Philip G. Janicak · Stephen R. Marder
Rajiv Tandon · Morris Goldman *Editors*

Schizophrenia

Recent Advances in Diagnosis and Treatment

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ISBN 978-1-4939-0655-0 ISBN 978-1-4939-0656-7 (eBook)
DOI 10.1007/978-1-4939-0656-7
Springer New York Heidelberg Dordrecht London

Library of Congress Control Number: 2014936416

Printed on acid-free paper

Springer is part of Springer Science+Business Media (www.springer.com)

For Rodney and Jude who taught me so much

Phil

To Paula for her support and her patience

Steve

For Gitanjali, Anisha, Neeraj, and Nammi
for their love and support

Rajiv

For Hilarie, Frank DeHaan, and Paul Tolpin
to whom I am forever grateful

Morrie

Preface

Over 60 years ago, chlorpromazine dramatically changed our understanding and treatment of patients suffering from schizophrenia. Clozapine reemerged over 20 years ago, representing both our most effective drug for refractory schizophrenia and most vexing in terms of its disadvantages. While some would argue that there has been little progress since, an enormous amount of research into the underlying pathoetiology of schizophrenia has been conducted. This body of knowledge sets the stage for future progress in:

- Parsing out the heterogeneity associated with the umbrella term "schizophrenia," allowing for subgroups to emerge with major implications for more effective treatment approaches.
- Early identification of at-risk individuals who may be prophylactically treated to prevent or attenuate the disease process.
- Developing therapies which are more targeted and less deleterious in terms of unwanted effects.
- Translating symptom reduction into improved functionality and quality of life.

At present, the most promising initiatives to facilitate these goals are in the areas of genetics, neuroimaging, and psychosocial rehabilitation approaches.

This book is divided into four sections. Part I summarizes our present state of knowledge about the diagnosis and treatment of schizophrenia. Part II considers recent discoveries into its pathoetiology, including the status of biological markers, genetics, and neuroimaging as they relate to diagnosis and potential novel therapeutic approaches. Part III explores the optimization of our present therapeutic approaches, novel treatments, and management of the substantial risks associated with both the illness and its present therapies. Part IV discusses progress in the long-term management of schizophrenia, focusing on biological and psychotherapeutic strategies to improve functioning and facilitate recovery. Finally, Part V considers future directions and predictions of how diagnosis and treatment of schizophrenia will change.

While the sense of being in a "holding pattern" is inevitable given the pace of progress in the clinical arena, there is also a growing recognition that the significant strides taken in basic research will usher in a second renaissance in the care of patients suffering from schizophrenia.

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Part I
Overview

Chapter 1
Introduction

Philip G. Janicak, Stephen R. Marder, Rajiv Tandon, and Morris Goldman

Clinical Features

Schizophrenia is a heterogeneous disorder with a broad range of symptoms and a variable course. It typically afflicts younger individuals, often leading to lifelong disability. The most dramatic aspect of this disease is the periodic episodes of psychotic symptoms (e.g., auditory hallucinations, paranoid delusions) which at times require emergent interventions to protect the individual and others. This illness, however, also includes more persistent impairment in multiple areas of cognition, substantial deficits in interpersonal relationships, and depressed mood, at times predisposing individuals to a heightened risk of suicide. The culmination of these symptoms may be a marked diminution in the ability to function adequately (e.g., socially, occupationally), as well as a greatly diminished quality of life.

The concept of schizophrenia continues to evolve with our expanding ability to detect genetic and environmental influences, as well as their interactions, advances in neuroimaging, and recognition of other biological factors that better inform our

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P.G. Janicak et al. (eds.), *Schizophrenia: Recent Advances in Diagnosis and Treatment*,
DOI 10.1007/978-1-4939-0656-7_1,

understanding of this condition. While the search for biomarkers has been frustratingly slow, it is important to the development of more targeted treatments and to better predict clinical outcomes.

In parallel, treatments for schizophrenia are evolving to accommodate this new information. Unfortunately, the pace of these initiatives leaves patients and clinicians with therapeutic approaches that presently fall far short of ideal. For example, functional impairment across multiple psychopathological dimensions continues to occur in most patients and life expectancies are dramatically shortened due to modifiable factors such as suicidality, substance abuse, and cardiovascular disease [1, 2].

Schizophrenia is characterized by multiple psychopathological dimensions (positive, negative, cognitive, mood, disorganization, and motor symptoms) whose severity varies across patients and course of illness. Each of these dimensions contributes to the significant distress and disability associated with this disorder. Additionally, these symptom dimensions appear to have different underlying neurobiological substrates and exhibit distinctive patterns of response to the various treatments utilized. The course of schizophrenia is characterized by a sequential trajectory that involves a *premorbid phase* with subtle and nonspecific cognitive, motor, and/or social dysfunction. The *prodromal phase* may include attenuated positive, negative, and cognitive symptoms and declining function. The *first psychotic episode* heralds the formal *onset* of schizophrenia, and often a lifelong course with the initial decade of illness sometimes marked by *repeated episodes of psychosis* with partial and variable degrees and duration of *inter-episode remission* and accrual of disability with each episode of illness. Finally, a *stable phase* or *plateau* may include psychotic symptoms that are less prominent while negative symptoms and cognitive deficits may increasingly predominate [3]. *Recovery* of varying degrees can occur at any stage of the illness and, in contrast to the original perspective of unalterably progressive deterioration, a significant proportion of patients do exhibit substantial improvement.

In Chap. 2, the description and definition of our current clinical understanding of schizophrenia in DSM-5 are summarized and its treatment implications discussed [4, 5].

Epidemiology and Genetic and Environmental Risk Factors

A comprehensive review of 150 studies from 33 countries indicated that between 1965 and 2001 the *mean incidence* of schizophrenia was 15.2 per 100,000 (range = 7.3–43 per 100,000) [6]. Further, the incidence was higher (i.e., a ratio of 1.4) and the onset of illness earlier (i.e., 2–3 years) in men than women [7]. A second review estimated that the *lifetime prevalence* was 4.0 per 1,000 [8].

As emphasized in Chap. 5, the central role of genetic factors in the etiology of schizophrenia has long been recognized. The role of environment in the development of schizophrenia, however, is now being increasingly appreciated. For example, existing data indicate that being raised in an urban versus rural setting confers an up

to twofold greater risk for developing this disorder and birth during winter and early spring increases the risk by 5–15 % [9, 10]. In addition, culture plays an important role in symptom presentation, course, and outcome leading to a decreased or increased chance of being diagnosed with schizophrenia [11].

Longitudinal and birth cohort studies are also providing a growing list of potential risk factors such as *prenatal* environmental (e.g., in utero infections, micronutrient deficiencies, obstetric complications such as preeclampsia or brain damage) or *postnatal* environmental (e.g., stress, inflammation, cannabis use) effects in the etiopathology of schizophrenia [12]. These factors appear to interact in complex ways with genetic, psychological, sociocultural, and economic issues to increase the risk of developing this illness. For example, four candidate genes for schizophrenia may play a role in obstetric-related hypoxic events (i.e., AKT1, BDNF, GRM3, DTNBP1) [13]. In the context of cannabis use, one meta-analysis of prospective studies found a pooled odds ratio of 2.3 (95 % CI = 1.7–2.9) for an association between cannabis use and increased risk for schizophrenia [14]. Another meta-analysis provided evidence that cannabis may play a role in an earlier onset of psychosis [15]. Yet a third study found an association between cannabis use and a more adverse course of schizophrenia over a 10-year follow-up period [16]. Further, as an example of gene x environment interaction, it appears the possession of the catechol-*O*-methyltransferase (COMT) valine 158 allele which increases vulnerability to psychosis may be exacerbated by cannabis use [17]. These studies offer the hope that environmental factors can be addressed with existing and future interventions, ultimately reducing the risk of developing or favorably moderating the course of schizophrenia.

Overview of Neurobiology

A range of neurobiological differences between individuals with and without schizophrenia have been defined and their relevance to the pathophysiology of schizophrenia is reviewed in Chaps. 3–6 [18]. These chapters provide summaries of our current knowledge regarding the neurobiology of schizophrenia, but are largely devoted to understanding some of the limitations of previous research approaches, as well as how current approaches address these challenges. All four chapters underscore the need to identify biomarkers and intermediate phenotypes in order to focus on future research efforts. Chapter 3 emphasizes the general need to characterize mechanisms of brain function to better distinguish adaptive from pathologic processes. The failure to consider the likelihood that many findings are a reaction to pathology rather than contributing to the pathology may in itself account for a failure to better integrate the massive amount of evidence supporting the view that schizophrenia reflects a diseased brain. Chapter 4 lays out some of the barriers which are beginning to be addressed, as well as providing a framework for integrating diverse findings by providing examples of how knowledge from several different domains can be integrated yielding more powerful models to investigate the illness(es). Chapter 5 provides an historical review of genetic findings in

schizophrenia and at the same time summarizes the logic, strengths, and weakness of these evolving approaches. It also attempts to provide a roadmap of how this field will incorporate multimodal approaches in the coming years. Chapter 6 addresses neuroimaging and focuses more on recent advances, again illustrating efforts to incorporate multiple modalities in the service of better characterizing the functional significance of findings and providing biomarkers of the illnesses. What follows next is background information about the different research domains which characterize current neurobiologic efforts. We anticipate this will help contextualize the chapters themselves.

Neurotransmission

Dopamine (DA) is a critical neurotransmitter in our conceptualization of schizophrenia. While existing antipsychotics all impact this system (i.e., primarily through antagonism of the DA_2 receptor), their greatest clinical benefit is in controlling DA mesolimbic hyperactivity and ameliorating positive symptoms. More recent data also indicates an ability to improve brain reward mechanisms [19]. Other neurotransmitters (e.g., serotonin, glutamate, GABA acetylcholine) also appear to play important roles, particularly for more difficult-to-treat symptoms (i.e., negative, cognitive). Indeed, these systems may alter DA neurotransmission and in turn be impacted by DA. In this context, specific genes related to these neurotransmitters may be associated with the pathoetiology of schizophrenia. Examples include glutamate (e.g., GRIN2B, SAP97) and serotonin (e.g., 5-HTT variants) [20–22]. Associations with immune system dysregulation (e.g., increased levels of proinflammatory cytokines, high levels of autoantibodies) and schizophrenia have also identified potential genetic links, including the IL-3 receptor (IL3RB) which may interact with polymorphisms of neuregulin (NRG1) to increase the risk of schizophrenia [23]. Another example is the observation of increased antibodies for the α7 nicotinic cholinergic receptor in patients with schizophrenia [24]. These issues are considered in greater detail in Chap. 4.

Genetics

Several genetic and nongenetic factors (i.e., multifactorial mode of inheritance) contribute to the risk of developing schizophrenia [25]. Family, twin, adoption, and candidate gene studies all support a genetic component for psychotic disorders. Further, genome-wide association studies (GWAS) suggest that submicroscopic chromosomal abnormalities (i.e., *copy number variants* (CNVs)) involving deletions and/or duplications may confer a higher risk for developing schizophrenia [26]. These studies provide evidence of a role for both common and rare, large CNVs in schizophrenia [27]. These abnormalities may occur de novo, be inherited, or involve both processes. Early findings of CNVs at the 22 q 11.2 locus indicate

they may play an important role in the susceptibility to complex disorders such as schizophrenia [28]. Such changes may interact with a polygenic liability and/or environmental factors to increase this risk [29]. There is also a signal for an association with genetic markers in the *major histocompatibility complex* (6 p 22.1) containing genes. Finally, more recent evidence from a genome-wide analysis indicates a greater overlap in specific *single-nucleotide polymorphisms* (SNPs) for five major psychiatric disorders (i.e., schizophrenia, bipolar disorder, autism spectrum, attention-deficit hyperactivity, and major depressive disorder) [30]. Despite these advances, most of the tentative heritability of schizophrenia is still unclear.

In this context, the exploration of *epigenetic variations* with recent technological advances may better inform us about the impact of environment on genetic expression associated with neuropsychiatric disorders [31]. Epigenetics involves the modification of chromatin (i.e., the DNA–histone complex in the nucleus). These phenomena can dynamically moderate gene expression separate from DNA sequence variation and may regulate important CNS neurobiological and cognitive processes [32]. Various external factors can promote lability in the epigenome (e.g., altered DNA methylation and histone modifications) predisposing an individual to develop schizophrenia. Certain antipsychotics (e.g., clozapine) may also alter the epigenome [33]. Although our understanding of this process is in its infancy, the dynamic and reversible qualities of the epigenome may facilitate the development of novel diagnostic and therapeutic approaches for schizophrenia. A more complete discussion of these issues is provided in Chap. 5.

Neuroimaging

The use of emerging *neuroimaging technology* to determine the pathoetiology of schizophrenia has expanded dramatically over the last 30 years. Techniques such as positron emission tomography (PET); single-photon emission computed tomography (SPECT); structural, real-time functional and spectroscopic magnetic resonance imaging (MRI); and diffusion tensor imaging (DTI) are all contributing to a better understanding of neurodevelopmental and neurodegenerative aspects of this illness. For example, there is a growing appreciation of dysregulated neural connectivity which moves beyond identification of associated structural and functional abnormalities [34]. The field of "connectomics" has recently identified such impairments in first episodes of schizophrenia [35]. A recent meta-analysis of 44 studies (618 patients; 606 controls) using PET or SPECT imaging indicated that the largest dopamine abnormalities in patients with schizophrenia may be *presynaptic* (i.e., DA synthesis capacity, baseline DA synaptic levels, DA release) [36]. Ironically, the authors note that all presently available antipsychotic agents target *postsynaptic* activity. Another meta-analysis of 27 studies (928 patients; 867 controls) found that over time (up to 10 years) patients with schizophrenia had significantly larger decreases in whole brain volume; whole brain and frontal gray matter; and frontal, parietal, and temporal white matter [37]. A recent high resonance MRI study ($n=156$) detected disruption in white matter tracts in patients with deficit (i.e., negative

symptoms) schizophrenia (i.e., right inferior, right arcuate, and uncinate fasciculi) in contrast to nondeficit patients and healthy controls [38]. In addition, there is evidence for accelerated aging in white matter tracts in schizophrenia using DTI-derived fractional anisotropy [39]. These issues are discussed in greater detail in Chap. 6.

Finally, combining various imaging approaches with molecular genetics provides a powerful tool to understand the origins of and the ability to develop more targeted therapeutic interventions for managing schizophrenia [40, 41]. These issues are touched on in Chap. 9.

Endophenotypes

A related area is the identification of *endophenotypes* which may serve as biomarkers for schizophrenia. These are molecular, neuropsychological, neuroimaging, and electrophysiological observations closely associated with the genetic basis of an illness [42]. They represent intermediate links between genetic variation and clinical presentation which can clarify genetically transmitted, brain-based deficits across patients and relatives [43, 44]. To qualify, these biomarkers should meet certain criteria, including heritability, trait stability, test–retest reliability, diagnostic stability, cosegregation of illness within families, and simplicity [45].

One potential example is the dysregulation of GABA inhibitory interneurons during brain maturation in schizophrenia [46, 47]. Another example is neuroimaging in schizophrenia which has identified both structural and functional dysregulation that may serve as endophenotypes for this disease [48]. These include prediction of transition to psychosis in high risk individuals, linking these abnormalities to specific symptoms of schizophrenia, and associating structural changes with clinical outcome.

Recently, the Consortium on Genetics for Schizophrenia reported on 12 regions meeting GWAS significant (e.g., antisaccade task; 3p14) and suggestive (e.g., emotion recognition; 1p36) criteria for potential endophenotypes related to schizophrenia [49]. Yet another area of inquiry has linked abnormal sleep with COMT mutations. Such disturbances during adolescence may impair cortical development leading to deficits in cognitive performance and sleep-related cognitive deficits and may also serve as an endophenotype for schizophrenia [50]. Chapter 5 contains a more complete discussion of these issues.

Management of Schizophrenia

The recent research regarding various environmental influences, neurotransmitters, genetics, neuroimaging, and other biological markers is providing important clues to the pathophysiology of schizophrenia with the hope of better informing our

treatment approaches. Thus, we increasingly recognize the need to employ creative strategies with a variety of therapies to alleviate the multiplicity of symptoms that characterize schizophrenia in both its acute and long-term management. These include the development of novel antipsychotic agents, adjuncts to existing antipsychotics (e.g., glutamatergic), a variety of novel psychotherapeutic interventions (e.g., cognitive remediation), and therapeutic neuromodulation (e.g., transcranial magnetic stimulation).

As our appreciation of the implications regarding clinical response, remission, and recovery also grows, the emphasis is shifting to earlier disease detection and interventions. The study of high risk (HR) states for psychosis focuses on those individuals with prepsychotic or potential prodromal symptoms [51]. In this context, a meta-analysis of 19 studies (1,188 HR patients; 1,029 controls) found evidence for impaired neurocognition and social cognition in this population [52]. In particular, deficits in verbal fluency and memory functioning appeared to increase the risk of transitioning to psychosis.

Such approaches offer hope for a better understanding about the origins of this disorder and the provision of more appropriate services to favorably alter its course. For example, a recent open-trial ($n=31$) considered the role of low-dose aripiprazole (i.e., up to 7.5 mg/d) in drug-naive or short-exposure patients with ultrahigh risk states or first-episode psychosis [53]. In this study, the use of lower doses was efficacious, but side effects were still prevalent. In another small trial ($n=31$), the authors found evidence for reduced efficacy with a second exposure to antipsychotics after a first episode, suggesting relapse may be biologically harmful to some patients [54].

Complications Associated with Schizophrenia and Its Treatment

Long-Term Management

Until recently, long-term management in schizophrenia focused on preventing psychotic relapse and helping patients remain out of the hospital. This approach has been reevaluated based on the observation from clinicians and patients that many patients were unable to meet their personal goals. As a result, interventions—both psychosocial and pharmacological—are increasingly focused on improving an individual's vocational and social outcomes as well as the quality of his or her life. New approaches to long-term management also address improving physical health. Individuals with psychotic illness are more vulnerable to premature death due to cardiovascular disease. In addition, obesity and type 2 diabetes are highly prevalent and can interfere with one's health and social adjustment. Decision-making about the selection of a pharmacological treatment should be guided by these health concerns. Moreover, regular interactions between clinicians and patients should focus on modifiable risk factors associated with poor health such as diet, exercise, and smoking.

Improving functioning and quality of life almost always requires combining an antipsychotic medication with a psychosocial intervention. As noted in Chap. 14 a number of psychosocial interventions have a strong evidence base. These include symptom-based interventions such as cognitive behavioral therapy for psychosis and treatments which directly affect functioning such as skills training and supported employment. Unfortunately, these treatments are often underutilized and suggest that implementing these practices can potentially improve outcomes.

It is also important to point out that there is strong evidence that psychosocial interventions are only effective when patients are stabilized on an antipsychotic medication [55, 56]. Assuring that individuals with schizophrenia remain on their medications is a continuing challenge during long-term treatment. As noted in Chap. 13, there are a number of approaches to improve adherence, including educating individuals as to why they should remain on medications even when they are feeling well. The recent introduction of new long-acting antipsychotic medications provides additional tools for assisting patients to continue their treatment.

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Chapter 2
The Evolving Nosology of Schizophrenia: Relevance for Treatment

Rajiv Tandon and Dawn Bruijnzeel

Introduction

The formulation of our current nosology for psychiatric disorders began in the late nineteenth century and culminated in publication of a section related to mental disorders (Section V) in the sixth revision of the International Classification of Disease (ICD-6) in 1949 and in the first edition of the American Diagnostic and Statistical Manual of Mental Disorders (DSM-I) in 1952 [1, 2]. In subsequent revisions of these texts (ICD-7–ICD-10 and DSM-II–DSM-5), substantial changes in diagnostic criteria were made but the basic structure was preserved. Differences between the two systems narrowed and there is now marked concordance between DSM-5 and ICD-10 [3, 4]. DSM-5 became operational in 2013, but ICD-10 is currently being revised and ICD-11 will likely be released in 2016. Schizophrenia is one of the major diagnostic categories in all versions of both manuals.

Although schizophrenia has been studied as a specific disease entity for the past century, its precise nature (core definition, boundaries, causes, and pathogenesis) remains undefined [5, 6]. Since its designation as dementia praecox by Kraepelin (1856–1926) and schizophrenia by Eugen Bleuler (1857–1939), its definitions have varied and its boundaries expanded and receded over the past century (Fig. 2.1) [7, 8]. Thus, it is instructive to examine the varying definitions of schizophrenia over the past 150 years and trace its evolution to the present DSM-5 and soon-to-be released ICD-11 [9, 10].

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P.G. Janicak et al. (eds.), *Schizophrenia: Recent Advances in Diagnosis and Treatment*,
DOI 10.1007/978-1-4939-0656-7_2,

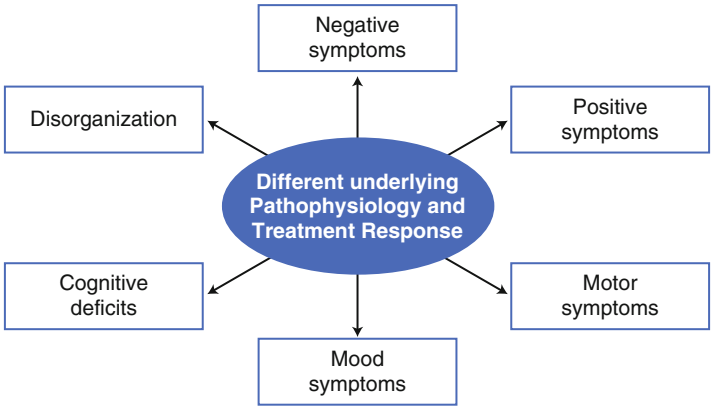

Fig. 2.1 Dimensions of schizophrenia (Adapted with permission from Tandon et al. [29])

The Concept of Schizophrenia from the Nineteenth Century to DSM-IV and ICD-10

The current concept of schizophrenia derives from Emil Kraepelin's formulation of dementia praecox in the late nineteenth century and his elaboration of this idea in the early part of the twentieth century [7, 11]. Until that time, there were two broad prevailing constructs of major psychiatric illness or psychosis. Griesinger postulated that there was only one basic form of psychosis with diverse manifestations attributable to endogenous and environmental factors (einheitpsychose), while others suggested that there were several distinct psychotic disorders (e.g., catatonia, hebephrenia, folie circulaire, dementia paranoides, melancholia) [12–15].

Kraepelin discerned two distinct patterns for the course of illness among the various psychotic disorders and used them to define and classify mental conditions. His approach was influenced by the contemporaneous classification of general paresis of insanity (neurosyphilis or tertiary syphilis). The distinctive course and outcome among patients with this illness in psychiatric hospitals led to its delineation, etiological identification, development of the diagnostic Wasserman test, and later to definitive treatment. Kraepelin concluded that course and outcome of illness are the best disease characteristics to use in defining and demarcating psychiatric disease entities. Based on his study of several hundred cases of hospitalized patients, he delineated two distinct disorders: *dementia praecox*, which included catatonia, hebephrenia, and paranoid states; and *manic-depressive insanity*, which comprised folie circulaire and melancholia [16]. Kraepelin identified schizophrenia on the basis of its onset (in adolescence or early adulthood), course (deteriorating), and outcome (demence or "mental dullness") [7, 11]. He distinguished dementia praecox from manic-depressive insanity on the basis of the chronicity and poor outcome of the former contrasted with the episodic nature and better outcome of the latter.

During the same time period, Eugen Bleuler renamed this condition "schizophrenia" because he considered the splitting of different psychic functions to be its defining characteristic [8]. He postulated that schizophrenia was defined by a set of basic or fundamental symptoms which were unique and always present in those with this group of diseases, whereas its course and outcome were variable [8, 11]. He called delusions and hallucinations accessory symptoms and considered them to be variable and nonspecific. He described fundamental symptoms (now identified as negative symptoms) which included autism, ambivalence, flat affect, and loosening of associations. He further believed that many mild cases existed and considerably broadened the scope of the disease construct. He included latent and simple forms as part of this entity which he called the group of schizophrenias.

Influenced by the thinking of Karl Jaspers, Kurt Schneider (1887–1967) believed that impairment of empathic communication was the fundamental defect in schizophrenia [17]. He considered "un-understandability" of the personal experience as pathognomonic. Based on this premise, he defined 11 first-rank symptoms which he considered diagnostic of schizophrenia [11, 17]. Given central importance in the Present State Examination, these symptoms were incorporated into both ICD-9 and DSM-III definitions of schizophrenia [18].

Definitions of schizophrenia over the past half-century from DSM-I–DSM-IV and ICD-6–ICD-10 all incorporated Kraepelinian chronicity, Bleulerian negative symptoms, and Schneiderian positive (first-rank) symptoms as part of their definition. The relative emphasis paid to these three roots, however, has varied. In the 1960s and 1970s, there was significant discordance between the DSM (I and II) and ICD (7 and 8) systems with regard to this issue. Whereas DSM-I and DSM-II highlighted the Bleulerian perspective (emphasis on negative symptoms and very broad definition of the schizophrenias, including latent, pseudoneurotic, pseudopsychopathic, and residual subtypes), ICD-7 and ICD-8 stressed Kraepelinian chronicity [1, 19]. This overly broad definition of schizophrenia in the DSM system led to poor reliability in diagnosing schizophrenia and a marked discrepancy between its diagnosis in the USA and the rest of the world which utilized the ICD system [20]. In reaction to these anomalies, the operationalized criteria of DSM-III provided the narrowest definition of schizophrenia with an emphasis on Kraepelinian chronicity and Schneiderian positive (first-rank) symptoms [21]. In fact, the imperative of improved reliability and the belief that positive symptoms could be more reliably diagnosed resulted in positive symptoms becoming the defining characteristic of schizophrenia in DSM-III and ICD-9. Further, certain positive symptoms such as Schneiderian first-rank symptoms were accorded special importance and the presence of any single bizarre delusion or special auditory hallucinations (voices arguing or commenting) was considered sufficient for a diagnosis of schizophrenia in DSM-III and DSM-IV and ICD-9 and ICD-10 [22, 23]. Although there were modest changes in the definition of schizophrenia from DSM-III to DSM-IV, the importance of positive symptoms with the special significance placed on bizarre delusions and special hallucinations in the diagnostic criteria remained.

The Present: DSM-5 and Towards ICD-11

The reliability of diagnosing schizophrenia improved substantially after the introduction of DSM-III in 1980, but several limitations in its definition and description became apparent over the past three decades [24]. Although the significant heterogeneity of schizophrenia was always recognized, with multiple etiological factors and pathophysiological processes, it has been treated as a singular entity [6, 25, 26]. Now, however, it is almost certain that our construct of schizophrenia encompasses not one but several diseases [27]. In the past, we tried to explain the heterogeneity of the illness by defining distinct subtypes—paranoid, disorganized, catatonic, simple, and undifferentiated. These classic subtypes, however, provided a very poor description of the enormous heterogeneity of this condition. Subtypes' stability is low, reliability of diagnosing them weak, their validity questionable, and only the paranoid and undifferentiated subtypes were utilized with some frequency [28, 29]. Because these subtypes have virtually no clinical or research utility, they are being eliminated from the classification system in DSM-5 and ICD-11 [10, 30, 31]. Instead, the heterogeneity of schizophrenia is now formally described in terms of psychopathological dimensions (discussed below) which will be measured in all patients throughout the course of the illness [32]. Since the severity of different symptom domains varies in each patient over the illness course and in response to treatment, such dimensional assessments will be an invaluable tool, allowing clinicians to provide individualized, measurement-based care [33].

Another significant limitation in definitions of schizophrenia until DSM-IV and ICD-10 was the inability to characterize the distinct stages of the illness [34]. The classification system did not allow clinicians to adequately describe the course of their patient's illness (e.g., first episode, chronic) or denote the patient's current clinical status (e.g., active symptoms, in partial or full remission). The provision of modified course specifiers in both DSM-5 and ICD-11 helps to redress this anomaly [10]. Additionally, there was no provision in DSM-IV or ICD-10 to describe the early or late prodromal phases of the illness when there is the possibility of arresting active pathology and preventing disease progression [35, 36]. The addition of Attenuated Psychosis Syndrome as a condition for further study in Section 3 of DSM-5 will partly address this deficiency.

Revisions in DSM-5 and currently proposed changes in ICD-11 will correct the major failure in properly characterizing the clinical heterogeneity of schizophrenia and denoting stages in the evolution of the disease. Additionally, revisions in DSM-5 and ICD-11 correct other discrepancies in the DSM-IV and ICD-10 description of schizophrenia. The four major changes made in DSM-5 (and likely to be made in ICD-11) are separately summarized below.

Changes in Characteristic Symptoms of Schizophrenia in DSM-5 and ICD-11

The changes in the diagnostic criteria of schizophrenia in DSM-5 were modest and continuity with DSM-IV is broadly maintained. No changes were made in the

Table 2.1 Characteristic symptoms of schizophrenia (Criterion A) in DSM-IV and DSM-5

DSM-IV-TR criterion A	*DSM-5* criterion A
Schizophrenia	
Criterion A. *Characteristic symptoms*:	Criterion A. *Characteristic symptoms*:
≥2 of the following, each present for a significant portion of time during a 1-month period (or less if successfully treated)	≥2 of the following, each present for a significant portion of time during a 1-month period (or less if successfully treated). *At least one of these should include 1–3*
1. Delusions	1. Delusions
2. Hallucinations	2. Hallucinations
3. Disorganized speech	3. Disorganized speech
4. Grossly disorganized or catatonic behavior	4. Grossly disorganized or catatonic behavior
5. Negative symptoms, i.e., affective flattening, alogia, or avolition	5. Negative symptoms, i.e., restricted emotional expression 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 behavior or thoughts, or ≥2 voices conversing with each other	*Note*: Deleted

Source: Reprinted with permission from Tandon R, et al. [51]

minimum duration (6 months), functional impairment (necessary), and exclusion (psychotic mood disorder, schizoaffective disorder, substance-induced psychotic disorder, psychosis secondary to a general medical condition) criteria. Two key changes, however, were made in the definition of characteristic symptoms required in the active phase of the illness (Table 2.1):

- Elimination of special treatment of *bizarre delusions and other Schneiderian first-rank symptoms*. In DSM-IV, only one characteristic symptom was required if it was a bizarre delusion or special hallucination (voices arguing or commenting). Since Schneiderian first-rank symptoms are not pathognomonic for schizophrenia, do not have diagnostic specificity or prognostic significance, and the reliability of distinguishing bizarre from non-bizarre delusions is poor, they will be treated like any other "positive symptom" with regard to their diagnostic implication in DSM-5 and ICD-11 [37–40]. Thus, two characteristic symptoms will be necessary to make a diagnosis of schizophrenia even if one of them is a bizarre delusion or "special hallucination." This change affects a very small number of patients, who will now more appropriately receive a diagnosis of delusional disorder [41].
- Requirement in both DSM-5 and ICD-11 that at least one of the two required symptoms to meet characteristic criterion A be delusions, hallucinations, or disorganized thinking. These are core "positive symptoms" diagnosed with high reliability and might reasonably be considered necessary for a diagnosis of schizophrenia. Less than 1 % of patients with DSM-IV schizophrenia will be affected by this change and in such patients a necessary exploration of other causes of catatonia will be required [41–43].

Elimination of Classic Subtypes of Schizophrenia in DSM-5 and ICD-11

As noted previously, the schizophrenia subtypes had limited diagnostic stability, low reliability, poor validity, and little clinical or research utility. Further, except for the paranoid and undifferentiated subtypes, the others were rarely utilized in most mental healthcare systems. Consequently, these subtypes are eliminated in DSM-5 and ICD-11. This change should simplify clinical description of schizophrenia.

Addition of Psychopathological Dimensions of Schizophrenia

Schizophrenia is characterized by several psychopathological domains which have distinctive courses, patterns of treatment response, and prognostic implications (Box 2.1 and Fig. 2.1). The relative severity of these symptom dimensions varies across patients, as well as within patients at different stages of their illness. Measuring their relative severity through the course of illness and in the context of treatment can provide useful information to the clinician about the nature of the illness in a particular patient and the specific impact of treatment on different aspects of the illness (e.g., analogous to measuring pulse, temperature, blood pressure, respiratory rate). As a simple rating scale (akin to a thermometer or a sphygmomanometer), it should encourage clinicians to explicitly assess and track changes in the severity of these dimensions and to use this information to guide treatment. Six symptom domains with a total of eight items are described in DSM-5 and each item is scored on an anchored 0–4 scale (see Box 2.1) [32]. In addition to their clinical utility, dimensional measurement should prove useful from a research perspective and thereby permit studies on etiology and pathogenesis which cut across current diagnostic categories [44, 45]. Such approaches are consistent with recent findings in genetics and neuroscience and the recent Research Domain Criteria (RDoC) project initiated by the National Institutes of Mental Health [46, 47].

Box 2.1 Dimensions of Psychotic Disorders: Assessment of Severity

All dimensions will be assessed on a 0–4 scale cross-sectionally, with severity assessment based on symptoms in the past 7 days.

1. Delusions
2. Hallucinations
3. Disorganization
4. Negative symptoms
5. Impaired cognition
6. Depression
7. Mania
8. Psychomotor symptoms including catatonia

Attenuated Psychosis Syndrome

It is believed that the still unsatisfactory outcome of schizophrenia in a significant proportion of individuals with the disorder is due to the identification of the illness and initiation of treatment late in its course after a substantial amount of damage has occurred. The introduction of Attenuated Psychosis Syndrome (Box 2.2) in Section 3 of DSM-5 will support the efforts of clinicians to recognize and monitor psychotic symptoms early in the course of their evolution, and, if necessary, intervene during these crucial stages [35, 36, 48]. Early recognition and intervention are important in other branches of medicine and these changes in DSM-5 should stimulate the development of a similar practice in psychiatry. Although recognition of Attenuated Psychosis Syndrome is important, the ability to reliably diagnose the condition in routine practice is not demonstrated and its nosologic relationship to other psychiatric diagnostic entities is not precisely defined [36, 49]. Consequently, it is not in the main body (Section 2) of the DSM-5 but in Section 3 as a condition needing further study [35]. It should be emphasized that its diagnosis is *not* an indication for routine antipsychotic treatment but should instead prompt a careful search for comorbidities (e.g., anxiety, depression, substance use disorder) and their appropriate treatment along with close monitoring for a possible transition to psychosis.

Box 2.2 Criteria for Attenuated Psychosis Syndrome in DSM-5 [3]

All six of the following:

1. *Characteristic symptoms*: at least one of the following in attenuated form with intact reality testing, but of sufficient severity and/or frequency that it is not discounted or ignored.
   (a) Delusions
   (b) Hallucinations
   (c) Disorganized speech
2. *Frequency/currency*: symptoms meeting criterion A must be present in the past month and occur at an average frequency of at least once per week in past month.
3. *Progression*: symptoms meeting criterion A must have begun in or significantly worsened in the past year.
4. *Distress/disability/treatment seeking*: symptoms meeting criterion A are sufficiently distressing and disabling to the patient and/or parent/guardian to lead them to seek help.
5. *Exclude other DSM-5 disorder*: symptoms meeting criterion A are not better explained by any DSM-5 diagnosis, including substance-related disorder.
6. *Exclude prior psychotic disorder*: clinical criteria for any DSM-5 psychotic disorder have never been met.

Treatment Implications of Current Conceptualization of Schizophrenia: 2014 and Beyond

For the past century, schizophrenia was conceptualized as a singular disorder with a distinctive pathology, albeit with multiple etiological factors and diverse manifestations. This formulation dictated a single specific treatment directed at the common pathology (i.e., antipsychotic medications). These agents, however, are ineffective against some core features of the illness, such as negative symptoms and cognitive deficits [50]. Although researchers assiduously searched for an alternative core pathology in schizophrenia, no single mechanism has been found and no single treatment is effective against all aspects of the illness. With DSM-5, schizophrenia is explicitly conceptualized as a multidimensional illness with each dimension potentially explained by a distinct pathophysiology and the target of a unique treatment [51].

In DSM-5, six distinct dimensions of schizophrenia are defined (Fig. 2.1). Whereas positive symptoms and mood symptoms have two items (delusions and hallucinations for positive symptoms, and depression and mania for mood symptoms), the other four dimensions have one item (Box 2.1). Each item is scored on an anchored 0–4 scale (Section 3 of DSM-5) [3]. Different schizophrenia patients exhibit varying admixtures of symptom severity across the six dimensions. Additionally, these dimensions respond differently to various treatments and different patients show dissimilar patterns of treatment response. Unique measurement of how each of these distinct dimensions responds to specific treatments in individual patients enables monitoring of response and appropriate treatment adjustments. The availability of a simple scale which provides measures of symptom severity across these distinct dimensions enables measurement-based, individualized treatment.

Antipsychotic medications are particularly effective for treating positive symptoms and disorganization in schizophrenia. Specific treatments are in development to address negative symptoms and cognitive deficits in schizophrenia. Hopefully, some of these will be effective and safe, becoming available for clinical practice in the near future. Antidepressants and mood stabilizers are moderately effective for the mood symptoms in schizophrenia. Antipsychotic medications, benzodiazepines, and electroconvulsive therapy all demonstrate efficacy for motor symptoms (including catatonia) in schizophrenia. As better treatments for various symptom dimensions are developed, more effective, "evidence-based" pharmacotherapy will be possible.

It is clear that schizophrenia is not one but several disorders. The delineation of unique psychopathological dimensions facilitates the identification of distinct etio-pathophysiological pathways to schizophrenia; development of specific biological tests for the "different schizophrenias"; elaboration of specific treatments for the "different schizophrenias"; construction of an etio-pathophysiological nosology of the schizophrenias; and most importantly, better outcomes for our patients [47, 52–54]. As DSM-5 provides a better bridge to this anticipated future, it also provides tools for more effective treatment of schizophrenia today [24, 45, 55].

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Part II
Recent Research into the Pathophysiology of Schizophrenia

Chapter 3
Overview of Neurobiology

Rajiv Tandon and Morris Goldman

we must strive to divide things by classes, where the natural joints are, and not try to break them apart after the manner of a bad carver

Plato, Phaedrus 265e

Introduction

In a *Nature* Perspective called "Rethinking Schizophrenia," the head of the National Institutes of Mental Health, Thomas R. Insel, acknowledged, "For schizophrenia our knowledge base in 2010 is mostly based on clinical observation" [1]. He observed "we still do not have a basic understanding of the pathophysiology of the disorder and therefore lack the tools for curative treatment." How, despite the several thousand scientific articles per year on schizophrenia reporting myriad evidence of brain dysfunction at multiple levels of analysis, has this situation arisen? A recent review noted that the situation is quite analogous to the blind men probing different parts of an elephant, each coming up with their own provisional assessment based on what they perceive [2]. In a subsequent article, Insel and others go on to identify some of the issues which in part are reflected in the revisions to the nosology of psychiatric disorders (i.e., DSM-5, ICD-10); the renewed effort to integrate pathologic findings into disordered brain functioning; and current priorities of funding agencies (i.e., R-Doc) [3]. These include:

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P.G. Janicak et al. (eds.), *Schizophrenia: Recent Advances in Diagnosis and Treatment*,
DOI 10.1007/978-1-4939-0656-7_3,

1. *Categorizing illnesses by reliably identifying collections of symptoms based on longitudinal observations* (*e.g., DSM-III, DSM IV*) *may be counterproductive*. Current evidence suggests that important biologic findings cross boundaries to the extent that persons with different disorders may share a common pathophysiology while the pathophysiology of different persons with the same disorder may be completely different. This should not be so surprising, given the complexity of the human mind and the many steps from genes to molecular mechanisms to neural circuits to behavior and psychopathology.
2. *Very few neurobiological findings in schizophrenia have been truly replicated.* For example, over 1,000 genes and 8,000 polymorphisms, as well as 25 imaging measures, are linked to schizophrenia. Non-replications and approximate replications are common. A major problem is the lack of an adequate sample size to account for the multiple comparisons intrinsic to studies of genes and brain structure when not guided by a specific hypothesis tested by a specific outcome measure. This provides opportunities for "approximate replications" which appear to (pseudo-) confirm a previous finding because so many different measures related to the original finding are obtained in the follow-up study.
3. *Schizophrenia is a heterogeneous disorder*. While this view has been asserted for decades and generally accepted by the neuroscience community, it does not have a major impact on research beyond leading to larger patient samples and multi-site studies. Among the reasons for not acknowledging this reality are that previous efforts to categorize the disorder have proven to be of no utility, and that it is much more difficult to balance groups of schizophrenia patients (compared with balancing groups of healthy controls). Over time, a general consensus developed that schizophrenia must be reconceptualized and investigators must "deconstruct the concept of schizophrenia, and then reconstruct the defined elements." Specifically, heterogeneity in clinical expression must be resolved by mapping phenotypic dimensions to markers of biological processes (intermediate phenotypes or endophenotypes) and eventually to causative etiological factors [4]. Precisely how this will be accomplished is not yet established, though several possible routes are proposed.
4. *The vast majority of studies compare a group of patients with a group of healthy individuals*. One does not need a biological test in most cases to make this distinction. These "extreme" comparisons are of little use to clinicians and do not advance our understanding of the illness(es). Furthermore, finding a biological difference between patients and controls does not tell us whether that difference reflects pathology, a restitutive process, or an epiphenomenon (i.e., *a finding is not necessarily pathology*).

In the remainder of this chapter, we discuss some of the implications which arise from these four critical issues. In particular, we point out how this recognition challenges basic assumptions guiding neuroscience research. When possible, we provide examples demonstrating the potential relevance to studying the neurobiology of schizophrenia.

Identifying Findings Is Not the Same as Identifying an Abnormality

Part of the logic of using healthy persons as controls is the belief that findings that cannot be accounted for by controlling for demographic (e.g., age, sex, race) and treatment factors (drug exposure, years of illness) are abnormalities. Surprisingly, with few exceptions, this assumption is rarely challenged, and one can easily identify examples by scanning the content of most clinic neuroscience journals [2]. The brain is a remarkably adaptive organ, and most activity is likely compensatory, perhaps designed around maintaining a specific psychological state(s) [5, 6]. It is likely that the vast majority of findings at all levels of analysis in schizophrenia are not abnormalities but instead reflect adaptive efforts which are quite distant from the initial insult(s).

To Determine If a Finding Reflects Pathology, Learn About Its Regulation

To determine whether a "finding" is adaptive (e.g., physiological response) or pathological, one needs to understand what normally regulates it. Often, this information is ignored even if available. For instance, many studies were interested in the possible association between plasma levels of the neurophysiologic peptides arginine vasopressin and oxytocin and severe mental illness [7]. Vasopressin serves primarily as the antidiuretic hormone maintaining plasma tonicity in a narrow range and plasma levels are largely determined by plasma tonicity (i.e., sodium concentration, osmolality). Of the 15 psychiatric studies published from 2000 to 2006 in which arginine vasopressin was the major outcome variable, only six provided a measure of plasma tonicity. Only two reported any of the other easily obtainable measures which modulate vasopressin levels (e.g., blood pressure, smoking, cortisol) and only one acknowledged that any of this was of possible relevance. Indeed, one asserted that "plasma osmolality was not measured because it is not associated with plasma vasopressin in depression" [8]. It seems quite possible that most biological functioning, even that related to severe mental illness, is only subtly disrupted, and that it may be very difficult to isolate even fundamental abnormalities if one does not concurrently measure factors known to modulate them. Thus, clinical researchers are well advised to measure confounding factors outside of the demographic and treatment-related variables usually assessed in current studies, especially if they are known to modulate the outcome variable of interest. It is quite possible, as discussed below, that follow-up studies assessing these modulatory influences might lead to a delineation of mechanisms and a better understanding of pathogenesis.

Some Abnormalities May Be Epiphenomena But Still Provide Clues About Mechanisms

While most of what goes on in the brain likely reflects compensatory processes, there still may be considerable "collateral damage" which has little to do with the mental illness. Such information may, however, provide clues to help identify the pathophysiology. This approach seems particularly promising for limbic functions which cover multiple domains, some of which can be reliably assessed (e.g., neurophysiologic, behavioral) and others which are more obscure (e.g., affect, cognition). For instance, a sequence of studies identified that polydipsic schizophrenia patients have subtle impairments in peripheral vasopressin regulation which are attributable to hippocampal volume loss but are unrelated to the mental illness [9, 10]. Concurrent work, however, suggests that this abnormality is closely associated with a generalized stress diathesis, as well as other neuroendocrine findings which contribute to these patients' social deficits [11]. Thus, while an abnormal finding per se may not contribute to a mental illness, it could direct you to the right "neighborhood."

Heterogeneity Obscures Findings by Mixing Patients with Deficient and Adaptive Function

The schizophrenia literature is full of studies showing patients are both higher and lower on a given neurobiologic measure, or that groups of patients exhibit a larger standard deviation than controls. While these results are often attributable to either small sample sizes, a failure to control for confounding variables or nonspecific factors associated with the mental illness; they may also reflect real differences which warrant further exploration. Measures of cortisol responses to psychological stress provide a good example of this. It is widely appreciated that patients with schizophrenia exhibit both hypo- and hypercortisolemia, and specifically elevated and blunted responses to psychological stress [12–14]. While some findings may reflect acuity of the illness or confounding effects of antipsychotic medications on the hypothalamo-pituitary axis, others may reflect real differences critical to understanding the mental disorder [15]. Schizophrenia patients experience more stressful events than controls which in healthy persons would blunt their responses to future stressors [16–18]. Furthermore, this blunting is proportional to indices of psychological resilience and the integrity of the hippocampus [19, 20]. Indeed, Brenner found that most schizophrenia patients with blunted responses exhibit evidence of greater resilience consistent with the response in healthy persons. Others, however, exhibited enhanced responses unaffected by the subject's psychological resilience [21]. These observations may be particularly relevant to understanding differences between polydipsic and nonpolydipsic schizophrenia patients. Polydipsic patients exhibit enhanced responses and nonpolydipsic patients exhibit blunted cortisol responses to psychological stress [22]. The polydipsic enhanced responses are

proportional to deformations in hippocampal structure not seen in those without polydipsia, while the blunted responses in nonpolydipsic patients may be linked to their higher level of functioning [10, 14]. Thus, this example demonstrates how failing to distinguish groups of schizophrenia patients whose findings "cancel each other out" potentially obscures data critical to understanding the pathophysiology of the illness for one group (i.e., hippocampal-modulated stress diathesis) and a potential treatment intervention for another (i.e., teaching coping skills to enhance resilience).

Compensatory Responses May Identify Potential Treatment Interventions for Other Patients

The identification of a particular "finding" in schizophrenia as a compensatory response to some known or unknown pathological insult might lead to a potentially effective treatment. For example, compensatory increased cholinergic activity during an acute psychotic phase of schizophrenia provides some of the impetus for the current interest in the evaluation of muscarinic and nicotinic cholinergic agents to treat schizophrenia (see Chap. 7) [23, 24].

How Does One Relate Underlying Neurobiology to Treatment of Schizophrenia

Despite the note of caution emphasized in this chapter, even the limited current understanding of the neurobiology of schizophrenia is still of value to the clinician. The range of etiological and pathophysiological factors considered relevant to the disorder is reviewed in the next three chapters. Many of the most consistent neurobiological findings are summarized in Chap. 4. Genetic findings in schizophrenia and the best way to understand their relevance are reviewed in Chap. 5. Neuroimaging findings in schizophrenia and their current and future clinical application are considered in Chap. 6. Although very little of this information has provided useful clinical tools to-date, changes in our current research paradigm warrant optimism for the future which is likely to expand clinical applicability because of both methodological and conceptual advances. Neurobiological research is also likely to benefit from improvements in nosology, with further refinements in the DSM criteria and incorporation of objective measures [25]. As neuroimaging and electrophysiological technologies mature, dysfunctions are more likely to become apparent. Better integration of neuroimaging, neurochemical and electrophysiological data, as well as the combined use of biomarkers may be more useful than single markers used in isolation. Multimodal imaging (e.g., combining fMRI with ERP data) may also be more useful than individual modalities alone. Better delineation of

endophenotypic markers and susceptibility genes are likely to yield more valid animal models for further hypothesis testing. Larger, multisite studies should improve statistical power to confirm or refute the tantalizing observations currently limited by small sample sizes.

Conclusion

The past three decades of research in the neurobiology of schizophrenia point to brain structural, functional, and neurochemical alterations in multiple regions and their connecting circuitries. These alterations appear to begin early in development and evolve during the course of the illness, suggesting a sequential derailment of developmental processes. While the precise meaning of these brain changes in schizophrenia currently remains unclear, conceptual and methodological refinements augur well for a better understanding in the near future.

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Chapter 4
Pathophysiology of Schizophrenia

Jaya Padmanabhan and Matcheri S. Keshavan

Introduction

The neurobiological basis of schizophrenia has been suspected for over a century, beginning with Kraepelin's description of *dementia praecox* [1]. Unlike other neurological disorders such as Alzheimer's disease, however, few clear-cut neuropathological observations emerged. This led to an eminent neurologist's comment that "schizophrenia is the graveyard of neuropathologists" [2]. Scientific research in this area stagnated for much of the early twentieth century as psychodynamic theories dominated our understanding of mental illness. Beginning in the 1960s, however, neurobiological approaches to schizophrenia reemerged, starting with the landmark finding of ventricular enlargement [3].

As Weinberger stated, the challenge of finding verifiable brain changes in schizophrenia no longer exists given the advent of sophisticated neuroimaging, electrophysiological, and neuropathological techniques over the past three decades which led to an improved, albeit incomplete, understanding of the pathophysiology of this illness [4]. Thus, we review the current understanding of the neurobiology of schizophrenia with a focus on the substantive body of literature largely accumulated over the past 30 years. We conclude with a summary of the prevailing theoretical models of its pathophysiology, gaps in our knowledge, and promising directions for future research (Box 4.1).

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P.G. Janicak et al. (eds.), *Schizophrenia: Recent Advances in Diagnosis and Treatment*,
DOI 10.1007/978-1-4939-0656-7_4,

Box 4.1 Key Facts in the Pathophysiology of Schizophrenia

- Structural brain findings:
  - Ventricular enlargement [3]
  - Subtle reductions in total gray matter volume [6]
  - Reductions in gray matter volume of the hippocampus and other medial temporal and limbic regions [7]
- Functional brain findings:
  - Decreased activation of prefrontal cortex (hypofrontality) [27]
  - Increased activation of temporal regions during hallucinations [31]
- Electrophysiological findings:
  - Diminished prepulse inhibition of startle response (PPI) [39] and diminished P50 suppression [46]
  - Decreased amplitudes of the P300 response [34] and mismatch negativity [54]
  - Abnormalities in gamma oscillations [58]
- Neuroendocrine, Oxidative, and Immunological
  - Elevated markers of oxidative stress, varying by clinical status [62]
  - Dysfunction of the hypothalamic–pituitary–adrenal axis (abnormal dexamethasone suppression) [74, 131]
  - Abnormal levels of inflammatory cytokines [68]
- Neuropathology
  - Reductions in dendritic spines and size of pyramidal neurons [98]
  - Relative preservation of total number of neurons [97]
  - The absence of gliosis and other neurodegenerative features [89, 97]
  - Reduced expression of GAD-67 in the dorsolateral prefrontal cortex [88]
- Neurochemical
  - Reduced *N*-acetyl aspartate in frontal and temporal regions [77]
  - Reduced PME (marker of membrane phospholipid synthesis) in prefrontal regions [80]
  - Elevated presynaptic dopamine function [83]

Brain Structure

Gray Matter

There are a number of well-established structural brain alterations in schizophrenia. The most consistent findings include enlargement of the third and lateral ventricles and slight reductions in total brain volume and total gray matter volume [5–7].

Additionally, regional reductions are reported consistently in the hippocampus, amygdala, parahippocampus, superior temporal gyrus, anterior cingulate, insula, and inferior and medial frontal gyri [7, 8].

Patients with first-episode psychosis also exhibit volumetric reductions in whole brain and hippocampus; enlargement in the third and lateral ventricles; and longitudinal loss of total cortical gray matter and gray matter in frontal, temporal, and parietal regions [9, 10]. Although further study is required, first-generation antipsychotic (FGA) exposure appears to correlate with enlargement of the caudate over time, while cumulative antipsychotic exposure may be associated with gray matter loss over time [11, 12].

Alterations are observed in other aspects of structural morphology. These include reductions in cortical thickness of the temporal and frontal lobes and reduced cortical surface area in multiple regions [13, 14]. Cerebral asymmetry is also reduced in both affected individuals and healthy relatives, particularly in the planum temporale which shows diminished left–right asymmetry in patients with schizophrenia compared with healthy controls [15].

Structural measures show some correlations with severity of symptoms and cognitive deficits. The most consistent finding is the association between gray matter reductions of the superior temporal gyrus and positive symptom severity, specifically hallucinations [16]. Hippocampal volume reduction is correlated with greater severity of positive and negative symptoms and poorer social function [17]. Prefrontal alterations are associated with impaired executive function, while temporal and hippocampal structural abnormalities correlate with deficits in performance speed, working memory, and abstraction [18].

High-risk individuals (variously defined as individuals with prodromal symptoms or a family history of schizophrenia) also exhibit reduced volume in structures such as the insula, superior temporal gyrus, and cingulate [19, 20]. Conversion to psychosis among high-risk individuals is associated with relative gray matter deficits in frontal, temporal, and parahippocampal regions, although this finding is not consistent [20, 21]. Nonpsychotic relatives of individuals with schizophrenia also demonstrate volumetric reductions in the anterior parahippocampus and hippocampus and enlargement of the third ventricle when compared with healthy controls [22, 23].

White Matter

White matter changes are documented in schizophrenia through use of diffusion tensor imaging (DTI), a form of magnetic resonance imaging (MRI) that evaluates its structure by measuring characteristics of water diffusion in the brain. DTI studies in schizophrenia have identified numerous regions with decreased fractional anisotropy (FA), a measure that reflects axonal diameter and myelination in white matter [24]. Meta-analyses of DTI studies in schizophrenia report FA reductions of the left deep frontal lobe, right deep frontal lobe (including the right cingulum), and left deep temporal lobe [24, 25]. FA is also generally reduced in the corpus callosum, suggesting deficits in interhemispheric communication [24]. These white matter

changes were used to propose a model of schizophrenia as a syndrome of "functional disconnection," resulting from abnormalities in the connectivity between brain regions which may ultimately be relevant in understanding the cognitive deficits in this disorder.

Summary

Although structural imaging has produced a rich data set uncovering a number of consistent brain alterations, several questions merit further study. The neurodevelopmental timeline of observed alterations is not fully understood. Though there has been an increasing focus on high-risk and first-episode patients, further longitudinal data is needed to determine which brain alterations mark the conversion to psychosis. Additionally, it is unclear whether structural changes result from intrinsic disease pathology or reflect adaptations to the disease state. Continued research with healthy relatives and first-episode populations may disentangle the effects of environmental factors (e.g., antipsychotic exposure) from intrinsic disease effects on brain structure. Lastly, the current knowledge base is limited regarding the relationship between structural brain changes and long-range network connectivity. Ongoing integration of structural data with functional imaging may provide insight into these issues.

Brain Function

Functional and Molecular Imaging

Over the past several decades, functional MRI (fMRI) has been used extensively to examine brain activation in schizophrenia during specific cognitive and emotional processes (e.g., tasks of working memory, attention, and decision-making) [26]. One of the most consistent findings is diminished activation of frontal regions during cognitive tasks (i.e., "hypofrontality"), with meta-analyses of both first-episode and multiepisode patients finding reduced activation in the dorsolateral prefrontal cortex during these tasks [27–29].

Further, functional studies of social cognition and emotional processing suggest dysfunction of the amygdala and hippocampus. Individuals with schizophrenia demonstrate decreased limbic activation during tasks, but abnormally increased limbic activation when presented with fear-inducing stimuli such as pictures of angry faces [30]. Functional studies also focus on neural correlates of hallucinations and other symptoms, demonstrating that real-time auditory hallucinations correlate with increased activation of fronto-temporal regions such as Broca's area and the middle and superior temporal gyri [31]. Another area of research focuses on the

"default mode network" which is active during rest. While activity in these regions is normally suppressed during cognitive tasks, it is under-suppressed in schizophrenia, perhaps reflecting attentional and other cognitive impairments [32].

Summary

Schizophrenia is associated with abnormal limbic activation in response to emotional stimuli and frontal dysfunction during cognitive tasks. Despite its extensive research use, functional imaging is far from achieving clinical utility in diagnosis or treatment for several reasons. fMRI signals are subtle and require specialized analysis, making it difficult to detect robust signals at the level of the individual patient [33]. Lack of standardized image acquisition and analysis techniques also impedes efforts to establish the clinical utility of fMRI [33]. As with structural alterations, the pathogenesis of functional alterations is poorly understood. Two lines of research which may address these issues are multimodal studies integrating functional imaging with structural imaging, DTI, or electrophysiology and functional connectivity analyses evaluating temporal correlations in networks of brain regions [26]. These developments may ultimately yield clinically relevant biomarkers which are robust enough to identify high-risk individuals and guide treatment choices.

Neurophysiology

Neurophysiological research in schizophrenia largely focuses on event-related potentials (ERPs), which are electrophysiological responses observed in an EEG after presentation of a stimulus. ERP data is collected by applying electrodes to the scalp and recording brain electrical activity during tasks or stimuli. Electrophysiological markers are based on variations in latency, amplitude, and scalp localization of waveforms generated by various auditory stimuli. These markers differ in their anatomical substrate, their association with cognitive and clinical measures, and their putative genetic influences. Electrophysiology has several important advantages as a clinical and research tool: it is noninvasive, presents fewer technical challenges than functional and molecular imaging methods, and has a long history of use with established paradigms and analysis methods.

P300

P300 is one of the most studied electrophysiological markers. It is a large, positive voltage response evoked about 300 ms after presentation of a salient stimulus.

Its amplitude is consistently lower in individuals with schizophrenia compared with healthy controls [34]. A subset of the P300, the P3b, localizes to the inferior parietal cortex, while the other component of the P300, the P3a, localizes to frontal regions [35]. P300 abnormalities may correlate with negative symptoms, cognitive dysfunction, and gray matter reductions in temporal regions [36]. A meta-analysis of 46 studies of P300 alterations in schizophrenia found a pooled effect size of 0.85 for the amplitude of the P300 measure but did not find any impact of antipsychotic medication on this measure [37]. P300 reduction is also observable in relatives of patients with schizophrenia and in other psychiatric disorders [38].

Prepulse Inhibition of Startle

Abnormal prepulse inhibition of a startle response (PPI) is a well-established electrophysiological finding in schizophrenia. The startle response is typically measured as the amplitude of electromyographic response of the orbicularis oculi muscle when it contracts after an unexpected stimulus. PPI is the reduction in the amplitude of this wave which occurs when the startling stimulus is preceded by a weak stimulus [39]. Individuals with schizophrenia do not exhibit the same degree of reduction in the startle response as healthy controls, suggesting defects in the brain's ability to selectively filter stimuli [39]. This abnormality correlates with thought disorder and disruption in global functioning but may normalize with second-generation antipsychotic (SGA) treatment [40, 41]. Abnormal PPI is highly heritable and present in unaffected first-degree relatives [42, 43]. PPI also has a direct association with gray matter volume in the right superior parietal cortex of first-episode patients and healthy controls [44].

P50 Auditory-Evoked Potential Suppression

The P50 wave is an evoked potential which occurs 50 ms after a stimulus. When two auditory clicks are presented 500 ms apart, generating two P50 waves, the amplitude of the second wave is reduced in comparison to the first. This phenomenon is known as P50 suppression and is abnormal in patients with schizophrenia who demonstrate a smaller reduction in amplitude of the second P50 wave compared with normal controls [45, 46]. Cholinergic neurotransmitter pathways may mediate P50 suppression, as indicated by the apparent ability of nicotine to briefly normalize suppression in people with schizophrenia [47]. P50 suppression localizes to the hippocampus, is estimated to have a heritability around 68 %, and is observed in first-degree relatives of patients with schizophrenia [48–50]. Treatment with clozapine, but not other antipsychotics, may normalize P50 suppression [51].

Mismatch Negativity

Mismatch negativity (MMN) refers to an ERP component which is measured when a series of repetitive auditory stimuli are punctuated by deviant or "oddball" stimuli. MMN is believed to reflect pre-attentive sensory processing and the response of the brain to changes in consecutive stimuli [52]. It localizes to the primary and secondary auditory cortices, as well as the dorsolateral prefrontal cortices [53]. MMN abnormalities appear specific to schizophrenia among psychiatric disorders and are consistently associated with cognitive activity and the ability to function independently [54, 55].

Cortical Oscillations and Neural Synchrony

Neural oscillations allow networks of brain regions to coordinate activity essential for cognitive processes. Gamma band oscillation, which is normally in the range of 30–80 Hz, reflects coordination of neuronal activity and appears highly heritable [56, 57]. Compared to healthy controls, individuals with schizophrenia demonstrate reduced power of gamma band oscillations and are less able to modulate these oscillations in frontal regions during tests of cognitive function [58, 59]. Because cortical synchrony matures during adolescence, gamma band abnormalities may reflect a failure of normal neurodevelopment. A number of studies support a correlation between positive symptoms, particularly auditory and visual hallucinations, and changes in gamma band activity [60].

Summary

The existence of electrophysiological abnormalities in schizophrenia is well established but their clinical and research implications require further study. Electrophysiological markers hold the potential to serve as "endophenotypes" (i.e., heritable, objective disease characteristics that bridge the gap between genetic factors and clinical phenotype). These markers fulfill some of the criteria for endophenotypes as they appear to be highly heritable and present in unaffected relatives. They do not, however, consistently fulfill other endophenotype criteria such as stability over time. In addition, the clinical utility of electrophysiological markers is currently limited because of the expense of EEG equipment, the need for subjects to cooperate with complex task instructions (for some markers), and the lack of diagnostic specificity or treatment implications for most existing markers [61]. Nevertheless, electrophysiology is highly relevant for future study, as markers may correlate with elements of early information processing disrupted in schizophrenia. Electrophysiology can also be applied to the study of simple neural processes in other mammals, thus expanding the role of animal models in schizophrenia research.

Oxidative, Immunological, and Neuroendocrine Abnormalities

Schizophrenia may involve abnormalities in the oxidative stress response. Oxidative stress results from the body's inability to fully neutralize free radicals generated by normal metabolic processes [62]. This can ultimately lead to cell membrane damage and impaired neurotransmission. Markers of elevated oxidative stress are observed in schizophrenia (e.g., diminished levels of the antioxidant glutathione in the brain and cerebrospinal fluid) [63]. A meta-analysis found decreased levels of the antioxidant red blood cell superoxide dismutase across the illness course, implying it may be a trait marker for schizophrenia [62]. Other antioxidants in this study varied by patients' clinical status or stage of disease. Antioxidant deficits may affect interneuron function and cortical synchrony. For example, in a mouse model, impaired synthesis of glutathione led to reductions in high-frequency gamma oscillations [64]. Thus, oxidative stress may play a critical role in the neurodevelopmental pathways leading to schizophrenia, while enhancement of antioxidant function may represent a novel therapeutic pathway. Further investigation is needed to explore whether antioxidant abnormalities explain the link between schizophrenia and certain environmental risk factors (e.g., psychosocial stress or viral infections) [65]. Additional trials also are necessary to validate the clinical potential of antioxidant treatment, although studies using *N*-acetyl cysteine show promise in the treatment of negative symptoms (see Chap. 7) [66].

Immunological theories propose that autoimmune dysfunction or infections may contribute to the etiology of schizophrenia. Epidemiological studies observe a correlation between prenatal exposure to infections and later development of schizophrenia [67]. Studies report a number of immunological findings, including changes in the levels of cytokines (signaling molecules that coordinate the inflammatory response), elevated levels of autoantibodies, and associations between autoimmune disorders and risk for schizophrenia [68–70]. A meta-analysis found that some cytokines (such as IL-6 and TGF-β) were associated with psychotic exacerbations, while others (IL-12, TNF-α) may be trait markers for schizophrenia [68]. In addition, anti-inflammatory medications may augment antipsychotic response and improve psychotic symptoms in randomized controlled trials (see Chap. 7) [71]. These findings lend support for immunological theories of schizophrenia and fit well with known prenatal risk factors. The current literature on immunological markers is often limited by inadequate control for confounding factors such as clinical status, body mass index, and smoking. Thus, many studies were unable to determine if abnormalities represented state or trait markers [68]. Additional research is necessary to clarify the role of cytokines in the pathogenesis of schizophrenia and whether they hold potential as therapeutic targets in addition to biomarkers.

Dysfunction in the hypothalamus–pituitary–adrenal (HPA) axis may mediate interactions between stress and psychosis. The stress response appears blunted in individuals with schizophrenia, as reflected in studies showing decreased cortisol response to psychological and physical stress [72, 73]. Multiple studies also demonstrate a relatively high rate of dexamethasone non-suppression (i.e., the absence of

cortisol suppression after a dexamethasone suppression test) in chronic schizophrenia, indicating failure of the HPA negative feedback mechanism [74]. Subgroups of patients (e.g., those with primary polydipsia) have higher rates of dexamethasone resistance and HPA overactivity which may result from abnormal hippocampal regulation of the stress response (see Chap. 11) [75]. Function of the HPA system is likely preserved overall, despite some abnormal input from the limbic system. One major challenge for neuroendocrine research in schizophrenia is distinguishing adaptive responses from intrinsic disease pathophysiology. To place neuroendocrine findings in an appropriate context, future studies will need to identify where abnormalities occur in the regulatory pathway and connect observed abnormalities with clinical symptoms.

Neurotransmitter Systems

Neurochemical Imaging

Proton magnetic resonance spectroscopy (^{1}H MRS) is a noninvasive imaging method which assesses the chemical composition of brain tissue in vivo by measuring magnetic resonance signals produced by atomic nuclei within molecules [76]. This form of imaging can estimate concentrations of several biologically relevant compounds including *N*-acetyl aspartate (NAA) which is a marker of neuronal integrity; glutamate and glutamine (Glu + Gln), which correlate with glutamatergic neurotransmission; and choline metabolites (Cho) which are an indicator of cellular turnover [76]. One of the most consistent findings in this area is a reduction in NAA in frontal, temporal, and thalamic regions. This is seen in both first-episode and multiepisode patients, indicating neuronal abnormalities in these regions [77]. Another consistent finding, which was reported in a meta-analysis of studies on Glu + Gln, is a reduction in frontal glutamate and increase in glutamine [78]. Possible reasons for reduced glutamatergic function include hypo-activation of *N*-methyl-D-aspartate (NMDA) receptors and abnormal expression of glutamate transporters [78]. These hypotheses require clarification, however, perhaps through animal models.

The current MRS literature is also limited by the paucity of longitudinal studies, making it difficult to assess the relationship between neurochemical alterations and disease course [78]. Because of long scanning times, studies typically limit themselves to small samples of cooperative subjects [79]. Scanner resolution is constrained by the size and strength of spectroscopy magnets [79]. Studies also differ in their choice of MRS techniques, and many did not control for variables such as antipsychotic medication status or duration of illness [76, 78]. Future studies will need to develop and use more standardized methods. Newer forms of MRS (e.g., proton echo-planar spectroscopic imaging (PEPSI)) are able to scan multiple brain regions in a short amount of time. These advances allow for the imaging of

agitated or uncooperative subjects, enhancing the potential clinical utility of MRS. Recent studies are also using more powerful magnets which permit greater spatial and temporal resolution [79].

MRS with ^{31}P (phosphorus-31) is also used to examine cell membrane phospholipids (i.e., PME (phosphomonoester), a phospholipid precursor; and PDE (phosphodiester), a metabolite of phospholipid breakdown). PME and PDE can provide information about membrane phospholipid synthesis and turnover which in turn may reflect the condition of neuronal membranes [80]. Studies utilizing ^{31}P have reported reductions in PME in prefrontal and medial temporal regions in schizophrenia, implying reduced production of membrane phospholipids [80]. As with ^{1}H MRS, studies with ^{31}P are limited by small sample sizes, inconsistencies in imaging and analysis techniques, and differences in subject populations [79]. ^{31}P MRS, however, continues to be relevant given its unique ability to examine processes of lipid metabolism and cell membrane turnover.

Two forms of molecular imaging are used to explore neurotransmitter systems in schizophrenia: positron-emission tomography (PET) and single-photon emission-computed tomography (SPECT). In both methods, radioactive-labeled tracers are injected into the bloodstream and emitted rays are measured. PET demonstrates better spatial resolution and more sensitivity to subtle brain changes than SPECT, and presently appears to be a more powerful brain imaging technique [81]. Two meta-analyses of SPECT and PET studies found elevations in striatal dopamine synthesis capacity but found no significant difference in dopamine transporter availability [82, 83]. Additionally, prefrontal hypo-activation is correlated with increased striatal dopamine function [84]. These findings support a modified version of the "dopamine hypothesis" (to be discussed below) in schizophrenia. Altered striatal dopamine synthesis may hold potential as a biomarker for risk of psychosis, but additional research is needed to determine how it changes over the illness course and whether it is specific to schizophrenia rather than affective psychosis [82]. In addition to clarifying these issues, future studies could integrate PET and SPECT methods with electrophysiology and structural imaging to identify dysfunctional networks [85]. As with MRS, PET and SPECT research is limited by small sample sizes, differences in technical methods, and variations in subject characteristics.

Dopamine

The dopamine hypothesis has persisted as a pathophysiological theory of schizophrenia for several decades. Various lines of evidence support this theory. These include the efficacy of D2 receptor antagonists in treating the acute symptoms of psychosis, as well as the ability of amphetamines to stimulate psychosis by increasing extracellular dopamine. Initial models theorized simply that increased dopamine transmission led to psychosis, and later, that defects in mesocortical dopamine activity resulted in overactivity of the mesolimbic system [86]. Further, depletion in prefrontal dopamine was believed to disinhibit subcortical regions, resulting in

dopaminergic excess in striatal regions [87]. More recent models proposed that presynaptic dopamine dysfunction is the primary path to psychosis, in accordance with recent PET studies [82, 83]. These more recent findings point to presynaptic dopamine synthesis as a potential therapeutic focus (see Chap. 7) [83].

The ultimate place of dopaminergic dysfunction in the pathogenesis of schizophrenia is unclear with the literature increasingly implying that dopamine dysfunction is a downstream consequence of other deficits. One weakness of initial dopamine models was their relative difficulty in accounting for cognitive deficits and negative symptoms in schizophrenia. Altered D1-mediated transmission in the prefrontal areas or changes in glutamatergic neurotransmission may influence striatal dopamine systems and could underlie cognitive and negative symptoms [83, 84]. However, these theories await further confirmation.

Gamma Aminobutyric Acid

Gamma aminobutyric acid (GABA) is the primary inhibitory neurotransmitter in the brain and an increasing focus of attention in the pathophysiology of schizophrenia. Inhibitory control by GABA interneurons is believed to coordinate subsets of pyramidal neurons which comprise the majority of cortical neurons [56]. Thus, GABA interneurons are crucial for synchronized neural activity [56]. While the overall number of GABA interneurons is not reduced in schizophrenia, those which contain parvalbumin demonstrate reduced production and uptake of GABA [88]. In particular, levels of glutamic acid decarboxylase 67 (GAD-67), an essential enzyme for GABA synthesis, are diminished in several cortical regions in parvalbumin-containing GABA interneurons [88]. Deficiencies in GAD-67 and decreased expression of parvalbumin appear to correlate with alterations in gamma band oscillations, thus linking electrophysiological phenomena and neurotransmitter systems. Synaptic alterations in the dorsolateral prefrontal cortex may disrupt the balance of inhibitory control by GABA interneurons, leading to deficits in working memory [89]. It is not known whether the observed abnormalities in the GABA-ergic system represent primary deficits in schizophrenia or compensatory mechanisms for other deficits [56]. For example, increases in postsynaptic GABA-A receptors and reductions in presynaptic parvalbumin may compensate for reduced GABA release from chandelier neurons which serve to inhibit pyramidal neurons [90]. This viewpoint is supported by evidence from animal models showing that such alterations tend to improve GABA transmission [91].

Glutamate

Unlike dopamine, glutamate is present throughout the entire nervous system and is the main excitatory neurotransmitter in mammals [92]. The potential relevance of glutamate to the pathophysiology of schizophrenia was discovered through research

on NMDA receptor antagonists such as phencyclidine (PCP) and ketamine. NMDA receptors are normally activated through the binding of glutamate or aspartate, but synthetic NMDA antagonists bind specifically to the NMDA receptor. When administered to healthy subjects, NMDA antagonists can induce psychotic symptoms, cognitive deficits, and defects in MMN which mimic those observed in schizophrenia [93, 94]. From this and other data, it was initially proposed that schizophrenia involved diminished function or density of NMDA receptors caused by abnormalities in glutamate neurotransmission [92]. Studies on postmortem brains report reductions in the NMDA receptor density in the prefrontal cortex and hippocampus [95]. Reduction in the density of dendritic spines, which receive excitatory glutamatergic synapses, may also reflect inadequate glutamate neurotransmission and resulting defects in connectivity [96]. Subsequent research, however, suggests that glutamatergic excess may actually be a driving force in the disease process. One promising pharmacotherapeutic application is the use of metabotropic glutamate 2/3 receptor agonists, which could balance excitatory and inhibitory systems by normalizing presynaptic glutamate levels (see Chap. 7) [92].

Summary

Dopaminergic dysfunction remains a consistent finding in schizophrenia and may be due primarily to alterations in presynaptic synthesis and transmission. While the relative place of dopaminergic dysfunction in the pathogenesis of schizophrenia remains unclear, it may play an early role in neurodevelopmental processes or it may reflect downstream consequences of other abnormalities. Recent investigations focusing on glutamatergic and GABA-ergic neurotransmitter systems may generate novel therapeutic targets.

Neuropathology

Schizophrenia is historically a challenging area in neuropathology, initially yielding few definite findings. As stated earlier, it is associated with subtle reductions in total brain volume and total gray matter volume [6]. Notably, these reductions are not attributable to loss of neurons, but to reductions in the size of neuronal cell bodies and in cortical neuropil [97]. Specifically, pyramidal cell bodies are about 10 % smaller in layer three of the dorsolateral prefrontal cortex and dendritic shafts and spines are reduced, resulting in diminished dendritic arborization [98]. Dendritic spines receive excitatory synapses throughout the central nervous system and reductions in their density may underlie connectivity defects between regions [96]. In addition, reductions and altered gene expression in the microglia, support cells of the nervous system which include astrocytes and oligodendrocytes, may contribute to white matter abnormalities [99].

Another consistent finding is the lack of gliosis. This is the proliferation of glial cells in response to nervous system damage which is observed in many neurodegenerative disorders [89]. Its absence in schizophrenia suggests a neurodevelopmental rather than a neurodegenerative process at work [97]. Postmortem studies observe higher densities of cortical neurons in deep rather than superficial layers of the limbic and prefrontal regions. This indicates that there may be early failures in the migration of neuronal precursor cells from subcortical to cortical regions during gestation [100]. Neuropathological studies have a number of limitations including the effects of variable postmortem intervals, heterogeneity within the schizophrenia diagnostic spectrum, and the confounding effects of antipsychotic medication [97].

Neuroplasticity

The presence of widespread gray matter deficits and synaptic alterations without apparent neuronal loss raises the question of whether these abnormalities are remediable. Neuroplasticity refers to the ability of the brain to adapt to the environment and reorganize aspects of neuronal circuits, such as synaptic density [101]. Neuroplasticity may be abnormally reduced in schizophrenia, as suggested by studies showing diminished long-term potentiation in response to transcranial magnetic stimulation and lowered stimulus-specific plasticity in response to electrophysiological tetanic stimulation [101, 102]. Recent findings indicate that levels of brain-derived neurotrophic factor (BDNF), a protein responsible for neuronal development and synaptic plasticity, may be altered in schizophrenia [103]. BDNF may closely interact with glutamatergic, dopaminergic, and GABA-ergic neurotransmitter systems and may mediate the gray matter improvements observed following cognitive remediation [104, 105].

Models of Pathogenesis

Although various neurobiological abnormalities are now well established in the schizophrenia literature, it is important to synthesize these findings to develop models of pathogenesis. The majority of evidence supports the conceptualization of schizophrenia as a neurodevelopmental disorder. This evidence includes the onset of schizophrenia in adolescence and the presence of premorbid cognitive deficits, minor physical anomalies, and neuromotor abnormalities during childhood [106–108]. The timeline of neurodevelopmental alterations, however, remains unclear.

One model posits that the pathogenesis of schizophrenia begins pre- or perinatally, perhaps through early environmental insults or genetically mediated defects in neuronal migration [86]. As mentioned earlier, postmortem studies imply alterations in neuronal migration from subcortical to cortical regions, a process which occurs during the second trimester [100]. Studies of high-risk individuals find a

high prevalence of motor coordination issues in childhood, further supporting an early timeline of pathogenesis [108]. An exclusive focus on perinatal or prenatal abnormalities, however, does not explain why the characteristic symptoms of schizophrenia emerge in late adolescence.

Another model addresses this issue by focusing on neurodevelopmental abnormalities in late adolescence. Excessive synaptic or axonal pruning may underlie longitudinal changes reported in young high-risk and first-episode patients. These include gray matter reductions and reductions in NAA observed in MRI studies [10, 77]. Findings from neuropathology, such as reductions in dendritic arborization and synaptic density, are also consistent with this model [98].

Schizophrenia does not appear to be a neurodegenerative disorder, as demonstrated by lack of gliosis or other neurodegenerative signs in postmortem studies [97]. There still remains a question of whether a subgroup of individuals experience progressive deterioration. The first few years of illness in particular are marked by a decline in function and some individuals recover incompletely or take longer to recover after each successive psychotic episode [109].

Diminished neuroplasticity may fit well with existing neurodevelopmental models of pathogenesis. Dysfunction in GABA-ergic systems could reduce plasticity in cortical areas, while changes in NMDA receptor-mediated neurotransmission may disrupt long-term potentiation, a crucial process for learning and memory [101, 110]. Altered neuroplasticity may serve as a biological mechanism for environmentally mediated longitudinal changes in schizophrenia.

Summary

Although divergent in their timelines, these models could be integrated with the current understanding of neurotransmitter systems to create a "three-hit" model that longitudinally describes the pathogenesis of schizophrenia [111]. Early genetic or environmental "hits" may disturb glutamate-mediated processes of neuronal migration and survival during gestation. This could lead to cell death and loss of glutamatergic neurons, manifesting as premorbid cognitive and neuromotor deficits. In adolescence, hypofunction of NMDA receptors, whose sustained activity is necessary for synaptic survival, could result in excessive synaptic pruning and reduced neuroplasticity. Diminished neuronal connectivity could worsen cognitive and social function during this time period. Additionally, glutamatergic dysfunction could disrupt phasic and tonic dopamine release and upregulate subcortical dopaminergic neurons, ultimately precipitating the onset of psychotic symptoms [111, 112]. During the years following the first episode of psychosis, glutamatergic dysfunction could lead to increased phasic dopamine release during psychotic episodes, which could then *increase* glutamate release, resulting in oxidative stress and neuronal damage. Neurotoxicity caused by glutamatergic excess could then account for disease progression during the first years of illness. In addition, deficits in neuroplasticity may help explain chronic cognitive impairments. This model draws support from genetic

studies showing association of schizophrenia with glutamate- and neuroplasticity-related genes (see Chap. 5). Further research using animal models and longitudinal brain imaging is likely to refine neurodevelopmental theories of pathogenesis.

Conclusion

Knowledge Gaps and Future Steps

As this review indicates, many facts about the pathophysiology of schizophrenia are being discovered at a rapid pace. This progress, however, is not matched by their translation to advances in treatment of schizophrenia. In general, treatments for schizophrenia were largely discovered by astute, yet serendipitous, observations. Thus far, few treatments are based on knowledge of pathophysiology (Fig. 4.1). Yet, some trends may be delineated.

Toward neuroscience-based classification of psychoses. While successive revisions of the Diagnostic and Statistical Manual of Mental Illness (DSM) serve to improve the reliability and clinical utility of a symptom-based classification of psychiatric disorders, there remains a critical lack of *validity* in the current categorization of psychoses. The century-old distinction between schizophrenia and affective psychoses remains in the DSM-5 despite the considerable overlap in symptoms, cognition, neurobiology, genetics, treatment response, and outcome characteristics across these disorders [113–117]. Emerging new data on pathophysiology of the psychotic disorders spectrum can eventually help move the field

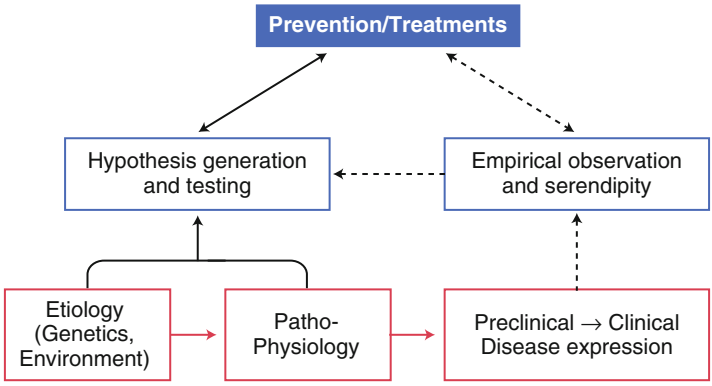

Fig. 4.1 Pathways to treatment discovery. Treatments for schizophrenia have traditionally been developed by clinical observation and serendipity (*dashed lines*) but need to be increasingly informed by etiopathological observations and hypothesis testing (*solid lines*) (Adapted from Tandon et al. [132])

toward a neuroscience-informed nosology. Such progress is only possible if disease dimensions of what we now call schizophrenia, spanning molecular to behavioral domains across the psychosis spectrum, are deconstructed [118, 119]. The cross-cutting pathophysiological dimensions can then be used to identify new, perhaps more valid categories of the psychosis spectrum. Relevant to the pursuit of this goal are the NIMH Research Domain Criteria (R-DoC) which seek to map translationally relevant behavioral phenotypes to biomarkers in physiological and molecular domains [120]. The introduction of dimensional measures which cut across diagnoses in DSM-5 is a good step in this direction. It is critical for the field, however, to utilize such measures in large populations, agnostic to DSM diagnoses, and examine their relationships to biology [121].

Toward diagnostic and predictive biomarkers. Despite accumulating data on several altered biological processes, few diagnostic or predictive biomarkers exist for psychiatric disorders, other than those to rule out "other" medical disorders (e.g., testing to rule out hypothyroidism). Even "proxy" biomarkers such as cognitive deficits, which are widely prevalent, pervasive across multiple domains, persistent, map onto biology, and may predict outcome in schizophrenia, are not yet incorporated into standard psychiatric assessments [122]. At least in part, this impasse stems from a continued reliance on symptom-based categories as the gold standard for developing diagnostic tests [121, 123]. In striking contrast, there is unprecedented progress in imaging, genomics, and computational abilities which could deliver clinically useful tests in the near future. Given the lack of validity of symptom-based classifications in psychiatric disorders as discussed earlier, simple comparisons of imaging or other biomarker data between diseases and between disease and healthy subjects are unlikely to yield much. In contrast, examining etiological differences across biologically defined subgroups of disease may be much more valuable. For example, using data-driven approaches on phenotypically diverse subjects, it may be possible to derive subgroups characterized by distinctive biological features, quantifiable through neuroimaging and electrophysiology. These subgroups could then be compared in etiology and pathophysiology, ultimately generating targeted therapeutic approaches.

Multimodal approaches and automated machine learning algorithms (e.g., support vector machines (SVMs) which utilize multivariate pattern recognition methods) can robustly distinguish early course of schizophrenia and its progression [124]. Such classification approaches in the future may also incorporate information from other biomarker domains, including electrophysiology, metabolomic, proteomic, genomic, and gene expression profiles. Cellular markers derived from induced pluripotent stem cells are another exciting direction in the not-too-distant future [125].

Toward theory-driven therapeutic interventions. Stratifying psychosis spectrum disorders into neurobiologically separable entities will help develop more targeted interventions [119]. Molecular stratification of disease is already standard practice in the rest of medicine. Thus, the presence of "actionable" mutations such as BRCA1 gene in breast cancer can lead to prevention efforts [126]. In another example,

specific treatments can lead to substantial clinical benefit for cystic fibrosis for individuals with CFTR mutations [127]. Several examples of such theory-driven interventions in schizophrenia may now be mentioned. It is important to look beyond simply modulating the dopamine receptor. Recent thinking on the role of glutamatergic and GABA pathways discussed earlier suggests trials of several novel pharmacological agents which may impact these systems (see Chap. 7) [128]. One needs to look beyond neurotransmitter systems as well to treatments which address increased oxidative stress, such as *N*-acetyl cysteine [66]. Anti-inflammatory agents such as aspirin may be of value in treating psychosis [129]. Improvement in cognitive deficits in schizophrenia patients positive for herpes simplex antibody titers is reported with the antiviral agent valacyclovir [130]. Treatments that directly upregulate BDNF or improve neural plasticity, such as computer-based cognitive enhancement therapies, also hold promise as novel therapeutic approaches [105].

In conclusion, our understanding of the pathophysiology of schizophrenia has made remarkable progress, but much work remains to translate these observations into real differences for managing and potentially preventing this devastating illness. Future researchers will benefit from both a creative application of cutting-edge neuroscience knowledge and having an open mind to look beyond current conceptual models of this disease.

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Chapter 5
Genetics of Schizophrenia

Alan R. Sanders

Abbreviations

22q11.21DS	22q11.21 deletion syndrome
ANK3	*Ankyrin 3*
ASD	Autism spectrum disorders
BP	Bipolar disorder
CACNA1C	*Alpha subunit of the L-type calcium channel*
CNV	Copy number variant
DISC1	*Disrupted in schizophrenia 1*
DSM	Diagnostic and Statistical Manual of Mental Disorders
eQTNs	Expression quantitative trait nucleotides
GWAS	Genome-wide association study
GWLS	Genome-wide linkage scan
GWS	Genome-wide significant
ISC	International Schizophrenia Consortium
ITIH	*Inter-alpha-trypsin inhibitor heavy chains*
LD	Linkage disequilibrium
LOD	Logarithm of the odds ratio
MGS	Molecular Genetics of Schizophrenia
NRGN	*Neurogranin (protein kinase C substrate, RC3)*
NRXN1	*Neurexin 1*
SGENE	Schizophrenia Genetics Consortium
SNP	Single nucleotide polymorphism
MAF	Minor allele frequency

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P.G. Janicak et al. (eds.), *Schizophrenia: Recent Advances in Diagnosis and Treatment*,
DOI 10.1007/978-1-4939-0656-7_5, © Springer Science+Business Media New York 2014

PGC-SZ	Psychiatric Genomics Consortium for Schizophrenia
TCF4	*Transcription factor 4*
VCFS	Velocardiofacial syndrome
VIPR2	*Vasoactive intestinal peptide receptor 2*
WGS	Whole-genome sequencing
xMHC	Extended major histocompatibility complex

Introduction

The broad goals of psychiatric genetics are to locate susceptibility genes, understand how implicated genetic variants contribute to illness, and generally increase knowledge of pathophysiology. Researchers hope such advances will contribute to improved diagnostics, perhaps enabling prevention efforts and the development of new treatments. The general inaccessibility of the organ of interest (brain), the relative lack of specific well-defined neuropathology (e.g., compared with Parkinson's disease), and the immense complexity of the brain further heighten the appeal of genetic approaches to schizophrenia research which do not require substantial pathophysiological knowledge beforehand. Many human neuropsychiatric disorders, as well as behavioral traits, have substantial genetic components. These include diseases as diverse as alcoholism, Alzheimer's dementia, antisocial personality disorder, attention-deficit hyperactivity disorder, autism spectrum disorders (ASD), bipolar disorder (BP), depression, substance abuse/dependence, anorexia nervosa, bulimia nervosa, Huntington's chorea, obsessive–compulsive disorder, panic disorder, schizophrenia, intellectual disability (ID), and Tourette's syndrome. These conditions (and many common nonpsychiatric disorders with partial genetic causation) are mostly considered as complex (multifactorial) genetic disorders. This means many and diverse genetic contributions are present along with significant environmental contributions and perhaps interactions among these components. Research approaches used to study the genetics of schizophrenia are also similarly employed with other complex genetic disorders and all benefit from the knowledge and technology derived from big science efforts, exemplified by the Human Genome Project (www.genome.gov/10001772). These approaches are roughly divided into the earlier (still ongoing) approaches which depend only on reliable phenotyping (diagnosing) and accurate characterization of familial relationships, and later approaches which also require working with biomaterials, most typically, DNA. The earlier approaches are often referred to as genetic epidemiology, while the later approaches start with linkage and progress through and beyond DNA re-sequencing. This chapter discusses highlights of each of the main approaches, summarizes current knowledge, and comments on future directions.

Genetic Epidemiology

Genetic epidemiological approaches include family studies, twin studies, adoption studies, and segregation analyses. Family studies compare the risk for illness in first-degree relatives of probands (first identified ill individual) to the risk for illness in family members of controls. Family history of schizophrenia is the strongest common predictor of illness elevating risk (~tenfold in first-degree relatives); however, most patients have no first-degree relatives with the disorder (called sporadic cases) [1, 2]. An early clue to schizophrenia being a complex genetic disorder (as opposed to a simpler Mendelian single gene disorder) was that family studies showed the risk for illness diminished much more quickly than the degree of biological relationship did. Indeed, the risk for third-degree relatives approaches the prevalence found in the general population. *Twin studies* compare the diagnostic concordance (agreement) rate by twin type (i.e., monozygotic or identical twins) where phenotypic differences are attributed to the environment versus dizygotic or fraternal twins (the latter typically being same-sex twin pairs) where genetic differences are also in play. Many twin studies were conducted (see examples), which consistently showed high heritability of around 80 %; however, there are many examples of identical twin pairs where one twin has schizophrenia and the co-twin does not—another clue to complex genetics [3–8]. *Adoption studies* compare the risk for illness in biological versus adoptive relatives of probands. Though there are fewer studies as one progresses from family to twin to adoption studies, schizophrenia has a substantial number of the latter. The general conclusions are that risk for illness travels with the biological relationship and not the adoptive relationship. Further, this risk does not depend on the rearing environment, including whether or not a parent with schizophrenia is present [9]. *Segregation analyses* attempted to fit observed families with known modes of inheritance (e.g., autosomal versus sex-linked; dominant versus recessive). While such analyses were much more successful for Mendelian disorders, they did not bear fruit for schizophrenia genetics.

In summary, over many decades using various methods of ascertainment, assessment, and phenotyping/diagnosis (i.e., Kraepelin to the Diagnostic and Statistical Manual of Mental Disorders), epidemiological studies of schizophrenia consistently found genetic contributions to be of primary importance [10, 11].

Molecular Approaches: Linkage

Molecular approaches burgeoned over recent decades as technological capabilities grew exponentially and costs decreased. While earlier molecular approaches (e.g., linkage and especially association) continue to be employed, more recent molecular approaches, such as exome sequencing and whole-genome sequencing (WGS), and a variety of other "omics" (transcriptomics, methylomics, proteomics,

metabolomics), in addition to genomics and pharmacogenetics, are beginning to make larger contributions to our knowledge base. *Linkage studies* seek to find a linked genetic marker which is inherited with illness within a pedigree. Association studies seek to find an associated DNA sequence which occurs more frequently in patients than in controls. Both approaches assay for the degree of crossing over (or meiotic recombination) between homologous chromosomes which occurs between a polymorphic genetic marker and a putative risk variant contributing to illness. If these two loci are very close to each other on a chromosome, they would likely remain linked if looking at one or two generations (as in a linkage study) or in linkage disequilibrium (LD) over many generations if very close to each other (as in an association study). Earlier linkage studies used parametric logarithm of the odds ratio (LOD) methods to study one or a few large pedigrees with a high density of illness in the hopes this would reduce genetic heterogeneity. Later linkage studies employed nonparametric allele sharing methods, most typically focusing on affected sibling pairs from many more families. Linkage mapping studies are geared to search for one or a few common major gene effects. Over the years, numerous genome-wide linkage scans (GWLS) were performed, but genome-wide significant (GWS) linkage loci remain elusive. The strongest linkage evidence from the largest study, which was a meta-analysis of GWLS, suggested chromosome 8p as being linked to schizophrenia; this was previously supported by some individual dataset GWLS, meta-analyses, and a combined (jointly genotyped) GWLS [12–18]. Many other regions in the genome had lower and less consistent levels of support from various GWLS. Thus, the dearth of significant findings from GWLS supports the notion that common major gene effects are not present to any large extent, even though there may be very rare families with a major gene effect (e.g., *DISC1*, *disrupted in schizophrenia 1*) [19].

Molecular Approaches: Candidate Gene Association

Association studies were initially mostly population-based in which a group of unrelated cases were compared to a group of unrelated controls otherwise matched to the case group for differing allele frequencies at the studied genetic markers. Particularly for ancestral differences (race, ethnicity, population history), however, it was difficult to fully match the two groups. Thus, family-based association approaches compared alleles transmitted to affected offspring versus alleles not transmitted by parents in many trios of parents and child, a situation where population history is very well matched. Subsequently, much better methods of controlling for this population stratification were developed and most association studies were done using the population-based approach which enabled much larger sample sizes (case–control pairs being easier to collect than parent–child trios, especially for disorders where most of the cases are adults), resulting in better statistical power. For association studies, often an hypothesis (e.g., dopamine hypothesis) would nominate candidate genes to be tested (akin to a gene having a motive). At other times candidate genes would be

tested because they were in the right position (e.g., under a linkage peak; akin to being at the scene of the crime). Since LD acts over much shorter distance than linkage (in a linkage study a few hundred highly informative genetic markers can assay the entire genome), multiple testing becomes a much larger statistical concern in an association study (since many more independent markers can be tested). Meta-analyses of some candidate gene association studies were performed, though overall results were limited. This is especially because the frequently underpowered sample sizes (which due to instability of findings in small samples would sometimes suggest large effects or odds ratios) and often inadequate or loose statistical thresholds contributed greatly to frequent non-replications. The largest unified candidate gene testing study of that era which focused on thoroughly testing 14 of the leading candidate genes of the time by analyzing 789 single nucleotide polymorphisms (SNPs) found no evidence of association [20]. With some rare exceptions, classical candidate genes for schizophrenia have not been upheld in genome-wide association studies (GWAS). Of note, this is a general pattern seen in GWAS of other complex disorders and bolsters the need for adequately powered samples and stringent statistical thresholds for declaring an association [21].

Molecular Approaches: Genome-Wide Association Studies

Continuing technological developments (especially microarrays) enabled hundreds of thousands of genetic markers, mostly tag SNPs (i.e., "tagging" much of the common variation by means of LD, but not necessarily themselves being "causative" SNPs), to be assayed, thus paving the way to search for common variation on a genome-wide scale, resulting in the advent of GWAS [22]. These commercial GWAS SNP arrays are further complemented by imputation, the computational prediction of non-genotyped SNP genotypes from the patterns of genotyped ones [23, 24]. The first combined GWAS in schizophrenia (2009) involved ~27,000 subjects from the Molecular Genetics of Schizophrenia (MGS) collaboration, International Schizophrenia Consortium (ISC), and the Schizophrenia Genetics Consortium (SGENE) [25–27]. This approach provided the first GWS evidence for association [25–27], typically defined as $p < 5 \times 10^{-8}$ [28]. The strongest result was for SNPs at the extended major histocompatibility complex (xMHC) region on chromosome 6p21.3-p22.1 where genes with immune functions and histone genes predominate [25–27]. Two other GWS loci which emerged from this meta-analysis were near *NRGN* (*neurogranin* [*protein kinase C substrate*, *RC3*]) on chromosome 11q24.2 and at *TCF4* (*transcription factor 4*) on chromosome 18q21.2 [27]. All of these individually detectable common variant GWS loci were of low effect (i.e., odds ratios around 1.1–1.3). Besides these common risk variants, even lower effect variants which are undetectable individually but with observable effects *en masse*, (i.e., polygenic contributions) were also highlighted in these studies [26, 29]. GWAS also greatly enabled the detection of a large and increasing number of schizophrenia risk copy number variants (CNVs). These structural variants are submicroscopic

deletions or duplications detectable by a number of adjacent SNPs showing alterations in signal intensities. These included 1q21.1, 2p16.3 (*NRXN1*, *neurexin 1*), 3q29, 7q36.3 (*VIPR2*, *vasoactive intestinal peptide receptor 2*), 7q11.23, 15q13.3, 16p11.2, 17q12, and 22q11.21. Many of these CNVs span multiple and even dozens of genes with some exceptions such as *NRXN1* and *VIPR2* (see reviews) [30, 31]. These schizophrenia risk CNVs are often de novo (though some were inherited) and rare, but showed higher penetrance (higher odds ratios) than common loci (i.e., intermediate between Mendelian diseases and complex disorders) [32]. Genotype:phenotype correlations, however, are modest for these CNVs (e.g., the same CNV might lead to different phenotypes such as schizophrenia, ID, ASD, and epilepsy). This is referred to as pleiotropy where variation in a gene may contribute to different though often somehow related phenotypes—with the neurodevelopmental hypothesis of schizophrenia being echoed in many of these pleiotropy examples [33, 34]. CNVs can be more straightforward pointers to pathophysiology than GWAS associations to common SNPs because of the "indirect association" with GWAS. Subsequently, additional samples were reported and an even larger meta-analysis of schizophrenia GWAS (i.e., the Psychiatric Genomics Consortium for Schizophrenia, Part 1 [PGC-SZ-1]) found five more GWS loci and further confirmed the xMHC locus and *TCF4* [35]. It also provided further support for substantial polygenic contributions to schizophrenia risk [35, 36]. A large multistage GWAS starting with a Swedish national sample provided support for previously detected GWS loci and also yielded 13 additional new GWS loci, some of which implicate calcium signaling in schizophrenia risk [37]. PGC-SZ-2 is currently in progress and reports from meetings indicate it is yielding many more GWS loci. It seems clear for many complex genetic disorders such as schizophrenia that increasing the sample sizes of GWAS meta-analyses will yield even more common low effect loci. Such implicated loci can then be fed into downstream analyses (e.g., network and pathway analyses) aimed at groups of genes, as well as studied on an individual gene level when appropriate. The well-established association of schizophrenia to variation at the xMHC locus is intriguing, given the many immune-related genes located there and previously known associations of schizophrenia to various autoimmune disorders [38, 39].

Still, our knowledge of the specific genes and the biology underlying statistical associations from GWAS remains tentative. For example, the high gene density, strong long-range LD, and the many haplotypes of the xMHC region make classical fine-mapping difficult. The case can be made that gene regulation may underlie some GWAS susceptibility loci. Most common SNP GWAS hits lie outside of genes or are not in LD with polymorphisms affecting the amino acid sequence of a protein; CNVs and trait-associated SNPs from GWAS are usually enriched for expression quantitative trait nucleotides (eQTNs); and GWAS SNPs are enriched in regulatory sequences (DNase I hypersensitive sites, ENCODE). Thus, transcriptomics (mRNA expression) analysis provides data which is closer to function than GWAS and less limited by diffuse boundaries typical of association data [40]. Other "omics" approaches (methylomics, proteomics, metabolomics) may also yield additional insight (see recent reviews) [41–44]. Despite these issues, it is worthwhile to note

that GWAS are far more successful than any previous approach to finding new susceptibility loci for complex disorders, including schizophrenia [21, 45, 46]. One of the main limitations of GWAS, however, is that their statistical power to detect an association with rare alleles (minor allele frequency, MAF < 1 %) is very low. To assay for such rare variation, deep re-sequencing (i.e., exome sequencing and WGS) is much more useful. While some initial deep re-sequencing findings indicate that exonic de novo mutations are enriched in schizophrenia, larger samples are needed [47–49].

Genetic Relationships to Bipolar Disorder

There are diagnostic/symptom overlaps between schizophrenia and BP (especially psychosis) which are posited as having some genes in common, with schizoaffective disorder serving as a "bridge" [50–52]. Further, family studies show that schizoaffective disorder is enriched in families of schizophrenia and BP probands [53–58]. Later, larger studies found familial coaggregation of schizophrenia and BP mostly derived from additive genetic effects in common [59, 60]. GWAS for BP found several loci (i.e., detected individual common variants within/near genes), some of which were implicated in a joint GWAS meta-analysis of schizophrenia and BP, including *ANK3* (*ankyrin 3*), *CACNA1C* (*alpha subunit of the L-type calcium channel*), and the region of *ITIH1-ITIH3* (*inter-alpha-trypsin inhibitor heavy chains*) [35, 61]. GWAS for BP also show a polygenic contribution and some overlap with polygenes for schizophrenia [26, 62, 63]. Thus, there is some overlap of susceptibility between BP and schizophrenia for both some individually detectable risk alleles and for polygenic risk. By contrast, CNVs seem to play a smaller part in BP than in schizophrenia.

Clinical Applications and Future Directions

Upcoming clinical applications using knowledge derived from genetic research bear mentioning. Testing for CNVs is increasingly used for ASD and ID and is of some utility for schizophrenia. This is most notable in the setting of symptoms suggestive of 22q11.21del (e.g., psychosis, developmental delay, learning disability, facial and palatal dysmorphology). This is also known as 22q11.21 deletion syndrome (22q11.21DS) or velocardiofacial syndrome (VCFS) due to its comorbidities (especially cardiac) [64]. Identification of individual genes or groups of genes (from network or pathway analyses) can both inform pathophysiology and guide pharmaceutical industry development. Pharmacogenomics and pharmacogenetics should increasingly provide some clinical guidance (medication efficacy, specificity, metabolism), though as of now this is rather limited (see Chap. 9) [65]. Due to the multitude of genetic variants contributing to risk, from individually detectable ones

(now shading into the oligogenic area with PGC-SZ-2) to polygenes, it is likely that any future genetic tests for schizophrenia risk prediction will largely be composite tests assaying for many variants at once. Finally, as we acquire more knowledge about genetic contributions to schizophrenia, we may be able to improve prediction and prevention efforts by tying some of them into environmental risk factors for schizophrenia (e.g., obstetrical complications; urban birth/residence and migrant status; famine; seasonal effects via prenatal infections such as influenza; adolescent cannabis use; and advanced paternal age) [66–74].

Conclusion

With the relatively recent advent of the GWAS era, schizophrenia genetics research has yielded an unprecedented accumulation of new risk loci. Further, our knowledge is aided greatly by technological developments and improved and more rigorous statistical analyses. This is further supported by the large scale cooperation of the scientific community via rapid data sharing and very large meta-analyses. Future progress looks promising as these trends continue and are complemented by the addition of next-generation sequencing (WGS and exomic) in much deeper samples; functional study of statistically implicated variants; and eventually the study of human cellular models such as via neurons differentiated from induced pluripotent stem cells [75].

Glossary

ENCODE Refers to the *Enc*yclopedia *O*f *D*NA *E*lements project to identify all functional elements in the human genome sequence

Exome sequencing The DNA sequencing of the exons in the genome, most often referring to the protein coding exons, i.e., not including all untranslated regions (UTRs)

Expression quantitative trait nucleotides (eQTNs) Are SNPs that regulate expression levels of mRNAs or proteins

Genomics Refers to mapping or sequencing of whole genomes (as opposed to focusing on an individual gene)

Linkage disequilibrium Abbreviated LD, the nonrandom association of alleles (alternative forms) at two or more loci, which descended from an ancestral chromosome

Metabolomics The study of the whole set of metabolites (small molecule end products of cellular processes, i.e., metabolism) of a biological unit (cell, tissue, organ, individual)

Methylomics The study of DNA methylation (which affects gene expression) on a genome-wide scale

Network or pathway analyses The study of a biological system with subunits connected into a larger patterns (networks, pathways), such as a protein–protein interaction network or a gene regulatory (e.g., DNA–protein interaction) network

Nonparametric linkage analysis A type of linkage analysis where no assumptions or specifications are made regarding the genetic model for the disorder

Parametric linkage analysis A type of linkage analysis where the genetic model for the disorder must be specified, i.e., allele frequency and penetrance (likelihood a risk genotype will be phenotypically expressed) parameters

Pharmacogenetics The study of genetic differences affecting metabolic pathways important for drug response (including both therapeutic and side effects)

Polygenic contributions The situation when variants at many genes contribute to a phenotype, as opposed to the phenotype arising from variation at one (monogenic) or a few genes (oligogenic)

Polymorphic Having more than one form, as in a genetic maker with more than one allele (alternative form)

Proteomics The study of an entire complement of proteins of a biological unit

Transcriptomics The study of the set of all RNA (mRNA, rRNA, tRNA, and other noncoding RNA) of a biological unit (typically a collection of cells or a tissue), though in many instances limited to the study of mRNA

Whole-genome sequencing The DNA sequencing of the whole genome of an individual, i.e., all chromosomes and also mitochondrial DNA

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Chapter 6
Recent Advances in Neuroimaging Biomarkers of Schizophrenia

Lei Wang and John G. Csernansky

Abbreviations for fMRI Tasks

CP	Context processing
CPT	Continuous performance task
DMS	Delayed match to sample
EF	Executive function, including DMS, GNG, MA, NB, OB, SR, ST, WCS, and WG
EL	Emotion-labeling
EME	Episodic memory, encoding
EMR	Episodic memory, retrieval
FF	Fearful faces
FN	Fear and neutral faces
GNG	Go/No-Go
MA	Mental arithmetic
NB	N-Back
NF	Negative faces
NI	Negative images vs. neutral images
NV	Nonvisual speech
OB	Oddball

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P.G. Janicak et al. (eds.), *Schizophrenia: Recent Advances in Diagnosis and Treatment*,
DOI 10.1007/978-1-4939-0656-7_6,

PC	Pavlovian conditioning
RI	Response inhibition
RP	Reward prediction
SA	Speech appraisal
SL	Listening to speech
SP	Speech/non-speech
SR	Sequence recall
ST	Stroop
VB	Verbal fluency
WCS	Wisconsin card sorting
WG	Word generation
WM	Working memory

Abbreviations for Gray Matter ROIs

ACC	Anterior cingulate cortex
AG	Amygdala
BG	Basal ganglia
CD	Caudate
CG	Cingulate gyrus
DLPFC	Dorsolateral prefrontal cortex
ERC	Entorhinal cortex
GP	Globus pallidus
HG	Heschl's gyrus
HP	Hippocampus
IFG	Inferior frontal gyrus
IPL	Inferior parietal lobule
MPFC	Medial prefrontal cortex
MSFG	Medial superior frontal gyrus
MTG	Middle temporal gyrus
MTL	Medial temporal lobe
NAc	Nucleus accumbens
OFG	Orbitofrontal gyrus
PCC	Posterior cingulate cortex
PFC	Prefrontal cortex
PHG	Parahippocampal gyrus
PPC	Posterior parietal cortex
PT	Planum temporale
PUT	Putamen
STG	Superior temporal gyrus
TH	Thalamus
VLPFC	Ventrolateral prefrontal cortex
VSTR	Ventral striatum

Abbreviations for White Matter ROI

AF Arcuate fasciculus, connecting STG and IPL with inferior frontal gyrus. AF is important in language processing
ALIC Anterior limb of the internal capsule
CB Cingulum bundle, connecting paralimbic-neocortical brain regions, also connecting limbic structures including DLPFC, CG, PHG, and AG. CB is involved in a number of functions, including pain perception, emotion, self-monitoring, and spatial orientation and memory
CC Corpus callosum
FX Fornix
ILF Inferior longitudinal fasciculus, connecting the anterior temporal and occipital regions
IOF Inferior occipitofrontal fasciculus, connecting the frontal with occipital and temporal lobes
PLIC Posterior limb of the internal capsule
SLF Superior longitudinal fasciculus, connecting the frontal, occipital, parietal, and temporal lobes
UF Uncinate fasciculus, connecting OFG and IFG with the anterior pole and the AG. UF is involved functionally in decision making, autobiographical and episodic memory, as well as in social behavior

Abbreviations for White Matter

FA Fractional anisotropy
MD Mean diffusivity

Abbreviations for Other

DMN Default mode network

Overview

Since Kraepelin (1917) first described "dementia praecox" and Bleuler (1911) coined the term "schizophrenia," and until Johnstone and colleagues (1976) conducted the first neuroimaging study in schizophrenia with computerized tomography (CT), the search for the cause(s) and cure of schizophrenia has been primarily conducted in the dark [1–4]. This is because investigators were unable to image the living brain. In the ensuing three decades, numerous advances in neuroimaging were introduced. These included positron emission tomography (PET) for brain energy (glucose)

consumption (1979); structural magnetic resonance imaging (MRI, sMRI) for brain structure (1980); functional MRI (BOLD, or blood oxygen level dependent, fMRI) for brain activity (1990); and diffusion-weighted imaging (DWI) for white matter tracts that connect different regions of the brain (1990) [5–15]. The development of other neuroimaging technologies, such as magnetic resonance spectroscopy (MRS) and arterial spin labeling (ASL), combined with evolving data analysis methods and software tools, pushed open a window to the brain [16, 17]. Since the first MRI study of schizophrenia, neuroimaging research has provided insights into the neural underpinning and heterogeneity of the illness [18].

Decades before modern technology discerned anatomic and functional connections in the living brain, Geschwind put forth the visionary suggestion that connections between regions that subserved specific behavioral functions are critical to overall mental functioning [19]. The latest developments in modern neuroimaging technology and analytic methods are revealing the overall organization of the functional brain network, and Geschwind's inference on the "disconnexion syndromes in animals and man" has evolved into "the disconnection hypothesis" that schizophrenia is a syndrome of disconnection of neural networks [20–23].

Many excellent reviews have been published on the topic of schizophrenia and neuroimaging (PubMed search revealed close to 700 reviews since 1988 and over 175 since 2010), starting with early comprehensive reviews of brain structure by Pearlson and Marsh, McCarley et al., Shenton et al., and Buckley [4, 24–26]. More recent reviews include Shenton et al. on gray matter; Karlsgodt et al. and Thomason and Thompson on white matter; Waddington, McGuire et al., and Mueller et al. on function; and Fornito et al. and Pettersson-Yeo et al. on connectivity [23, 27–33]. There are now close to 3,000 papers reporting schizophrenia neuroimaging studies in the last 25 years and close to 1,000 since 2010.

In this chapter, we describe more recent developments of neuroimaging measures of regions of interest (ROIs) and functional networks, as well as multimodal integration and pattern analysis in schizophrenia.

Distributed Patterns of Widespread Abnormal Structure and Function

Volumetric measurement of manually traced ROIs in structural MRIs was the predominant method in the first decade of schizophrenia neuroimaging research. Andreasen et al. published the first quantitative MRI study of schizophrenia (e.g., see reviews by Lawrie and Abukmeil, McCarley et al., and Pearlson and Marsh) [24, 25, 34, 35]. These early studies unequivocally demonstrated that schizophrenia is associated with patterns of fundamental anatomic abnormalities almost everywhere in the brain. These patterns are subtle, but widespread, and include enlarged ventricular spaces and gray matter losses predominantly in the medial temporal and frontal lobes, but also in the midline limbic structures and the deep thalamic and striatal nuclei [24–26, 35]. Chapter 4 of this book

provides a more comprehensive summary of brain structural abnormalities and their clinical correlates.

In the ensuing decades, structural MRI research benefited from increases in scanner field strength from 1.5 T to 3 T and subsequent increased resolution down to 1 mm. In addition to measuring volume, the emerging field of computational anatomy (Box 6.1) also allowed for automated segmentation and quantification of structural shape and cortical thickness. Studies employing these new technologies confirmed earlier observed patterns of distributed gray matter loss in the frontal, temporal, limbic, and striatal regions [27, 36–44]. Visualization of these overall patterns became possible with the development of meta-analysis tools such as ALE (Activation Likelihood Estimation, http://www.brainmap.org/ale/) and SDM (Signed Differential Mapping, http://www.sdmproject.com/software/). Figure 6.1 shows visualization of the spatial patterns of gray matter loss in schizophrenia across prefrontal/dorsolateral prefrontal cortex, temporal/medial temporal lobe, anterior cingulate cortex, and thalamus, based on meta-analysis using these tools [44].

Box 6.1 Computational Anatomy

Although manual methods are still considered the gold standard for structural delineation today, they are unsatisfactory for a number of reasons:

- *Manual tracing* is time-consuming and quite often suffers from rater bias, drift, and attrition.
- *Anatomic abnormalities* appear to be very subtle in schizophrenia, often not exceeding 5 % in ROI volume reductions.
- *Structural size* is not precise or specific enough to provide biological insights to disease pathophysiology.

To overcome these limitations, computational anatomy was developed by several labs in the late 1990s to provide automatic or semiautomatic, computerized approaches for the understanding of biological shape variation, cortical thickness, and cortical folding patterns.

The origin of computational anatomy can be traced back to 1917 when Sir D'Arcy Wentworth Thompson emphasized the roles of physical laws and mechanics as determinants of the form and structure of living organisms [111]. Grenander and Miller coined the term computational anatomy (and later computational functional anatomy for brain function) which focuses on the quantitative analysis of shape variability in biological structures [112, 113]. Its basic principles are: building atlases and computing large-deformation maps to represent biological shape space; computing empirical probability laws on that space to represent biological shape average and variation; and making inferences based on the probability laws for hypothesis testing and classification. An early review of several of the computational anatomy methods is found in

(continued)

Box 6.1 (continued)

Ashburner et al. and a more complete collection of these methods in a NeuroImage Special Issue on Mathematics in Brain Imaging [114, 115].

The field of computational anatomy has flourished with an abundance of methods including deformation-based morphometry (DBM), voxel-based morphometry (VBM), tensor-based morphometry (TBM), surface-based morphometry (SBM), and pattern-based morphometry (PBM). For example, a 2003 review presented three nonlinear deformation methods and a 2009 review listed and compared 14 [114, 116]. Freely available software packages that utilize these methods are now easily accessible and user-friendly. These packages, including FreeSurfer (http://surfer.nmr.mgh.harvard.edu/), Slicer (http://www.slicer.org), Brain Voyager (http://www.brainvoyager.com/), BRAINS (http://www.nitrc.org/projects/brains), and SPM (http://www.fil.ion.ucl.ac.uk/spm/), offer automatic registration, ROI delineation, cortical measurements, white matter fiber tract tracing, and statistical hypothesis testing.

These methods and software tools represent more than 15 years of research combining mathematics, engineering, and computer vision. They provide unprecedented precision and repeatability, thereby alleviating rater bias and drift. Additionally, they are increasingly automated and are able to evaluate ever larger datasets to allow for the detection of subtle biological differences. They employ sophisticated state-of-the art algorithms to identify shape or localized changes in all areas of the brain and provide biologically meaningful information about the underlying disease process [117].

The next advance in neuroimaging research in schizophrenia included functional imaging and diffusion imaging techniques, which allowed for the quantification of brain activities in these regions and the integrity of the white matter that connects them. The first set of (fMRI) studies in individuals with schizophrenia reported elevated responses to photic stimulation in the primary visual cortex; reduced activation in the sensorimotor cortex and supplementary motor area during a finger-to-thumb task; and reduced frontal activation and increased temporal activation during a word fluency task [45–49]. The first set of diffusion tensor imaging (DTI) studies reported reduced white matter anisotropy extending from frontal to occipital regions, along with a lack of normal asymmetry in the uncinate fasciculus which connects the frontal and temporal regions [27, 50–53].

Since then, a wealth of fMRI studies revealed patterns of widespread abnormal task-induced activity that are similar to patterns of gray matter abnormalities. Most consistent are decreases in the dorsolateral prefrontal cortex during working memory and executive functioning tasks, followed by altered activity in the lateral and medial temporal lobe during retrieval tasks, and in the cingulate gyrus during cued verbal recall and Stroop tasks [54]. However, some studies have also shown

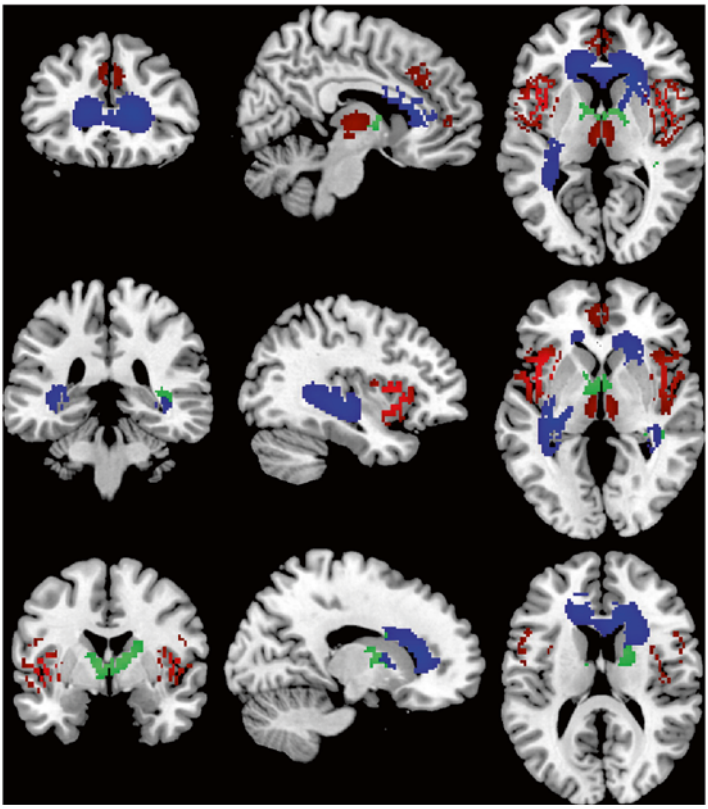

Fig. 6.1 Distributed patterns of gray and white matter abnormalities in schizophrenia from meta-analyses (Reproduced with permission from Bora et al. [44]). Meta-analysis of voxel-based morphometry studies indicates reduced gray matter density in bilateral medial frontal and temporal regions, dorsal and rostral anterior cingulate cortex, insula, and thalamus; left lateral prefrontal areas, superior frontal gyrus, and orbitofrontal and fusiform regions. Meta-analysis of DTI studies indicates reduced white matter volume in the anterior limb of the internal capsule (ALIC), right inferior frontal occipital fasciculi, and the inferior longitudinal fasciculi (ILF), and increased white matter volume in the left superior longitudinal fasciculi (SLF). Meta-analysis of DTI studies also indicates reduced fractional anisotropy (FA) in the bilateral genu of the corpus callosum, anterior cingulate cortex/medial frontal white matter, right ALIC, right external capsule/corona radiate, left temporal white matter and retrolenticular internal capsule, external capsule including fibers from the left inferior frontal occipital fasciculi, ILF and fornix/stria terminalis, and right temporal WM including fibers from right inferior frontal occipital fasciculi and ILF. *Red*: gray matter, *Blue*: DTI, and *Green*: WM volume (Color figure online)

increased activities in these regions (see Table 6.1 for a more detailed description of increased and decreased activities found in different studies). Similarly, DTI studies revealed consistently decreased white matter integrity in these regions, as well as in the regions that connect them, including frontotemporal, fronto-occipital, temporo-occipital, thalamocortical, and interhemispheric connections [27]. However,

Table 6.1 Distributed and heterogeneous pattern of widespread abnormal structure and function in schizophrenia

ROI	Review	fMRI: Measure Change, no. of studies	DTI: Measure Change, no. of studies	Notes
Frontal/prefrontal				
PFC	[45, 57, 139, 140]	EF ↓, 17 ↑, 7 ↓ ↑, 13 EME, EMR ↓, 6 Language ↓, 1 L	MD ↑, 2	↑ MD
MPFC	[141]	EL, FF, NF, NI ↓, 1L, 2R ↑, 1L, 1R		
DLPFC	[45, 55, 141]	NB ↓, 4 ↑, 2 Language, VB, WM, RI, CP ↓, 7L, 4R ↑, 2L, 1R		
VLPFC	[141]	WM, CP ↓, 1L, 2R ↑, 1L, 1R		
OFG				
White matter	[57, 142]		FA, MD ↓, 11 ↔, 1	
Temporal/MTL				
AG	[141]	EL, FN, FF, NI ↓, 6L, 2R ↑, 1L		
HP/PHG	[141]	EL, FN, FF, NI ↓, 3L, 2R ↑, 2R		
HP	[57, 140]	EME, EMR ↓, 4	FA ↓, 1	
PHG	[57]		FA, MD ↓, 1 ↑, 1	↑ MD
ERC				
STG	[45, 57]	Language, VB SA, SL, SP, NV ↓, 4L, 1R ↑, 1L, 2R	FA ↓, 1	

(continued)

Table 6.1 (continued)

ROI	Review	fMRI: Measure Change, no. of studies	DTI: Measure Change, no. of studies	Notes
MTG	[57]	SA, SL, SP, NV ↓, 3L, 2R ↑, 2R	FA ↓, 1	
White matter	[57, 142]		FA ↓, 5 ↔, 1	
Parietal				
IPL	[57]		FA ↓, 1	
White matter	[142]		FA ↓, 2 ↔, 1	
Occipital				
White matter	[57, 142]		FA ↓, 3 ↔, 1	
Limbic				
CG	[55, 57]	NB ↑, 1	MD ↑, 1	↑ MD
ACC	[57, 143]	CPT ↓, 1	FA ↓, 1	
Deep nuclei				
TH	[57, 140]	EMR ↓, 2	MD ↑, 1	↑ MD
VSTR	[141]	RP, PC ↓, 2L ↑, 1L, 1R		
Connections				
CC	[57, 142, 144]		FA, MD ↓, 7 ↔, 3	
FX	[57]		FA, MD ↓, 1 ↑, 1	↑ MD
ALIC	[57, 142]		FA ↓, 3 ↔, 1 ↑, 1	
PLIC	[57, 142]		FA ↓, 2 ↔, 1 ↑, 1	

(continued)

Table 6.1 (continued)

ROI	Review	fMRI: Measure Change, no. of studies	DTI: Measure Change, no. of studies	Notes
Frontal–temporal				
AF	[27]		FA ↓, 3	Reduced left-lateralized
CB	[27, 57, 142]		FA, MD ↓, 10 ↔, 3 ↑, 1	↑, MD
UF	[27, 57, 142]		FA, MD ↓, 4	FA decrease in left > right asymmetry
			↔, 1	↑, MD
			↑, 1	
Frontal–occipital–parietal–temporal				
SLF	[57]		FA, MD ↓, 5 ↔, 1 ↑, 1	↑, MD
Fronto-occipital				
IOF	[57]		FA, MD ↓, 2 ↔, 1 ↑, 1	↑, MD
Temporal–parietal				
White matter	[57, 142]		FA, MD ↓, 2	
Temporal–occipital				
ILF	[27, 57, 144]		FA ↓, 4	
Parietal–occipital				
White matter	[142]		FA, MD ↓, 1	

Structurally, reduced volume, altered asymmetry, and abnormal shape of gray matter are predominantly found in the medial and lateral temporal lobe, followed by frontal regions. Functionally, task-induced abnormal activities are seen in prefrontal regions most often, followed by the medial and lateral temporal lobe. These structural and functional changes are accompanied by similar changes in white matter integrity, in these particular regions and in the regions that connect thems
Symbols
↓: reduced when compared with controls
↑: increased when compared with controls
↓ ↑: both reduced and increased when compared with controls
↔: no difference when compared with controls
N/A: not available/not reported

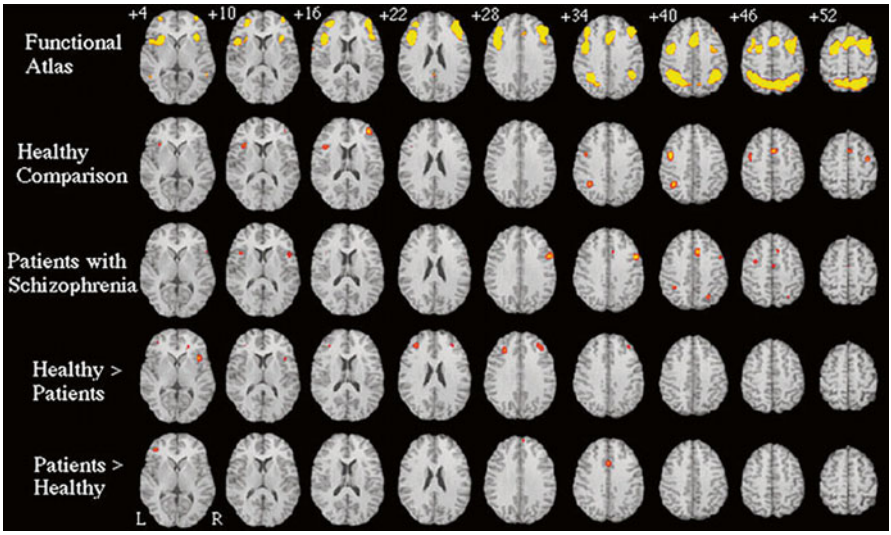

Fig. 6.2 Distributed patterns of fMRI activation abnormalities in schizophrenia from meta-analyses (Reproduced with permission from Glahn et al. [55]). Meta-analysis of N-Back studies indicates reduced activation in bilateral dorsolateral prefrontal cortex, rostral prefrontal cortex, and right ventrolateral/insular cortex. Brain regions showing greater patient activation include left frontal pole, right dorsomedial prefrontal cortex (BA9), and anterior cingulate

some studies have observed increased white matter integrity measures, particularly in interregional connections.

Table 6.1 provides a detailed summary of the patterns of abnormal structure and function in studies of schizophrenia. The table is arranged by brain regions commonly found to have abnormal gray matter structure in sMRI studies. Findings from recent reviews of fMRI and DTI studies in these regions are then summarized in separate columns. Findings of abnormal interregional anatomic connections are listed in the bottom portion of the table. Similar to sMRI studies, advanced meta-analysis tools now allow for the visualization of spatial patterns of functional and anatomic connection alterations (Fig. 6.2: reduced activation in bilateral dorsolateral prefrontal cortex, rostral prefrontal cortex, and right ventrolateral/insular cortex during N-Back working memory paradigm [55]; reduced activation in the right superior frontal gyrus, left and right inferior frontal gyri, right inferior parietal gyrus, right lingual gyrus, and right posterior cingulate gyrus during episodic memory encoding; and reduced activation in the left inferior frontal gyrus, left precentral and middle frontal gyri, right anterior cingulate gyrus, left middle temporal gyrus, right cuneus, bilateral thalamus, right posterior cingulate gyrus, and bilateral cerebellum during episodic memory retrieval [not shown] [56]; Figs. 6.1 and 6.3: reduced anisotropy and white matter volume in the anterior thalamic radiation, inferior longitudinal fasciculi, inferior frontal occipital fasciculi, cingulum and fornix, cingulate, corpus callosum, frontal, temporal, parietal, and occipital lobes; as well as intralobar and interlobar connections of the superior longitudinal fasciculus,

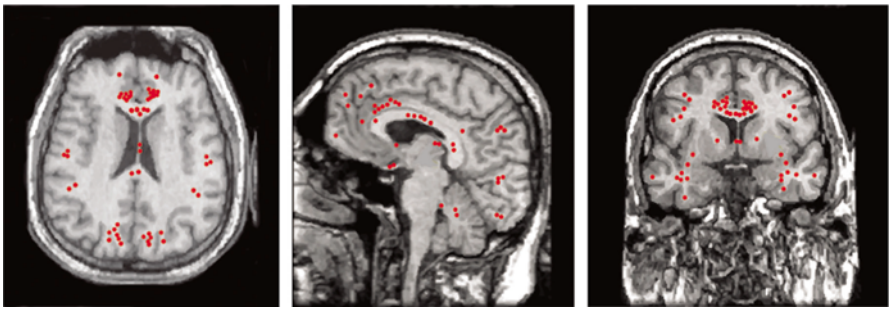

Fig. 6.3 Distributed patterns of DTI abnormalities in schizophrenia from meta-analyses (Reproduced with permission from White et al. [57]). Meta-analysis of DTI studies indicate reduced anisotropy and white matter volume in the anterior thalamic radiation, inferior longitudinal fasciculi, inferior frontal occipital fasciculi, cingulum and fornix, cingulate, corpus callosum, frontal, temporal, parietal, and occipital lobes, as well as intralobar and interlobar connections of the superior longitudinal fasciculus, fronto-occipital longitudinal fasciculi, uncinate fasciculi, frontal longitudinal fasciculus, and the arcuate fasciculus

fronto-occipital longitudinal fasciculi, uncinate fasciculi, frontal longitudinal fasciculus, and arcuate fasciculus [44, 57]).

Disorganization of Brain Networks

Individuals with schizophrenia exhibit a wide range of clinical symptoms such as delusions, hallucinations, loss of emotion, and disorganized thoughts. These symptoms are accompanied by profound difficulties in a broad spectrum of cognitive functioning including working memory, episodic memory, and attention to stimuli, as well as the ability to control these cognitive processes [58]. Despite demonstrable abnormalities, however, studies of individual brain regions are unable to answer questions related to the pathophysiology of schizophrenia. This is because the methods employed by these studies are limited to the traditional view that cognitive functions are subserved by individual or separate brain regions. For example, studies of the dorsolateral prefrontal cortex could not completely account for the cognitive deficits exhibited in individuals with schizophrenia [59]. Recently, this traditional view has given way to a new paradigm in which cognitive constructs are viewed as being subserved by complex, interconnected, large-scale brain networks that segregate and then reintegrate to work together [60–64]. In this light, schizophrenia may be a disorder of neural and cognitive integration and that multifocal abnormalities in the brain, although subtle, likely involve brain networks or systems rather than a simple collection of disparate brain regions [21, 65–68].

A brain network is a set of brain systems that together subserve a specific or a set of specific cognitive behaviors such as working memory, attention, and executive function. A brain system is a set of cytoarchitectonically or functionally distinct brain regions along with the connections between these regions. Components and

their links are defined based on measurement methods. (A broader, graph-theoretical concept of global, large-scale brain networks is described later in this chapter.) Accordingly, the schizophrenia neuroimaging research field is moving in the direction of network, multimodal, and pattern analyses (Box 6.2).

Below we summarize neuroimaging evidence that brain regional structural and functional impairments, as well as disruptions in the structural and functional connections between these regions, occur in a coordinated, network-wide fashion (i.e., schizophrenia is a disorder of disruptions in neural circuitry) [20, 21, 65, 69–71].

Box 6.2 Emerging Technologies and Characterization of Brain Networks

The theoretical prediction that healthy mental functioning depends on the existence of interregional connections and cooperation was set forward by Norman Geschwind (1965) in his seminal paper "Disconnexion syndromes in animals and man. I" [19]. In vivo neuroimaging support for this prediction started to gather only after technology advanced to the point where this was possible. Nora Volkow (1988) and colleagues provided the first neuroimaging evidence in a study of 12 healthy volunteers using PET scans [65]. She discovered covariations in the amount of regional deoxy [^{11}C] glucose uptake in the frontal and occipital regions, thalamus and frontal regions, and thalamus and occipital regions, and she proposed meaningful interactions in the forms of fronto-occipital, thalamo-frontal, and thalamo-occipital brain organization. The concept of a "functional connectivity" was solidified 5 years later when Friston et al. coined this term in a [^{15}O] PET study of six healthy male volunteers [118]. Functional connectivity was subsequently defined as "temporal correlation between two neurophysiological (functional) measurements made in different brain areas". In vivo neuroimaging investigation of functional connectivity made its biggest breakthrough with the invention of fMRI by Seiji Ogawa (1990) and the discovery of resting state connectivity by Bharat Biswal (1995), seven years after the initial PET study by Volkow et al. [12, 119].

While correlation-based characterization of functional connectivity requires a priori definition of pairs of brain ROIs, a recently adapted multivariate approach, independent component analysis (ICA), does not have such a requirement. It allows for the automatic discovery of functional connectivity in the entire brain. ICA was originally used in signal processing in 1995 to solve "cocktail party" problems separating individual voices from recordings of many people speaking at once [120]. It was first applied to neuroimaging on groups of subjects to identify temporally coherent intrinsic brain networks by Vince Calhoun in a series of studies [121–123]. ICA extensions were later developed for functional network connectivity (FNC) analysis and

(continued)

Box 6.2 (continued)

structure–function joint analysis (jICA) [124, 125]. Using both correlational analysis and ICA methods, fMRI studies made great contributions to the discovery of the brain's many resting state networks (RSN) which are temporally coherent, are spatially distributed, and correspond to functional behaviors. These networks include the default mode network (DMN), somatomotor network, visual network, language network, dorsal attention network, ventral attention network, and fronto-parietal control network [78, 126, 127]. In Fig. 6.4 we show examples of these networks as obtained from an ICA analysis of resting state data [126].

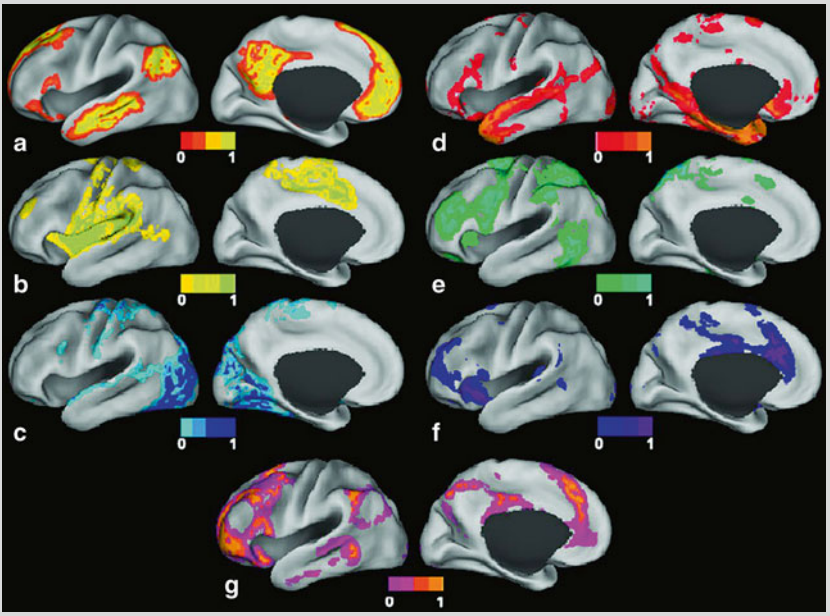

Fig. 6.4 Representation of different ICA components from resting state fMRI analysis. Resting state networks projected onto the cerebral surface. (**a**) Default mode network. (**b**) Somatomotor network. (**c**) Visual network. (**d**) Language network. (**e**) Dorsal attention network. (**f**) Ventral attention network. (**g**) Fronto-parietal control network. Reproduced with permission from Lee et al. [126]

Disrupted Regional Networks

Relationships between functional networks in schizophrenia were first interrogated by Volkow et al. in a PET study [65]. Compared with controls, individuals with schizophrenia showed reductions in what was later termed functional connectivity between frontal and occipital cortices and between the thalamus and frontal, occipital cortices. Using PET and word generation paradigms, Friston later reported a disruption of prefronto-temporal functional connectivity in individuals with schizophrenia [72]. In individuals with schizophrenia, the normal correlations between prefrontal and superior temporal cortices were absent, and the normal correlations between prefrontal and middle temporal cortices were increased. These prefrontal–temporal connectivity disruptions were later replicated in functional connectivity studies using PET and fMRI [68, 71, 73–76]. Further, dorsolateral prefrontal cortex–superior temporal gyrus/parahippocampal connectivity was reduced while ventrolateral prefrontal cortex–superior temporal gyrus/parahippocampal connectivity was increased during verbal encoding [77].

The default mode network (DMN), consisting of the medial temporal lobe, medial prefrontal cortex, posterior cingulate cortex, precuneus, and medial, lateral, and inferior parietal cortices, is among the most studied networks in schizophrenia [78]. Individuals with schizophrenia show disruption in the localized spatial patterns of activation during task, i.e., reduced activation in the precuneus, both reduced and increased activation in different parts of the posterior cingulate, and the inability to properly suppress medial prefrontal cortex activity [79, 80]. They also show disrupted connectivity among the DMN regions while at rest, although some inconsistencies exist. For example, Zhou et al. and Whitfield-Gabrieli et al. found increased connectivity, while Bluhm et al. found the opposite [80–82]. Despite these discrepancies, which may be due to inherent disease heterogeneity and differences in patient cohorts and analysis methods, hyper-connectivity within the DMN regions is the most consistent finding [83, 84].

More recent fMRI studies of schizophrenia extend these findings to the interconnections between the rest of the brain regions. Connectivity between the DMN and the frontal, parietal, and fronto-parietal networks is increased, while DMN connectivity with dorsolateral prefrontal cortex and orbitofrontal gyrus networks is decreased [80, 85, 86]. Also, a decrease in functional connectivity exists between the frontal/prefrontal areas (including the dorsolateral prefrontal cortex) and other networks; and between the temporal network and other networks [73, 80, 81, 85–90]. These disruptions are thought to weaken frontal–temporal connectivity [71, 73–76]. They also corroborate the notion that the frontal–temporal white matter connections are weakened (i.e., the finding of "hypofrontality"), as well as the shifting of frontal to nonfrontal hubs (described in the next section).

The literature is not without inconsistencies. For example, Jafri et al. and Sakoglu et al. both reported changes between the frontal–visual networks but in opposite directions [85, 86]. While the DMN–frontal connectivity was increased in one study, the DMN–dorsolateral prefrontal cortex connectivity was decreased in another [80, 86]. Table 6.2 provides a summary of findings on the disruption in between-network functional connectivity from these studies.

Table 6.2 Disrupted between-network functional connectivity in schizophrenia

Connection	Study	Correlation/ anticorrelation (+/-)	Increase/ decrease (↑/↓)	Notes
Frontal to other areas				
Frontal–DMN	[86]	+	↑	
Frontal–visual	[86]	+	↑	
Frontal–visual	[85]	+	↓	Medial visual
Frontal–MTL	[85]	+	↓	Task modulated
Frontal–other lobes	[89]	+	↓	Graph theory
Frontal–temporal	[71, 74–76]	+	↓	
Prefrontal/DLPFC to other areas				
Prefrontal–temporal	[73]	+	↓	
Prefrontal–cingulate	[87]	+	↓	Task modulated, MSFG-ACC
Prefrontal–cerebellum	[73]	+	↓	
DLPFC–parietal	[81]	+	↓	Bilateral
DLPFC–PCC	[81]	–	↓	Right
DLPFC–PPC	[90]	+	↓	
DLPFC–DMN	[80]	–	↓	
DLPFC–other brain areas	[88]	+	↓	Absence of normal connectivity
DLPFC–OFG, insula	[81]	–	↑	Left DLPFC
VLPFC–PPC	[90]	+	↑	
Fronto-parietal to other areas				
Fronto-parietal—other areas				
Fronto-parietal—DMN	[86]	+	↑	
Fronto-parietal—visual	[86]	+	↑	
Fronto-parietal—OFG	[85]	+	↑	Right lateral fronto-parietal
Fronto-parietal—MTL	[85]	+	↑	Task modulated, right lateral fronto-parietal
Temporal to other areas				
Temporal–occipital	[73]	+	↓	
Temporal–cerebellum	[73]	+	↓	
Temporal–parietal	[86]	+	↓	
Temporal–parietal	[85]	+	↓	Medial temporal
Temporal–visual	[85]	+	↓	Medial temporal, medial visual
Medial temporal–anterior temporal	[85]	+	↓	
Other connectivities				
OFG–DMN	[85]	+	↓	Task modulated, posterior DMN
Parietal–DMN	[85]	+	↑	Task modulated, posterior DMN
Parietal–visual	[85]	+	↓	Medial visual

(continued)

Table 6.2 (continued)

Connection	Study	Correlation/ anticorrelation (+/-)	Increase/ decrease (↑/↓)	Notes
ACC–other brain areas	[145]	+	↓	Normal connectivities absent
Cerebellum–other brain areas	[73]	+	↑	

We note: (1) reduction of connectivity is most acute in the pairings of frontal to other areas and temporal to other areas, and this corroborates the weakening of the frontal–temporal connection as mentioned previously in DTI studies; (2) relatively few studies reported changes other than the frontal and temporal networks, and this corroborates the "hypofrontality" mentioned earlier and the shifting of frontal to nonfrontal hubs below; (3) changes in inter-network connectivities involving the DMN specifically depend on what the other network is: increases with frontal, parietal, and fronto-parietal, and decreases with DLPFC and OFG; (4) some inconsistent findings are also reported. For example, Jafri et al. and Sakoglu et al. both reported changes between the frontal–visual networks but in opposite directions [85, 86]
Symbols
↓: reduced when compared with controls
↑: increased when compared with controls
N/A: not available/not reported

Disrupted Large-Scale Global Networks

Overwhelming evidence exists that schizophrenia is associated with widespread disruptions in normal structural and functional coherence, notably in the prefrontal, temporal, parietal, and limbic regions. Additionally, connections between these regions, both structurally via white matter pathways and functionally via synchronized neural oscillations, are also disrupted. Recent developments in large-scale brain network analysis methods, particularly those based on graph theory approaches (Box 6.3), allow for the examination of these disruptions in a coordinated, global fashion.

Box 6.3 Development of Large-Scale Brain Network Methods

Adapted from the graph-theoretic framework, interregional brain networks were first characterized in cats and macaques where connections between brain regions could be anatomically verified [128–130]. Organizations of mammalian brain networks use a combination of high levels of local clustering (i.e., cliques) and overall short path lengths to link all nodes of the

(continued)

Box 6.3 (continued)

network [91]. This type of network is said to have "small-world properties," a concept originally described in social networks [131]. A network with small-world properties balances local segregation (modular processing) and global integration (distributed processing) with high signal-propagation speed, computational efficiency, and information synchronizability [132]. Virtually all complex, real-world networks have small-world properties (e.g., social networks, road maps, gene and neuron networks).

The characterization of brain organization in humans greatly improved with recent developments in neuroimaging techniques, especially white matter tract tracing and fMRI connectivity methods which quantify structural and functional connections. The application of graph-theoretical approach demonstrates that human brain structural and functional networks also exhibit small-world properties [132]. This approach usually includes the following steps of analysis: network nodes are defined as anatomic ROIs, such as subcortical or cortical structures in MRI or electrode sensor locations in the electroencephalogram (EEG); associations between nodes are then defined by structural or functional connectivity (i.e., correlations in cortical thickness or volume, DTI tractography-derived connection probability, correlations between fMRI BOLD time series, or spectral coherence between sensors); an adjacency matrix or undirected graph is then generated by compiling all pairwise associations (e.g., correlation); and finally, network parameters of interest are calculated [60, 132, 133]. The most commonly used network parameters are the small-world parameters (i.e., clustering coefficient, characteristic path length, and degree of connectivity). Other parameters include hierarchy, assortativity, connection distance, centrality, and identification of network hubs. A formal definition of "small-worldness" is that a network's level of clustering should be greater than that of a comparable random network, and the clustering coefficient to characteristic path length ratio is also greater than that of a comparable random network, where clustering coefficient is a measure of how much neighbors of each network node are also neighbors of each other and characteristic path length is the average length of the shortest path between any two nodes [91, 128, 134]. In Figs. 6.5, 6.6, and 6.7 we show illustrations of network analysis pipeline and outcomes using graph theory approaches [33, 91].

The first graph-theoretic application of network analysis in schizophrenia was performed by Micheloyannis et al. using EEG [135]. The first structural network analysis was performed by Bassett et al. using regional volumes measured in structural MRI, while Liu et al. were the first group using fMRI [89, 91]. Earlier EEG and magnetoencephalography (MEG) studies showed discrepant findings regarding small-worldness (decreased; preserved) and may be related

(continued)

Box 6.3 (continued)

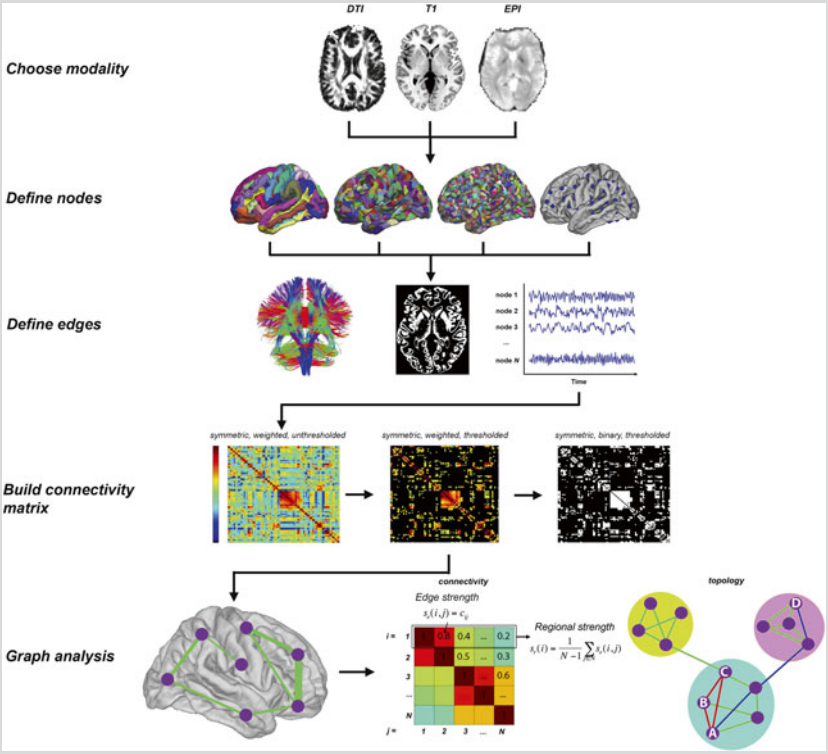

Fig. 6.5 Representations of graph theory network analysis pipeline and outcomes: Illustration of the main steps involved in graph analysis of human neuroimaging data (Reproduced with permission from Fornito et al. [33]). Top row: imaging modalities. Second row: imaging data are parcellated into distinct network nodes—e.g., anatomic parcellation (*left*), random parcellations of 500 (*middle left*) and 2,000 (*middle right*) regions, and functionally defined parcellation (*right*). Third row: interconnecting edges are defined—tractography for DTI (*left*), cross correlations for T1 (*middle*); time course dependencies for EPI (*right*). Fourth row: connectivity is represented as a continuously weighted matrix–time course correlations for resting state fMRI (left), thresholded to create either a weighted (*middle*) or binary (*right*) adjacency matrix. Bottom row: the adjacency matrix is used to construct a brain graph—e.g., a weighted, undirected graph where nodes are represented as purple circles and their interconnecting edges as green lines sized in proportion to edge weight (*left*), connectivity measures (*middle*): edge strength, regional strength, etc., and network topology (*right*) measure of connectivity: nodal degree, clustering coefficient, characteristic path length. Note that the nodes are grouped into three distinct modules, defined by the large *colored circles*. Nodes within modules have higher connectivity with each other than with the rest of the network (Color figure online)

(continued)

Box 6.3 (continued)

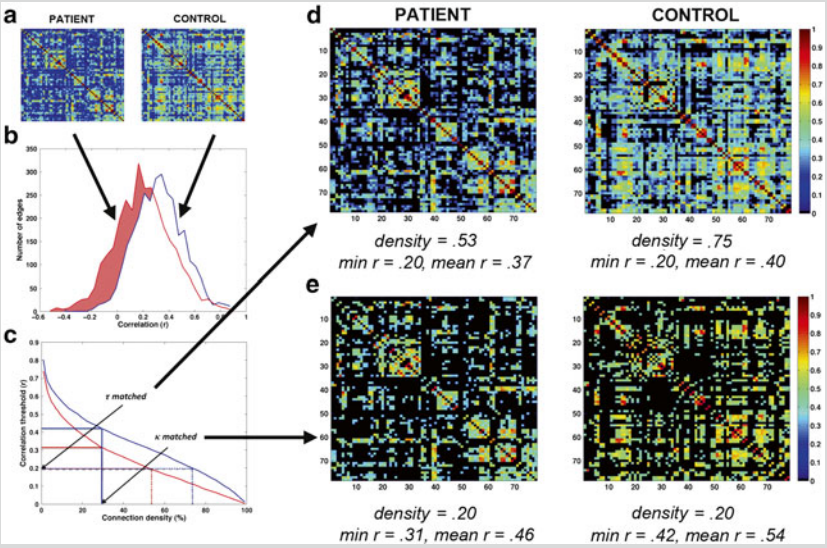

Fig. 6.6 Representations of graph theory network analysis pipeline and outcomes: Illustration of the relationship between thresholding and connectivity weight (Reproduced with permission from Fornito et al. [33]). (**a**) A representative functional connectivity matrix from a single patient (*left*) and control (*right*). (**b**) The distribution of connectivity weights is shifted towards lower values in the patient (*red*) relative to the control (*blue*); the area shaded in red highlights the excess number of low weighted values in the patient's connectivity matrix. (**c**) Applying weight-based threshold τ (*solid lines*) to the patient and control results in different connection densities; applying connection density-based threshold κ (*broken lines*) results in a different minimum correlation weight threshold. (**d**) Correlation matrices after τ-matched thresholding have different connection densities. (**e**) Correlation matrices after κ-matched thresholding have different minimum and mean weights (Color figure online)

to different thresholds across studies [97, 135–137]. In the quantification of network links and path lengths, various threshold values are used and they affect the group differences in overall path lengths more drastically than differences in clustering coefficients [100]. Since individuals with schizophrenia exhibit increased interdependence on long-distance nodes, both from functional connectivity (above) and from electrophysiology studies, it is reasonable to deduce that larger, but looser network clusters may have survived thresholding, contributing to decreased overall path length [138]. Since the early days of EEG, recent neuroimaging modalities of choice for investigating brain network organizations in schizophrenia shifted to DTI or fMRI, where connections (i.e., edges in a graph) can be explicitly quantified using measures of fiber tracts or functional connectivity throughout the brain, as opposed to being limited to the cerebral surface as measured in an EEG. In a

(continued)

Box 6.3 (continued)

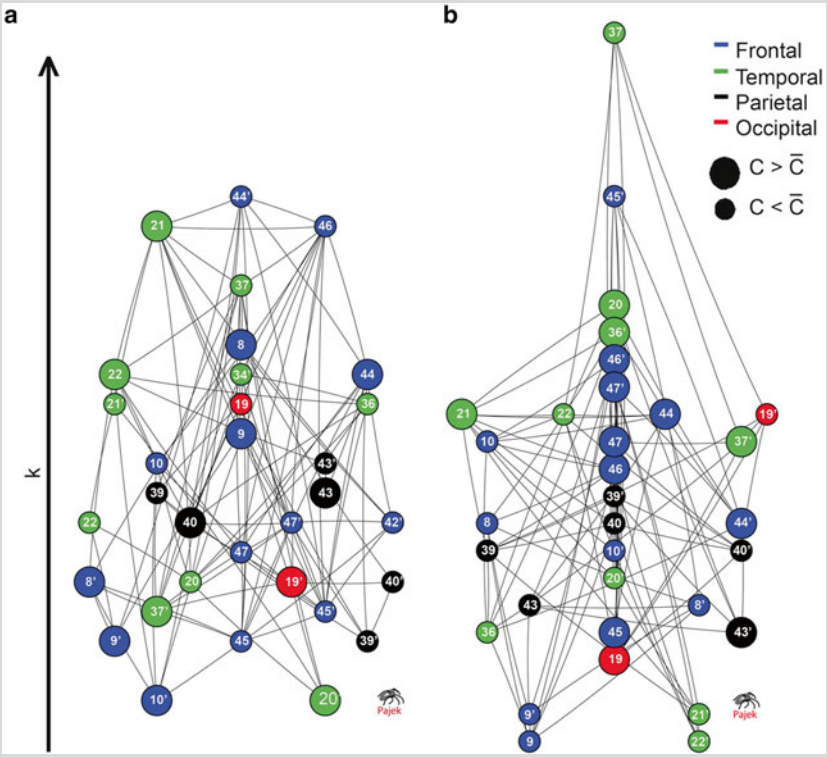

Fig. 6.7 Representations of graph theory network analysis pipeline and outcomes. Graphical visualization of multimodal network hierarchy (Reproduced with permission from Bassett et al. [91]). (**a**) Normal control subjects; (**b**) Individuals with schizophrenia. Nodes are ordered according to their degree (*y*-axis). Size of nodes indicates greater than (large) or less than (small) average clustering. Color of the nodes indicates lobe location: frontal (*blue*), temporal (*green*), parietal (*black*), or occipital (*red*). Lettering indicates approximate Brodmann area, and the overbar denotes left-sided regions. Note that highly clustered nodes are concentrated at the bottom of the normal hierarchy, which is dominated by highly connected nodes (many of them frontal) with low clustering; conversely, in individuals with schizophrenia, highly clustered nodes are more evenly distributed in terms of their degree, and frontal hubs are less prominent (Color figure online)

thorough review of the graph-theoretical analysis of disturbances in the structural and functional networks in schizophrenia, Fornito et al. provide a summary of MRI, DTI, and fMRI studies up to 2011 [33].

MRI studies based on sMRI, DTI, or fMRI and network analysis methods show that despite being "a putative neurodevelopmental disorder with profound effects on complex brain functions," the overall global network architecture in schizophrenia appears to be preserved. This suggests that key aspects of brain organization are highly conserved in schizophrenia [91]. Interestingly, however, virtually all of the local measures of this global network architecture differ from healthy controls. Reduced hierarchy, increased regional path length, reduced local efficiency, and loss of hub properties are all reported in individuals with schizophrenia [91–99]. Most notably, these patients show diminished hub properties in the frontal lobe and a shift of hubs from frontal to nonfrontal areas [91]. Table 6.3 summarizes findings from studies on network analysis in schizophrenia, including fMRI, electroencephalogram (EEG), and magnetoencephalography (MEG) studies. Based on these observations, the theory that schizophrenia is a "fragmentation of brain pathologies" was put forth to understand its pathophysiology as a breakdown in local network organization rather than a loss of global coherence [100].

Multimodal and Pattern-Analytical Neuroimaging Biomarkers

The observation that schizophrenia is a syndrome of dysfunctional neural networks created a framework for understanding how brain structural attributes relate to functional attributes, and how brain dynamics relate to behavioral manifestations of the syndrome. Within this framework, analytic approaches that combine different neuroimaging modalities and examine patterns of disease-related alternations in these modalities are providing a deeper understanding of the neural mechanisms of, and improved biomarkers for disease pathophysiology [101].

Multimodal analysis primarily involves two approaches:

- Measures collected in ROIs or finer-grained image elements (e.g., voxels or surface vertices) from different imaging modalities (e.g., sMRI and fMRI) are used to find correlations between the modalities.
- Data are fused first before statistical analysis.

Recent studies demonstrate a significant overlap between spatial distribution patterns of individual modalities, and a positive association between stronger alterations in one imaging modality and stronger disturbances in another. For example, increased disturbance in white matter connectivity of the superior temporal cortex is associated with thinning of the posterior cingulate cortex. This reflects a complex disruption of gray and white matter integrity within a cingulo-temporal network in schizophrenia [102]. Reduced functional activity in prefrontal and parietal cortices is associated with thinning of the same regions during a problem solving Tower of London task [103]. Reduced functional activity in the dorsal anterior cingulate cortex is associated with thinning of prefrontal–temporal cortices during a working

Table 6.3 Brain network organization findings in schizophrenia

Studies in chronological order	Modality	Small-world properties			Other findings
		Small-worldness	Clustering coefficient	Characteristic path length	
[135]	EEG Resting state and working memory	Decreased	↓	↑	• Differences were observed in different frequency bands
[136]	EEG Working memory	Decreased trend	↓	↑	• Differences were observed in different frequency bands
[89]	fMRI Resting state	Decreased	↓	↑	• Decreased regionally and globally
[91]	sMRI	Preserved globally but regionally disrupted	↔	↔	• Multimodal cortex shows reduced hierarchy, increased connection distance • Multimodal cortex shows shifting of hubs from frontal to nonfrontal areas including premotor, prefrontal, orbitofrontal, inferior temporal, medial temporal, cingulate, and insular cortex
[97]	EEG Resting state	Preserved subtle trend towards decrease	↓	↓	• Lowered centrality of major hubs
[93]	fMRI	Preserved	N/A	N/A	• Reduced local efficiency • Reduced gray matter volume in hub regions • Loss of hub properties in medial superior frontal gyrus and bilateral dorsal cingulate gyrus
	Episodic memory				• Different hubs than controls

(continued)

Table 6.3 (continued)

Studies in chronological order	Modality	Small-world properties			Other findings
		Small-worldness	Clustering coefficient	Characteristic path length	
[92]	DTI	Preserved	↔	↔	• Increased path length in olfactory, medial, and superior frontal regions, anterior cingulate, medial temporal pole, and superior occipital regions • Indicating a less strongly integrated structural network and reduced central role of key frontal hubs
[94]	fMRI Resting state	Decreased	↓	↑	• Increased characteristic path length only at lower cost points • Global efficiency showed lower value only at lower cost points • Local efficiencies were increased only at the higher cost points
[98]	fMRI Resting state	N/A	↓	N/A	• More and smaller modules • Different hubs than controls
[95]	DTI	Preserved	↔	↔	• Reduced global network efficiency, probably driven by reduced nodal degree in frontal, parietal, and occipital regions
[96]	DTI	N/A	N/A	N/A	• Increased global efficiency • Reduced regional efficiency of the prefrontal cortex, the paralimbic/limbic regions, and subcortical structures

(continued)

Table 6.3 (continued)

Studies in chronological order	Modality	Small-world properties			Other findings
		Small-worldness	Clustering coefficient	Characteristic path length	
[146]	fMRI Resting state Auditory oddball	Preserved	↓	↓	
[99]	fMRI		↓	↓	• Reduced local efficiency • Increased global efficiency
	Working memory				• Processing in schizophrenia may be more concurrent across different brain regions
[137]	MEG Resting state	Preserved	↔	↔	

Symbols
↓: reduced when compared with controls
↑: increased when compared with controls
↔: no difference when compared with controls
N/A: not available/not reported

memory task [104]. Further, structural changes in gray matter regions are associated with functional changes from a different location, serving as a morphological substrate for changes in functional connectivity [105–107]. These results directly support the notion that functional consequences in schizophrenia are closely related to, or may even constitute a consequence of, aberrant gray matter structure. Multimodal approaches provide useful information on whether and how disparate pathophysiological features influence each other and how schizophrenia alters these relationships.

Pattern analysis primarily involves methods adopted from the machine learning community applied to neuroimaging data. The basic idea is that the relationship between multiple parameters from multiple neuroimaging modalities can be combined to identify key differences between groups which in turn aid individual classification. In this pattern-analytical approach, data are constructed into training and validation sets in various schemes of classifier algorithms, including support vector machines (SVM), Bayesian networks, and artificial neural networks. Compared with traditional general linear model (GLM)-based approaches for detecting group differences, high-dimensional machine learning techniques show promise for improving the characterization of individual-based classification and finding subtle but significance features undetectable by traditional approaches. A review of recent machine learning studies in schizophrenia revealed that classification accuracy ranging from 81 to 92 % could be achieved. These are higher than rates usually achieved using GLM-based methods [108].

The amount of data in these types of analysis is immense. For example, structural or functional MR data will result in parameters which can number up to hundreds of thousands of voxels. Multiplied by the number of different statistical data reduction and analysis approaches, the complexity makes the outcomes difficult to interpret, especially from one study to another. Therefore, while showing much promise, replication is needed to validate the findings from multimodal and pattern analysis studies.

Critical Questions

While advances in neuroimaging data collection and analysis greatly improve our understanding of the pathophysiology of schizophrenia at a group level, they do not yet translate into reliable neuroimaging biomarkers at an individual level useful to the clinician. New developments of neuroimaging technology will continue to push the boundary on how we understand in vivo brain structure, function, and the interactions of neuronal cells and complex neural networks in both time and space. Development of new technologies, including the complete description of the structural connections between elements of the brain—the Human Connectome Project [109]; the complete understanding of activities of the brain—the NIH BRAIN (Brain Research through Advancing Innovative Neurotechnologies, http://www.nih.gov/science/brain/) initiative; and the mapping of genetic vulnerabilities onto brain structure and function, may help us address the following critical questions:

- Can we achieve *individualized diagnosis and treatment* monitoring?
- Can we disentangle *effects of disease from effects of drug treatment and substance* use, and predict functional outcome?
- Can we *reconcile discrepancies and characterize psychosis spectra* which include schizophrenia and bipolar disorder?

For now, the field remains unsettled with regard to clinically relevant issues such as prodromal prediction of emerging symptoms, diagnosis of disease spectrum, and clinical course and specificity regarding overlapping symptoms with other related neuropsychiatric disorders. Despite its unproven clinical utility, neuroimaging as a tool for predicting disease course, treatment response, and identifying risk factors shows much promise [110]. It has served, and will continue to serve, as a validation tool for linking disease in the brain with clinical symptomatology and cognitive deficits. Thus, neuroimaging may soon become a biomarker for diagnosis, monitoring progression, and predicting treatment response in schizophrenia.

List of Key Facts

- Schizophrenia is associated with subtle but widespread abnormalities of brain structure, function, and connectivity.

- These abnormalities are part of dysfunctional large-scale brain networks which together give rise to the cognitive deficits observed in individuals with schizophrenia.
- For now, there remains much we do not understand about the neural mechanisms of schizophrenia.

Acknowledgements The authors would like to acknowledge the following NIH grants: 1R01 MH084803, 1 U01 MH097435, P50 MH071616, and R01 MH056584. The authors would like to thank Eva C. Alden, Katherine D. Blizinsky, and Daniel B. Stern for assistance on literature search.

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Part III
Medical Management of Schizophrenia

Chapter 7
Acute Management of Schizophrenia

Philip G. Janicak

Introduction

The largest database for the treatment of acute schizophrenia involves antipsychotic drug therapy, primarily to manage multiepisode patients. Ironically, management of high-risk, first-episode, and early-onset patients is less well studied but may be more critical to ultimately achieve recovery.

Strategies to optimize outcome at any phase of schizophrenia should consider the various levels of improvement. *Response* is typically defined as at least a 20–30 % reduction in symptom severity (e.g., positive, negative) based on various assessment metrics used in antipsychotic drug trials. In clinical settings, it typically implies sufficient improvement of symptoms in an adherent patient to reduce or eliminate the need for hospitalization. *Remission* refers to sustained (e.g., ≥6 months) maintenance of minimal symptoms in dimensions such as psychosis and disorganization. It typically requires a comprehensive strategy beyond medication including case management, psychosocial interventions, psychotherapy, and vocational training. Ideally, this should involve the patient, family and other caregivers. *Recovery* requires improvements in cognitive, social, and vocational functioning over sustained periods of time, allowing individuals the opportunity to realize their personal goals (e.g., friends, employment, marriage).

This chapter considers the data and clinical experience with various strategies for acute management of schizophrenia. Since inadequate response and treatment-resistance are common, augmentation of or alternatives to standard antipsychotics are also reviewed.

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P.G. Janicak et al. (eds.), *Schizophrenia: Recent Advances in Diagnosis and Treatment*,
DOI 10.1007/978-1-4939-0656-7_7,

Choice and Dosing of an Antipsychotic

The choice and dosing of an antipsychotic are critical to maximizing benefit and take into account the quality and quantity of the evidence base, the clinical experience with a specific agent and the risk-to-benefit ratio [1]. The results from large "pragmatic trials" such as the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) and the Cost Utility of the Latest Antipsychotic Drugs in Schizophrenia Study (CUtLASS) and expert consensus guidelines such as the Schizophrenia Patient Outcomes Research Team (PORT) project also help guide clinicians in this choice [2–4]. Important factors in choosing an antipsychotic may include personal or physician preference, history of treatment response or resistance, sensitivity to certain adverse effects, comorbid substance use and/or medical disorders, available formulations, long-term planning, and cost.

In time, pharmacogenetics and pharmacogenomics will increasingly clarify how inheritance and acquired genetic variations (e.g., epigenetics) alter a drug's effects, promising to facilitate:

- Identification of *biomarkers to optimize treatment*
- Avoidance of treatments likely to produce *adverse effects*
- Improved understanding of a drug's *mechanism of action*
- Development of *new targets for drug therapy*
- Prediction of *metabolic profiles* to help with the choice of drug, duration of treatment, and/or dose
- *Enhancement of medication adherence* and the subsequent reduction in relapse rates [5]

Pharmacogenetics identifies single nucleotide polymorphisms (SNPs) associated with a drug's action and then tests for an association to clinical response [6]. As an example, this strategy was used to study dopamine and serotonin transporter gene polymorphisms to assess for the potential response and the risk for EPS with clozapine (CLZ) [7, 8]. *Pharmacogenomics* uses a genome-wide association study (GWAS) approach to interrogate thousands of SNPs randomly distributed across the genome [9]. This may identify "profiles" of SNPs with additive predictive value for clinical efficacy. In one study, six genetic loci were associated with response to iloperidone [10]. More recently, however, their specificity was questioned, since two of these SNPs also appeared predictive of response to risperidone (see Chap. 9) [11].

Twenty-seven antipsychotics are available in the United States. They are grouped into typical or first-generation antipsychotics (FGAs) and atypical or second-generation antipsychotics (SGAs). The validity of such a classification, however, is debated since there are many similarities between drugs within these two groups. In this context, adverse effects may still help to distinguish them [12]. For example, neuromotor toxicity is more characteristic of high potency FGAs (e.g., haloperidol, fluphenazine, thiothixene), while weight gain and metabolic dysregulation are more characteristic of certain SGAs (e.g., CLZ, olanzapine, quetiapine). Given our present knowledge about the relative efficacy of the various antipsychotics, the initial choice

of a specific agent is often based on safety and tolerability considerations. This is discussed in greater detail in Chaps. 10–12.

In the context of dosing, neuroimaging (e.g., positron emission tomography (PET), single photon emission computer tomography (SPECT)) and dose/plasma level response studies can provide guidance for certain agents. For example, a recent meta-analysis of neuroimaging studies supports a role for D_2 occupancy levels in achieving optimal dosing of antipsychotics with the exception of CLZ and quetiapine [13]. Studies also indicate plasma levels of certain agents such as haloperidol (e.g., 3–15 ng/mL range) are optimal and usually achieved at much lower doses than initially recommended [14]. Existing data also indicates that optimization of CLZ's efficacy may occur with levels of 350–800 ng/mL [15].

Table 7.1 lists the antipsychotics presently available in the United States with information about their recommended dosing range and alternate routes of administration. Further, although not recommended for routine clinical use, plasma level data may help guide dosing in certain circumstances (e.g., suspected adherence problems, potential for drug interactions, unexpected adverse effects, insufficient benefit with adequate dosing) and results of preliminary trials are provided [15–19].

Acute Treatment of Psychosis

High-Risk Individuals

Patients who develop schizophrenia may experience subtle changes in behavior and cognition for long periods prior to their first psychotic exacerbation. Early recognition (e.g., high-risk phase) and appropriate interventions can facilitate symptom reduction and possibly delay or prevent psychosis onset [20, 21]. The accurate identification of those who will transition from this "prepsychotic phase" to schizophrenia, however, is problematic [22, 23]. Thus, while individuals with potential prodromal symptoms are at an increased risk to transition to a psychotic disorder, less than 40 % will and some recent data indicates a decline in these transition rates [20]. Further, many individuals go on to develop other psychiatric disorders or their symptoms will resolve before experiencing a full psychotic episode. Complicating this issue is the potential for schizophrenia to develop later than the timeframes studied to date.

In this context, a number of centers are developing criteria to characterize this phase. For example, the ultra-high risk (UHR) criteria require the presence of one or more of the following:

- *Attenuated* psychotic symptoms
- *Brief*, *limited*, *intermittent* psychotic episodes
- *Trait vulnerability* (i.e., genetic risk)
- *Psychosocial functioning decline*
- *Prodromal symptoms* [24, 25]

Table 7.1 Commonly used first- and second-generation antipsychotics

Name	Oral dosing range (mg)	Alternate formulations/putative therapeutic plasma levels[a]
First-generation agents		
Phenothiazines		
Chlorpromazine	100–1,000	Parenteral; rectal suppository
Thioridazine	30–800	Oral concentrate; oral suspension
Fluphenazine	5–40	Oral concentrate; acute parenteral; LAI (12.5–25 mg/2–3 week); plasma level of 1–3 ng/mL
Trifluoperazine	2–60	Plasma level of 1–2.3 ng/mL
Perphenazine	2–60	Plasma level of 1.5–3 mmoL/L
Thioxanthenes		
Thiothixene	6–60	Oral concentrate; plasma level of 2–15 ng/mL
Dibenzoxapines		
Loxapine	20–250	Acute inhalant (single dose of 5 or 10 mg)
Butyrophenones		
Haloperidol	3–50	Oral concentrate; acute parenteral; LAI (50–200 mg/4 week); plasma level of 3–15 ng/mL
Dihydroindolones		
Molindone	15–225	Oral concentrate
Second-generation agents		
Dibenzodiazepines		
Clozapine	100–900	Oral rapid dissolving; plasma level of 350–800 ng/mL
Benzisoxazoles		
Risperidone	2–8	Oral: liquid and rapid dissolving; parenteral: LAI (150–405 mg/2–4 week); plasma level of 20–60 ng/mL
Paliperidone	3–12	Oral extended release; parenteral LAI (117 mg/4 week); plasma level of 20–52 ng/mL
Iloperidone	12–24	
Lurasidone	40–80	
Thienobenzodiazepines		
Olanzapine	5–20	Oral rapid dissolving; parenteral LAI (150–405 mg/2–4 week); plasma level > 20 ng/mL
Dibenzothiazepines		
Quetiapine	75–800	Oral immediate and extended release
Benzisothiazolyls		
Ziprasidone	40–160	Acute parenteral
Quinolinones		
Aripiprazole	5–30	Oral: liquid and rapid dissolving; parental: acute and LAI; plasma level 150–210 ng/mL
Dibenzo-oxepinopyrrole		
Asenapine	10–20	Sublingual formulation only

[a]Based on preliminary data

The North American Prodrome Longitudinal Study also identifies other potential predictors of psychosis, including high levels of unusual thought content, high suspicion/paranoia, and a history of substance abuse [26]. There is also preliminary data indicating presynaptic striatal dopamine abnormalities may precede the onset of

psychosis [27]. Various assessment tools are available, such as the Structured Interview for Prodromal Symptoms (SIPS), to help identify these individuals [28]. To qualify for high risk using this metric requires at least one fully positive psychotic symptom several times per week for at least 1 month; or for at least 1 day if the symptom causes significant disorganization or is dangerous.

In testament to the substantial progress made in this area over the past 20 years, the Diagnostic and Statistical Manual of Mental Illness (DSM)-5 will include the category of Attenuated Psychosis Syndrome in its Sect. 3 [29]. This means the category is of note but requires further study (see Chap. 2).

Treatment of High-Risk Individuals

There are preliminary data to guide clinicians in helping these individuals. Two reviews identified five controlled studies of focused treatments for those at high risk [30, 31]. These trials indicated that both pharmacological and psychological approaches may be beneficial. For example, both intensive community care with family psychoeducation and omega-3 polyunsaturated fatty acid (PUFA) supplementation reduced the transition to psychosis at 12 months [32]. Other "neuroprotective strategies" such as *N*-acetyl cysteine (NAC) are also possible candidate treatments for these individuals [33, 34]. In general, these strategies carry less risk of adverse effects than standard antipsychotics and might be first-line approaches if these early results are replicated [35, 36]. The use of antipsychotics should be reserved for more complicated or resistant individuals. In this context, a small ($n=59$) controlled trial combining low-dose risperidone (mean dose = 1.3 mg) with cognitive behavioral therapy (CBT) reported a reduction in the risk of early transition to psychosis [21]. The dilemma, however, is that a small decrease in the conversion rate to psychosis involves a substantial risk of adverse effects associated with antipsychotics.

First-Episode and Early-Onset Patients

Recognizing the earliest signs of clear psychosis and introducing various interventions can reduce the duration of untreated symptoms and positively impact long-term outcome. While an average of 1 year elapses from the onset of psychotic symptoms to first treatment, two meta-analyses found that a shorter duration of untreated psychosis was associated with a better response and subsequent reduction in negative symptoms [37, 38]. Conversely, there is evidence demonstrating an association between longer duration of untreated psychosis in first-episode patients and worse outcomes in terms of psychotic symptoms, cognition, functioning, and quality of life [39–41].

In addition, imaging studies indicate that a subset of these patients demonstrate significant decreases in gray matter, white matter, and increases in cerebrospinal fluid during the early years after illness onset [42]. Complicating these observations are conflicting reports of an association between antipsychotic drug exposure and

either neuroprotective or neurotoxic effects. While these findings suggest a possible causal relationship, ethical issues preclude more definitive study designs and leave unclear whether such effects are deleterious or beneficial [43, 44].

Treatment of First-Episode and Early-Onset Patients

Several studies consider the benefit of earlier intervention in first-episode and early-onset patients with schizophrenia and related psychotic disorders. In one intensive program (i.e., OPUS), 369 first-episode patients were followed for 2 years and 301 for 5 years [45]. In comparison with standard treatment, the addition of assertive community treatment, family involvement, and social skills training demonstrated better clinical outcomes at 2 but not 5 years (see Chap. 14). The investigational group, however, had fewer patients in supportive housing and experienced fewer days hospitalized over the 5-year period. A second study ($n=281$) found a significantly lower rate of serious suicidal behavior (i.e., $p<0.01$) in first-episode patients participating in an early detection program which shortened the duration of untreated psychosis from 16 to 5 weeks compared with those not involved [46, 47]. A third program in Norway for first-episode patients (TIPS) followed 101 subjects for up to 10 years [48]. This approach initially achieved a reduction in the duration of untreated psychosis from a median of 26 to 5 weeks. In comparison with 73 usual care patients, the early detection group had a significantly greater recovery rate ($p<0.01$), largely due to higher employment. The authors concluded that the early detection approach increased the chances of milder deficits and superior functioning over this time period. Recently, Wunderink et al. [49] reported that dose reduction/discontinuation (DR) in remitted first-episode patients ($n=103$) was superior to standard maintenance treatment in terms of recovery rates (i.e., 40 % versus 18 %). While the study confirmed an initial higher relapse rate in the DR group, surprisingly, this was not reflected in remission rates (equal between the two groups) or in the recovery rates (superior on the DR group; $p<0.01$) after 7 years.

Other studies also consider the relative benefits of various antipsychotics in treating first-episode or early-onset schizophrenia. One trial ($n=263$) compared olanzapine with haloperidol for up to 2 years in first-episode patients [50]. Both agents demonstrated substantial and similar improvement in overall symptoms. Olanzapine, however, produced greater decreases in symptom severity based on the Positive and Negative Symptom Scale (PANSS) total, negative, and general psychopathology subscale scores and had a greater percentage of patients complete the 12-week acute phase. A controlled trial ($n=160$) conducted in China, found an initial benefit for CLZ versus chlorpromazine (CPZ) in treatment-naïve, first-episode patients after 12 weeks. This difference, however, disappeared at the 1-year and 9-year follow-up time points [51, 52]. Median doses at 1 year were 300 mg for CLZ and 400 mg for CPZ. Of note, patients receiving CLZ remitted significantly faster, remained in remission longer and experienced fewer adverse effects compared with CPZ. Another small, controlled trial ($n=39$) found that CLZ was superior to "high dose" olanzapine (i.e., up to 30 mg/day) in refractory, early-onset schizophrenia with

response rates of 66 % and 33 % ($p < 0.04$), respectively [53]. Both agents, however, were associated with significant weight gain and metabolic dysregulation.

A large, long-term study ($n = 555$) randomized first-episode patients to low-dose risperidone (mean modal dose = 3.3 mg) or low-dose haloperidol (mean modal dose = 2.9 mg) [54]. While both groups demonstrated improvement in cognitive functioning over a 3-month period, risperidone improved more aspects (e.g., global functioning) to a greater degree than haloperidol. Further, the median time to relapse was 466 days with risperidone versus 205 days with haloperidol [55]. A second study ($n = 104$) compared haloperidol (mean dose = 2.7 mg/day), risperidone (mean dose = 3.9 mg/day), and olanzapine (mean dose = 10 mg/day) [56]. After 1 year, all three treatment groups demonstrated significant and similar improvements in cognition. In a 52-week, randomized, double-blind, flexible-dose, multicenter study ($n = 400$), patients early in the course of their psychotic illness received olanzapine (mean modal dose = 11.7 mg), quetiapine (mean modal dose = 506 mg), or risperidone (mean modal dose 2.4 mg) [57]. Based on all-cause treatment discontinuation, these agents were similarly effective. All three agents also produced significant and similar modest improvements in neurocognition which were associated with improved functional outcomes [58].

The Treatment of Early-Onset Schizophrenia Spectrum Disorders Study (TEOSS) randomized 116 youth with schizophrenia or schizoaffective disorder to olanzapine (2.5–20 mg/day), risperidone (0.5–6 mg/day), or molindone (10–140 mg/day) plus benztropine (1 mg/day) [59]. While the degree of symptom reduction and response rates was comparable among the three agents, adverse effects differed. Indeed, olanzapine was discontinued due to its adverse effects in this population. Given their results, the authors questioned the nearly exclusive use of SGAs in this population in light of the associated greater risk for weight gain and metabolic issues. The European First-Episode Schizophrenia Trial (EUFEST) compared five antipsychotics in 498 patients (ages 18–40 years) with first-episode schizophrenia, schizoaffective disorder, or schizophreniform disorder [60]. In a 1-year, randomized, open-label, multicenter design, patients received haloperidol (1–4 mg/day), amisulpride (200–800 mg/day), olanzapine (5–20 mg/day), quetiapine (200–750 mg/day), or ziprasidone (40–160 mg/day). Based on all-cause treatment discontinuation, the SGAs had a lower risk compared with haloperidol, while symptom improvement was similar for all drugs. In a post hoc analysis, the authors concluded that the results favor the SGAs given the importance of continuing treatment at this phase of the illness [61]. In contrast, a meta-analysis of 15 controlled trials ($n = 2{,}522$) found no differences in discontinuation rates or symptom improvement between FGAs and SGAs in this patient population [62]. Adverse effects of SGAs (i.e., weight gain) and FGAs (i.e., EPS), however, clearly distinguished these two groups.

In summary, effective treatment is critical in the first 5 years after the onset of psychosis since maximal disability may occur during this period. Addressing known predictors of treatment nonadherence (e.g., depression; substance abuse) is also important to assure optimal outcomes during the recovery from a first episode [63]. When antipsychotics are prescribed, low doses of SGAs with less propensity to cause weight gain and metabolic complications are recommended first-line

approaches. In this context, the PORT recommendations relegate olanzapine and CLZ to second-line choices. In appropriate patients, long-acting injectable (LAI) formulations may be warranted. After two failed adequate trials, CLZ should be considered. The goal is to achieve remission (i.e., mild levels of key symptoms for at least 6 months) whenever possible [64].

Multiepisode Patients

For multiepisode patients responsive to prior treatment, common strategies for acute exacerbations include starting with the previously effective agent or certain generic FGAs (e.g., perphenazine) and SGAs (e.g., olanzapine, risperidone). Many of these antipsychotics also have alternate formulations (e.g., acute parenteral, oral liquid, disintegrating tablets) which may be used in emergencies for uncooperative patients or for those who cannot swallow tablets or capsules. Some also have LAI formulations, which makes the transition from oral medication easier if such a maintenance strategy is pursued.

For agitation and disruptive behaviors, non-pharmacological de-escalation techniques are the preferred first option. If this approach is insufficient, the short-term use of an adjunctive benzodiazepine (e.g., oral or acute parenteral lorazepam) can calm the patient and reduce the dose of antipsychotic. Alternate strategies include acute parenteral FGAs and SGAs, as well as acute loxapine inhalation therapy, all of which may be combined with a benzodiazepine [65, 66]. The goal is to optimize the intended antipsychotic effect with the minimally effective dose. Lessening longer-term exposure to polypharmacy is also a goal. This may be particularly true for benzodiazepines given the high rates of substance use disorders in these patients and whose extended exposure may be associated with increased mortality rates [67]. The hope is that such a strategy will substantially reduce adverse effects (e.g., acute EPS) and facilitate longer-term adherence.

Patients should demonstrate acceptable improvement during the first 2 weeks. If not, an alternate agent or augmentation of the initial but insufficient benefit is usually appropriate. Augmentation may include additional medications (e.g., combined antipsychotics), alternate nonpharmacologic, biological treatments (e.g., therapeutic neuromodulation), various types of psychotherapy (e.g., cognitive behavioral), and rehabilitation programs (e.g., social skills training).

After two or more failed adequate antipsychotic trials, CLZ is a reasonable next step [4]. Its advantages over other available antipsychotics include evidence for benefit in treatment-refractory, hostile, aggressive, violent, and suicidal patients. It may also lower the risk of death [68]. CLZ, however, has several disadvantages which require a careful risk-benefit assessment prior to its prescription. For example, its use requires ongoing blood count monitoring to minimize the risk of neutropenia and agranulocytosis. This increases the cost and complexity of managing patients on this agent (Table 7.2).

Table 7.2 Clozapine

Potential benefits	Potential risks[a]
Efficacy	*Box warnings*
• May benefit treatment-refractory patients	• Agranulocytosis
• May reduce suicidal, agressive, or violent behavior	• Seizures
• May increase life expectancy	• Myocarditis
Adverse effects	• Orthostasis
• Diminish extrapyramidal side effects	• Increased mortality in dementia
• Minimize risk for or improve tardive dyskinesia	*Serious adverse effects*
• Minimize hyperprolactinemia	• Weight/gain metabolic syndrome
	• Diabetic ketoacidosis
	• Gastrointestinal hypomotility

[a]See Chap. 12 also

Conclusion

Early intervention in high-risk individuals and first-episode patients leading to shortened duration of untreated psychosis appears to favorably impact the course of schizophrenia. While many of these individuals do not transition to psychosis, they may still experience a variety of problems such as anxiety, depression, heightened suicidality, substance use disorders, negative symptoms, impaired academic performance, poor occupational functioning, and interpersonal problems. Even when psychotic symptoms do not emerge, these issues can be the focus of treatment which may improve quality of life. Nonpharmacological approaches (e.g., psychosocial interventions, psychotherapy) and neuroprotective agents (e.g., omega-3 fatty acids) are appropriate first-line interventions in high-risk groups given the adverse effect burden of antipsychotics and since a substantial proportion of these individuals will not go on to develop schizophrenia (at least in the immediate future). With clear psychotic behaviors, however, the introduction of antipsychotic medication conservatively dosed is warranted to shorten the duration of untreated psychosis [69]. In multiepisode patients, the focus should be on optimizing the dose of antipsychotic, improving adherence, establishing a therapeutic environment, and developing a constructive alliance with patients, families and other support groups.

Management of Treatment-Resistance

Given the multiple psychopathological dimensions of schizophrenia, drugs acting primarily through dopaminergic D_2 mechanisms are usually not sufficient to address this entire spectrum of symptoms. For example, while existing agents are relatively effective for positive symptoms, they are far less helpful for primary persistent negative, neurocognitive, and mood symptoms [70]. In addition, safety and tolerability

Table 7.3 Combined antipsychotics

Potential benefits	Potential risks
• *Facilitate* switching antipsychotics	• Lack of adequate *evidence base*
• *Supplement long-acting agents*	• Increased *mortality*
• Improve *specific symptoms* (e.g., low-dose quetiapine for sedation)	• Increase risk for *adverse effects* or *drug interactions*
• *Lower doses* of two agents to avoid safety or tolerability issues with standard dose of a single agent	• Worsen *adherence issues*
• *Augment* efficacy of primary antipsychotic	• *Increase cost*

issues often prevent an adequate treatment course. Thus, when CLZ is not an option or proves intolerable or insufficient, there are a number of ongoing initiatives which may improve outcomes, including:

- *Refining existing agents* to increase efficacy and/or decrease adverse effects
- Developing drugs with *alternate mechanisms of action*
- *Augmenting* standard antipsychotics with novel agents [71].

While there are many potential approaches reported in the literature, those discussed in this chapter have shown promising results, primarily from controlled trials. The quality and quantity of evidence, however, is presently limited and usually based on proof-of-concept study data.

Antipsychotic Polypharmacy

Combining antipsychotics is a frequently employed strategy in clinical practice. One rationale given for this approach is the ability to augment the effects of the first agent by tailoring the neuroreceptor profile of actions for a specific patient [72]. The most frequent combination studied to date involves CLZ polypharmacy for patients inadequately responsive to CLZ monotherapy [73, 74]. While the results from most of these controlled trials were negative, their quality was usually not adequate to definitively address the question. A meta-analysis of controlled trials comparing other antipsychotic combinations versus antipsychotic monotherapy also did not produce firm recommendations about the value of this approach [75]. In general, the paucity of data dictates the need for further studies. Table 7.3 summarizes the relative risks and benefits of this approach.

Agents Impacting Other Neurotransmitter Systems/Receptors

Dopamine

Existing antipsychotics directly impact the dopamine (DA) system, primarily through the D_2 receptor. Given an inadequate benefit in many patients and/or safety and tolerability issues, other ways of modulating the DA system (e.g., D_1–D_5 receptors) are

being explored. D_1 receptors are abundant in the prefrontal cortex (PFC) and appear to play an important role in cognition (e.g., working memory) [76]. Several lines of evidence support a therapeutic potential by modulating these receptors. For example, hypofrontality is a common finding in schizophrenia, including medication-naïve first-episode patients [77]. In this context, a D_1 agonist (e.g., dihydrexidine) was found to produce increased perfusion in prefrontal and nonprefrontal areas in these patients [78]. Presently, however, clinical data to support its efficacy in schizophrenia is insufficient [79, 80]. Both CLZ and asenapine appear to facilitate glutamate *N*-methyl-D-aspartate (NMDA) receptor-induced currents through modulation of prefrontal D_1 receptors [81]. Conversely, genetic variants of the D_1 receptor may predispose to adverse effects of antipsychotics such as tardive dyskinesia [82]. In addition, agents acting at the D_3 and D_4 receptors are also considered potential targets for treating schizophrenia [83, 84]. For example, *cariprazine* is a partial agonist at the D_2/D_3 (with preference for D_3) and 5-HT_{1A} receptors. Preclinical models predict procognitive effects and there are now positive Phase II and Phase III trial results [85]. Some evidence also supports selective D_3 agonism at presynaptic autoreceptors and antagonism at postsynaptic receptors as potential but relatively unexplored therapeutic approaches [86–88].

Norepinephrine

Norepinephrine (NE) can increase DA activity in the medial PFC. In turn, this may improve vigilance, cognition, and mood, as well as moderate stress reactions. Blockade of reuptake transporters, antagonism of presynaptic α_2-NE receptors (preventing autoreceptor negative feedback on activity) and agonism of postsynaptic α_2-NE receptors are also potentially therapeutic [89, 90]. Controlled trials have generated mixed results, however, regarding the cognitive benefit of NE reuptake inhibition with agents such as reboxetine or atomoxetine, usually as adjuncts to standard antipsychotics [91–94].

Serotonin

SGAs have multiple neuroreceptor interactions with the serotonin (5-HT) system. Thus, much interest is focused on developing agents which impact 5-HT receptor subtypes [95]. Evidence suggests that 5-HT_{1A} receptor agonism varies among available agents and may enhance the antipsychotic effects of D_2 receptor antagonists [96]. Newer compounds (e.g., cariprazine) possessing these two properties are now in development. Targeting other receptor subtypes may also improve psychosis, negative symptoms, and certain cognitive dimensions, while reducing the dose of standard antipsychotic and lessening their adverse effect burden. Examples include selective 5-HT_{2A} inverse agonists (e.g., pimavanserin), selective 5-HT_{2A} antagonists, selective 5-HT_{2C} agonists (e.g., vabicaserin), 5-HT_3 antagonists (e.g., ondansetron; tropisetron), 5-HT_4 receptor agonists, and 5-HT_6 (e.g., latrepirdine) and 5-HT_7 antagonists [97–100]. The most recent SGAs, (i.e., iloperidone, asenapine, and lurasidone) all demonstrate several of these properties [101–103].

Glutamate

Glutamate (Glu) is one of the most abundant free amino acids in the central nervous system (CNS) and the primary excitatory neurotransmitter. Glutamate contributes to the formation, maintenance, and plasticity of synaptic function, as well as facilitation of sensory processing, memory and executive functioning [104]. In schizophrenia, dysregulation of the glutamate system can compromise neuroplasticity and produce neuronal toxicity. The Glu NMDA ionotropic receptor may be critical to these processes [105]. For example, drugs which block this receptor (e.g., phencyclidine, ketamine) produce psychotic symptoms closely resembling schizophrenia. Some postulate, however, that it is the resultant overactivity of Glu, particularly at the α-amino-3-hydroxy-5-methyl-4-isoxazle propionic acid (AMPA) ionotropic receptor, which produces or worsens psychosis [105]. In this context, a recent, placebo-controlled trial ($n=20$) reported a rapid decrease in various symptoms of schizophrenia (i.e., positive, negative, depressive, anxious) after a single IV dose of nitroprusside (0.5 μg/kg/min) given over 4 h [106]. This agent is believed to modulate the NMDA receptor. Metabotropic Glu receptors are also implicated in the pathophysiology of schizophrenia and as such serve as potential therapeutic targets. Glu also interacts with other important systems (e.g., DA, GABA, Ach) which are modulated by and in turn also modulate its activity. As a result, there is great interest in a *glutamatergic strategy* to treat various psychopathological dimensions of schizophrenia. Since direct impact on Glu receptors may produce neuronal excitotoxicity, various indirect approaches are being explored.

Facilitation of the *glycine* receptor site colocated near the Glu site on the NMDA receptor may enhance channel efficiency [104]. A recent meta-analysis concluded that adjunctive glycine improved positive and total symptoms of schizophrenia when combined with non-CLZ antipsychotics, but worsened symptoms when added to CLZ [107]. Not all studies, however, support this strategy. The Cognitive and Negative Symptoms in Schizophrenia Trial (CONSIST) involved 157 patients with schizophrenia or schizoaffective disorder [108]. Patients were randomly assigned to 16 weeks of adjunctive glycine (60 g/day), the selective partial NMDA receptor agonist, D-cycloserine (50 mg/day), or placebo. The authors did not find benefit for these add-on agents when compared with placebo for the treatment of negative symptoms or cognitive impairment. A more recent, 16-week, placebo-controlled trial ($n=195$) involving patients with schizophrenia or schizoaffective disorder also did not demonstrate benefit with an adjunctive, naturally occurring, allosteric modulator of the NMDA receptor, *D-serine* (2 g/day), for negative and cognitive symptoms [109].

Given the relatively poor CNS penetration and the resultant need for high doses of these amino acids, another strategy is to administer agents which act as glycine transport inhibitors, a strategy analogous to use of selective serotonin reuptake inhibitors [110]. A 6-week, double-blind trial ($n=60$) involving patients with schizophrenia found that 2 g/day of adjunctive *sarcosine* (*N*-methyl glycine), but not D-serine, was superior to placebo based on various clinical measures [111]. An earlier, controlled trial ($n=20$) also found scarcosine (2 g/day) was efficacious in drug-free patients with schizophrenia [112]. More recently, the glycine reuptake inhibitor bitopertin (RG 1678) at doses of 10 and 30 mg demonstrated efficacy

for negative symptoms in a placebo-controlled phase IIb trial ($n=323$) for schizophrenia [113]. Unfortunately, two recent Phase III trials found bitopertin was not beneficial for reducing predominant negative symptoms.

Another strategy is to modulate *metabotropic Glu 2/3 receptors*. Stimulation of presynaptic receptors inhibits further Glu release while postsynaptic receptor effects can further modify Glu activity. There was great initial excitement when *pomaglumetad methionil* (a mGlu 2/3 receptor agonist) at doses of 40 mg BID demonstrated a benefit for positive and negative symptoms significantly better than placebo ($p<0.001$) and similar to olanzapine (15 mg/day) [114]. This was a 4-week, Phase II, controlled study ($n=193$) involving patients with schizophrenia. Subsequent trials, however, did not demonstrate efficacy for this agent compared with placebo, leading to a suspension of Phase III development [115, 116]. Positive allosteric modulation at other receptors (e.g., mGlu5), however, may be an alternate approach [105].

Other strategies include NAC which stimulates these receptors indirectly by enhancing formation of glutathione, a neuroprotective free radical scavenger which may counter oxidative stress [34]. In this context, a 24-week, controlled trial ($n=140$) found that adjunctive NAC (1 g BID) was superior to placebo in terms of the PANSS total ($p<0.009$), negative symptoms ($p<0.02$), and general psychopathology ($p<0.04$) scores, as well as the Clinical Global Impression-Severity (CGI-S) ($p<0.04$) and Clinical Global Impression-Improvement (CGI-I) ($p<0.03$) scores in patients with chronic schizophrenia [117]. A more recent controlled trial found that NAC (up to 2 g per day) improved scores on the PANSS total and the negative symptom subscale significantly more than placebo ($p<0.006$ and $p<0.001$, respectively) when used in combination with risperidone [118]. As noted earlier, NAC may also play a "protective" role in at-risk individuals, preventing the evolution into schizophrenia [33].

Strategies involving adjunctive anticonvulsants such as *lamotrigine* (LTG) (an inhibitor of glutamate release) plus CLZ, *memantine* (a weak nonselective NMDA receptor antagonist) plus CLZ, and *AMPA-receptor modulators* (e.g., ampakines such as CX 516) have also been considered. While preliminary data support each of these approaches, design limitations and difficulty with or lack of replication of these initial results leave unclear their potential roles [119–121].

Gamma-Aminobutyric Acid

Gamma-aminobutyric acid (GABA) is the primary inhibitory neurotransmitter in the CNS. There is evidence that cortical and subcortical GABA activity is disrupted in schizophrenia, including first-episode and antipsychotic-naïve patients [122]. Preclinical and clinical evidence support a potential role for agonists of this system to improve various symptoms. For example, activation of GABA interneurons may decrease hyperactivity of mesolimbic dopamine and/or glutamate, reducing positive symptoms.

One approach is to use agents with both DA antagonist and GABA agonist activity (e.g., BL-1020). In a placebo-controlled trial ($n=363$), this agent was superior to placebo ($p<0.001$) and comparable to risperidone in overall improvement (i.e., PANSS total score). Further, the 20–30 mg dose was superior to both placebo and risperidone ($p<0.009$ and $p<0.019$, respectively) on a measure of cognitive function [123].

Unfortunately, results from an interim analysis of a Phase II/III trial failed to meet the pre-specified primary cognitive efficacy endpoint and the trial was discontinued.

Another strategy to modulate this system involves the use of anticonvulsants which work in part through GABAergic mechanisms. While an initial 4-week study ($n=249$) generated encouraging results using adjunctive divalproex sodium (DVPX; 15–30 mg/kg/day), a subsequent 12-week, controlled trial ($n=402$) did not demonstrate efficacy for this agent at doses of 20–35 mg/kg/day when used as an adjunct to olanzapine or risperidone [124, 125]. This agent, however, did rapidly control hostility and anxiety. A small, 12-week, controlled study ($n=24$) also did not find benefit for either adjunctive DVPX or LTG versus placebo [126].

Selective agonists of $GABA_A$ receptors represent an alternate strategy. Working memory deficits are associated with impairments in PFC function, possibly related to altered gamma band oscillations which reflect desynchronization of pyramidal cell activity. This process partially depends on $GABA_A$ receptor-mediated neurotransmission [127]. More recent data also indicates possible $GABA_A$ dysfunction in high-risk and first-episode patients [128]. Using transcranial magnetic stimulation, this group found evidence of reduced $GABA_A$-mediated inhibition in these individuals ($n=18$) compared with healthy subjects ($n=18$). In addition, a recent magnetic resonance spectroscopy (MRS) study ($n=54$) observed 30 % elevations in glutamate-glutamine and GABA levels in the medial PFC of unmedicated patients compared with controls ($p<0.03$) [129]. A positive, proof-of-concept, placebo-controlled trial ($n=15$) with MK-0777 (a relatively selective agonist of $GABA_A$ receptors containing α_2/α_3 subunits) led to a larger, 4-week, placebo-controlled trial ($n=60$) [128, 130]. Even though the results of the second study were negative, the investigators opined that a more potent, partial agonist with greater intrinsic activity at this site might improve cognition.

Acetylcholine

The cholinergic system is implicated in sensory processing and cognition, modulated through both its nicotinic ionotropic and muscarinic metabotropic receptors. In this context, the use of perinatal choline appeared to enhance development of cerebral inhibition which is deficient in patients with schizophrenia and is related to poor sensory gating and attention [131]. This controlled trial compared dietary phosphatidylcholine (6,300 mg/day) supplementation with placebo starting in the second trimester. The results indicated choline had no adverse effects and produced a greater rate of intact P50 sensory gating at the 5th postnatal week (i.e., 76 % versus 43 %) but this difference was gone by the 13th week. Results from trials like this raise the possibility that dietary supplementation during pregnancy may decrease the long-term risk of schizophrenia. In multiepisode patients, the potential role of adjunctive acetylcholinesterase inhibitors (e.g., rivastigmine, donepezil, galantamine) to enhance cognition and improve negative symptoms in schizophrenia is not clearly established in adequately powered RCTs but remains a possible approach. One review and meta-analysis (including six open-label and 13 double-blind trials)

concluded that the existing data suggested improvement in memory, and the motor speed and attention part of executive function, with these agents [132].

Heavy smoking patterns often seen in patients with schizophrenia may stimulate *nicotinic receptors*, temporarily improving sensory processing. Further, the α7 nicotine ACh receptor gene (CHRNA7) is associated with schizophrenia, as well as related cognitive and sensory gating problems [133]. Agonists at this receptor may improve abnormal suppression of the P50 auditory evoked potential which is associated with certain cognitive deficits and perceptual impairments [134, 135]. In a controlled trial ($n=40$), nonsmoking patients with abnormal P50 rates (i.e., >0.5) were stabilized on risperidone (3–6 mg/day) and then randomized to *tropisetron* (an α7 partial agonist and 5-HT_3 antagonist) or placebo [136]. All three tropisetron doses (5, 10, or 20 mg/day) improved P50 deficits after 10 days and this correlated with improvement in cognition. *DMXB-A* is an α7 partial agonist which may work by improving the default network function in schizophrenia [137]. A 4-week, proof-of-concept, controlled trial ($n=31$) found that adjunctive DMXB-A (150 mg BID) was significantly better than placebo ($p<0.01$) for negative symptoms (but not cognition) and generally well tolerated [138]. A more recent trial found that DMXB-A plus risperidone was superior to olanzapine monotherapy for improvement in neurocognitive function [139]. A controlled, exploratory trial ($n=185$) found that the addition of TC-5619 (another α7 partial agonist) to quetiapine or risperidone was superior to placebo ($p<0.03$) in terms of cognitive and negative symptom improvements [140]. Early signals for potential cognitive improvement and management of concurrent alcohol and nicotine dependence with adjunctive varenicline (a partial α_4-β_2 and full α7 agonist) must be balanced against its adverse effects and reports of behavioral toxicity [141–143]. Of note, galantamine has a more complex impact on the cholinergic system beyond anticholinesterase inhibition (i.e., also modulates α_7 and α_4-β_2 receptors) [144].

Antagonism of *muscarinic receptors* (M_1–M_5) may disrupt cognitive function. A controlled, crossover trial ($n=20$) found that monotherapy with xanomeline (75–225 mg/day) (a relatively selective M_1/M_4 cholinergic, orthosteric, receptor agonist) was significantly more effective than placebo ($p<0.05$) on various measures including improvement in verbal learning and short-term memory [145]. Gastrointestinal effects were common with xanomeline, but did not lead to discontinuation from the trial. Studies utilizing selective allosteric activators of the M_1 or M_4 receptors are needed to clarify if this potential benefit is due to actions at either or both receptor sites [146–148]. Whether activation of M_2, M_3, or M_5 receptors might also be efficacious is not clear at this time.

Histamine

The activity at four identified histamine receptor subtypes contributes to the modulation of arousal and cognitive function. Thus, activity at autoreceptors may increase alertness and activity at heteroreceptors may modulate levels of neurotransmitters such as DA, NE, 5-HT, Glu, GABA, and Ach [149, 150]. Preliminary preclinical and clinical evidence support a therapeutic potential with histamine (e.g., H_3 receptor antagonists

and inverse agonists) for cognitive deficits associated with schizophrenia [151]. As an example, pitolisant, an H_3 receptor inverse agonist, demonstrated potential procognitive activity. Further, a pharmacokinetic study ($n=129$) in Chinese patients with schizophrenia indicated that histamine H_3 receptor polymorphisms may aid in predicting the efficacy of risperidone [152]. More recently, the H_2 receptor antagonist, famotidine, was reported to be superior to placebo based on the change in PANSS total, general psychopathology subscale, and CGI scores ($p \leq 0.05$) [153].

Other Approaches

Antidepressants

Antidepressants are often used to manage depression in schizophrenia. They may, however, also benefit other psychopathological dimensions. For example, a 6-week, controlled trial ($n=54$) found amoxapine (150–250 mg/day) (an agent with both 5-HT_2 and D_2 receptor antagonism properties) was as effective as haloperidol (5–15 mg/day) in improving PANSS total and positive symptom subscale scores in patients with schizophrenia [154]. An earlier meta-analysis considering only SSRIs as add-on therapy to treat negative symptoms concluded there was no global support for benefit, but subsequent meta-analyses which included SSRIs plus other antidepressants found support for this approach [155, 156]. For example, a large, 12-week, controlled trial ($n=198$) found that adjunctive citalopram (20 mg/day) was superior to placebo in improving depression ($p<0.002$), negative symptoms ($p<0.05$), mental functioning ($p<0.0001$), and quality of life ($p<0.05$) in middle-aged or older (i.e., 40 years of age) patients with schizophrenia or schizoaffective disorder [157]. In a 12-week, controlled trial ($n=60$), oral adjunctive selegiline (5 mg BID) was superior to placebo in improving negative symptoms ($p<0.009$), Brief Psychiatric Rating Scale (BPRS) total scores ($p<0.02$), and CGI-S scores ($p<0.002$) [158]. A 16-week, controlled trial ($n=33$) reported that duloxetine (60 mg/day) augmentation of CLZ was superior to placebo in benefiting the PANSS negative ($p<0.004$), general psychopathology ($p<0.001$), and total scores ($p<0.001$) [159]. The best evidence to date supports a potential role for *mirtazapine* to improve negative, cognitive, and depressive symptoms [160–164]. For example, a recent review found that five of six randomized trials supported the use of mirtazapine in treating negative symptoms of schizophrenia [160–164].

Glucocorticoids/Neurosteroids

The hypothalamic–pituitary axis (HPA) may play an important role in the pathophysiology of and stress vulnerability associated with schizophrenia. In this context, *mifepristone* (a glucocortoid receptor antagonist) has shown initial promise for improving cognition in schizophrenia [165]. *Pregnenolone* and *dehydroepiandrosterone* (DHEA) are neurosteroids whose various actions (e.g., neuroprotection, stress response, mood

regulation, cognitive performance) predict the potential to improve symptoms of schizophrenia [166]. Promising results from preliminary trials demonstrated benefit as add-on therapies for positive, negative, and certain cognitive symptoms, as well as for relief of extrapyramidal side effects (EPS) [167]. For example, pregnenolone (30 mg/day) (but not DHEA) produced significant decreases in positive symptoms ($p<0.01$); improved attention and working memory ($p<0.04$); and reduced EPS in an 8-week, double-blind, placebo-controlled trial ($n=58$) involving patients with chronic schizophrenia [168].

Anti-Inflammatory Agents

Inflammatory processes (e.g., abnormal levels of cytokines, autoantibodies, and lymphocytes in serum and CSF) are implicated in the pathophysiology of schizophrenia [169, 170]. A recent meta-analysis concluded that add-on, *nonsteroidal, anti-inflammatory drugs* (NSAIDs) such as *celecoxib* could reduce symptom severity, and noted a potential added benefit for *aspirin* to reduce the increased cardiac and cancer mortality in this population [171–173].

Minocycline is the second-generation tetracycline with anti-inflammatory, antimicrobial, and possible neuroprotective properties through modulation of Glu-induced excitotoxicity. Results of a 6-month, longitudinal, placebo-controlled trial ($n=54$) demonstrated an augmenting effect when minocycline (200 mg/day) was added to an antipsychotic, improving negative symptoms ($p<0.01$) and cognitive functioning ($p<0.01$) in early-onset schizophrenia [174]. A more recent study ($n=94$) found that minocycline plus TAU was significantly ($p<0.001$) more effective than TAU alone in improving negative symptoms in an early-onset population [175]. These results support earlier case reports and open-label trial data.

Cannabinoids

Central cannabinoid receptors are among the most abundant G protein-coupled receptors in the CNS, appear relevant to working memory, modulate both GABA and Glu release and are targets for delta-9-tetrahydrocannabinol (THC), the primary psychoactive substance in cannabis [176]. Stimulation of central cannabinoid receptors (e.g., CB_1) can produce transient psychotic symptoms, exacerbate preexisting psychotic disorders, and with early exposure may increase the risk of developing schizophrenia in vulnerable individuals [177]. Preliminary data suggest a positive cognitive effect (e.g., working memory) with CB_1 antagonists, through modulation of PFC GABA release [178].

Hormonal Agents

Decreases of *estrogen* during the postpartum and perimenopausal periods appear to increase the risk for a first episode or relapse of schizophrenia. Conversely, increases

in estrogen during pregnancy and certain phases of the menstrual cycle can ameliorate psychosis and reduce the risk of relapse [179]. The "estrogen protective hypothesis" is supported by preliminary results from controlled trials with add-on estradiol and possibly the selective estrogen modulator, raloxifene [180, 181]. A more recent, 4-week study ($n=32$) involving women of childbearing age with chronic schizophrenia compared conjugated estrogen (0.625 mg/day) with placebo to augment standard antipsychotics [182]. In contrast to placebo, those receiving estrogen experienced a significant decrease in positive ($p<0.003$), negative ($p<0.001$), general ($p<0.001$), and total PANSS ($p<0.001$) scores.

Oxytocin functions as both a hormone and peptide neurotransmitter and is linked to both social and reproductive behaviors [183, 184]. There is data from controlled trials indicating a potential role for oxytocin nasal spray as an adjunct to antipsychotics [185–187]. For example, an 8-week, controlled study ($n=40$) found oxytocin nasal spray (20–40 IU BID) superior to placebo based on change in the PANSS positive ($p<0.001$), negative ($p<0.01$), general psychopathology ($p<0.02$), and total ($p<0.001$) scores in patients with schizophrenia on a stable dose of risperidone [185]. More recent preliminary reports indicate oxytocin (40 IU) may also facilitate social cognition training (e.g., improve empathic accuracy) [188, 189].

Neutraceuticals

Omega-3 Fatty Acids

Given their role in neurodevelopment, neurodegeneration, and behavioral neurobiology, long-chain omega-3 PUFAs may play a role in schizophrenia. In a controlled trial ($n=81$), individuals at ultra-high risk of transitioning to a psychotic disorder received omega-3 PUFA (1.2 g/day) or placebo for 12 weeks and were then followed for an additional 40-weeks [32]. At 12 months, 2/41 (4.9 %) who initially received the active treatment had transitioned to a psychotic disorder versus 11/40 (27.5 %) who had initially received placebo ($p<0.07$). Further, the active treatment group experienced fewer positive symptoms ($p<0.01$), negative symptoms ($p<0.02$), and general symptoms ($p<0.002$) compared with placebo. By contrast, a subsequent meta-analysis of controlled trials considering omega-3, specifically eicosapentaenoic acid (EPA), found no benefit when used as an augmentation in patients with multiepisode schizophrenia [190].

Folate

Folate and other micronutrient deficiencies during fetal development may be risk factors for schizophrenia [191]. A recent, 16-week, controlled trial ($n=140$) compared folic acid (2 mg/day) plus vitamin B12 (400 μg/day) to placebo in patients with chronic schizophrenia [192]. Active treatment was superior to placebo in improving negative symptoms when genotype was taken into account but not when

excluded ($p<0.02$). The authors concluded that folate plus B12 may improve negative symptoms, but the results were influenced by genetic variation in folate absorption. There is also data indicating that genetic and epigenetic factors which influence folic acid metabolism are associated with an increased risk of metabolic syndrome in patients taking SGAs [193].

Vitamin D

Nutritional deprivation increases the risk of schizophrenia [194]. Further, low vitamin D levels affect neuronal differentiation, axonal connectivity, dopamine ontogeny, and brain structure and function [195]. In this context, low prenatal concentrations of vitamin D are associated with neurobiological and neuropsychiatric disorders, such as schizophrenia [196]. Following up on the hypothesis that developmental vitamin D deficiency may contribute to the risk for schizophrenia, dried neonatal blood samples of vitamin D levels were compared between 424 individuals with schizophrenia and 424 matched controls [197]. Surprisingly, both low and high concentrations were associated with an increased risk. Such findings raise the possibility that vitamin D supplementation may prevent schizophrenia in some populations. This is supported by a Finnish birth cohort study ($n=9,114$) which observed a reduced risk of schizophrenia by age 31 years in males with vitamin D supplementation provided during the first year of life [198].

Cognitive and Psychosocial Therapies

Most studies of psychosocial and psychotherapeutic interventions for schizophrenia focus on the phases after acute symptoms are reasonably well controlled. In this context, there is good evidence that augmentation with cognitive behavioral therapy (CBT) may be as effective as polypharmacy in managing persistent positive symptoms [199]. There are, however, some data on their use to augment acute antipsychotic drug therapy, focusing primarily on behavioral and educational interventions. In one study ($n=315$), the use of adjunctive CBT to manage acute symptoms demonstrated that a 5-week course had transient benefits over treatment as usual (TAU) or supportive counseling in patients during their first or second hospital admission [200]. Further, at 18 months follow-up, both CBT and supportive counseling produced significantly greater symptom reduction versus TAU ($p<0.005$) [201]. A second report ($n=100$) included patients who were experiencing an acute psychotic exacerbation which required hospitalization [202]. These patients were randomly assigned to a TAU plus CBT (up to 25 sessions) or a TAU control group. In the TAU plus CBT group, 60 % experienced a significantly better resolution of symptoms and improvement in social function over 12 months compared with 40 % in the TAU group ($p<0.04$). At the 2-year follow-up, the TAU plus CBT continued to demonstrate significantly better improvement in negative symptoms ($p<0.004$) and social functioning ($p<0.009$) with no difference in cost [203]. A more recent study ($n=18$)

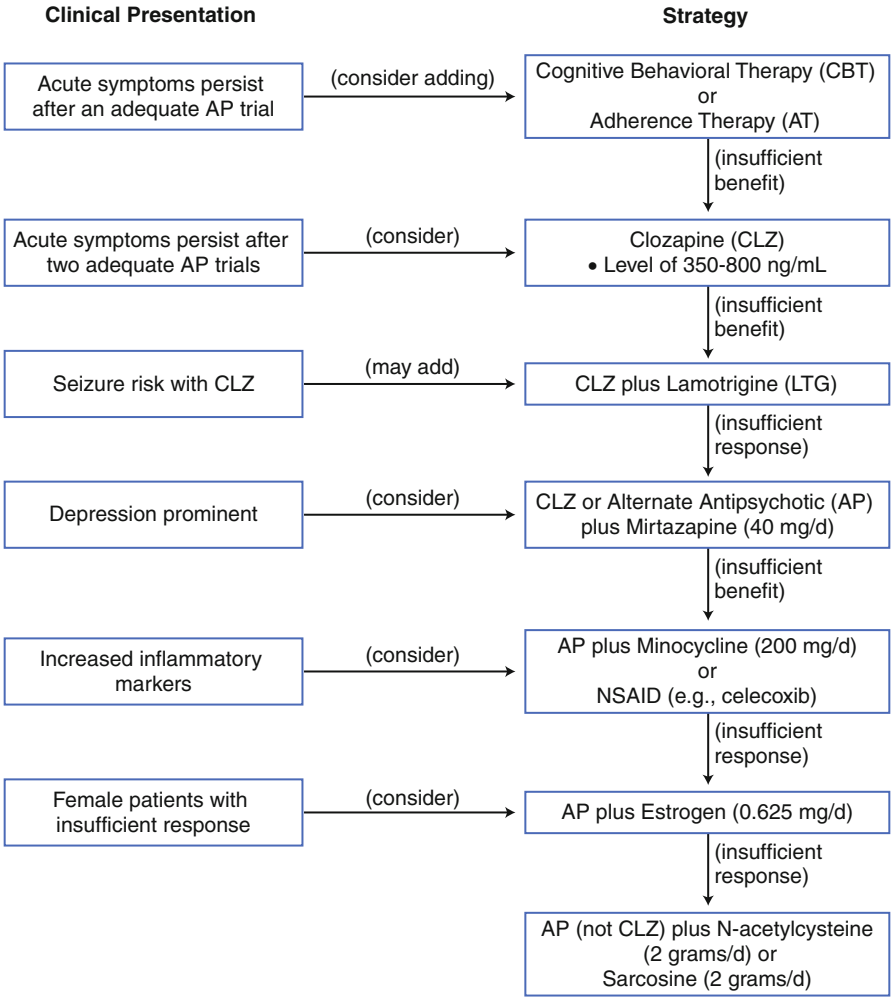

Fig. 7.1 Strategy for treatment-resistant multiepisode schizophrenia

in hospitalized patients with schizophrenia found that both group CBT (16 sessions) and group psychoeducation (8 sessions) significantly improved quality of life measures after acute treatment and at 6 months follow-up [204]. Finally, adherence therapy (AT) utilizes motivational and CBT techniques to modify patient's beliefs about treatment to improve medication adherence [205]. In a European trial ($n = 161$) comparing AT versus TAU, AT was superior to TAU in improving PANSS total scores 12 weeks after discharge from the hospital ($p < 0.05$).

Clinical Strategy with Other Approaches

While there is insufficient data to support an FDA-approved indication for the novel approaches discussed, their relative safety and tolerability, ready availability and positive, preliminary, controlled trial data suggest they may benefit some patients. Figure 7.1 outlines a clinical strategy which incorporates some of these options.

Conclusion

The introduction of antipsychotic drug therapy for schizophrenia and related psychotic disorders has improved the lives of many patients. Some argue, however, that there has been little progress since the advent of CPZ and CLZ. As a result, the focus is increasingly on detection of high-risk individuals and utilization of appropriate treatments early in the course of illness. After a first episode of psychosis and during the critical period characterized as early-onset, strategies to improve efficacy, tolerability, and adherence are also important to prevent the deterioration seen during this phase. Initiatives involving genetics, neuroimaging, early identification, and psychosocial interventions to control acute symptoms, sustain remission, and ultimately achieve recovery are now being actively pursued. These topics are discussed elsewhere in this book and will hopefully lead to more specific, more effective, and better tolerated therapies.

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Chapter 8
Therapeutic Neuromodulation for Treatment of Schizophrenia

Jeffrey T. Rado and Edgar I. Hernandez

Introduction

Antipsychotics are the primary pharmacologic treatment for schizophrenia, yet many patients do not achieve a clinically meaningful response. Approximately 25–30 % are refractory to these medications and up to 40 % of previously unresponsive patients also fail a trial of clozapine [1, 2]. As a result, nonpharmacologic approaches are increasingly being considered as potentially safe and effective adjunctive strategies. Therapeutic neuromodulation is a growing field of study for refractory auditory hallucinations (AHs), the deficit syndrome, and other symptoms such as catatonia. This chapter discusses its emerging role in the treatment of schizophrenia.

Positive Symptoms

Electroconvulsive Therapy

Electroconvulsive therapy (ECT) was first introduced in 1938 by Ugo Cerletti who applied electrical current to the head to elicit seizures as a treatment for various mental illnesses, including schizophrenia [3]. With the introduction of antipsychotics

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P.G. Janicak et al. (eds.), *Schizophrenia: Recent Advances in Diagnosis and Treatment*,
DOI 10.1007/978-1-4939-0656-7_8,

in the 1960s, ECT fell out of favor. Given the substantial subset of patients who still did not achieve sufficient benefit from medication, however, interest in ECT resurfaced in the 1980s [4].

Mechanism of Action

ECT's proposed mechanisms of action include modulation of monamines; change in neurotrophic factors (e.g., increased BDNF); and changes in GABA transmission and receptor antagonism [5]. Interestingly, in a review by Bolwig on the prevailing theories, the author states that "ECT is effective in various illnesses such as depression, mania, schizophrenia, and catatonia, but it remains an unresolved issue whether ECT exerts differential effects, or whether these obviously different disorders have common pathophysiological bases" [6].

ECT for Positive Symptoms

While direct comparisons between ECT and antipsychotic drugs for treating schizophrenia are limited, numerous studies have evaluated ECT as an adjunct to antipsychotics. For example, Goswani et al. randomized 25 chlorpromazine-treated adults with schizophrenia to either active ECT or a control group (anesthesia was induced in these patients but no ECT treatments were given) [7]. The authors reported that weekly Brief Psychiatric Rating Scale (BPRS) scores significantly improved ($p \leq 0.002$) from baseline in the active ECT-treated patients ($n = 15$) after at least six treatments. Kupchik and colleagues reviewed 36 cases of patients treated with ECT plus clozapine [8]. Of these cases, 23 patients were diagnosed with schizophrenia or schizoaffective disorder, while the rest were diagnosed with mood disorders. Clozapine was added to ECT in 18 patients, while in 17, ECT was introduced after the initiation of clozapine. The ECT electrode placements, number of treatments, and stimulus intensity were not reported. This combination was highly effective in 24 patients with 67 % demonstrating marked improvement from baseline. The authors point to a possible synergistic effect by enhancing brain electrophysiological changes. Chanpattana et al. found benefit for refractory patients who received 20 bilateral ECT treatments (three times per week) in addition to flupenthixol [9]. Refractory patients were defined as those who failed two separate trials of antipsychotic treatment from two different classes for a minimal duration of 6 weeks. Flupenthixol was started simultaneously with ECT after other psychotropics were discontinued. Patients received 12 mg daily during the first week and then the dose was increased to 24 mg daily (depending on tolerability). Those achieving a BPRS score of ≤ 25 entered a 3-week stabilization period where patients received three ECT treatments in the first week followed by once weekly treatments during the subsequent 2 weeks. Patients were considered responders if they completed this period with no worsening in their scores. Response was achieved in 160 of 293 (54.6 %) participants. In particular, five symptoms demonstrated marked improvement

after ECT: conceptual disorganization (effect size (ES) = 0.94); tension (ES = 0.89); mannerisms and posturing (ES = 1.06); hostility (ES = 0.83); and unusual thought content (ES = 1.02). By contrast, motor retardation, blunted affect, and disorientation worsened. In summary, the ECT–flupenthixol combination resulted in marked improvement for specific positive symptoms, an intermediate improvement for affective symptoms, and no benefit for negative symptoms.

Nothdurfter et al. conducted a retrospective analysis of 455 patients receiving ECT combined with first- (FGAs) or second-generation antipsychotics (SGAs) versus ECT monotherapy [10]. Patients with schizophrenia ($n = 170$) received 11.59 (±5.3) ECT treatments (76 % bilateral electrode placement). The authors suggest that the ECT–antipsychotic combination improves electrophysiological indices, particularly the postictal suppression index (PSI), which may predict treatment response to ECT. The PSI demonstrates how fast and complete the EEG amplitude flattens directly after a seizure, with a correlation between high percent suppression and a more robust therapeutic response [11]. The outcome measure was assessed by the Clinical Global Impression Scale (CGI-S). The authors report that the PSI of treatments done with SGAs was significantly higher than the PSI of treatments done with low potency FGAs ($p \leq 0.0001$; actual values not reported), supporting the notion that the index appears to be a reliable parameter of response. Compared with FGAs, CGI score improvements were superior for SGAs and this correlated to a higher percent suppression ($p \leq 0.0001$; actual values not reported). Finally, they found no differences in adverse effects among the antipsychotics.

Reviews and Meta-analyses of ECT for Positive Symptoms

Tharyan et al. conducted a Cochrane review of 26 studies comparing active versus sham ECT, ECT combined with antipsychotics, and ECT versus other interventions [12]. Improvement was measured by various outcomes, and the authors describe the definition of a "clinically meaningful benefit" based on the individual study's scale. The data was then made binary to calculate a relative risk (RR) when possible. Overall, greater improvement occurred in patients treated with active versus sham ECT ($n = 392$; 10 RCTs; RR = 0.71 [CI = 0.59–0.98]; NNT = 6 [CI 4–12]). Although results favor the medication group when ECT is compared directly with antipsychotics, there is evidence to suggest that the *combination* treatment results in greater improvement of symptoms in the short term ($n = 203$; 7 RCTs; RR 0.76 [CI 0.52–1.10]). Further, the authors found data supporting the ECT–antipsychotic combination as a viable option for adult patients with schizophrenia, particularly when rapid global improvement and reduction of symptoms are necessary ($n = 40$; 1 RCT, Weighted Mean Differences BPRS −3.9 [CI −2.28 to −5.52]). The review noted that these results are less relevant for those with schizophreniform disorder or unspecified psychosis.

A review and meta-analysis conducted by Painuly et al. found the combination of ECT plus antipsychotic to be more efficacious than antipsychotic monotherapy [13]. For the review, 11 open and controlled trials were selected ($n = 651$), while the meta-analysis only included four RCTs ($n = 113$). The benefit was seen primarily in

the first 3–6 weeks when ECT appeared to cause an "acceleration of treatment response" during an acute exacerbation as measured by changes in BPRS scores. The effect of combined treatment was most pronounced on affective and behavioral disturbances, yielding an additional five-point reduction in BPRS scores with combination treatment versus an antipsychotic alone.

Matheson et al. conducted a meta-analysis which found that adjunctive ECT provided a small but significant improvement in global symptoms compared with a sham procedure (RR = 0.76) [14]. Further, ECT plus antipsychotic demonstrated a moderate benefit over sham ECT plus antipsychotic based on BPRS scores ($d = -0.75$) for up to 6 weeks posttreatment. Gazdag et al., however, point to the heterogeneity of study samples due to changes in the diagnostic criteria for schizophrenia over the years and variability in study designs as limitations in assessing ECT's effectiveness to treat schizophrenia [15]. A more recent review article by Zervas et al. concluded that ECT is most effective in treating catatonia, paranoid delusions, and other positive symptoms [16].

Despite decades of utilizing ECT for the treatment of various psychiatric diseases, the literature reports inconsistencies when it comes to its role in schizophrenia. This may be due to the lack of well-controlled study designs, heterogeneous samples, and small sample sizes. Despite these acknowledged limitations, the evidence supports the use of ECT in the treatment of schizophrenia, particularly if combined with antipsychotics in patients who demonstrated limited response to an antipsychotic alone. As the authors of the Cochrane review declared, "The efficacy of ECT, when schizophrenia is diagnosed using operationally defined criteria, indicates a specific effect on schizophrenic symptoms, rather than causing an improvement in those with affective disorder misdiagnosed as schizophrenia" [12].

ECT for Catatonia

Several case reports support ECT's efficacy and safety for patients with catatonia, especially if symptoms do not improve with benzodiazepines [17–19]. In a retrospective study ($n = 22$), Rohland et al. reported no difference in the effectiveness of ECT for the resolution of catatonic symptoms in patients with mood disorders versus schizophrenia [20]. By contrast, it has also been reported that patients with catatonia secondary to mood disorders obtain a greater improvement compared to those with catatonia associated with schizophrenia [21].

In a randomized, controlled study of 14 non-affective, catatonic patients ($n = 9$ schizophrenia; $n = 5$ psychosis NOS), ECT plus oral placebo was compared with sham ECT plus risperidone (4–6 mg) in nonresponders to lorazepam [22]. ECT demonstrated significant improvement over risperidone on both outcome measurements (i.e., the Bush-Francis Catatonia Rating Scale ($p \leq 0.035$) and Positive and Negative Symptom Scale (PANSS) ($p \leq 0.04$)). The study concluded that ECT may be safely used as a monotherapy for catatonia. The Cochrane review by Tharyan et al., however, concluded that "there is no clear evidence to support or refute the use of ECT in catatonia given the lack of randomized controlled trials" [12].

Table 8.1 Predictors of response to adjunctive ECT in treatment-resistant schizophrenia: interaction between clinical variables and gender

Variable	Male	Female
Age	Younger	Younger
Duration of current episode	Short duration	Short duration
Symptom profiles	Delusions, blunted affect, suspiciousness	Anxiety, depressed mood, hallucinations
Diagnostic subtype	Paranoid	–
Psychiatric admissions	More frequent admissions	–
Duration of illness	–	Short duration
Family history	–	Negative family history

Source: Data from Chanpattana et al. [25]

ECT for Adolescents

In a prospective study of seven antipsychotic-treated patients with intractable first-episode schizophrenia or schizophreniform disorder (age 15–34 years), Suzuki et al. reported improvement in symptoms when bilateral ECT was administered two or three times per week (total number of sessions was limited to 20) [23]. BPRS and Global Assessment of Functioning (GAF) scores improved significantly after the acute treatment course ($p \leq 0.018$ and $p \leq 0.018$, respectively). Based on Chanpattana et al.'s criterion of a final BPRS score ≤25 after 1 week of an acute ECT treatment, all seven patients were considered responders (10.7 ± 8.0 after the first ECT course versus 44.4 ± 5.3 before the course) [9]. Further, ECT was safe and well tolerated. Similarly, in a retrospective study of 13 adolescents (ages 13–17), Baeza et al. demonstrated that an acute course of bilateral ECT (mean number of sessions = 13.9 (±4.3)) combined with an antipsychotic was effective and safe in treating schizophrenia spectrum disorders [24]. In addition, the mean endpoint PANSS scores after 6 months of completing the first acute ECT course demonstrated significant improvement in the positive and general subscale scores ($p \leq 0.004$), while negative symptoms were unchanged.

Predictors of Response

In a prospective study of 253 patients, Chanpattana et al. considered factors which may predict response to ECT plus flupenthixol in treatment-resistant schizophrenia (see Table 8.1) [25]. The authors report that frequent psychiatric admissions and paranoid subtype were associated with better response on the BPRS (primary outcome) in males, while shorter duration of illness and a negative family history for schizophrenia were associated with better response in females. Finally, greater severity of positive or affective symptoms compared with more severe negative symptoms also predicted greater response as measured by the BPRS.

ECT for Maintenance Treatment

In a retrospective chart review of 19 patients with schizophrenia or schizoaffective disorder, Levy-Rueff et al. considered maintenance ECT (M-ECT) plus medication as a treatment strategy in refractory patients [26]. The authors note a "substantial, although moderate" efficacy for M-ECT on symptom intensity (although no standardized measures were provided); duration of hospitalizations (80 % reduction); and quality of life. No factors predicted relapse. Similarly, in a chart review ($n=79$) conducted by Kristensen et al., the authors report that no predictive factors were identified, but most patients treated with bilateral ECT (acute treatment 2–26 sessions; M-ECT duration 3 months to 12 years; once every 1–3 weeks) experienced good or moderate outcomes ($n=66$ and $n=8$, respectively) with only five patients experiencing a poor outcome [27]. The outcomes were defined by assessing severity of illness and degree of improvement by categorizing the wording in each patient's chart. The authors note that these categories correlated well with the CGI Scale (Item 3.1). Specifically, of the 18 patients treated with M-ECT, 16 (88 %) showed excellent or good response based on the degree of relief from psychosis and disruptive behavior, while two demonstrated only a moderate benefit.

ECT Administration

Important issues when using ECT to treat schizophrenia include optimal electrode placement; stimulus intensity and frequency; and number of ECT sessions. While successful treatment with both bilateral and unilateral electrode placement is documented, bilateral ECT may result in a quicker response. The existing data, however, does not conclusively support the use of either electrode placement. Thus far, the stimulus intensity requirement for patients with schizophrenia has not differed from those with major depression. Chanpattana et al., however, proposed that doses 2–4 times the seizure threshold are more likely to speed recovery with bilateral ECT [28]. They also support the use of 20 ECT treatments to elicit full response. Further, in line with studies in major depression [29, 30], the authors concluded patients receiving thrice weekly ECT treatments responded faster than those on twice weekly schedules based on the improvement in BPRS and GAF scores [31].

ECT Guidelines for Treating Schizophrenia

There is no general consensus regarding the clinical use of ECT in schizophrenia. In a review by Pompili et al., the authors conclude that the most common indication for ECT in schizophrenia was to augment pharmacotherapy (particularly in treatment-resistant patients), while the most common symptoms treated were catatonia, aggression, and suicidal ideation [32]. Further, the American Psychiatric Association Guidelines (2001) propose that patients with acute onset of predominantly depressive or catatonic symptoms would benefit most from ECT, implying that

Table 8.2 Parameters used with adjunctive ECT in schizophrenia

Electrode placement	Bilateral[a]
Stimulus intensity	1.5–4 times seizure threshold
Number of treatments	6–20
Dosing frequency	3 times per week[b]
Adjunct medication	Second-generation antipsychotics[c]

[a]Noted to result in faster response
[b]Faster onset of improvement
[c]Clozapine in treatment-resistant cases

predominant delusions or hallucinations are less likely to benefit [33]. The review by Zervas et al. concludes, however, "these studies have indicated that one should not exclude patients with refractory schizophrenia from a trial of ECT only on the basis of lack of affective symptoms, especially if the so called 'positive' symptoms of psychosis are present" [16]. Finally, the 2009 Schizophrenia Patient Outcomes Research Team (PORT) review concluded that "there is insufficient evidence to support a recommendation for the use of ECT for the core symptoms of schizophrenia in treatment-resistant individuals" [34]. The authors, nonetheless, acknowledge the role of ECT in treating acute positive psychotic symptoms.

Conclusion

Adjunctive ECT may be an effective therapy for positive symptoms such as refractory auditory hallucinations (AHs) or catatonia; when rapid reduction of symptoms is needed; as both an acute and maintenance treatment; and in both adults and adolescents. Although more research is necessary to clarify its mechanisms of action, predictors of response, and optimal application, ECT remains an important treatment option in clinical practice. Table 8.2 provides a general summary of parameters which were successful in the treatment of schizophrenia.

Transcranial Magnetic Stimulation

Transcranial magnetic stimulation (TMS) delivers intense, intermittent, magnetic pulses generated by an electrical charge into a ferromagnetic coil. Applied to the scalp, rapid repetitive TMS ($\geq$1 Hz) causes neuronal depolarization in a localized area under the coil, as well as distal effects [35]. In contrast, slow repetitive TMS (<1 Hz) inhibits neuronal depolarization. TMS is generally a safe and well-tolerated procedure, with application site discomfort and mild headaches being the most common adverse effects. While inadvertent seizure occurrence is more serious, its incidence is far less than 1 %. This novel device-based therapy is approved for the treatment of depression, but has demonstrated benefit for other neuropsychiatric disorders, including positive and negative symptoms in schizophrenia. While high

frequency (≥1 Hz) TMS has FDA approval for depression and may also benefit negative symptoms, it is suggested that low frequencies (<1 Hz) with extended duration of treatment (e.g., >15 min) may benefit treatment-resistant auditory hallucinations (AHs).

Mechanism of Action

Functional magnetic resonance imaging (fMRI) studies implicate left temporoparietal cortex (TPC) hyperactivity in the etiology of hallucinations [36]. Further, it is postulated that low frequency TMS may attenuate excitability in this region, while high frequency stimulation generates the opposite effect. Thus, most treatment studies with TMS for AHs stimulated with low frequency over the region between T3 and P3 as described in the International 10-20 EEG System of Electrode Placement [37].

TMS for Positive Symptoms

Early studies by Geller et al. and Feinsod et al. employed low frequency TMS (<1 Hz) in patients with depression or schizophrenia [38, 39]. The authors demonstrated improvement in mood and anxiety but not in the core symptoms of schizophrenia. Neither report looked at the effects of TMS specifically for AHs.

To investigate TMS for the treatment of medication-resistant AHs, Hoffman et al. conducted a double-blind, crossover study ($n=3$) with low frequency TMS at 80 % motor threshold (MT) over the left TPC given on 4 days during a 2-week period [40]. Stimulation was initiated at 4 min on day 1 with increases of 4 min each day to a maximum of 16 min duration on day 4. Active versus sham TMS stimulation took place on separate weeks with 2–3 days off between trials. The authors reported a significant decrease in hallucination severity based on an individualized rating scale for each patient which corresponded to a composite score incorporating loudness, frequency, content, and level of distress. Following active but not sham stimulation, all three patients reportedly experienced significant improvement in AHs (p value not reported).

Subsequently, Hoffman et al. conducted a second, double-blind, crossover trial ($n=12$) using the same design as in their first study [41]. Again, hallucination severity was significantly decreased with active versus sham stimulation ($p \leq 0.006$). This group then published additional data in two separate reports which included a total of 50 patients randomized to low frequency, active TMS (90 % MT; 132 min of total stimulation) or sham TMS over the left TPC [42, 43]. Patients received 8 min of continuous stimulation on day 1, 12 min on day 2, and 16 min daily for the next 7 days. Responders had a Hallucination Change Scale (HCS) score of 5 or lower at the end of treatment. Fourteen patients in the active group (51.9 %) versus four in the sham group (17.4 %) met this criterion ($p \leq 0.01$). In addition, the frequency quality item of the Auditory Hallucination Rating Scale (AHRS) demonstrated a significant linear decrease over time in the active versus sham group ($p \leq 0.0001$). There were no

differences in other AHRS variables or PANSS scores. Of note, Fitzgerald et al. were unable to replicate Hoffman's results using the same parameters in a randomized, controlled study with 33 patients [44]. The authors, however, did find that eight patients in the active group met response criteria compared with only four in the sham group ($p \leq 0.05$) using the HCS scores as the primary outcome measure. In addition, except for a significant reduction in the volume of hallucinations in the active versus sham group ($p \leq 0.01$), no significant differences were observed in change scores on the Psychotic Symptom Rating Scale (PSYRATS). Finally, a randomized, double-blind controlled study ($n = 83$) by Hoffman et al. recently investigated the use of TMS over Wernicke's area anterior to the T3/P3 site and its right homologous site to treat refractory auditory/verbal hallucinations (AVHs) [45]. This was based on fMRI studies linking AVHs with activation at these sites which are involved in the processing of external speech and acoustic processing. The TMS parameters used for this study included 1 Hz; 90 % MT; 16 min per session; and 960 pulses over a 15-day course. The stimulations were administered during five weekday sessions at one site and then switched to the opposite hemisphere for another five sessions. A final five-session block was delivered to the site associated with greater initial improvement in AVHs based on change in scores in the HCS. Hallucination severity at endpoint did not differ between the active or sham groups ($p \leq 0.09$), but the hallucination frequency difference (i.e., baseline minus endpoint score) was significantly less in the active treatment group (−1.32 active versus −0.26 sham), as were the CGI scores ($p \leq 0.005$ and $p \leq 0.045$, respectively). Interestingly, by eliminating patients for whom the MT could not be consistently detected, there was a statistically significant improvement in the active condition ($p \leq 0.044$) attributed to a reduction in sham response. The authors concluded that a bilateral site-optimization protocol using active TMS reduced AVHs.

Other groups have also pursued the use of TMS for positive symptoms. McIntosh et al. conducted a placebo-controlled, crossover study of TMS (1 Hz; 80 % MT) over the left TPC in 16 patients given on 4 days over a 2-week period [46]. Stimulation was initiated at 4 min on day 1 with increases of 4 min each day to a maximum of 16 min duration on day 4. Of note, a 15 s pause was allowed between each continuous minute of treatment. The authors found a trend for improvement on the PANSS hallucination subscale score after the second week of stimulation, suggesting that a longer period of treatment may be more effective. Poulet et al. conducted a double-blind, crossover study ($n = 10$) of active (1 Hz; 90 % MT; 1,000 stimulations per day) versus sham TMS delivered twice daily over the left TPC on 5 days [47]. All seven items of the AHRS were significantly reduced during active versus sham treatment ($p \leq 0.008$). They also found that 50 % of the actively treated patients achieved response (i.e., improvement of ≥20 % compared to baseline severity) after 8 weeks. Of note, instead of delivering sham treatment with an active coil angled at 45 or 90° away from the skull, this study was the first to use a sham coil which produced the same sound but no superficial scalp stimulation, making it less distinguishable from the active coil.

Chibarro et al. conducted a randomized, controlled study in 16 schizophrenia patients treated with SGAs [48]. Low frequency TMS (1 Hz; 90 % MT; one

continuous 15-min period; 900 total stimulations) over the left TPC was administered on four consecutive days. The Scale for the Assessment of Positive Symptoms (SAPS) and Severity of Auditory Hallucinations (SAH) scores were significantly decreased in both the active ($p \leq 0.04$ and $p \leq 0.001$, respectively) and sham groups ($p < 0.02$ and $p < 0.01$, respectively). The reduction in AHs in the active group, however, was sustained 6 weeks after treatment completion, whereas the sham group returned to baseline.

Saba et al. conducted a double-blind study ($n = 18$) of 10 daily active (1 Hz; 80 % MT; five trains; 1 min; 1 min intertrain interval (ITI)) or sham TMS treatments over the left TPC [49]. All patients demonstrated the same pattern of improvement with no difference between active and sham treatment on the PANSS AH items. Lee et al. conducted a double-blind study (left, right, or sham TMS) administering 10 daily treatments (1 Hz; 100 % MT; 20 continuous minutes; 1,600 stimulations) applied bilaterally over the TPC in 39 patients [50]. The study found significant changes in frequency of AHs ($p \leq 0.001$) and in PANSS positive symptom scores ($p \leq 0.001$) over the course of treatment. The greatest improvement was noted in frequency and attentional salience. The study was also the first to observe that TMS over the right side may be beneficial in improving global symptoms based on the CGI-I Scale ($p \leq 0.002$), implying that its effects may spread to the opposite hemisphere.

Jandl et al. compared the effects of TMS (1 Hz; 100 % MT; one continuous 15 min stimulation; 900 stimuli per session) over the left or right TPC for 5 days in a randomized, three-armed, sham-controlled study ($n = 16$) [51]. While PSYRATS change scores were not significantly different between the groups, only the five patients who received active left TPC stimulation achieved complete or partial response. The authors note that the number needed to treat (NNT) (i.e., three) at the end of the left TPC stimulation period falls within the range seen for other psychiatric treatments. The NNT after 4-week follow-up, however, increased to 8.

In a double-blind trial ($n = 24$), Brunelin et al. delivered twice daily active (1 Hz; 90 % MT; 10 sessions; 1,000 stimulations) or sham TMS over the left TPC for 5 days [52]. The authors reported that AHRS scores in the active group were significantly improved versus the sham group ($p \leq 0.002$). Positive symptoms as measured by the SAPS, however, did not differ between groups. Finally, the authors were the first to report a trend, noting that as AHs improved, source monitoring performance (e.g., discriminating between internally generated thoughts and externally generated events) also improved.

Rosa et al. conducted a randomized, controlled study in 11 clozapine-resistant patients [53]. TMS (1 Hz; 90 % MT; one continuous 16-min period; 9,600 pulses) was delivered over the left TPC for 10 days. Reality and attentional salience scores on the AHRS significantly decreased at endpoint and at 6 weeks of follow-up in the active TMS group ($p \leq 0.049$ and $p \leq 0.036$, respectively). By contrast, the sham group's initial linear decrease over time was not sustained after 2 weeks (suggesting a possible placebo effect).

Vercammen et al. randomly assigned 38 patients to TMS (1 Hz; 90 % MT; 20 min of continuous stimulation; 12 sessions with a minimum of 5 h delay between sessions; 14,400 pulses) on six consecutive work days [54]. Patients received

bilateral TPC, left TPC, or a sham condition. The authors reported no difference in total AHRS change scores between the stimulation conditions; however, the frequency subscale of AHs was significantly reduced in the left and bilateral TPC groups only after the 1-week follow-up assessment ($p<0.043$ and $p<0.043$, respectively).

In a double-blind, crossover trial ($n=18$), Loo et al. assessed the effects of TMS over the right and left temporal cortex versus the vertex (control site) using low frequency stimulation (1 Hz; 110 % MT) [55]. Participants received three consecutive days of TMS over each site (with a gap of 4 days in between stimulation conditions) for 4 min on days 1–2 and 8 min on day 3. There was a nonsignificant trend for decreasing the quality of distress level on the AHRS in the active versus sham group ($p<0.087$). There was no difference between stimulation over the left or right temporal cortex.

de Jesus et al. conducted a randomized study in 17 patients with clozapine-refractory schizophrenia who received active TMS (1 Hz; 90 % MT; 20 sessions over 4 weeks) over the left TPC, while the sham procedure angled the coil at 45° and reduced intensity to 80 % MT [56]. Patients received one continuous 8-min stimulation period on day 1, 16 min on day 2, and 20 min daily for the next 18 days. Changes in BPRS scores from baseline to endpoint were significantly greater in the active versus sham group ($p \leq 0.002$). This study also found a positive effect in general psychopathology.

Meta-analyses of TMS for Positive Symptoms

Four meta-analyses summarized these results, reporting moderate to high mean ES ranging from 0.54 to 1.0 [57–60]. In their most recent meta-analysis, Slotema et al. included 15 randomized controlled studies utilizing TMS over the left TPC ($n=337$) [60]. The mean weighted ES was 0.44 (i.e., moderate effect). In two additional studies (whose primary site of stimulation was not the left TPC; $n=122$), a mean weighted ES of 0.33 was obtained. This analysis also looked into the long-term effects of low frequency TMS for AHs 1 month after the end of treatment. Five studies ($n=118$) were included and produced a mean weighted ES of 0.40. All of these studies applied TMS over the left TPC.

A recent review of five meta-analyses considering TMS for treatment of schizophrenia was published by Hovington et al. [61]. The authors report that the data for AVHs support the efficacy of active versus sham TMS when applied over the left TPC (i.e., ES ranged from 0.54 to 1.04). When considering global positive symptoms, the ESs were more modest and varied from 0.17 to 0.51. Of note, when the SANS was the primary outcome measure (versus the PANSS), it appeared to be more sensitive in detecting changes in negative symptoms (i.e., ES=0.73 and E=0.35, respectively). The authors concluded that TMS over the left TPC was the most common site of stimulation for AVHs, using low frequencies and treatment durations lasting between 4 and 15 days (pulses per session ranged from 120 to 2,000). Finally, the authors note that given the limited number of RCTs for positive symptoms, "there does not appear to be a dose-dependent increase in effect sizes with more treatment sessions." Overall, the procedure was well tolerated and safe.

TMS for Adolescents

In a case series of childhood-onset schizophrenia (COS), ten adolescents underwent twice daily TMS treatment (1 Hz; 90 % MT; 1,200 continuous pulses) applied over the left TPC for five consecutive days [62]. AHRS scores significantly decreased from baseline to acute endpoint and from baseline to 1-month posttreatment (i.e., $p \leq 0.007$ and $p \leq 0.004$, respectively). GAF scores were also significantly improved at both time points (i.e., $p \leq 0.002$ and $p \leq 0.009$, respectively). The authors concluded that larger controlled trials are needed to validate these results.

TMS for Maintenance Treatment

There is limited evidence regarding the use of maintenance TMS in schizophrenia. Thirthalli et al. described a patient with clozapine-treated refractory AHs [63]. This patient underwent an acute course of TMS over the left TPC (1 Hz; 100 % MT; once daily five times a week; 900 continuous stimulation) followed by once weekly maintenance treatment for 6 weeks, then once every 2 weeks for 3 months, and then once every 4 weeks for 3 months. The patient reported almost total remission of AHs after week 4 with frequency, intensity, duration, intrusiveness, and overall severity all improved.

TMS Administration

While many TMS studies demonstrate efficacy for treating schizophrenia, there are several limitations. For example, in the Fitzgerald, McIntosh, and Loo studies, the authors suggest that the pause within the stimulation trains may contribute to a reduction in efficacy compared with other protocols which did not employ these breaks [44, 46, 55]. In addition, the Hoffman and Vercammen studies included patients who were on anticonvulsants which may attenuate the effects of TMS [41, 54]. In this context, Poulet et al. noted that none of their seven responders received anticonvulsant drugs [47]. A challenge to device-based research is that the putative neuroanatomical substrate for hallucinations may differ between subjects, making one stimulation target impractical for all patients. It may also be that only a subgroup of patients with schizophrenia benefit from this approach. Another problem is the difficulty in creating an adequate sham procedure.

Conclusion

Despite the limitations noted, low frequency TMS over the TPC holds promise as a potential treatment for refractory AHs and possibly other positive symptoms. While it is difficult to identify a definitive set of ideal treatment parameters, Table 8.3 provides a general summary of parameters which were successful in the treatment of auditory hallucinations.

Table 8.3 Parameters used with adjunctive TMS for auditory hallucinations

Frequency	1 Hz
Stimulation location	Left temporoparietal cortex
Duration	4–15 days
Number of pulses per session	12–2,000
Motor threshold	80–90 %

Negative Symptoms

Electroconvulsive Therapy

Few trials with ECT report a formal outcome measure for negative symptoms (e.g., the SANS). In an open-label, add-on trial of 8–20 ECT sessions in 15 patients with schizophrenia on a stable antipsychotic regimen, Tang et al. reported a significant improvement in SANS scores ($p \leq 0.05$) [64]. By contrast, no improvement in negative symptoms was observed in 253 patients with treatment-resistant schizophrenia who received a combination of ECT and flupenthixol [9]. Matheson et al. analyzed five systematic reviews conducted since 2000 [14]. They concluded the evidence supported a "medium size" benefit for overall clinical improvement as measured by the BPRS in schizophrenia, but the authors did not comment on ECT's specific effect for negative symptoms.

Transcranial Magnetic Stimulation

Mechanism of Action

Since several neuroimaging studies indicate an association between negative symptoms and frontal cortical hypoactivity, the potential for TMS to excite the dorsolateral prefrontal cortex (DLPFC) is the rationale for its treatment of these symptoms [65].

Open-Label Studies

Treatment with TMS for negative symptoms was first reported in six inpatients with schizophrenia on a stable antipsychotic dose for 3 months [66]. Ten daily TMS treatments (20 stimulation trains; 2 s duration; 20 Hz; 80 % MT; 58 s ITI) over the prefrontal cortex (side not defined) decreased PANSS negative subscale scores significantly ($p \leq 0.02$). Subsequently, an open-label study administered TMS (20 stimulation trains; 3.5 s duration; 10 Hz; 100 % MT; 10 s ITI) over the left DLPFC to 10 patients with schizophrenia and prominent negative symptoms [67]. Mean baseline SANS scores decreased from 49.0 (±10.7) to 44.7 (±11.8) posttreatment ($p \leq 0.001$). In another study, Sachdev et al. administered daily TMS (24 stimulation trains; 5 s duration; 15 Hz; 80 % MT; 25 s ITI) over the left DLPFC for 20 days to four patients with

schizophrenia [68]. PANSS negative subscale scores decreased from a mean of 29.25 at baseline to 19.5 following treatment (p value not reported). In 27 patients, Jin et al. provided 2 weeks of daily bilateral TMS (20 stimulation trains; 2 s duration; 80 % MT; 58 s ITI) over the DLPFC at 3 Hz, 20 Hz, or a stimulation set individually at each subject's EEG-derived alpha frequency [69]. A subject's alpha wave frequency refers to any rhythmic activity detected between 8 and 12 Hz on an EEG. The alpha frequency-derived stimulus produced the greatest reduction in PANSS negative symptom subscale scores (i.e., 29.6 %) versus the other two groups (i.e., <9 %; $p \leq 0.007$).

Controlled Studies

The majority of the published, sham-controlled studies applied TMS over the left DLPFC, since this brain region is believed to play a role in negative symptoms.

Holi et al. randomized 22 medicated inpatients with schizophrenia in double-blind fashion to either ten daily TMS treatments (20 stimulation trains; 5-s duration; 10 Hz; 100 % MT; 30 s ITI) or a sham procedure [70]. No significant improvement in PANSS negative subscale scores was detected in the active versus sham groups. Hajak et al. employed identical TMS treatment parameters (except 110 % MT) and duration in a similar study of 20 inpatients with schizophrenia or schizoaffective disorder on stable doses of antipsychotics [71]. While significant improvement in the PANSS negative subscale scores was reported for the active versus sham group, neither raw scores nor p values were provided.

Novak et al. applied 10 days of higher frequency TMS (40 stimulation trains; 2.5 s duration; 20 Hz; 90 % MT; 30 s ITI) to 16 patients with schizophrenia [72]. Neither active nor sham TMS produced any benefit. Mogg et al. randomized 17 subjects with schizophrenia in a double-blind fashion to either 10 daily active (20 stimulation trains; 10 s duration; 10 Hz; 110 % MT; 50 s ITI) or sham TMS treatments [73]. Again, no significant difference was detected between the active or sham groups for the primary outcome measure (i.e., PANSS negative subscale score).

When Prikryl et al. administered a greater number of treatments, however, benefit for negative symptoms was observed with active TMS [74]. Twenty-two patients with schizophrenia were randomized to active (15 stimulation trains; 10 s duration; 10 Hz; 110 % MT; 30 s ITI) or sham TMS for 15 consecutive daily treatments. Active TMS was associated with significant improvements (i.e., 29 % reduction in the PANSS negative subscale score and a 50 % reduction in the SANS score ($p \leq 0.01$ and $p \leq 0.01$, respectively)).

Goyal et al. randomized 10 patients with schizophrenia to 10 days of active (10 stimulation trains; 4.9 s duration; 10 Hz; 110 % MT; 30 s ITI) or sham TMS [75]. An ANOVA between-groups analysis demonstrated significant improvement in the PANSS negative symptom scale scores with active versus sham TMS ($p \leq 0.008$). Unique to this study is that the authors included depression assessments (Calgary Depression Scale Schizophrenia (CDSS)) at baseline and follow-up to evaluate the possible confounding effect of mood on improvements in negative symptoms. Changes in negative symptoms scores, however, did not correlate with changes in the CDSS.

In one of the largest and longest trials to date, Schneider et al. randomized 51 patients with schizophrenia to active (20 stimulation trains; 5 s duration; 1 or 10 Hz; 110 % MT; 15 s ITI) or sham TMS [76]. After 20 daily treatments, a significantly greater improvement on the SANS was observed in the 10 Hz group compared with the 1 Hz and sham groups ($p \leq 0.031$) which persisted 4 weeks posttreatment. No significant changes were noted on the HAM-D, again providing support that the observed changes were not attributable to improvements in depression.

Other investigators have employed bilateral and right-sided TMS for negative symptoms, but neither was found efficacious [77, 78]. Finally, Levkovitz applied deep TMS (20 Hz; 120 % MT) over the lateral prefrontal cortex in 15 patients and observed a mean SANS score decrease of 16.83 % after 20 daily treatments [79].

Meta-analyses of TMS for Negative Symptoms

TMS for the treatment of negative symptoms was evaluated in two meta-analyses. Freitas and colleagues included only those trials employing greater than one session of high frequency stimulation over the left DLPFC [80]. The final analysis included 107 patients. The authors reported an ES of 0.58 using a random effects model to analyze only the active arms of all studies, while a mixed effect model revealed an ES of 0.49. They concluded that high frequency TMS over the left DLPFC provided a "modest to moderate" reduction in negative symptoms. When only considering sham-controlled data, however, the pooled weighted ES was 0.27 with no significant difference in improvement for negative symptoms observed in patients receiving active versus sham stimulation. Of note, lack of sufficient data led to two positive trials being excluded from this analysis. Dlabac-de Lange et al. included two previously unpublished trials in a more recent meta-analysis [81]. Thus, the authors analyzed nine controlled trials involving 213 patients. Inclusion of only those studies utilizing high frequency (>10 Hz) TMS generated a mean ES of 0.63 (96 % CI 0.11–1.15) with the authors concluding that TMS for negative symptoms warrants further study.

Conclusion

As with TMS for positive symptoms, the preliminary data are inconsistent but promising and await more definitive studies which are adequately powered and well designed.

Cognitive Symptoms

Transcranial Magnetic Stimulation

Cognitive symptoms in schizophrenia impair function, adversely impact quality of life, and substantially contribute to overall disability. Further, antipsychotic medications are usually insufficient to control these symptoms. In this context, TMS has been

considered as a possible option. Fitzgerald et al., however, did not detect cognitive improvement after 10 sessions of daily TMS over the left temporal-parietal region [44]. A review including three studies evaluating cognition in schizophrenia treated with TMS also found no improvement in cognitive speed, Mini Mental State Exam scores, digit span, or verbal fluency [82]. A study primarily focused on treating negative symptoms (Mogg et al., described earlier) did report significant improvement in verbal learning [73]. In the Levkovitz et al. study described earlier, the application of open-label, bilateral deep TMS (20 Hz; 120 % MT) in 15 subjects also resulted in improvements in executive function (i.e., spatial working memory ($p \leq 0.001$); sustained attention ($p \leq 0.01$)) [79].

In more recent studies, Guse et al. applied TMS (10 Hz; 110 % MT) over the left posterior middle frontal gyrus daily for 15 days [83]. No improvement was noted in the verbal letter 2-back task, a measure of working memory. Further, Barr et al. randomized 27 patients on antipsychotics to 20 daily active (25 stimulation trains; 1.5 s duration; 20 Hz; 90 % MT; 30 s ITI; 1,500 pulses/session) or sham TMS sessions bilaterally over the DLPFC [84]. Compared with the sham procedure, patients receiving active TMS significantly improved on the verbal working n-back task (Cohen's $d = 0.92$).

Conclusion

Future studies need to clarify the ideal neuroanatomic targets for TMS which may produce improvement in various aspects of cognition.

Other Neuromodulation Approaches

Transcranial Direct Current Stimulation

Transcranial direct current stimulation (tDCS) produces a weak current flow through the cerebral cortex via two scalp electrodes: the anode which increases neuronal activity and the cathode which reduces activity [85]. The technique was established in the 1950s, primarily in animal studies. Since the 1960s, tDCS has been studied for its effects on mood and depressive symptoms in humans with promising results.

tDCS for Acute Psychotic Symptoms

tDCS for treatment of schizophrenia is based on the premise that excitatory stimulation delivered via the anodal electrode over the left DLPFC may improve negative symptoms. Conversely, inhibitory stimulation delivered via the cathodal electrode over the left TPC could reduce AHs. In a report of two patients, Brunelin et al. utilized

tDCS to treat refractory symptoms of schizophrenia [86]. The authors hypothesize that with tDCS, cortical excitability will be increased in the vicinity of the anodal electrode (analogous to high frequency TMS) and decreased near the cathodal electrode (analogous to low frequency TMS). Stimulations were delivered at an intensity of 2 mA for 20 min twice a day (with a 3 h break in between) for five consecutive days. A significant decrease in AHRS scores and a slight improvement in the total PANSS scores were noted (no p value reported). Further, clinical benefit was maintained over 3 months.

Brunelin et al. expanded their initial study by investigating the efficacy of tDCS in reducing the severity of AH and negative symptoms in a randomized, double-blind study ($n = 30$) [87]. Twice daily stimulations (2 mA; 20 min; 3 h break in between) were also conducted on five consecutive days. Active tDCS resulted in a significant improvement in AHRS scores versus the sham procedure ($p \leq 0.001$). Further, improvements remained significant at 1 month ($p \leq 0.001$) and 3 months ($p \leq 0.001$) posttreatment. A significant ES was observed for the PANSS negative subscale score ($d = 1.07$), while the positive and depressive subscale scores demonstrated medium ESs (i.e., $d = 0.64$ and $d = 0.61$, respectively). The treatment was well tolerated with the most common adverse events being a transient mild tingling or itching sensation at the beginning of stimulation.

tDCS for Maintenance Treatment

In terms of maintenance treatment using tDCS, there is one case report of a clozapine-refractory patient with severe AHs whose symptoms improved after 1–2 daily stimulations (1–3 mA; 30 min) over 3 years of treatment at the patient's residence with frequency determined by her day-to-day needs [88]. Improvements in cognitive, psychosocial, and occupational functioning were maintained over this period. Adequately powered maintenance studies are needed to confirm this observation.

Conclusion

While initial pilot data is promising, large, well-designed, controlled studies are needed to clarify the potential role of tDCS in treating schizophrenia.

Deep Brain Stimulation

Deep brain stimulation (DBS) involves the implantation of stimulating electrodes into brain sites such as the thalamus for essential tremor or the globus pallidus internus or the subthalamic nucleus for Parkinson's disease and intractable primary dystonia [89]. Depending on the brain target site, DBS can exert excitatory

(by facilitating neuronal activity/conduction) or inhibitory (by blocking neuronal activity/conduction) effects. To our knowledge, its only use in schizophrenia involves a case report of a woman whose comorbid OCD symptoms improved after receiving DBS, with no worsening of psychosis [90].

Conclusion

ECT is currently used to treat refractory positive and mood symptoms in schizophrenia, as well as catatonia. While large definitive studies are lacking, its usefulness for these indications has been demonstrated over many years in clinical practice. TMS may benefit both positive and negative symptoms, but presently remains investigational. Further studies with larger samples, optimized parameters, and adequate number of treatments are needed. The use of tDCS also appears promising in treating refractory symptoms, but further studies with larger samples are needed to confirm these preliminary results. Finally, there is an inadequate database to suggest a therapeutic role for DBS or other device-based approaches in treating schizophrenia.

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Chapter 9
Pharmacogenetics in the Treatment of Schizophrenia

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Introduction

Pharmacogenetics/pharmacogenomics is the science of interindividual genetic differences which contribute to variation in drug efficacy and adverse effects [1]. Understanding the role of genetic and epigenetic variation in drug response is key to achieving the goal of personalized medicine for mental disorders. As yet, there are no commonly available laboratory methods to establish diagnosis. For any psychiatric diagnosis, diverse pharmacologic and non-pharmacologic treatments are available. Further, with the emphasis on diagnosis in decline despite the 2013 publication of the American Psychiatric Association Diagnostic and Statistical Manual of Mental Disorders—5th edition, the treatment focus is shifting to specific domains of psychopathology and behaviors (e.g., delusions, negative symptoms, specific types of cognitive impairment, suicide) which often are relevant to various diagnostic categories (see Chap. 2).

Even though psychotropic drugs are usually approved by regulatory authorities (e.g., the US Food and Drug Administration) for specific diagnoses, they are often prescribed off-label based on symptoms rather than diagnosis. For example, second-generation antipsychotics (SGAs) are more widely used for indications other than schizophrenia, and only recently is their labeling being extended to some of these other indications. There is also great heterogeneity in response to psychotropic drugs. Since biological variation is largely due to individual genetic and epigenetic factors, the identification and use of genetic biomarkers offer great promise for providing an effective means to identify the most appropriate drug for a given patient.

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P.G. Janicak et al. (eds.), *Schizophrenia: Recent Advances in Diagnosis and Treatment*,
DOI 10.1007/978-1-4939-0656-7_9,

Identification of these markers for APD response utilizes candidate gene, genome wide association studies (GWAS), whole exome, and theoretically, whole genome sequencing. In addition, there is an array of databases available to validate the biological significance of putative genetic markers. These include BrainCloud (braincloud.jhmi.edu), Brainspan (www.brainspan.org), ENCODE (encodeproject.org/ENCODE/), and other bioinformatics. Reductions in the cost of such testing make it economically feasible to intensively investigate biomarkers for psychotropic drugs. Current commercial chips have as many as 5,000,000 single-nucleotide polymorphisms (SNPs) and millions of additional mutations can be imputed from these SNPs through use of linkage disequilibrium.

Presently, the genetic biomarker discovery process is best approached with a GWAS (see Chap. 5 for further discussion and other methodologic approaches). A GWAS examines many common genetic variants in a group of individuals (hundreds to thousands) seeking variants (usually SNPs) for associations with a trait, including response to a specific drug, resistance to treatment, or adverse events. These studies normally compare the DNA of those with and those without the trait of interest. A GWAS is an economically viable means to identify novel genetic associations. Follow-up studies with the SNPs identified can then be used to verify the findings from the GWAS. Candidate gene studies are also widely utilized to identify possible biomarkers but are limited by our current understanding of the biology of schizophrenia and APD mechanisms of action. The clinical data available for testing associations between genetic variation and drug response using GWAS or candidate genes must be accurate and all important covariates (e.g., ethnicity, drug dose, concomitant medications) must be taken into account. Both the discovery and replication samples must be sufficiently large to provide enough statistical power to find relevant biomarkers. Additionally, since most drug responses are the result of a cluster of pharmacodynamic and pharmacokinetic influences, polygenetic methods of analysis are critical for finding clinically useful markers [1].

In this context, we examine methodological issues in identifying gene variants of clinical utility in psychiatry, review the most clinically useful genetic biomarkers currently available, address the practical implementation of pharmacogenetics and pharmacogenomics into practice, and speculate about their future promise for psychiatry.

Genetic Biomarkers of Drug Response

The known targets for psychotropic drugs are mainly proteins (e.g., monoamine receptors such as DA D_2 receptors; transporters of neurotransmitters such as the serotonin (5-HT) transporter; or enzymes which inactivate neurotransmitters such as monoamine oxidase inhibitors). The degree of expression of a target protein is under genetic control which affects its overall level of activity and resulting physiological impact. Genetic variants also result in changes in protein function (e.g., differences in receptor activation) which also impact drug effectiveness. Likewise, pharmacogenetic information predictive of response to drugs which share

a given pharmacophore (i.e., the essential features of the drug which bind it to the protein site which produces its effect) can guide drug selection prospectively. This can increase the probability of a therapeutic response, reduce treatment failures, and decrease associated suffering.

Synaptic Vesicle (SV2C)

Synaptic vesicle 2 proteins (SV2) which include SV2A, SV2B, and SV2C are localized on the surface of synaptic vesicles in all neurons [2–4]. SV2C protein is expressed in the ventral tegmental area, nucleus accumbens, olfactory bulb, and olfactory tubercle which comprise most of the mesolimbic dopaminergic system (i.e., the region of the brain believed to be the basis for the role of DA in psychosis). SV2C is important for exocytosis in glutamatergic and GABAergic neurons [5]. SV2C may contribute to the regulation of DA release in limbic and striatal terminal regions and for glutamate and gamma amino butyric acid (GABA) release in many areas of the brain. It may also be important for cholinergic striatal interneurons which play a role in extrapyramidal side effects (EPS) and cognition [6]. SV2C knockout mice exhibit large increases in tyrosine hydroxylase mRNA production, indicating SV2C decreases tyrosine hydroxylase expression [7]. Tyrosine hydroxylase is the rate limiting enzyme in the biosynthesis of DA and norepinephrine. Thus, SV2C may modulate the availability of DA which is involved in psychosis, cognition, motor function, and hormone secretion; and norepinephrine which is involved in psychosis, mood, anxiety, and hormone secretion [6, 7].

SV2C also appears to be involved in GABA–glutamate interactions in the prefrontal cortex, preferentially co-localizing with GABA, but not glutamate vesicles [5]. Instead, glutamate vesicles show enrichment of SV2B protein levels [5]. Down-regulation of mRNAs encoding glutamic acid decarboxylase 67 and reelin decreases the co-expression of cognate proteins in prefrontal cortex GABAergic neurons in schizophrenia and bipolar disorder, perhaps through the release of reelin from GABAergic neurons [8]. Reelin can interact with integrin receptors on cortical pyramidal neurons and regulate mRNA translation [8]. Such down-regulation of cognate proteins may be associated with the hypoplasticity of the prefrontal cortex in schizophrenia and bipolar disorder.

SV2C and Schizophrenia

Analysis of data from the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) study revealed that two SNPs of SV2C were associated with inadequate response to olanzapine and quetiapine, but not to risperidone and ziprasidone [9]. Thus, patients possessing these SV2C variants experienced a worsening of their symptoms when receiving olanzapine or quetiapine [9]. Of note, these findings have not yet been replicated.

Sulfotransferase Family (SULT) 4A1

Another effort to use pharmacogenetics to guide treatment is based upon sulfotransferase 4A1 (SULT4A1), a unique member of the sulfotransferase family. Most members of this family are not located in the brain and are involved in detoxification. While, the function of SULT4A1 in the brain is unknown, a number of neurotransmitters (e.g., norepinephrine, DA, 5-HT) which are central to brain function are sulfonated by one or more other cytosolic sulfotransferases, leading to their inactivation and renal excretion [10, 11]. SULT4A1, however, is not involved in the inactivation of any known neurotransmitter or neuromodulator, differing from the other human sulfotransferases, in that it shares less than 36 % amino acid sequence homology with other known cytosolic sulfotransferases [12, 13]. Nevertheless, SULT4A1 is highly conserved between species (i.e., human, mouse, and rat isoforms sharing 97 % sequence homology), suggesting it plays an important physiological role. In both human and rodent brains, it is highly expressed in areas thought to be involved in the etiology of psychosis (e.g., cerebral cortex, cerebellum, pituitary brainstem) [14]. Although no coding variants are identified in man, there is genetic variation in the region that regulates expression which is in line with much evidence that gene expression rather than variation in gene product is relevant to functional effects of genetic variation [15]. Additional research to identify the biological function of SULT4A1 is needed.

SULT4A1 and Schizophrenia

An association between SULT4A1 and susceptibility to schizophrenia was initially established in a family-based study [16]. A SULT4A1 SNP was associated with greater impairment in working memory and executive function in schizophrenia patients [17]. Subsequently, a common haplotype, SULT4A1-1, was associated with greater improvement in total psychopathology during treatment with olanzapine in the CATIE study. SULT4A1-1 was significantly correlated with higher baseline psychopathology measured by the total Positive and Negative Symptom Scale (PANSS) score. Further, SULT4A1-1(+) patients treated with olanzapine had greater improvement in psychopathology compared with olanzapine-treated SULT4A1-1(−) and quetiapine- and risperidone-treated SULT4A1-1(+) patients [18]. Thus, SULT4A1-1(+) patients receiving olanzapine were three times more likely to exhibit a clinically significant therapeutic response than olanzapine-treated SULT4A1-1(−) subjects. Indeed, these patients had the best response to any treatment in the CATIE study. These results were corroborated in a retrospective analysis of an independent study of 160 patients with schizophrenia or bipolar disorder randomized to treatment with olanzapine or risperidone. In that trial, SULT4A1-1(+) patients had a superior response compared with olanzapine-treated SULT4A1-1(−) and risperidone-treated SULT4A1-1(+) patients [18]. SULT4A1(+) and (−) patients

did not differ in response to risperidone, similar to the results in the CATIE study. A subsequent follow-up retrospective analysis of the CATIE sample showed that SULT4A1-1(+) patients receiving olanzapine had an approximate 80 % reduction in re-hospitalization events during CATIE compared with SULT4A1-1(–) patients receiving olanzapine [19].

Prospective studies of the ability of SULT4A1-1 to guide treatment assignment in schizophrenia and bipolar patients are needed to confirm these interesting results. If verified, they might help to determine the risk–benefit ratio of prescribing olanzapine which produces significant weight gain, since it was superior in efficacy only in SULT4A1-1(+) patients.

The association of SULT4A1-1(+) with olanzapine response was strengthened by an expression quantitative trait loci (eQTL) analysis. This analysis utilized the previously cited gene expression database, BrainCloud, for a relevant disease tissue [i.e., dorsal lateral prefrontal cortex (DLPFC)]. Two SNPs, rs470089 and rs138079, in linkage disequilibrium with the SULT4A1 haplotype which predicted response to olanzapine, had a significant cis-association with gene expression of a splicing variant of SULT4A1. This suggests that the common variants associated with olanzapine response could be an eQTL for SULT4A1 (Li et al., in preparation). The BrainCloud database suggests this isoform is uniquely overexpressed at the prenatal stage, implying an important role in neurodevelopment. According to the National Center for Biotechnology Information (NCBI) AceView database, this alternative splicing variant was identified specifically in cortex, but not in subcortical regions such as the hippocampus, striatum, thalamus, and cerebellum, indicating a unique importance for cortex. This finding was confirmed by microarray data from the Sestan Lab Human Brain Atlas.

In summary, the existing data suggests that the previously identified genetic markers associated with treatment response to olanzapine are DNA sequences in the vicinity of the structural portion of the SULT4A1 gene. These sequences may be required for gene expression (cis-acting) and code for a specific alternative splicing variant.

Genetic Biomarkers of Drug Metabolism

Most drugs are subject to enzymatic processes which alter their chemical structure (i.e., metabolism), thus changing their biological activity. These changes result in metabolites with altered biological activity, usually more hydrophilic and more easily eliminated from the body. Metabolic reactions are categorized into two broad classes: *Phase I reactions* which add polar groups to the parent compound by oxidation, reduction, or hydrolysis; and *Phase II conjugation reactions* (i.e., acetylation, glucuronidation, sulfation, or methylation) via transferases, resulting in polar conjugates.

Genetic variants affect the function and expression level of individual metabolic enzymes, impacting the rate and extent of their activity. Of clinical importance, the rate of metabolism determines the duration and extent of a drug's pharmacological

activity by affecting the blood levels of the parent compound and metabolites. Dosing to achieve drug and/or metabolite levels within the therapeutic window (i.e., the range of concentrations between the lowest efficacious level and the level at which toxicity emerges) is critical to achieving a successful outcome. Since drug effects and toxicity are concentration dependent, the direction of change in efficacy or safety depends upon the nature (active or inactive; toxic) and concentration (elevated or decreased) of the parent compound and its metabolites. When capacity of a particular enzyme is decreased, resultant metabolite levels are decreased and the concentration of the parent compound is elevated compared with normal activity. Conversely, when the metabolic capacity of a particular enzyme is increased, resultant metabolite concentrations are increased and the parent compound concentrations are decreased. By including pharmacogenetic information in the decision process for drug and dose selection, the prescriber can choose doses with increased precision, resulting in concentrations within the therapeutic window and improved outcomes.

Of the currently available pharmacogenetic tests for metabolism of psychotropic drugs, the most relevant for psychiatry assesses the functional status of cytochrome P450 isozymes. Clinical guidance surrounding specific drug and dose recommendations based on genotype is published by the Royal Dutch Pharmacists Association–Pharmacogenetics Working Group and can be found at www.pharmgkb.org. In the following sections, we discuss the most clinically relevant genes which encode metabolic enzymes of the cytochrome P450 family and the antipsychotics which are metabolized by these isoenzymes.

Cytochrome P450 2D6 (CYP2D6)

CYP2D6 metabolizes a number of commonly used antipsychotic and antidepressant drugs and is primarily expressed in the liver [20, 21]. CYP2D6 metabolizes both risperidone and aripiprazole, as well as several first-generation APDs, including haloperidol and perphenazine. A number of functional variants of the gene CYP2D6 are identified and included in most commercially available pharmacogenetic tests. Patients classified as poor metabolizers (PMs) do not process these drugs well, often requiring alternate metabolic routes for biotransformation and achieving higher than expected steady-state concentrations of the parent compound. Thus, patients have a greatly elevated risk for serious adverse events [21]. Conversely, ultra metabolizers (UMs) rapidly metabolize drugs compared with the general population, leading to lower-than-expected blood concentrations of the parent drug. Concomitant use of drugs that act as CYP2D6 inhibitors or inducers can produce a metabolic state similar to either PM or UM status via drug–drug interactions. It is also important to note that the administration of multiple drugs, which use the same metabolic enzymatic pathways, can lead to lowered metabolism of some of these drugs due to competition for the isoenzyme.

Cytochrome P450 1A2

Cytochrome P450 1A2 (CYP1A2) is an isoenzyme responsible for the metabolism of a number of drugs (e.g., clozapine is metabolized to norclozapine by CYP1A2). Genetic variations which produce PMs or UMs appear to be very rare [21]. Cigarette smoking induces the expression of CYP1A2, leading to a more rapid clearance of drugs metabolized by this isoenzyme [21]. Since a large number of psychotic patients smoke, it is important to consider this when prescribing a CYP1A2-metabolized drug as lower-than-expected blood concentrations may result, especially if there is also a genetic propensity for rapid CYP1A2 metabolism.

Clozapine, olanzapine, and promazine are commonly used antipsychotics metabolized by the CYP1A2 isozyme.

Cytochrome P450 3A4/5 (CYP3A4/5)

CYP3A4 and CYP3A5 are isozymes responsible for the metabolism of a number of antipsychotic, anxiolytic, and antidepressant drugs, with both having similar activities. CYP3A4 is the predominant isoform in Caucasians and CYP3A5 the predominant isoform in African Americans.

Quetiapine and ziprasidone are commonly used antipsychotics metabolized by CYP3A4/5 isoenzymes.

Genetic Biomarkers of Antipsychotic-Related Adverse Effects

Antipsychotic-Induced Weight Gain

Weight gain and the associated metabolic syndrome are some of the most common adverse effects associated with APDs, especially clozapine, olanzapine, and quetiapine [22]. Antipsychotics target multiple neurotransmitter systems and brain regions involved in the regulation of food intake, metabolic rate, and body weight. Extensive pharmacogenetic investigations indicate an SNP in HTR2C, the gene that encodes for the 5-HT_{2C} receptor, may play an important role in antipsychotic-induced weight gain (AIWG) [23–25]. Another gene which impacts the 5-HT_{2C} receptor, MC4R, is also strongly implicated in AIWG. In studies of four independent populations, an SNP near MC4R (the gene that encodes for the melanocortin 4 receptor) was associated with AIWG with risk allele homozygotes gaining twice the weight as other patients [26–28]. In addition, MC4R regulates 5-HT_{2C} receptors, further implicating them in AIWG [28]. The strength of the associations with HTR2C and MC4R indicates that genetic testing for these variants may prove

clinically useful. For example, patients may be genotyped prior to initiation of APD treatment to see if they carry a risk allele for drug-induced weight gain. If so, antipsychotics which are less weight-inducing should be considered along with non-pharmacological interventions to prevent or attenuate weight gain (see Chaps. 10 and 12) [28].

Agranulocytosis

Clozapine is the most efficacious agent for treatment-resistant and suicidal schizophrenia or schizoaffective disorder patients [29, 30]. Despite superior efficacy, its use is limited due to potentially fatal drug-induced agranulocytosis which occurs in approximately 0.5–1 % of patients (see Chap. 12). Clozapine-induced agranulocytosis (CIA) is defined as a decrease in the absolute neutrophil count to less than 500 cells/mm^3. This neutrophil deficiency greatly increases the risk of infection and possible fatality unless the drug is stopped and treatment with growth factors and antibiotics started. If these interventions are initiated, the fatality rate is 1:10,000. Current treatment guidelines restrict clozapine use to those patients who failed two previous trials of other antipsychotic drugs (APDs) or have made a serious suicide attempt. Patients are also required to have periodic blood cell monitoring. If this is done, several studies with clozapine found this agent reduced overall mortality due to its profound effect on suicide. There is no biomarker for the ability of clozapine to reduce the risk of suicide despite attempts to identify one.

Pharmacogenetic studies indicate that CIA is associated with a variation in genes that encode for the human leukocyte antigen (HLA) [31]. In an initial study of HLA gene variants in Ashkenazi Jews, a strong association was found between a specific HLA haplotype and CIA, despite the small study population [32]. Another study analyzed the whole exome sequence of a small sample of Finnish schizophrenia patients suffering from CIA (25 cases and 27 controls) and found a nominal association between multiple coding variants in the HLA-C gene and CIA [33]. Although the study was underpowered, carriers of an allelic variation in the HLA-B/HLA-C region were approximately twofold less likely to develop CIA, indicating that HLA genes warrant further investigation [34]. In this context, a recent study of HLA genes found that a single SNP, 6672G>C, was associated with an extremely elevated risk for CIA (i.e., the odds were 16.9 times greater in patients who carried the marker as compared with those who did not) [34].

Tardive Dyskinesia

Tardive dyskinesia (TD) is a group of delayed-onset, iatrogenic movement disorders (most notably oral-bucco-lingual stereotypy) associated with APD treatment (see Chap. 12) [35]. TD is caused by inherent vulnerability and chronic DA receptor

blockade. First-generation antipsychotics (FGAs) with high DA D_2 receptor occupancy are associated with a higher risk of TD than SGAs which produce lower levels of D_2 receptor occupancy when used appropriately. TD is reported to occur in approximately 20 % of patients treated chronically with FGAs, especially older females [36]. While the use of SGAs greatly reduces the risk, even these drugs can cause TD, but at much lower rates than with the FGAs [37]. Indeed, the greatly reduced risk of TD with the SGAs is a major reason for their adoption as preferred first-line therapy. The severe morbidity and increased mortality associated with TD, however, provide a rationale for developing genetic tests to detect susceptibility.

Familial studies showing a hereditary association with TD provide compelling evidence for genetic susceptibility in its etiology [38]. Promising pharmacogenetic associations are reported for genetic variants of CYP2D6, CYP1A2, the dopamine receptor genes DRD2 and DRD3, and manganese superoxide dismutase (MnSOD) [39–41]. The DRD2 A1 allele at rsl800497 is associated with a 40 % reduction in striatal D_2 receptor density and appears to be protective against TD [42]. Meta-analyses based on overlapping sets of studies, however, strongly support increased rates of TD in carriers of the DRD2 A2 allele [43, 44]. These results indicate a 30 % increase in risk for TD per A2 allele (i.e., A2/A2 homozygotes are nearly 80 % more likely to develop TD as A1/A1 homozygotes). While genetic variants of DRD3 (the gene that encodes for the DA D_3 receptor) also showed an association with TD risk, this did not hold up to replication in all studies [42].

Oxidative stress is hypothesized as contributing to the development of TD [45]. Enzymes which scavenge free radicals (e.g., the mitochondrial enzyme MnSOD) are associated with TD. The gene encoding MnSOD possesses one polymorphism which results in its less efficient transport [44]. Pharmacogenetic studies, however, produced mixed results with one meta-analysis actually showing a protective association between this MnSOD polymorphism and TD, with the genotype associated with less efficient MnSOD exhibiting an approximate 50 % risk reduction [44].

Since many antipsychotics are metabolized by CYP2D6 and CYP1A2 and many adverse effects are concentration dependent, variants of the genes encoding for these isoenzymes which result in metabolic deficiencies may be useful in determining TD risk [42]. In this context, a meta-analysis of eight studies demonstrated that CYP2D6 PMs had a 64 % greater risk of developing TD [46]. Investigations into genetic variants of CYP1A2 related to isoenzyme induction have thus far provided inconsistent results [47].

Clinical Use of Pharmacogenetics in Psychotropic Drug Selection

Although pharmacogenetic testing is commercially available and offered by a growing number of laboratories, it has not been widely adopted in psychiatric practice. Guidance regarding the use of these tests must be enhanced before more clinicians will utilize them. The experience in implementation obtained by early adopters

needs to be carefully evaluated and reported in peer reviewed journals. This is no substitute, however, for prospective effectiveness trials in a variety of clinical settings. These studies must compare the outcome on a wide range of measures including time to discontinuation, change in psychopathology, and adverse effect burden from treatment as usual versus the choice of medication based upon genotypic data [28]. Other clinical trial methodological issues specific to schizophrenia (e.g., poor adherence) should also be considered in the design of such studies. In addition, improvements in pharmacogenetic clinical trial methodologies are needed to overcome various shortcomings such as confounding factors (e.g., race, ethnicity, and environment).

Ethnicity and Pharmacogenomics

Ethnicity and race are used to categorize groups of people with shared ancestry and inherited physical traits [48]. Ideally, pharmacogenetic biomarkers should apply across an entire population to maximize clinical utility. There is great racial and ethnic variability, however, in the incidence of pharmacogenetic biomarkers, including the expression of cytochrome P450 isoforms and their variants [21]. Self-reported race/ethnicity identification corresponds well to major genetic clusters, suggesting that self-identification of race is of considerable value in dividing populations for the development and utilization of genetic biomarkers [49]. There are errors, however, perhaps in the 5–10 % range in this regard. The introduction of race/ethnicity categorization into the study of pharmacogenetics is not without confounding limitations. For example, in addition to recognized group physical characteristics, ethnicity and race often include shared behavioral, dietary, cultural, linguistic, or religious characteristics [48]. Thus, ethnicity and race encompass both genetic and environment influences. Since an individual's biological status is the result of these complicated and intertwined influences, the exact contribution of each to one's biological status is complex and difficult to determine. Thus, these complex interactions confound many studies which try to identify the specific connections between pharmacogenetics and race/ethnicity.

The limitations of race/ethnicity categorizations are illustrated in the findings of a study by Wilson et al. which investigated the interactions of genetic variation, drug response, and race [50]. In this study, pharmacogenetic associations were investigated by assigning people to different groups depending on shared genetic regions and comparing to self-reported race/ethnicity. They found that microsatellite analysis-based genetic groupings were more informative regarding differences in CYP2D6 drug metabolism than the groupings based on self-reported race/ethnicity [50]. Whether such genetic grouping categorization techniques could generally improve the results of pharmacogenetic studies is unknown. There are significant obstacles to including such techniques, as they increase the complexity and cost of conducting such studies. While racial and ethnic categorization in pharmacogenetic studies facilitates the discovery of associations to drug response, it also limits the applicability of these findings as they are race/ethnicity dependent.

Conclusion

The treatment of patients with schizophrenia will surely benefit from advances in pharmacogenetics and pharmacogenomics. The large variation in clinical presentation and response to APDs seen in patients with schizophrenia engenders an opportunity for these approaches to meaningfully improve therapeutic outcomes. Current use of genetic testing is limited but seems likely to grow as prescribers become more familiar with the benefits of incorporating drug metabolism information into their choices of drugs and dosages. As with many new technologies, there are barriers which slow adoption (e.g., lack of familiarity among physicians; lack of prospective outcome studies to confirm utility; uncertainty on how to interpret results). The convergence of many factors (e.g., more accurate and faster genotyping technologies; reductions in cost of testing; and confirmation of the clinical utility of pharmacogenetic biomarkers) will help to facilitate more extensive clinical implementation.

Disclosures **Bill W. Massey** is Chief Scientific Officer for MyGenesRx and a Shareholder at SureGene and MyGenesRx. He is a previous consultant for Neurotherapeutics and Mallinckrodt. **Herbert Y. Meltzer** reports the following financial relationships: (1) ownership/investment interests in Suregene, ACADIA, and GlaxoSmithKline; (2) industry activities (such as speaking, advising, consulting, and providing educational programs) with Janssen Pharmaceuticals, Lundbeck Inc., Sunovion Pharmaceuticals Inc. (Dainippon Sumitomo Pharma Co., Ltd.), TEVA, BiolineRx, BI (Boehringer Ingelheim Pharma GmbH & Co. KG), Envivo, and Companion Diagnostics; (3) expert testimony with Janssen; and (4) current grants: Sunovion Novartis, Dainippon Sumitomo, Envivo, NeuroTherapeutics Pharma, Inc., Otsuka, Takeda, Alkermes, Naurex, Inc., and Astellas Research Institute of America.

Jiang Li has no disclosures.

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Chapter 10
Management of Comorbid Medical Conditions in Schizophrenia

Jeffrey T. Rado

Scope of the Problem

Patients with schizophrenia are at greater risk than the general population for developing a variety of diseases, including asthma, chronic obstructive pulmonary disease (COPD), diabetes, hepatitis C, and congestive heart failure [1]. For example, a 2-year, prospective study of 602 patients with schizophrenia in the UK found increased rates of angina and respiratory symptoms [2]. A study of Swedish patients with schizophrenia ($n = 8{,}277$, drawn from a database of more than six million adults) followed for 7 years found increased rates of COPD (women: hazard ratio = 2.16, CI = 1.80–2.34; men: hazard ratio = 1.53, CI 1.32–1.76) and diabetes (women: hazard ratio = 2.15, CI = 1.96–2.36; men: hazard ratio = 1.68, CI = 1.54–1.83) [3]. A third study of nearly 7,000 Taiwanese patients with schizophrenia found elevated rates of COPD, diabetes, and stroke [4].

Mortality

Numerous epidemiological studies document an increased mortality rate in patients with schizophrenia. One of the earliest and longest of these studies assessed 510 patients admitted to the University of Iowa Psychiatric Hospital between 1934 and 1944 and then followed them for 40 years [5]. The standardized mortality ratio (SMR, ratio of observed to expected deaths) in the third and fourth decades of follow-up was 4.21 for males and 7.89 for females, indicating a mortality rate 4 to nearly 8 times higher than the general population. Another prospective cohort study

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P.G. Janicak et al. (eds.), *Schizophrenia: Recent Advances in Diagnosis and Treatment*,
DOI 10.1007/978-1-4939-0656-7_10,

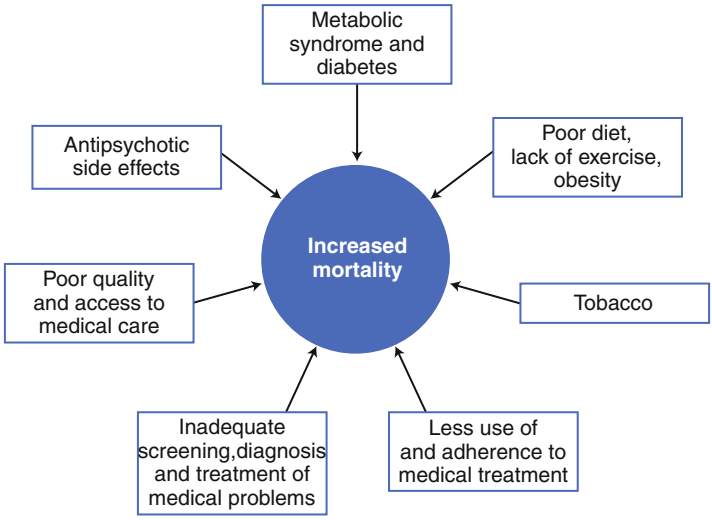

Fig. 10.1 Factors contributing to increased mortality in schizophrenia

included 370 patients followed for 13 years in England [6]. The SMR for all causes was 2.98 (CI = 2.36–2.72) and also elevated for specific disease states including circulatory (2.49, CI = 1.64–3.63), respiratory (3.17, CI = 1.16–6.90), and endocrine (11.66, CI = 3.79–27.21). Enger et al. conducted a retrospective cohort review of 1,920 antipsychotic-treated patients in a health plan general membership database compared with 9,600 patients without schizophrenia [7]. The mortality rate in these patients was four times the general population and the rate of new-onset diabetes was more than two times higher (Fig. 10.1).

More recent cohort studies draw similar conclusions. Ran et al. conducted a 10-year follow-up of 510 patients drawn from a larger population of 123,572 rural Chinese [8]. The calculated all-cause SMR for the entire cohort was 4.0 (CI = 2.4–5.8). For men it was 4.9 (CI = 2.8–8.1) and for women it was 3.3 (CI = 1.9–6.1). Fors et al. followed 255 Swedes with schizophrenia over a 10-year period and compared them to 1,275 age- and sex-matched patients from a national population registry [9]. The mortality rate (i.e., 23.0 %) was double that of the comparator group (i.e., 11.2 %) with the largest portion of excess mortality attributable to cardiovascular disease. A large Swedish cohort study found elevated all-cause mortality in both women (adjusted hazard ratio = 2.75; CI = 2.52–3.00) and men (adjusted hazard ratio = 2.44; CI = 2.25–2.64) with the leading causes of death being coronary artery disease (CAD) and cancer [3].

A meta-analysis of 18 studies involving more than 66,000 schizophrenia patients followed for 2–30 years found an aggregate SMR of 1.51 (1.48–1.54) [10]. A second meta-analysis of 20 schizophrenia studies found an SMR of 2.2 for all-cause mortality [11].

Reduced Life Expectancy

As a result of this increased mortality, patients with schizophrenia have a 20 % shortened life expectancy compared with those without the disease (i.e., from 76 to 61 years) [12]. The majority of this excess mortality is attributed to CAD, with suicide accounting for approximately 10–15 %. More premature deaths are attributable to heart disease than any other cause. This is due, in part, to an overabundance of poorly controlled cardiac risk factors such as hyperlipidemia, metabolic syndrome, and obesity.

Medical Care of Patients with Schizophrenia

Before reviewing the specific medical conditions prevalent in this population, it is important to examine their quality of and access to medical care, since several epidemiological studies attribute the elevated mortality rates to these issues. In a 9-year prospective study of 253 institutionalized patients (80 % schizophrenia) in Finland, the elevated all-cause mortality risk (SMR = 1.9 for males; 3.2 for females) was attributed partially to suboptimal care of physical illnesses [13]. A prospective analysis of 73 Irish patients with schizophrenia followed for 7.5 years found a twofold elevated mortality risk with the authors postulating that disengagement from health services is an important contributing factor [14].

Access to Care

Access to health care is the focus of several studies in schizophrenia. Utilizing data from the National Health Interview Survey (NHIS), Bradford et al. compared individuals with psychotic disorders, bipolar disorder, or major depression to persons without mental disorders [15]. Those with psychotic disorders were less likely to have a primary care physician and reported greater difficulties accessing care. Retrospective analysis of medical services obtained by 175,653 patients in the Veterans Administration system found that those with diabetes or hypertension and comorbid schizophrenia, bipolar disorder, or anxiety had substantially fewer medical visits than those without these disorders [16]. In another study, 60 % of veterans with serious mental illness (including schizophrenia) perceived barriers to accessing medical care [17]. Among these barriers were the lack of recognition of health complaints by providers, reluctance of non-psychiatrists to provide comprehensive care to psychiatric patients, screening procedures not provided to these patients, and lack of continuity of care due to unstable domiciles common in this population [18]. Even when patients were screened for common ailments such as hypertension or hyperlipidemia, psychiatric providers struggled to obtain referrals for appropriate care or were unable to provide general medical care on site [19].

Underdiagnosis

Even when care is accessible, underdiagnosis of common conditions may occur. Briskman et al. evaluated blood pressure, lipid levels, and fasting blood sugar in 200 hospitalized psychiatric patients (primarily schizophrenia) compared with a nonpsychiatric group [20]. Diabetes, hypertension, and dyslipidemia were all underdiagnosed in the psychiatric patients. In a 7-year cohort study carried out in more than 6,000 Swedes with schizophrenia, the authors reported elevated mortality due to cancer and ischemic heart disease compared with the general population [3]. Despite having twice as many contacts with the health care system, these patients were less likely than those without schizophrenia to have had their cancer (73.9 % versus 83.3 %) or heart disease (26.3 % versus 43.7 %) previously diagnosed.

Undertreatment

The Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) Study ($n=1{,}460$) attempted to mimic naturalistic antipsychotic treatment patterns in schizophrenia. Baseline point prevalence of diabetes, hypertension, and hyperlipidemia was measured with rates of non-treatment being 30.2 %, 62.4 %, and 88 %, respectively [30]. Of note, these patients were engaged in regular, ongoing psychiatric care. Vahia et al. conducted a cross-sectional study of 198 community-dwelling patients (age 55 or older) [22]. Compared with nonpsychiatric patients, those with schizophrenia were less likely to receive treatment for their hypertension (75 % versus 93 %), heart disease (28 % versus 75 %), or gastric ulcers (53 % versus 100 %) and were more likely to have their diabetes treated (86 % versus 81 %). A retrospective analysis of 113,653 patients (age 65 or older) from a national database examined those hospitalized for acute myocardial infarction [19]. Patients with a comorbid mental disorder ($n=5{,}365$; 41 % schizophrenia) were significantly less likely to undergo percutaneous transluminal angioplasty (11.8 % versus 16.8 %, $p<0.001$) or coronary artery bypass graft (CABG) surgery (8.3 % versus 12.6 %, $p<0.001$). A comparative meta-analysis involving 22 studies (10 in patients with schizophrenia), including a total of 825,754 patients, examined inequalities in coronary procedures for patients diagnosed with a psychiatric disorder [23]. Those with schizophrenia were less likely to receive invasive coronary interventions (relative risk (RR) of CABG = 0.69, CI = 0.55–0.85; RR of cardiac catheterization = 0.50, CI = 0.34–0.75). Not all studies, however, find disparities in care. For example, Whyte et al. reviewed the electronic charts of 481 UK general medicine practices and did not find differences in quality of diabetes care for those with schizophrenia [24].

Screening

Recommended screening may also occur at lower rates. Data from a free psychiatric clinic in San Diego followed 47 patients (age 45 or older) for 1 year [25]. Compared with age- and gender-matched patients from the same clinic, those with schizophrenia had fewer medical visits and were less likely to receive a detailed physical exam, lipid screening, or colon cancer screening. In another study, Martens et al. utilized the Population Health Research Data Repository in Manitoba, Canada, to determine factors associated with obtaining the papanicolaou (PAP) smear, a standard screening procedure for early detection of cervical cancer [26]. Compared with nonpsychiatric patients, women with schizophrenia were less likely to be screened with a PAP smear (58.8 % versus 67.8 %, $p<0.001$).

Medical Adverse Events

Acute medical and surgical hospitalizations among 1,746 patients with schizophrenia were compared to 732,158 non-schizophrenia patients in a Maryland database [27]. Diagnosis of schizophrenia was associated with increased risk of postoperative respiratory failure (OR 2.08, CI = 1.41–3.06), postoperative deep venous thrombosis (OR = 1.96, CI = 1.18–3.26), postoperative sepsis (OR 2.29, CI = 1.49–3.51), and an increased risk of ICU admission and death. Outcomes data from the Taiwanese National Health Insurance Research Database (NHIRD) described postoperative outcomes in 8,967 patients with schizophrenia [4]. Compared with the general population, patients had higher 30-day postoperative complications, including stroke (2.6 % versus 1.6 %, $p<0.0001$), bleeding (1.6 % versus 1.2 %, $p<0.002$), pneumonia (1.3 % versus 0.4 %, $p<0.0005$), sepsis (0.8 % versus 0.3 %, $p<0.0001$), and acute renal failure (0.3 % versus 0.1 %, $p<0.0005$). Overall, the postoperative complication rate was higher (6.2 % versus 3.9 %, $p<0.0001$) and perhaps most concerning, there was a greater risk of dying 30 days after surgery (i.e., 1.1 %) versus those without schizophrenia (i.e., 0.4 %, $p<0.0001$).

In summary, the quality of care that patients with schizophrenia receive is often subpar. Specifically, access to medical care is limited, rates of screening for common medical conditions are low, and patients are too often underdiagnosed. Even when a diagnosis is made, these patients frequently do not receive appropriate treatment. Finally, patients with schizophrenia experience higher rates of medical adverse events compared to the general population.

Coronary Artery Disease and Its Risk Factors

As noted earlier, numerous studies report a higher mortality rate in patients with schizophrenia, much of which is attributed to cardiovascular disease. Not surprisingly, patients experience cardiac risk factors, such as hypertension and hyperlipidemia, at higher rates than the general population.

Hypertension

Hypertension (HTN) is classified by the World Health Organization (WHO) as one of the most important global mortality risk factors [28]. Kilbourne et al. found that hypertension in patients with schizophrenia conferred a nearly 40 % increase in mortality (hazard ratio = 1.38 (1.32–1.46)) [29]. A high prevalence (i.e., 33 %) of hypertension was found in the CATIE Study, while the Comparison of Atypicals in First Episode of Psychosis (CAFÉ) Study found up to 25 % of patients at baseline had mild hypertension (systolic BP > 130) [30, 31]. After 1 year of treatment with olanzapine, risperidone, or quetiapine, rates of mild hypertension further increased to 41 %. De Hert also found similar elevated rates of hypertension (i.e., 25.9 %) in a retrospective chart review of patients with schizophrenia which increased after 3 years of antipsychotic drug treatment (i.e., 41.7 %) [32]. Not all studies, however, find increased rates of hypertension. A chart review of 125 patients with schizophrenia did not find elevated rates of hypertension compared with 1,721 age-matched, nonpsychiatric primary care patients [33]. Further, 6 months of treatment with antipsychotics was not associated with an increased prevalence in 130 outpatients with schizophrenia or schizoaffective disorder [34]. For additional discussion of this issue, see Chap. 12.

Treatment of hypertension is based on the 2014 Evidence-Based Guideline for the Management of High Blood Pressure in Adults [35]. For persons age ≥60 years, the goal blood pressure is <150/90 mmHg. The goal for those under age 60 is <140/90 mmHg. Thiazide-type diuretics, angiotensin converting enzyme (ACE) inhibitors, angiotension receptor blockers (ARBs) or calcium channel blockers alone or in combination are among the recommended initial treatment options for nonblack individuals. Thiazide-type diuretics or calcium channel blockers alone or in combination are the initial recommended treatment for blacks.

In summary, hypertension is common in schizophrenia. Lifestyle changes and the addition of antihypertensive medications, if needed, are the standard treatment approach.

Hyperlipidemia

The WHO reported that hyperlipidemia accounts for 4.5 % of global deaths. Rates of hyperlipidemia are higher in schizophrenia with elevated triglycerides occurring in 47.3 % of CATIE participants [30]. A large population-based study of 766,427 Taiwanese found that individuals with schizophrenia had a small but significant increase in hyperlipidemia prevalence (i.e., 8.15 % versus 8.10 % in the general population) [36]. Worse lipid profiles were noted in patients with acute phase schizophrenia, while community-dwelling clozapine-treated patients had hyperlipidemia rates of 2–4.6 % [37, 38]. The CAFÉ Study found rates of hyperlipidemia between 22 and 28 % at baseline [31]. Insurance claims data from 1,631 schizophrenia patients was

Table 10.1 2013 ACC/AHA Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults

Groups who are will benefit from statin therapy:
1. Individuals with known clinical atherosclerotic cardiovascular disease (ASCVD).
2. Individuals with primary elevations of LDL-C³190 mg/dL.
3. Individuals 40–75 years of age with diabetes with LDL-C 70–189 mg/dL.
4. Individuals without clinical atherosclerotic cardiovascular disease or diabetes who are 40–75 years of age with LDL-C 70–189 mg/dL and an estimated 10-year ASCVD risk of 7.5 % or higher (risk calculator: http://tools.cardiosource.org/ASCVD-Risk-Estimator/).

Source: [147]

reviewed and a slight but significant increase was found in hyperlipidemia with second-generation antipsychotics (SGAs) (HR = 1.41, CI = 1.09–1.83) but not with first-generation antipsychotics (FGAs) [39]. Of note, some studies in this population have not found baseline-elevated cholesterol levels [40].

The 2013 ACC/AHA Guidelines on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adult established revised guidelines for the management of hyperlipidemia. Treatment involves a combination of low-fat diet counseling (e.g., reducing intake of fried foods, red meat, and other animal fat) and/or statin medications. Statins (e.g., atorvastatin, simvastatin) inhibit HMG CoA reductase, the main enzyme that produces cholesterol in the liver. The most common adverse effect is myalgia, which can be managed by lowering the statin dose or changing to a lower risk agent such as pravastatin. Four groups of patients have been identified who are recommended to be treated with statin therapy (see Table 10.1). In contrast to prior guidelines, statin therapy is no longer tied to a specific low-density lipoprotein (LDL) goal.

In summary, patients with schizophrenia are at greater risk of hyperlipidemia. Treatment usually involves a combination of lifestyle changes and statin medications.

Diabetes Mellitus

Diabetes is such a strong risk factor for CAD that it is considered a "coronary artery disease equivalent." Diabetes is diagnosed by one of the following:

- *Hemoglobin* $A_{1C} \geq 6.5$ %.
- *Fasting plasma glucose* ≥ 126 mg/dL.
- Two-hour plasma glucose ≥ 200 mg/dL during an *oral glucose tolerance test*.
- *Random plasma glucose* ≥ 200 mg/dL in a patient with symptoms of hyperglycemia.

In addition to physical activity, initial treatment recommendations include weight loss with either low-carbohydrate, low-fat, calorie-restricted or Mediterranean diets. Metformin is the preferred initial pharmacologic agent.

Schizophrenia is associated with high rates of impaired glucose tolerance and diabetes. Even first-episode, drug-naïve patients exhibit impaired fasting glucose tolerance and increased insulin resistance [41]. This finding, however, is not entirely consistent [42]. Bresee et al. studied a population-based cohort of 28,755 patients with schizophrenia using an administrative database in Alberta, Canada [43]. Compared with non-affected controls, diabetes (age 30–39; 3.8 % versus 1.4 %) and CAD occurred at higher rates (i.e., 27 % versus 17 %) in patients with schizophrenia. A retrospective cohort study in a Saskatchewan health database compared 3,022 subjects with schizophrenia with an age- and sex-matched control group without psychiatric illness. Rates of diabetes were more than doubled (OR = 2.1, CI = 1.8–2.4) in those with schizophrenia [44].

Lifestyle Factors

Obesity is a major risk factor for diabetes and rates are higher in schizophrenia [45]. The reason for this is multifactorial. Obesity is associated with low socioeconomic status and low education, both of which are more prevalent among the seriously mentally ill [46]. Further, negative symptoms and cognitive impairment are associated with low motivation, suboptimal self-care, and poor dietary habits, all of which impact body mass index (BMI) and increase the risk for metabolic derangements. Sedation from antipsychotics or other psychotropics may also decrease motivation to exercise. Most clinicians who work with these patients are familiar with their unhealthy eating habits. Thus, those with schizophrenia are less likely to be physically active and do not eat adequate amounts of fruits and vegetables [47]. In their study of the dietary intake of 88 chronic, mentally ill patients in an urban mental health clinic, however, Henderson et al. found diets lower in calories, fat, carbohydrates, and sodium, suggesting that poor dietary habits are not universal [48].

In summary, unhealthy lifestyle is common in schizophrenia and negatively impacts cardiometabolic risk.

Metabolic Syndrome

The presence of metabolic syndrome greatly increases the risk for developing diabetes and CAD. According to the National Cholesterol Education Program Adult Treatment Panel III Guidelines, the diagnosis of metabolic syndrome requires three of the five criteria:

- *Waist circumference* ≥ 40 in. (men) or ≥35 in. (women).
- *Fasting triglycerides* ≥ 150 mg/dL.
- *High density lipoprotein* (HDL) ≤ 40 mg/dL (men) or ≤50 mg/dL (women).
- *Blood pressure* ≥ 135/85 mmHg.
- *Fasting blood glucose* ≥ 110 mg/dL.

Studies in schizophrenia report higher rates of metabolic syndrome, which significantly increases the risk of CAD, myocardial infarction, and stroke [48, 49].

Antipsychotic-Induced Weight Gain

A meta-analysis of 80 randomized controlled trials involving SGAs found that after 10 weeks of treatment, patients taking clozapine gained an average of 4.5 kg, olanzapine 4.2 kg, risperidone 2.1 kg, haloperidol 1.0 kg, and fluphenazine 0.4 kg [50]. A more recent meta-analysis of 21 placebo-controlled trials examined short-term (<12 weeks; $n = 1{,}742$) and long-term (1 year; $n = 1{,}649$) outcomes in subjects receiving amisulpride, haloperidol, olanzapine, risperidone, and ziprasidone [51]. With short-term treatment (i.e., 4–12 weeks), significant weight gain was associated with risperidone (17 %) and olanzapine (48 %; both $p < 0.05$ versus placebo) but not with haloperidol (12 %) or ziprasidone (9 %, both NS). Studies of 1-year treatment duration demonstrated clinically significant weight gain (defined as >7 % change from baseline) in those taking risperidone (39 %) and olanzapine (57 %, both $p < 0.05$ versus placebo) but not ziprasidone (17 %, NS). The CATIE Study demonstrated weight gain of ≥7 % from baseline in 30 % of those on olanzapine, 16 % on quetiapine, 14 % on risperidone, 12 % on perphenazine, and 7 % on ziprasidone [52]. Similar risk differentials appear to exist for hyperlipidemia, diabetes, and CAD. While many studies indicate that SGAs pose a higher risk compared with FGAs, the accuracy of this finding is debated in the scientific literature [53].

In summary, antipsychotics are associated with varying degrees of weight gain. For additional discussion of this issue, see Chap. 12.

Stroke

Higher rates of hypertension, hyperlipidemia, and diabetes lead to a higher risk for stroke. Tsai et al. examined 80,569 Taiwanese patients with schizophrenia over a 4-year period using a national health database [54]. Compared with 241,707 age- and sex-matched controls, stroke incidence (1.71 %) was higher than in the comparison population (1.22 %; no p value reported). After controlling for demographic variables and comorbid conditions, this still resulted in a small but significant increased risk (adjusted hazard ratio = 1.13, CI = 1.05–1.22). Similarly, a retrospective cohort study of 3,022 schizophrenia patients in Canada revealed adjusted relative risk for stroke of 1.5 (CI = 1.2–2.0). While older age is a strong risk factor, younger age groups were also studied. A database review of 5,001 Taiwanese patients under 45 years of age hospitalized for schizophrenia found a stroke incidence of 2.46 % versus 0.96 % in the comparison group [55]. By contrast, Kang et al. found a reduced mortality rate (hazard ratio = 0.35, CI = 0.21–0.57) in schizophrenia patients hospitalized for stroke compared with non-schizophrenia patients, even when adjusting for age, sex, stroke type, and comorbidity [56].

Management of Cardiometabolic Disorders

There are three main approaches to address the outsize burden of cardiometabolic disease in these patients. The first two are preventive in nature and involve improved screening for common medical illnesses and increased utilization of strategies for risk factor modification. The third, discussed later in the chapter, is to improve the access to and quality of medical care.

Screening

The American Psychiatric Association and the American Diabetes Association issued joint guidelines for regular, systematic screening and monitoring of weight, cholesterol, blood sugar, blood pressure, and waist circumference for patients treated with antipsychotics; adherence to these guidelines, however, is suboptimal [57, 58]. These guidelines include monitoring for:

- Personal and family at the start of treatment and then yearly.
- Weight (BMI) at the start of treatment, monthly for 3 months, and then every 3 months.
- Waist circumference at the start of treatment and then yearly.
- Blood pressure at the start of treatment, at 3 months, and then yearly.
- Fasting blood glucose at the start of treatment, at 3 months, and then yearly.
- Fasting lipids at the start of treatment, at 3 months, and then every 5 years [57].

Psychiatric providers who prescribe these medications are typically the ones most in contact with the patient and need to be more cognizant of these guidelines. In this context, the advent of electronic medical records and the potential for computer-based reminders may help.

The authors also highlighted the obesity and metabolic risk differential among the various SGAs. Clozapine and olanzapine were considered highest risk, risperidone and quetiapine middle risk, and aripiprazole and ziprasidone lowest risk. A recent meta-analysis included 56 (mostly short-term) trials of the newer SGAs (i.e., asenapine $n=9$; iloperidone $n=11$; lurasidone $n=8$; paliperidone $n=28$) in schizophrenia ($n=19{,}299$) and bipolar disorder ($n=2{,}392$) [59]. The overall risk of weight gain was low. Among these agents, the greatest risk of clinically meaningful weight gain was associated with asenapine (RR = 4.09, CI 2.25–7.43) followed by iloperidone (RR = 3.13, CI 2.08–4.70) and paliperidone (RR = 2.17, CI 1.64–2.86). Subjects on lurasidone did not demonstrate statistically significant weight gain (RR = 1.42, CI 0.87–2.29).

In summary, mental health providers must be more proactive in following national guidelines for monitoring of metabolic parameters.

Risk Factor Modification

Approaches to reduce cardiometabolic burden include switching to a lower risk antipsychotic, adjunctive use of metformin or topiramate, and behavioral or nutritional counseling.

Several studies examined the benefit of switching antipsychotics, usually from a higher risk agent such as olanzapine to lower risk agents such as ziprasidone or aripiprazole. In one study, patients taking FGAs ($n=108$), olanzapine ($n=104$), or risperidone ($n=58$) were switched to ziprasidone (titrated up to 160 mg daily) for 6 weeks [60]. Mean weight decreased from 93.4 to 91.6 kg ($p<0.001$) for those originally on olanzapine. Weight loss was also noted in those switched from risperidone (i.e., 87.3–86.5 kg; $p<0.05$) but not from FGAs. In another study, patients with schizophrenia or schizoaffective disorder ($n=84$) experiencing glucose intolerance, dyslipidemia, type 2 diabetes, or weight gain with their current antipsychotic were switched to ziprasidone (mean dose = 120 mg) [61]. Mean weight decreased by 5.1 kg after 6 months ($p<0.0001$). Reductions were also seen in serum glucose, cholesterol, and triglyceride levels ($p<0.0001$).

Weight reduction also occurred when switching patients to aripiprazole. Two large, multicenter trials reported reductions in weight and other metabolic parameters. In one study ($n=173$), switching from the current antipsychotic to aripiprazole resulted in a mean weight reduction of 1.3–1.7 kg depending on the switch strategy (significance not reported) [62]. A second study enrolled 173 olanzapine-treated subjects with schizophrenia or schizoaffective disorder randomized to continue olanzapine monotherapy or switch to aripiprazole monotherapy [63]. Over 16 weeks, the aripiprazole group lost 1.8 kg versus a gain of 1.4 kg in the olanzapine group ($p<0.001$).

In summary, these studies indicate that it is important whenever possible to consider switching patients to antipsychotics with a lower cardiometabolic risk profile.

Pharmacologic Approaches

Metformin

Metformin is a first-line treatment for diabetes mellitus. It is associated with weight loss, as well as lower blood glucose and hemoglobin A_{1C} levels. It was studied for both prevention and reversal of antipsychotic-induced metabolic derangements.

The best evidence for metformin to treat *antipsychotic-induced weight gain* (*AIWG*) comes from three Chinese studies. The first involved patients with schizophrenia ($n=128$) who had gained ≥ 10 % of their baseline weight within 1 year of beginning an antipsychotic. Patients were randomized to placebo, metformin

(750 mg daily), metformin (750 mg daily) plus lifestyle intervention, or lifestyle intervention alone for 12 weeks [64]. Lifestyle intervention consisted of psychoeducation (e.g., roles of eating and activity in weight management, behavioral techniques); the American Heart Association Step 2 diet; and exercise sessions led by a physiologist. The lifestyle plus metformin group was superior to the metformin alone and lifestyle plus placebo for decreases in weight (4.7 kg (CI = 3.4–5.7) versus 3.2 kg (CI = 2.5–3.9) and 1.4 kg (CI = 0.7–2.0), respectively; $p < 0.05$) and BMI (1.8 (CI = 1.3–2.3) versus 1.2 (CI = 0.9–1.5) and 0.5 (CI = 0.3–0.8), respectively; $p < 0.05$). Similar trends were found for the insulin resistance index (a measure of glucose intolerance). All treatment groups had better outcomes in the above measures compared with placebo. A second Chinese study involved 84 first-episode women with schizophrenia randomized to 6 months of metformin (1,000 mg daily) or placebo in addition to their antipsychotic [65]. The metformin group experienced a mean weight loss of 2.3 kg while the placebo-treated patients gained a mean of 2.1 kg ($p < 0.01$). Finally, 72 first-episode patients who had gained >7 % of their baseline weight on an antipsychotic were randomized to metformin (1,000 mg daily) or placebo for 12 weeks [66]. Metformin led to a mean 3.3 kg weight loss while the placebo group gained a mean of 2.5 kg ($p < 0.001$). The insulin resistance index was also significantly decreased in the metformin group ($p < 0.001$). Of note, all patients in these studies had a normal baseline BMI (<25) which may not be representative of typical patients in the United States who tend to be overweight (BMI > 25) or obese (BMI > 30.0). A meta-analysis of metformin for AIWG included seven randomized, placebo-controlled studies ($n = 398$) [67]. Metformin was associated with a significant body weight reduction in adults (4.8 %, CI = 1.6–8.0). The most common adverse effects associated with metformin included gastrointestinal upset and diarrhea.

The best evidence supporting metformin for the *prevention* of antipsychotic-associated weight gain was conducted by Wu et al. [68]. Forty, never-medicated, first-episode patients were randomized to 12 weeks of olanzapine (15 mg daily) plus metformin (750 mg daily) or olanzapine (15 mg daily) plus placebo. The active treatment group gained 1.90 (±2.72) kg, compared with 6.87 (±4.23) kg in the placebo group ($p < 0.02$). Although this is an off-label use, metformin should be considered in any patient requiring an antipsychotic with a higher metabolic risk profile (e.g., olanzapine).

Topiramate

Topiramate is an antiepileptic associated with weight loss. Following several promising open-label studies, Narula et al. randomized 72 drug-naïve patients initiating treatment with olanzapine to also receive topiramate (100 mg daily) or placebo for 12 weeks [69]. Patients on topiramate lost an average of 1.27 (±2.28) kg versus a 6.03 (±3.16) kg weight gain with placebo ($p < 0.001$). A second study randomized 43 female patients (diagnosis not reported) who had gained weight on olanzapine to

also receive topiramate (250 mg daily) or placebo for 10 weeks [70]. Weight loss was more significant in the topiramate group, though specific changes in weight were only reported in graph form. An 18-month, open-label extension of this study continued in the same 43 subjects [71]. Patients in the former placebo group received no adjunctive medication, while the former topiramate group continued on open-label medication. Mean weight in the active treatment group decreased from 82.8 (±11.3) kg to 77.2 (±3.9) kg, while the placebo group increased from 86.2 (±10) kg to 90.6 (±8.8) kg. Finally, a 12-week placebo-controlled trial randomized 66 hospitalized patients with first-episode schizophrenia to topiramate (100 mg or 200 mg daily) or placebo for 12 weeks [72]. A significant decrease in body weight (−5.35 kg) occurred in the 200 mg group compared with the 100 mg group (−1.68 kg) or placebo (−0.4 kg) ($p < 0.01$).

In summary, although not FDA-approved, the best evidence for adjunctive pharmacotherapy to attenuate AIWG supports metformin. Topiramate may be a reasonable alternate choice.

Nonpharmacological Approaches

Nonpharmacologic interventions are also useful for weight loss and cardiometabolic risk reduction. These interventions involve cognitive behavioral therapy (CBT), nutritional counseling, and nutritional counseling combined with exercise interventions conducted in both individual and group formats. A meta-analysis of 10 randomized controlled studies of non-pharmacological interventions for AIWG included a total of 482 patients, 75 % with a schizophrenia spectrum diagnosis [73]. Six of the 10 studies targeted weight loss and four targeted prevention of weight gain. The length of the studies ranged from 8 weeks to 6 months with a 2- to 3-month follow-up. All but one study involved outpatients. The authors found a statistically significant reduction in mean body weight for those in the active treatment group versus a treatment as usual (TAU) condition (weighted mean difference = −2.5 kg; CI = −3.20 to −1.90).

Caemmerer et al. conducted a more recent meta-analysis, adding an additional six, nonrandomized studies to examine the effect of nonpharmacologic interventions for antipsychotic-induced metabolic abnormalities [74]. Their analysis included 810 patients with schizophrenia, schizoaffective disorder, schizophreniform disorder, unipolar depression, or bipolar disorder (42 % unknown). Compared with the control conditions, CBT and nutritional and/or exercise interventions resulted in significantly less weight gain over 12 months (weighted mean difference = −3.48 kg, CI = −6.37 to −0.58). In addition, there were significant reductions in percent body fat, insulin levels, glucose, total cholesterol, LDL-cholesterol, and triglycerides.

In summary, evidence supports nonpharmacologic intervention for AIWG. Implementation of these interventions in real world settings, however, is limited by lack of access to services, the relative paucity of appropriately trained providers, and lack of reimbursement for such services. Nonetheless, clinicians should counsel their patients on healthy diet and exercise.

Infectious Diseases

The rates of human immunodeficiency virus (HIV) and hepatitis B and C are higher in schizophrenia than the general population. For example, Rosenberg et al. studied 931 inpatients and outpatients with severe mental illness (50 % schizophrenia, 20 % schizoaffective disorder, 17 % bipolar disorder) [75]. They found an HIV infection rate of 3.1 % which was eight times higher than the general population rate at that time. Further, there was a 23.4 % hepatitis B infection rate and a 19.6 % hepatitis C infection rate, both 5–11 times above general population rates. Studies confirm that the increased prevalence of high risk behaviors (e.g., intravenous drug use; unprotected sexual intercourse) in the mentally ill leads to higher infection rates [76]. A more recent review of 595 Belgian patients with schizophrenia, however, did not find a higher prevalence of hepatitis C compared with the general population, though HIV rates were elevated (i.e., 0.5 % or double the rate in the general population) [77].

Human Immunodeficiency Virus

HIV is a retrovirus that causes acquired immunodeficiency syndrome (AIDS). This syndrome is characterized by a weakening of the immune system leading to life-threatening opportunistic infections and cancers. A cross-sectional study of Medicaid recipients in Philadelphia found an HIV prevalence of 1.8 % among those with a schizophrenia spectrum disorder compared with 0.6 % in those without a psychiatric illness ($p<0.001$) [78]. A retrospective study from a national VA-based registry of HIV patients ($n=9{,}003$) found that having a chronic mental illness such as schizophrenia or bipolar disorder increased HIV-related all-cause mortality [79]. HIV infection is treated with highly active antiretroviral therapy (HAART).

Hepatitis C

Hepatitis C is a chronic liver infection which may lead to cirrhosis and hepatic failure. Studies describe higher rates of hepatitis C in chronic mentally ill patients. For example, in one study of patients ($n=1{,}556$) in a psychiatric hospital, 8.5 % were seroprevalent for hepatitis C versus 1.8 % in the general population [80]. Sockalingham et al. surveyed 110 patients in a Canadian clozapine clinic and found that 2.7 % were positive for hepatitis C, compared with 0.8 % in the general population [81]. HIV and hepatitis laboratory evaluations were conducted in 668 patients in four public sector clinics for the chronic mentally ill [82]. Eighteen percent ($n=122$) were positive for hepatitis C (of these, 53 had only hepatitis C; 56 had hepatitis B and C; and 13 had hepatitis C and HIV). More than 20 % of those had injected drugs, 14 % had shared needles, and more than 20 % used crack cocaine, all of which are associated with an increased risk of hepatitis C. Similarly, higher

than normal rates of hepatitis C (prevalence = 9.1 %) were described in hospitalized patients with schizophrenia and comorbid psychoactive substance abuse ($n = 1{,}193$) in Japan [83].

Compared with controls, schizophrenia patients in a large VA database were two times more likely to get tested for hepatitis C and also two times more likely to be infected [84]. Of note, patients in this study were as likely to receive treatment compared with controls. Butterfield et al. found that hepatitis C in the chronic mentally ill occurred twice as often in men versus women [85]. Higher rates of needle sharing and crack cocaine use occurred in men while women were more likely to report unprotected intercourse. In contrast to Osher et al., 2 years after a screening for hepatitis C in a cohort of 98 patients with schizophrenia none of the patients ($n = 8$) who tested positive had received treatment, again underscoring the inadequate access to care in this population [86].

Hepatitis B

Hepatitis B viral infection is spread via contact with infected blood and body fluids. Most patients develop subclinical or anicteric (no jaundice) hepatitis. In adults, most patients recover and do not develop chronic hepatitis B. Nonspecific constitutional symptoms consisting of fever, fatigue, headache, cough, nausea, and vomiting may be present [87]. Jaundice, commonly associated with hepatic diseases, develops in the next 7–14 days.

Management

There are recommendations for public sector mental health systems to better address infectious diseases in this population. The Centers for Disease Control (CDC) published guidelines addressing the increased risk for hepatitis and HIV [88]. All patients with a chronic mental illness should be screened for sharing of drug use paraphernalia and high risk sexual activity such as unprotected intercourse with a high risk person. Patients with any of these risk factors should be tested for the HIV-1 antibody, the hepatitis C antibody, and the hepatitis B surface and core antibodies and hepatitis B surface antigen [89]. The CDC recently expanded their recommendations, stating that all patients between the ages of 15 and 65, regardless of risk status, should be screened for HIV. In addition, all persons born between 1946 and 1965 should be tested for the hepatitis C antibody.

A brief intervention to increase screening and treatment in chronic mentally ill patients was undertaken by Rosenberg et al. in four community-based mental health clinics [90]. The investigators recruited 236 patients to the intervention, entitled Screening, Testing for HIV and Hepatitis, Immunization for Hepatitis A and B, Risk Reduction Counseling and Medical Treatment and Referral and

Support (STIRR), in the mental health clinic. The treatment group was more likely to be tested for hepatitis B and C, increase their knowledge about hepatitis, and reduce their substance use. High risk behaviors, however, did not decrease; patients were not more likely to be referred for specialty care and HIV knowledge did not increase [90].

Counseling patients on risk reduction—avoiding unprotected sexual intercourse and sharing of drug paraphernalia—is essential. While CBT-based group interventions for HIV risk reduction are effective for the chronic mentally ill, they are not widely available [91]. At a minimum, psychiatrists should educate patients about the risks and complications of these infectious diseases in an effort to motivate them to change associated behaviors.

Chronic hepatitis C infection is treated with ribavirin and pegylated interferon. Pegylated interferon is associated with various neuropsychiatric symptoms, including depression, suicide, and fatigue. This led to hesitation in providing these treatments for patients with schizophrenia. Huckans et al., however, reviewed a VA database of patients with schizophrenia who received hepatitis C antiviral treatment ($n = 30$) and compared them with hepatitis C patients without schizophrenia from the same database [92]. Patients with schizophrenia were equally likely to reach end of treatment response (ETR) and sustained viral response (SVR), indicating no differential in outcome of adverse effects. Further, patients with schizophrenia in a VA database ($n = 30$) who also received antiviral treatment for hepatitis C were followed over an 8-year period. Compared to controls, these patients did not experience higher rates of symptoms of schizophrenia, depression, or mania [93]. While interferon is not contraindicated in these patients, close monitoring is necessary for early detection of treatment-emergent depressive symptoms. Psychiatric symptom control should be optimized prior to starting treatment for hepatitis C.

The hepatitis B vaccine is delivered in a series of three injections. Anyone engaging in unsafe sex practices or sharing drug paraphernalia should receive the vaccine. In addition, the CDC recommends the hepatitis B vaccine for any sexually active person not engaged in a long-term monogamous relationship and men who have sex with men. Immunization and testing should be integrated into regular ongoing mental health care. Patients who test positive for any of these illnesses should be referred for treatment. Current treatment of chronic viral hepatitis B includes pegylated interferon, entecavir, or tenofovir [87].

Cancer

Studies in schizophrenia provide conflicting results with some finding a *lower* cancer incidence. For instance, an 8-year cohort of 59,257 patients with schizophrenia in the Taiwanese NIHRD was compared with 178,156 age- and gender-matched controls without schizophrenia [94]. Overall, cancer incidence was lower in those with schizophrenia (OR = 0.81, CI = 0.74–0.88). Lower rates were found for all types except breast and cervical/uterine cancer. Mortality, however, increased (hazard

ratio = 1.36, CI 1.24–1.50) which may reflect issues of quality and access to care. Similarly, a linkage study connecting national cancer and psychiatric databases found reduced cancer rates for both schizophrenia patients and their parents [95].

Other studies, however, found cancer rates similar to or greater than the general population. In this context, Goldacre et al. employed a cohort analysis of cancer incidence in schizophrenia compared with a reference population reporting that the rate ratio for cancer overall was 1.02 (CI = 0.90–1.08) [96]. Except for a significantly lower rate ratio for skin cancer (0.56, CI = 0.36–0.83), risk of individual cancers was not reduced. A population-based, nested, case–control study found that patients with schizophrenia experienced a 190 % increased risk of colon cancer (OR = 2.90, CI = 1.85–4.57) and a 52 % increased risk for breast cancer (OR = 1.52, CI = 1.20–2.11) [97]. Of note, the increased colon cancer risk was most pronounced in patients taking antipsychotics (OR = 4.08, CI = 2.43–6.08). Finally, a recent study calculated standard incidence ratios (SIRs) of total and site-specific cancers in more than 3,000 Maryland Medicaid beneficiaries over a 10-year period [98]. For those with schizophrenia, the SIR for all cancer sites was 2.6 (CI = 2.2–3.0) with the highest being for lung cancer (SIR = 4.7, CI = 3.1–6.8), though the authors did not control for tobacco use.

A meta-analysis of 16 studies involving patients with schizophrenia and their first-degree family members found that the effect of the illness on cancer rates depended on the type of cancer [99]. Thus, while the overall cancer incidence was not significantly increased (SIR = 1.05, CI = 0.95–1.15), the rate of lung cancer was (SIR = 1.31, CI = 1.01–1.71). This, however, no longer reached significance once the authors controlled for tobacco use. Breast cancer was also more common in schizophrenia (SIR = 1.02, CI = 1.02–1.23). Several cancers including colorectal, malignant melanoma, and prostate had a reduced incidence. Cancer incidence may also vary by age of onset. Lin et al. examined a nationwide cohort of 102,292 patients in the Taiwanese NHIRD during a 7-year period [100]. Overall, the SIR of any cancer declined with age (i.e., for ages 20–29, SIR = 1.97 (CI 1.85–2.33); for ages 60–69, SIR = 0.68 (CI 0.65–0.45)). Further, SIRs for cancers that develop at an older age were lower for prostate cancer (i.e., 0.35 (CI = 0.29–0.58); stomach cancer 0.62 (CI = 0.57–0.80); and pancreatic cancer 0.49 (CI = 0.39–0.84)). By contrast, cancers with a younger age of onset were more common (i.e., for nasopharyngeal cancer SIR = 1.18 (CI = 1.08–1.49); breast cancer SIR = 1.49 (CI 1.44–1.66); uterine cancer SIR = 2.15 (CI = 1.98–2.74)).

Cancer Mortality

Studies demonstrate that cancer is also a major contributor to the increased overall mortality in schizophrenia [3, 99]. Crump et al. followed 8,277 Swedes with schizophrenia over a 7-year period [3]. Despite frequent contact with the health care system, men died 15 years earlier and women 12 years earlier compared with the general population, suggesting suboptimal disease management. The two main causes of death

were heart disease and cancer. The authors concluded that improved screening and risk factor modification were needed. Capasso et al. described 319 Minnesota residents with schizophrenia followed for over 23 years [101]. Cancer was the number two cause of mortality (19 %) in this group which was significantly higher than the general population. A prospective cohort study included more than 3,000 French patients with schizophrenia followed for 11 years [102]. Mortality rates were four times higher than in nonpsychiatric patients, with cancer being the second most common cause. Compared with the general population, the global SMR for any type of cancer was 1.5 (CI = 1.2–1.9).

Less is known about cancer rates in schizoaffective disorder. One linkage study using a database in the Jewish-Israeli general population calculated SIRs for all types of cancer in patients with schizoaffective disorder and found no increased risk (SIR = 1.11, CI = 0.48–1.73) [103].

Breast Cancer

A systematic review of 13 studies concluded there was a higher incidence of breast cancer in schizophrenia [104]. Only 6 of the 13 studies, however, reported elevated incidence rates which varied from a 52 % increase to a 40 % decrease. Another review of breast cancer in schizophrenia identified the following relevant risk factors: obesity, elevated prolactin, low rates of screening with mammography, low parity, low rates of breastfeeding, high levels of smoking and alcohol use, and sedentary lifestyle [105].

Breast cancer treatment in schizophrenia is the subject of only a small number of studies. Using case examples, Cole and Padmanabhan described the challenges of treating breast cancer in women with schizophrenia [106]. Understanding their illness, medication adherence and dealing with psychiatric exacerbations during cancer treatment were among the issues cited by the authors. Nonetheless, a longitudinal study of 37 women with schizophrenia and breast cancer found no impact of the psychiatric illness for either treatment delivery or outcomes [107].

Lung Cancer

Most studies find a higher incidence of lung cancer in schizophrenia. Lichtermann conducted a large record linkage study in 27,000 Finn patients, reporting an elevated SIR of 2.17 (CI = 1.78–2.60) [108]. A large study ($n = 147{,}973$) in Danish patients reported an incidence rate ratio of 3.03 [109]. Neither of these studies, however, controlled for smoking. This is important, since the increased incidence typically disappears when studies control for tobacco use. A retrospective study of lung cancer in 29 patients with schizophrenia did not find a disparity in care, defined as less aggressive therapy prescribed for a potentially curable cancer [110].

Table 10.2 Screening recommendations for selected cancers (abbreviated)

Breast cancer	Recommends biennial screening mammography for women aged 50–74 years
Colorectal cancer	Recommends screening using fecal occult blood testing, sigmoidoscopy, or colonoscopy in adults beginning at age 50 continuing until age 75
Cervical cancer	Recommends screening women age 21–65 with PAP smear every 3 years or for women age 30–65 with combination of PAP and human papillomavirus testing every 5 years
Prostate cancer	Recommends against screening with PSA blood test
Lung cancer	Recommends annual screening with low-dose computed tomography in adults ages 55–80 years who have a 30 pack-year smoking history and currently smoke or have quit within the past 15 years
Ovarian cancer	Recommends against screening
Pancreatic cancer	Recommends against screening
Testicular cancer	Recommends against screening

Source: United States Preventive Service Task Force [148]

Management

Evidence indicates that patients with schizophrenia receive inadequate cancer screening [111]. Thus, all patients should receive age- and risk- appropriate screening for common cancers. Table 10.2 shows selected cancer screening recommendations from the United States Preventive Services Taskforce. Colorectal cancer screening should begin at age 50 and continue to age 75. Bienniel mammography is recommended for women between the ages of 50 and 75. Prostate cancer screening with prostate-specific antigen (PSA) testing is not currently recommended, though there is some controversy surrounding this. Screening for lung cancer with low-dose CT scan is recommended in adults ages 55 to 80 years who have a 30 pack-year smoking history and currently smoke or have quit within the 15 years. Psychiatric providers can play a proactive role in counseling patients to obtain age-appropriate cancer screening. In addition, bupropion is safe and effective for tobacco cessation in these patients.

In summary, studies find both elevated and decreased cancer rates in schizophrenia. Cancer-related mortality, however, appears to be consistently elevated in schizophrenia. The reasons for this are unclear, though delayed screening and diagnosis, inadequate risk factor modification, and suboptimal or incomplete treatment are possible reasons.

Substance Abuse

A full discussion of substance abuse in schizophrenia is beyond the scope of this chapter. It is important, however, to understand its health impact on patients. According to the Epidemiologic Catchment Area Study, nearly 50 % of patients with

schizophrenia or schizophreniform disorder have a diagnosis of substance abuse or dependence [112]. Studies report the following prevalences: nicotine 50–90 %; alcohol 20–60 %; cannabis 12–42 %; and cocaine 15–50 % [113]. Risk factors for substance use disorder include younger age, male gender, early age of schizophrenia onset, and lower levels of negative symptoms [114]. Substance abuse is associated with greater morbidity, greater deterioration in function, and reduced concentration [115]. Further, it is associated with increased risk for infectious hepatitis and HIV. Cannabis or cocaine use may lead to higher risk of tardive dyskinesia, while nicotine use increases the risk for lung cancer and CAD.

Management

All patients should be screened for substance use. Urine and blood toxicology may aid in detection. Development of a strong therapeutic alliance is important to increase awareness of the problem and help motivate the patient to change. Integrated treatment (by the same clinician or team of clinicians) of both schizophrenia and the substance use disorder is the most effective approach in this population. SGAs may be more beneficial in dual diagnosis patients, with clozapine in particular showing greater benefits for decreasing nicotine and alcohol use [116, 117]. Nicotine replacement, CBT, and bupropion are all successful in achieving tobacco cessation. For example, a 12-week trial of bupropion 300 mg daily or placebo added to transdermal nicotine patch 21 mg/24 h, nicotine gum, and CBT was conducted in 51 adults with schizophrenia. Bupropion achieved greater rates of 50–100 % smoking reduction (60 % versus 31 %, $p = 0.036$) compared with placebo [118]. Relapse rates were high, however, upon discontinuation. No worsening of psychosis was noted with bupropion. Naltrexone is effective for reducing alcohol intake. In this context, naltrexone 100–150 mg per day directly administered to 19 patients with schizophrenia for 8 weeks resulted in a significant reduction in number of drinks per week, number of drinks per drinking day, and alcohol craving [119].

Other Medical Conditions

Chronic Obstructive Pulmonary Disease and Pneumonia

Population studies demonstrate an increased risk of lung diseases such as COPD and pneumonia in patients with schizophrenia. Using a national Taiwanese database of nearly 800,000 people, researchers compared rates of COPD in schizophrenia versus the general population [120]. COPD was more prevalent in schizophrenia (3.8 % versus 2.9 %) with an OR of 1.66 (1.42–1.94) and the annual incidence of COPD was 2.21 % versus 1.43 % in the general population. Among veterans who

died while in the hospital, schizophrenia was associated with a diagnosis of COPD or pneumonia in the last year of life [121]. Similarly, a record linkage study of patient databases in England found that schizophrenia increased the likelihood of developing lobar pneumonia, pneumococcal pneumonia, or pneumococcal sepsis [122]. Increased rates of COPD are most likely linked to higher rates of nicotine use in this population.

There is no screening recommendation for asymptomatic individuals at risk for COPD. Addressing nicotine use, as already discussed, is essential. Patients with chronic medical conditions (i.e., heart or lung disease; cancer) and all patients over the age of 65 should receive the pneumonia vaccine.

Autoimmune Disorders

Immune dysregulation is implicated in the pathophysiology of schizophrenia. A cohort study linking two large Danish population-based registers examined the relationship between atopic disorders such as asthma and schizophrenia [123]. Of note, asthma appeared to increase the risk of having schizophrenia (RR = 1.59; 1.31–1.9). The authors, however, used a sibling comparator group instead of a general population comparison group. In contrast, a Taiwanese research group examined a large health insurance database and compared 44,187 individuals with schizophrenia with 132,561 matched nonpsychiatric controls [124]. Patients had a 30 % greater risk of developing asthma (RR = 1.3; 1.24–1.39). Interestingly, they were not at greater risk for other allergic disorders such as rhinitis or urticaria.

A linkage study in a Danish national patient register and a database of 7,704 patients with schizophrenia also found a 50 % higher prevalence of other autoimmune disorders compared with the general population [125]. Acquired hemolytic anemia, intestinal malabsorption, celiac disease, thyrotoxicosis, Sjogren's syndrome, interstitial cystitis, alopecia areata, and polymyalgia rheumatica were among the disorders found to occur more frequently in schizophrenia ($p < 0.05$). Shared disease-specific or non-disease-specific genetic loci are proposed as the putative cause. Thyroid dysfunction in antipsychotic-treated patients is also reported in several studies [126].

In contrast, rheumatoid arthritis (RA) is consistently shown to have a negative relationship with schizophrenia. A large review of 14 studies conducted between 1934 and 1985 found a negative association between schizophrenia and rheumatoid arthritis [127]. Twelve of the 14 studies found a reduced risk of rheumatoid arthritis in patients with schizophrenia, mirroring findings of other studies [128, 129]. Alterations in platelet activating factor (PAF) may explain this relationship [130]. PAF is pro-inflammatory and may predispose to RA, yet it is also responsible for neuronal migration and synaptic connectivity, so reduced bioavailability may predispose to schizophrenia.

Epilepsy

Psychosis is common among patients with epilepsy and may present with hallucinations and delusions, psychomotor retardation, and conceptual disorganization [131, 132]. In particular, patients with temporal lobe epilepsy are more likely to develop psychosis resembling schizophrenia [133]. In turn, epilepsy is more common in patients with schizophrenia [131]. Wotton et al. conducted a retrospective cohort study linking records within a national hospital statistics database in the United Kingdom [134]. Patients hospitalized for schizophrenia were twice as likely to have epilepsy while those admitted for epilepsy were five times more likely to have schizophrenia. Another study used the Finnish Hospital Discharge Register to follow parents and children born between 1947 and 1960 [135]. The authors found that individuals with a parental history of epilepsy had twice the risk of developing psychosis and those with parental history of psychosis had nearly three times the risk of developing epilepsy.

The co-occurrence of these disorders led some to propose a possible link based on shared genetic or neuropathologic etiologies. Ventricular enlargement in both conditions points to a shared neuropathologic etiology; left temporal lobe pathology may also be a shared putative factor [136]. Leucine-rich glioma-inactivated (LGI) family gene loci were also studied as potential causative factors [137]. Increased risk of seizure due to antipsychotics further complicates the issue.

Future Needs: Integrated Delivery of Medical Care

There is a need to improve screening of patients with schizophrenia for common chronic medical conditions such as diabetes and hypertension. Early interventions need to emphasize exercise and healthy diet and address nicotine use [138]. Improving quality and access to care is challenging and requires integrated models to better address patients' physical health [139]. Interventions to improve the integration of medical and psychiatric care are increasingly a focus of research. Co-located models of care may bring internists into psychiatric settings. Alternatively, mental health providers may be brought into medical settings to identify and treat psychiatric disorders, though these models more commonly target the primary care management of depression [140]. Finally, practicing psychiatrists may be trained in primary management of common medical conditions. This is a recent focus of various professional organizations. Of note, however, psychiatrists have been slow to implement metabolic monitoring guidelines for patients on antipsychotics [58].

Collaborative models involving a co-located primary care doctor or a consulting internist are one of the better studied approaches. Druss et al. randomized 120 patients in the VA system to a primary care medical clinic (contiguous to a mental health clinic) or care as usual (referral to general medical clinic in an adjacent building) [141]. The medical clinic was staffed with an on-site primary care physician, a nurse practitioner, and a nurse care manager. After 1 year, 15 of 17 measures of

quality of medical care were significantly better than the control group. Inpatient settings are also a focus of study. For example, 130 hospitalized patients with chronic mental illness were randomized to either medical care provided by a consulting internist (who conducted medical history and physical exam and communicated with the outpatient primary care provider) or medical care as usual provided by psychiatric house staff [142]. Twelve of 17 quality measures were improved in the intervention group and the cost between the two was similar (i.e., $8,558 versus $8,527). A variation on this approach is a model which employs a non-physician manager in a mental health clinic to facilitate medical care for chronic mentally ill patients [143]. In one study, patients with serious mental illness in an urban mental health clinic ($n = 407$) were randomized to medical care management or TAU for 1 year. Participants in the intervention group received 58.7 % of recommended preventive services versus only 21.8 % in the control group.

A systematic review of interventions for the chronic mentally ill concluded that regardless of whether services were co-located, the most important element was integration of the treatment team, as this has demonstrated improved quality of general medical and psychiatric care [144, 145]. Scharf et al. describe the early experiences of the 56 Primary and Behavioral Health Care Integration grantees, all of whom designed models for combined medical and psychiatric care within their current systems [146]. Data collection on the effect of these interventions is ongoing and should inform providers and mental health systems on how best to integrate medical and psychiatric care to enhance patient outcomes.

Conclusion

Patients with schizophrenia suffer from several medical disorders at higher rates and experience a shortened life-span than the general population. Causes are multifactorial and include lifestyle factors, delivery of medical care, and medication adverse effects. Thus, mental health providers need to play an increasingly proactive role in the physical health of psychiatric patients—including screening for chronic medical conditions and substance abuse and addressing modifiable risk factors. Finally, there is a need for innovative delivery approaches of medical care for patients with serious mental illness.

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Chapter 11
Management of Water Imbalance in Schizophrenia

Morris Goldman and Pichai Ittasakul

Introduction

Historical Overview

Since the 1930s, unexplained increases in water intake, impairments in water excretion which vary with severity of psychosis, and reports of water intoxication were linked to chronic psychotic disease [1–3]. In the following decades, hyponatremia was often unnoticed and patients were frequently thought to have a primary seizure disorder [4]. Beginning in the 1950s, the characterization of the syndrome of inappropriate antidiuretic hormone secretion (SIADH), the increased interest in distinguishing diabetes insipidus from primary polydipsia, and the development of a sensitive radioimmunoassay for the antidiuretic hormone, arginine vasopressin (AVP), all contributed to a renewed interest in water balance in psychiatric patients [5, 6].

Initial efforts to characterize the mechanism of chronic moderate hyponatremia and episodic water intoxication in schizophrenia were obscured by the different etiologies of the hyponatremia, as well as the complexities of antidiuretic function [7]. In the absence of a deficiency of salt or diminished blood volume, hyponatremia occurs when fluid intake overtakes renal water excretion thereby diluting the amount of sodium in the body. Early studies did not distinguish patients with idiopathic hyponatremia from those with iatrogenic hyponatremia (typically attributable to

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P.G. Janicak et al. (eds.), *Schizophrenia: Recent Advances in Diagnosis and Treatment*,
DOI 10.1007/978-1-4939-0656-7_11,

thiazide diuretics, carbamazepine, or antidepressants) or other recognized causes such as hypothyroidism or severe alcoholism [8, 9].

Iatrogenic hyponatremia and hyponatremia due to other recognized causes typically involved minimal or no excess fluid intake but fixed and relatively severe deficits in water excretion. In contrast, idiopathic cases typically involved marked polydipsia and transient, relatively mild, impairments in water excretion that were difficult to detect. While some reports indicated that patients with unexplained hyponatremia exhibited impaired water excretion or elevated AVP levels, others found normal water excretion [5–7]. Some asserted the hyponatremia in these patients was solely due to polydipsia, and labeled these patients as having psychogenic polydipsia and "self-induced water intoxication." Even when impaired excretion was apparent, this was often considered a consequence of hyponatremia (e.g., increased antidiuretic hormone secretion from seizures, vomiting), rather than a contributor [9].

Hariprasad et al. in 1980 were the first to reconcile the conflicting evidence regarding the role of impaired water excretion in patients with idiopathic hyponatremia [10]. Renal water excretion is primarily determined by the actions of AVP on the collecting ducts of the nephron. Plasma AVP normally increases linearly as plasma osmolality increases, and diminishes to undetectable levels as plasma osmolality drops (Fig. 11.1; normal). As AVP rises, urine concentration rises to five times that of plasma (~1,500 mOsm/kg), while undetectable AVP levels are associated with urine concentrations that are one-tenth of plasma (~30 mOsm/kg). At moderate or high AVP levels any amount of ongoing fluid intake will overwhelm renal water excretion, while with undetectable AVP levels renal water excretion can easily exceed ~20 L/day.

The plasma osmolality at which AVP becomes undetectable (and hence water excretion reaches maximal levels) is called the set point or osmotic threshold and is generally about 3–5 % below the actual plasma osmolality (normal 280–300 mOsm/kg) or plasma sodium (135–145 mEq/L). Hariprasad measured plasma osmolality and concurrent renal water excretion during enforced fluid restriction in a group with schizophrenia and idiopathic hyponatremia. At extremely low plasma osmolalities, these patients' water excretion appeared to be normal (i.e., ≥20 L/day), but as plasma osmolality began to rise their water excretion was diminished from normal. Hence, depending on the concurrent plasma osmolality, water excretion could appear impaired or normal. The findings implicated a condition called reset osmostat in which the relationship between AVP and plasma osmolality/sodium is maintained but shifted leftward (Fig. 11.1; type C). Several groups reproduced these findings and confirmed they were attributable to a shift in the set point for AVP, while other modulators of renal water excretion remained intact [10–13].

In an effort to distinguish psychotic patients with idiopathic hyponatremia attributable to reset osmostat from those whose hyponatremia was due to recognized factors (Fig. 11.1; type A or type B), Vieweg coined the term "psychosis, intermittent hyponatremia, polydipsia" (PIP) syndrome [14]. This initial clarification of the different mechanisms of hyponatremia provided the foundation for diagnosis and management of the disorders discussed below, as well as for subsequent research into the relationship of reset osmostat to the underlying mental illness. In contrast, little is still known about the mechanism of primary polydipsia.

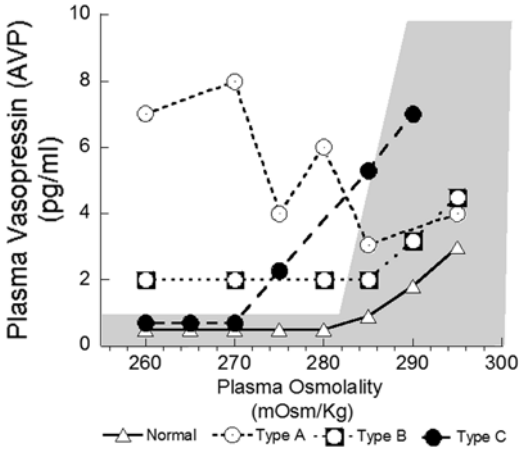

Fig. 11.1 Normal and abnormal regulation of arginine vasopressin (AVP). AVP is secreted from the brain into the peripheral circulation and binds receptors in the kidney which diminish renal water excretion. AVP is primarily determined by concurrent levels of plasma osmolality (and sodium). Increases in osmolality cause a linear rise in AVP concentration in plasma, while decreases diminish AVP to undetectable levels. The linear relationship is normally very precise ($r \sim 0.9$) and is characterized by its gain (slope of line) and set point (osmotic threshold). The white triangles are an example of a normal relationship. In most cases of abnormal osmoregulation attributable to medication or other unrecognized medical disorders, plasma AVP is unresponsive to plasma osmolality (i.e., syndrome of inappropriate antidiuretic hormone (SIADH; Type A) or only partially inhibited (Type B), producing relatively fixed and severe deficits in water excretion. In contrast, water excretion in patients with idiopathic hyponatremia/ PIP syndrome depends on the level of plasma osmolality (Type C = reset osmostat). At very low levels (i.e., near the set point) it will appear normal, while at slightly higher levels it will appear impaired. Moreover, the resetting itself varies with the acuity of the psychosis. Gray shading represents the normal range of levels, hence concurrent measures of AVP and plasma osmolality can help establish impaired water excretion which otherwise eludes detection

Epidemiology, Risk Factors, and Sequalae

Primary and Secondary Polydipsia

In individuals with chronic mental illness, 15–25 % have a "*primary*" *polydipsia* (i.e., oral intake >4 L/day, normal <3.0 L/day), exhibiting increased intake which is not attributable to impaired concentrating capacity (e.g., not nephrogenic diabetes insipidus, diabetes mellitus, or renal failure) [15, 16]. Genetic factors may contribute to this primary polydipsia [17, 18]. Patients also exhibit an increased incidence of alcoholism and smoking which appear to precede the mental illness and may further characterize the phenotype [16, 19]. *Secondary polydipsia* is commonly seen with nephrogenic diabetes insipidus attributable to lithium treatment (in about 30 % of those receiving lithium), and may occur more commonly in patients receiving serotonergic antidepressants [20]. The polydipsia is secondary to the increased

Table 11.1 Risk factors for hyponatremia

Primary polydipsia
Increasing age
Heavy smoking
Alcoholism
Polypharmacy
Chronic psychosis
Medications (e.g., use of diuretic, SSRI, TCA, venlafaxine, bupropion, carbamazepine, and calcium antagonist)
Medical conditions that decrease water excretion (e.g., diabetes mellitus, syndrome of inappropriate antidiuresis from lung cancer kidney disease, heart failure, cirrhosis, hypothyroidism, adrenal insufficiency)

Source: Modified from Ittasakul P, Goldman MB. Hyponatremia in Psychosis. In: Simon EE, editor. Hyponatremia: Evaluation and Treatment. New York: Springer; 2012, with permission from Springer Science + Business Media

SSRI selective serotonin reuptake inhibitor, *TCA* tricyclic antidepressants

water excretion which causes thirst. In the absence of lithium toxicity, irreversible nephrogenic diabetes insipidus and impaired glomerular filtration (e.g., elevated plasma creatinine) normally occur only after years of treatment. Recent findings indicate the lithium-induced tuberointerstitial nephritis which accompanies chronic polyuria may be directly responsible for this progressive renal failure [21]. Thus, polyuria is a risk factor for renal failure with lithium therapy, and physicians should consider treating it or switching medications (see Treatment). Secondary polydipsia does not predispose to hyponatremia, since the polydipsia is due to increased water excretion. Primary polydipsia in a patient with lithium-induced renal failure, however, would place the patient at markedly increased risk of hyponatremia.

Regardless of the etiology, over time excessive amounts of water flowing through the body may lead to systemic "plumbing" problems (i.e., dilated bowel, bladder, and kidneys as well as associated disorders such as obstruction, incontinence, urinary infection, and renal failure) [16]. Further, the increased intake and output seems to leech calcium from bones predisposing to osteoporosis and pathologic fractures [22].

Chronic Moderate Hyponatremia and Episodic Water Intoxication

Psychiatric disorders are associated with a higher risk of chronic hyponatremia and episodic water intoxication. The increased risk is primarily attributable to the prescribing of medications which impair water excretion, the elevated frequency of primary polydipsia, and the PIP syndrome (Table 11.1) [23–30]. Carbamazepine, thiazide diuretics, and antidepressants most commonly impair water excretion and are responsible iatrogenic hyponatremia [27]. Many of these patients may also have

primary polydipsia. Serotonin reuptake inhibitors (SSRIs) have a risk that is four times higher than other antidepressants [23, 31]. Elderly women during the first few weeks of therapy appear to be at highest risk [31]. It is likely that any antidepressant which enhances serotonin activity (e.g., trazodone, clomipramine) may increase the risk of hyponatremia, though reports have implicated all agents, including mirtazapine and buproprion [23–27, 29]. Other serotinergic agents, including street drugs such as methylenedioxymethamphetamine (MDMA: ecstasy), are also associated with hyponatremia, perhaps by directly enhancing vasopressin secretion [32]. While many psychotropic medications induce transient nausea and orthostatic hypotension (i.e., recognized AVP stimuli), these are not routinely implicated as causes for hyponatremia in this population.

The incidence of iatrogenic hyponatremia in polydipsic psychotic patients is not clearly established but is likely about the same or higher based on population surveys [33, 35]. About one in five patients with schizophrenia and primary polydipsia (i.e., about 3 % of all chronic patients) experiences intermittent hyponatremia due to the PIP syndrome [15, 33, 34]. In rare cases, hyponatremia may occur from primary polydipsia alone (i.e., "self-induced"), though this has never been conclusively demonstrated.

Other reported risk factors associated with hyponatremia (Table 11.1) include smoking which is a recognized stimulus for AVP release and contributed to impaired water excretion in case reports [36]. Smoking is extremely common in these patients (~70 %), especially in the hyponatremic subset [34]. Of note, this also places patients at increased risk for SIADH which is associated with small cell lung cancer. Alcoholism is also common in psychiatric patients and the associated malnutrition or cirrhosis in severe cases can predispose polydipsic patients to hyponatremia. Further, alcoholism is independently associated with polydipsia in schizophrenia [14, 37]. Finally, polypharmacy appears to be a risk, and may simply be due to the additive effects of two or more medications associated with impaired water excretion [38].

Clinical Presentation

Polydipsia is frequently undetected, though many patients are observed to have a cup at all times or may spend excessive time in proximity to water sources (potable or nonpotable). While moderate chronic hyponatremia may appear asymptomatic, most patients have impaired cognition characterized by deficits in attention, learning, memory, and executive function which may be difficult to distinguish from their underlying mental illness [30, 39, 40]. These patients also exhibit impaired fine motor skills and are at greater risk of falls and fractures [41–44].

Signs and symptoms of water intoxication are dependent on the severity and rapidity of its development [45]. Generally, the clinical presentation of symptomatic hyponatremia not only resembles that of nonpsychiatric patients (vomiting, nausea, ataxia, confusion, lethargy, seizures, and coma) but also includes

aggravation of the underlying psychiatric illness (e.g., increased paranoia and aggression). Conversely, patients may appear stable one moment and begin seizing the next [30, 46]. Neurological symptoms usually do not occur until the serum sodium concentration falls below 120 mEq/L or even lower with chronic hyponatremia [47]. Water intoxication is primarily attributable to acute cerebral edema (i.e., a water-saturated brain encountering a rigid cranium). Patients with chronic hyponatremia adapt to the excess brain water by excreting organic osmolytes (i.e., idiogenic osmoles) but will experience water intoxication if their sodium levels drop further (e.g., ~110 mEq/L) [48]. Hyponatremia may present with rhabdomyolysis (with or without compartment syndrome) and with neuroleptic malignant syndrome [49–52]. Rhabdomyolysis may also occur in patients whose hyponatremia was rapidly corrected [53].

Over the past 30 years there are many reports of death in severely mentally ill patients due to water intoxication [54, 55]. Once largely confined to medicated patients on extended stay units in public psychiatric hospitals, episodic water intoxication is now increasingly seen in unmedicated patients living in the community [56].

The PIP Syndrome

Primary polydipsia typically appears about 5 years after the onset of psychiatric illness, and hyponatremia appears about 5 years after that in patients with the PIP syndrome [14, 57]. Rarely, however, unexplained polydipsia and water intoxication can occur concurrently with the first psychotic break [58]. PIP patients usually have a severe unrelenting psychosis with marked social deficits [59]. Patients often hide their drinking, and symptomatic hyponatremia may be suspected only after someone notes a striking diuresis in a post-ictal patient. Because the impairment in water excretion is relatively minor and may even be transient, water accumulates over the course of the day and is excreted at night. Thus, hyponatremia is most marked in the mid-afternoon and is frequently not present when blood samples are obtained in the morning. This pattern of drinking and of water retention led to some unique clinical observations (i.e., institutionalized PIP patients in the winter tend to congregate at midday around heaters due to massive water drinking lowering their body temperature (so-called afternoon radiator sitting syndrome)) [60].

PIP patients and their first degree relatives differ from others with schizophrenia [18, 19, 37, 61] in that they are more severely debilitated by their illness and exhibit an increase in primary sensory deficits [62]. Hawken et al. recently examined the long-term effects of polydipsia and hyponatremia on mortality [63]. The median age at death was 57 years for hyponatremic polydipsia, 60 years for normonatremic polydipsia, and 68 years for matched non-polydipsia patients. Hyponatremic patients had a 74 % greater chance of dying before non-polydipsic patients. How much of the enhanced mortality is attributable to the water imbalance or other aspects of their schizophrenia (e.g., increased smoking) is not known.

Diagnosis

Polydipsia

Polydipsia of any origin typically presents with nocturia and incontinence. Since urine output normally matches up well with oral intake and the rate of solute excretion in the urine is fairly constant, urine tonicity provides a reasonable index of oral intake [64]. Despite the absence of fluid intake over the course of the night, morning urine tonicity may be diminished due to a concentrating defect (to be distinguished from the impaired excretion) attributable to the polydipsia (i.e., secondary to "renal medullary washout") [65]. Thus, afternoon measures are clearly more sensitive and hence preferred. Polydipsia is diagnosed by demonstrating diminished urine specific gravity (<1.008; normal 1.015–1.030) or diminished urine osmolality (<150 mOsm/kg; normal 500–1,400 mOsm/kg) on two of three spot urine samples taken over a week or more (Table 11.2).

PIP Syndrome

Because hyponatremia in PIP patients is intermittent and most apparent in the afternoon, morning serum sodium levels do not make the diagnosis [14]. The amount of retained water required to induce dilutional hyponatremia is significant. Because accumulation begins again each morning, patients at risk of water intoxication can be easily identified by obtaining diurnal measures of body weight. Acute water intoxication is commonly associated with a marked increase in body weight (i.e., 20 % decrease in plasma sodium typically accompanied by a 8 kg increase in body weight in the typical 70 kg person) [14], but on a typical day, patients gain 2–3 kg. Thus, determining the difference between morning and afternoon body weights is a reliable means of diagnosing the PIP syndrome, since diurnal weight rarely varies more than 1.5 kg in normals (Table 11.2). Care must be taken to use the same scale and make certain the patient is wearing approximately the same amount of clothing. Diagnosis of hyponatremia is confirmed by obtaining a concurrent sodium concentration or plasma osmolality with the afternoon weight (Table 11.2).

Concurrent plasma and urine concentration measures may or may not implicate reset osmostat in the hyponatremia. Given the transient nature of reset osmostat in this population, it is difficult to establish the diagnosis unless serial measures of plasma sodium and urine osmolality samples are obtained following water loading or fluid restriction when the patient is hyponatremic.

Medication-Induced Hyponatremia

Medication-induced hyponatremia is typically more stable than that seen in PIP patients, because of the more limited role of polydipsia and the more severe and

Table 11.2 Differential diagnosis and management of water imbalance in schizophrenia

Disorder	Causes	Diagnosis	Criteria	Clues	Management
Primary polydipsia	Hippocampal dysfunction	2–3 urine osmolalities or specific gravities in AM and PM	Two or more <1.008 or Uosm <150 (i.e., same criteria)	Worse in afternoon than AM	Usually none
Secondary polydipsia	Lithium			Minimal variation within or between days	Lower dose, amiloride, thiazide
Medication-induced hyponatremia	Thiazide, carbamazepine, antipsychotic	AM and PM weights for 1 week, two AM serum sodium with urine osmolalities	Na+ <130 mEq/L; Urine osmolality >220 mOsm/kg	Minimal diurnal variation in weight	Discontinue medication
PIP syndrome	Hippocampal dysfunction		Urine osmolality <220 mOsm/kg; PM weight 3 kg >AM weight	AM sodium levels may be normal	Target weight, clozapine

fixed impairment in water excretion. For these reasons, a single concurrent measure of urine and plasma osmolality at any time of the day is adequate to make the diagnosis. The role of one of the above noted agents is strongly implicated if treatment was initiated in the past 30 days and concurrent urine osmolality is greater than plasma osmolality (i.e., >300 mOsm/kg) (Table 11.2). Such levels are rarely if ever seen in PIP patients. Depending on the half-life of the medication (e.g., the half-life of fluoxetine is 2–7 days), these cases should rapidly resolve with discontinuation. In the absence of a rapid reversal, other factors noted in Table 11.1 should be considered.

Antipsychotic medication presents a particular challenge, since discontinuing them in PIP patients frequently worsens both the psychiatric disorder and the water imbalance [52, 66]. While antipsychotics may modestly enhance renal sensitivity to AVP in a dose-related manner, this effect, per se, does not appear to contribute to the hyponatremia [65, 67]. The mechanism of antipsychotic-induced hyponatremia is unknown but like other drug-induced cases, antipsychotic-induced hyponatremia is more stable than that seen in PIP patients and is attributable to severe impairments in water excretion [52]. A recent review of published cases found that persons with antipsychotic-induced hyponatremia tended to have concurrent urine osmolality levels >220 mOsm/kg. By contrast, levels are lower than this with the PIP syndrome. Persons with concentrated urine meet Naranjo Criteria (score based on a series of questions about the relationship of an adverse outcome to medication usage) for drug-induced disorder seven times as often as those with dilute urine. Further, duration of antipsychotic treatment was one-eighth as long, and recurrence of hyponatremia following antipsychotic rechallenge occurred exclusively in those with concentrated urine [66, 68–70] (Atsariyasing and Goldman, unpublished).

Pathophysiology of PIP Syndrome

Mechanism of Primary Polydipsia

The mechanism of primary polydipsia is unknown. Polydipsia does not seem attributable to increased thirst or to hydrophilic delusions [71, 72]. Most patients say they do not drink because of particular health beliefs but simply because it makes them feel better [73]. The osmotic set point for desiring water, like that for AVP, appears to be reset downward in polydipsic patients with or without hyponatremia [65]. This suggests that thirst regulation is generally intact but altered by an extrinsic factor [11, 65]. Initial studies indicated that the reset osmostat and primary polydipsia were independent of each other. More recent data, however, indicates abnormalities in fluid intake and excretion may both be related to hippocampal dysfunction [74]. Hippocampal lesions enhance the development of polydipsia and stereotypic behaviors in animal models [75], and polydipsic patients exhibit an increased incidence of stereotypic behaviors compared with other schizophrenia patients [76, 77].

Some evidence suggests that polydipsia (and perhaps other stereotypes) reduces arousal, constituting an adaptive response to the enhanced stress reactivity arising from the hippocampal dysfunction. This enhanced stress reactivity, in turn, underlies the reset osmostat and enhanced stress hormone responses as discussed below [78]. Another possibility, not inconsistent with that stated above, is that hippocampal dysfunction enhances the rewarding properties of water [79]. Further research into the mechanism of polydipsia may provide insights into the behavioral abnormalities associated with schizophrenia.

Mechanism of Reset Osmostat in PIP Syndrome

In addition to reset osmostat, PIP patients also exhibit enhanced renal sensitivity to low levels of AVP [11, 65]. Together with primary polydipsia they may account for the moderate chronic hyponatremia but are insufficient to produce episodic water intoxication. Previous observations suggested that impaired water excretion worsens during acute psychosis [5, 6], and one study specifically found that reset osmostat worsened during a psychotic relapse [80]. The mechanism of this association was addressed by giving a psychotomimetic to a group of clinically stabilized hyponatremic and normonatremic polydipsic subjects. Following the psychotomimetic, psychotic symptoms increased similarly in the two groups, but plasma AVP increased more in those with hyponatremia while the desire to drink did not change in either group [80]. The peak AVP response was predicted by basal positive psychotic symptoms in both groups. Moreover, it was proportional to concurrent plasma osmolality in those with hyponatremia (Fig. 11.2). This latter observation indicates that psychosis may further lower the set point in the PIP syndrome to a level capable of inducing water intoxication. Concurrent measures of recognized and putative physiologic factors did not explain why the set point shifted.

The anterior hippocampus normally restrains AVP and hormone responses to psychological stress [81, 82]. Further, the hippocampal segment is smaller [83, 84], stress hormone activity is elevated [85], and the reset osmostat normalizes with clinical stabilization [74, 80] in PIP patients relative to others with schizophrenia. This led to the hypothesis that hippocampal pathology might induce an enhanced AVP response to stress in PIP patients [74]. This hypothesis was supported by subsequent studies. One study demonstrated that both AVP and stress hormone responses to a psychological, but not a physical stimulus, were enhanced in PIP patients relative to healthy controls and nonpolydipsic patients [86]. Since AVP response to the psychological stressor was predicted by concurrent plasma osmolality, the hypothesis that a heightened response to stress lowers the AVP set point was supported. A second study reported that hippocampal-mediated negative feedback which contributes to braking the stress response was nearly absent in PIP patients, further linking the findings to hippocampal dysfunction [87]. A third study found these neuroendocrine findings were proportional to deformations on the surface of the hippocampus overlying the segment (i.e., anterior lateral) which projects to the anterior hypothalamus and normally restrains neuroendocrine release [88].

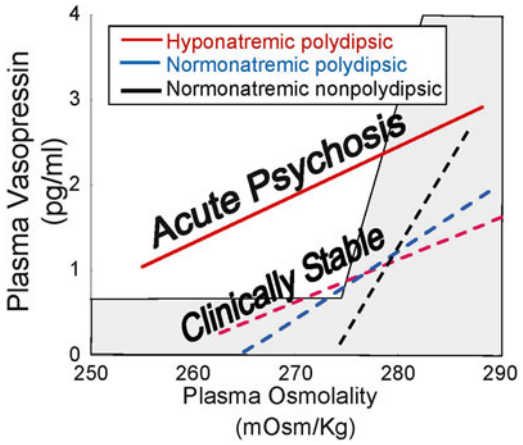

Fig. 11.2 Effect of acute psychosis on AVP regulation in polydipsic patients. An infusion of the psychotomimetic, methylphenidate, was given to hyponatremic and normonatremic polydipsic patients to induce a brief psychotic exacerbation. Peak AVP levels were higher in the hyponatremic patients and moreover were predicted by their concurrent plasma osmolality. In contrast, there was no significant relationship between peak AVP and plasma osmolality in the normonatremic patients (not shown). The mean linear relationships between AVP and plasma osmolality for the two groups when clinically stabilized is also shown, demonstrating how the set point (*x*-intercept) shifts in the hyponatremic group with acute psychosis without changing the slope of the relationship. The drop in the set point during acute psychosis (i.e., 242 mOsm/kg) is sufficient to produce water intoxication. The mean linear relationship of nonpolydipsic patients is also included, and highlights how "medullary washout" from polydipsia blunts the relationship between plasma osmolality and P_{AVP}

The hippocampal findings summarized above are also proportional to deformations on the amygdala and anterior hypothalamus [88]. These two structures, like the hippocampus, modulate both neuroendocrine activity to stress and are implicated in the pathophysiology of schizophrenia. In particular, the same hippocampal region that restrains these neuroendocrine responses also restrains dopamine release in the ventral striatum which many believe underlies acute psychosis and behavioral response to stress and is essential for coping efforts to buffer the impact of stress [79, 89]. Direct evidence linking hippocampal dysfunction to mental illness also comes from studies of plasma oxytocin, and the effects of intranasal oxytocin treatment on these patients' marked deficits in social functioning [59]. Taken as a whole, the data support the view that there are disruptions in both peripheral and central neuroendocrine function in polydipsic patients which are attributable to hippocampal dysfunction and contribute to a stress diathesis that accounts for the core features of their illness [74, 88].

Unlike the transient changes in the set point for AVP secretion, little is known about the mechanism of the enhanced renal sensitivity to AVP action and its relationship, if any, to its altered secretion or psychosis. One possibility is the effects of chronic antipsychotic treatment [90]. Polydipsia does not appear to be responsible,

although the possibility there is an idiosyncratic response (perhaps due to long-standing polydipsia) in PIP patients cannot be excluded. One potential explanation which has not been explored is variations in the genetic and functional properties of the renal AVP (V2) receptors.

Treatment and Prevention

Polydipsia

Primary polydipsia is typically not treated (Table 11.2). Efforts to restrict fluid intake, even in supervised settings, are rarely successful. In previous years, ongoing group and behavioral therapies were reported effective for inpatients on long-term units [20, 91]. Many putative therapeutic agents (e.g., beta-blockers, clonidine, ACE inhibitors, naltrexone) have been tried but their efficacy remains uncertain [92]. Clozapine's salutary effects on water imbalance in PIP patients may be due to its reduction of primary polydipsia, but using clozapine solely for this reason may not be appropriate due to its associated risks [93].

Because of the increased risk of renal failure, lithium-induced polydipsia must not be ignored. Lowering the lithium dose or changing to a single daily dose may help. Addition of a thiazide (e.g., 25 mg of hydrochlorthiazide) or potassium-sparing diuretic (e.g., 5 mg of amiloride) is generally effective in reducing polydipsia, though it is unclear whether this reduces the risk of renal disease (Table 11.2) [94]. If adding a thiazide diuretic, the lithium dose should first be reduced by about one third as more lithium will be retained by the kidney. Lithium levels should initially be followed at more frequent intervals to assure they remain therapeutic and safe. It is important to realize that these agents place patients at an increased risk of lithium intoxication (e.g., dehydration and salt loss during hot dry weather) which is also a risk factor for renal failure [28]. Theoretically, amiloride which blocks lithium uptake into renal tubule cells should lower the risk of nephrotoxicity [29]. In any case, patients need to maintain fluid and salt intake during heat spells or periods of intense exercise. Also, if polyuria is due to primary polydipsia rather than lithium treatment, a thiazide diuretic will predispose the patient to water intoxication.

Hyponatremia in the PIP Syndrome and with Recognized Causes

Following an acute episode of water intoxication, the appropriate response to most PIP patients is close observation and fluid restriction. This conservative approach is predicated on the relatively minor contribution of the impairment in water excretion to the hyponatremia, the rapid shifts in fluid balance and the increased risk of over-correction due to the concurrent concentrating defect. Thus, patients who have seized and regained consciousness or who are exhibiting symptoms of impending

water intoxication (tremors, ataxia, vomiting) can be fluid restricted for 3–4 h during which time they will excrete large amounts of the retained water. Patients must be closely monitored as they may continue to absorb ingested water from their gastrointestinal tract and (re)develop water intoxication. Monitoring changes in body weight is an effective means of assessing the efficacy of fluid restriction [14].

Prolonged fluid restriction should be avoided because of the concentrating defect and subsequent risk of overcorrection leading to central pontine myelinolysis (CPM). The risk of CPM in these patients may be, however, somewhat overstated because there is not adequate time for the patient to adapt to the lower sodium level (which is critical to CPM) [95]. Particular caution should be taken, however, in patients with alcoholism, malnutrition, medication-induced hyponatremia, or a subacute course of hyponatremia where the risk of CPM is high [47, 48]. While the risk of overcorrection or rapid correction producing CPM in PIP patients appears low, it does appear to induce rhabdomyolysis [53].

If the patient does not rapidly regain consciousness, standard measures of restoring water balance (e.g., saline infusion) should be considered. In the absence of reversible causes, preventive measures are appropriate following resolution of the acute episode.

Prevention

Targeted fluid restriction is an effective means of preventing water intoxication in PIP syndrome in an inpatient or nursing home setting and enables the patient and nursing staff to avoid the intensity of constant monitoring (Table 11.2) [14, 96]. The procedure relies on the fact that water retention leads to easily detected gains in body weight, and the "target weight" is based on an estimate of the weight gain at which the patient's hyponatremia is more severe than usual but not yet at a level likely to induce water intoxication. The procedure requires weighing patients twice a day (morning and afternoon) and whenever latent signs (light headedness, dizziness, bloating, or nausea) of water intoxication are observed. Initially, the target can be set at 7–10 lb above the average morning water weight, and a sodium level obtained when this target is exceeded. If the target is too conservative, it can be increased to a level more likely associated with symptomatic hyponatremia. Thus, it may take a few days to find a target weight that conforms to a sodium level which warrants fluid restriction. Fluid restriction for 2–6 h is usually sufficient to return a patient to the morning weight. Again, overcorrection should be avoided.

Pharmacologic Treatment

Until the introduction of clozapine and the vaptans, pharmacologic options were limited. While many agents were tested, with the possible exception of demeclocyline, they were not effective [72].

Clozapine

Many investigators report that clozapine reduces the risk of hyponatremia and water intoxication, even though there are no double-blind placebo-controlled studies [93]. The mechanism is unclear, but clozapine may lower water intake rather than enhance water excretion. The drug often normalizes sodium levels within several weeks, enabling patients to leave restricted settings and participate in therapeutic programming. Clozapine may be effective in low doses (approximately 100 mg/day), and there is no evidence that going above 300 mg/day will produce further improvements in water balance [93]. Water intoxication and other sequelae of polydipsia have, however, occurred in patients on clozapine [97]. In addition, clozapine requires monitoring not available to all physicians, and is associated with an impressive array of life-threatening adverse effects. Thus, the risk/benefit ratio must be examined, particularly in patients without a history of frank water intoxication, and whose chronic moderate hyponatremia does not appear to overtly impair cognition or contribute to altered balance and associated fractures.

Vaptans

A double-blind study documented the marked efficacy of tolvaptan which is a competitive vasopressin receptor 2 antagonist [98]. Nineteen PIP subjects were randomly assigned to receive placebo ($n=12$) or tolvaptan ($n=7$) once daily for 30 days at a dose of 15–60 mg, based on serum sodium changes. Baseline sodium levels were 130 mEq/L in both groups, and normalized (>135 mEq/L) within 24 h of treatment with tolvaptan while they did not change with placebo ($p<0.005$ at all samples after day 4). The salutary effects were apparent throughout the 30-day treatment period and subjects on tolvaptan returned to previous hyponatremic levels after treatment was stopped. Two subjects receiving active drug (28.6 %) became dehydrated and experienced hypotension, while five subjects receiving placebo (41.7 %) experienced symptoms associated with latent or overt water intoxication. The study included an open-label extension arm during which the salutary effects appeared to be maintained (Goldman and Josiassen; unpublished data). As of this writing, in the United States these medications are limited to acute inpatient settings but presumably will become integrated into routine outpatient care as well. Careful dose adjustment is needed to prevent dehydration, particularly in patients with concurrent medical problems (e.g., renal insufficiency).

Conclusion

Despite the clinical significance of the water imbalance and the effective interventions that are available, hyponatremia is frequently undetected in schizophrenia, making its recognition and proper management an important and neglected aspect

of patient care. Chronic moderate hyponatremia produces significant morbidity, while episodic water intoxication has caused many deaths in those with severe mental illness. Episodic water intoxication frequently occurs in the PIP syndrome and is a consequence of a marked primary polydipsia and transient mild impairments in water excretion that frequently coincide with psychotic exacerbations. A series of investigations have shown the impaired water excretion is attributable to resetting of the osmostat for AVP release and potentially characterizes a distinct subset of schizophrenia patients with enhanced stress reactivity.

Moderate chronic hyponatremia is frequently a consequence of medication-induced impairments in water excretion, which may or may not be compounded by primary polydipsia. The impairment in water excretion in these cases tends to be more marked and stable, resembling classic SIADH. When hyponatremia occurs outside of these scenarios other causes must be vigorously pursued.

Prevention of water intoxication in the PIP syndrome includes targeted fluid restriction, clozapine, and vasopressin antagonism. For medication-induced hyponatremia the offending agent should be discontinued and replaced. Antipsychotic medication is rarely responsible for hyponatremia in severe mental illness, and routine discontinuation may aggravate the water imbalance.

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Chapter 12
Management of Medication-Related Adverse Effects

Wanlop Atsariyasing and Morris Goldman

Introduction

The first part of this chapter reviews the major adverse effects (AEs) which typically influence antipsychotic selection: Sudden death, Movement disorders, Hyperprolactinemia, Sexual dysfunction, and Metabolic syndrome. For each of these AEs we divide the discussion into three parts: (1) *definition*, *significance*, *patient risk factors, and mechanisms*; (2) *risks of different antipsychotics*; *and* (3) *guidelines for prevention and treatment*. Since metabolic syndrome and other risk factors relevant to cardiovascular disease are discussed in detail elsewhere (Chap. 10), we restrict ourselves to those issues most relevant to antipsychotic therapy. Next, we consider advanced age because of specific concerns for this group of patients, especially those with dementia. There are many elderly patients who receive antipsychotics who do not have a history of schizophrenia, and most of the data reported here is not specific to the schizophrenic patient. Clozapine is also considered separately because its risk–benefit ratio differs from other agents. Finally, we consider less common but severe AEs which require immediate attention including neuroleptic malignant syndrome (NMS), laryngeal dystonia, thromboembolism, and respiratory distress in the newborn.

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P.G. Janicak et al. (eds.), *Schizophrenia: Recent Advances in Diagnosis and Treatment*,
DOI 10.1007/978-1-4939-0656-7_12,

Sudden Death

Definition, Significance, Patient Risk Factors, and Mechanisms

Since the 1960s, antipsychotics have been associated with an increased risk of sudden death (e.g., thioridazine) [1]. This is the unexpected death of an individual which occurs within 1 h of the onset of acute symptoms if there are witnesses, or the unexpected death of an individual who is known to have been medically stable less than 24 h previously if there are no witnesses [2]. The risk of sudden death in patients receiving antipsychotics is reported to be 2.4 times higher than those who did not receive these medications, and appears to increase with dose [3–7]. The incidence of sudden death is 2.9 events per 1,000 patient-years which is substantially higher than other recognized antipsychotic-related safety concerns (e.g., the rate of death from clozapine due to agranulocytosis is approximately 0.2 per 1,000 patient-years) [7, 8].

In addition to medication, other risk factors for sudden death in psychotic patients include female gender, hypertension, diabetes mellitus, increased age, cardiovascular disease, and electrolyte imbalance [1–3, 9]. Stroke, aortic dissection, and pulmonary embolism (PE) are also potential consequences of long-term antipsychotic therapy and may contribute to sudden death. The increased incidence, however, is largely attributable to the metabolic syndrome discussed here and in Chap. 10. Further, assessing the role of antipsychotics in sudden death is complicated by the approximate fourfold higher mortality risk of having schizophrenia, which at least over the typical 8- to 16-week, double-blind, placebo-controlled study time frame is similar in treated and untreated patients [10].

Antipsychotics likely contribute to some cases of sudden death due to their acute arrhythmogenic potential [2]. In most cases, other risk factors are typically present (Tables 12.1, 12.2, and 12.3). Because life-threatening arrhythmias are rarely observed, and their etiology even more rarely deduced, their role (i.e., primary or secondary) in sudden death is difficult to determine. Instead, primary arrhythmogenic risk is inferred from measures of the QT interval on an electrocardiogram (ECG). Increases in the QTc interval may trigger torsade de pointes (TdP), an arrhythmia which can cause ventricular fibrillation and death [1, 11–13].

The QT interval starts at the QRS complex and ends at the T wave (Fig. 12.1). It represents the time between the onset of ventricular depolarization and the end of repolarization. The QT interval varies with the heart rate (i.e., the lower the heart rate, the longer the QT interval). Various formulas correct for heart rate (QTc), the most commonly used being Bazett's formula (QTc = QT interval in seconds divided by the square root of the RR interval in seconds, $QT/RR^{½}$). QT measurement may be influenced by a number of factors including the shape of the U wave, ECG paper speeds, ECG lead placement, gender, time of day, and menstrual cycle [12]. QTc interval is considered prolonged if it is greater than 450 ms for men and 470 ms for women [14]. Most, but not all evidence, supports the inference that QTc interval prolongation increases the risks of TdP and sudden cardiac death [1, 12, 15–18].

Table 12.1 Risk factors of QTc prolongation and TdP [1, 12, 13, 17, 22, 242–245][a]

Cardiovascular disease
Congenital long QT syndrome
Bradycardia
Ischemic heart disease
Myocarditis
Myocardial infarction
Congestive heart failure
Left ventricular hypertrophy
Electrolyte imbalance
Hypokalemia
Hypomagnesemia
Hypocalcemia
Pharmacokinetic factors
Poor metabolizer
Inhibition of specific cytochrome P450 enzymes
Competition of specific cytochrome P450 enzymes
Others
Older age
Female gender
Extreme physical exertion
Restraint and psychological stress
Anorexia nervosa
Renal and hepatic impairment
Obesity (BMI > 25)

QTc corrected QT interval, *TdT* Torsades de Points
[a]See Table 12.2 for additional medications which prolong the QT interval

Table 12.2 Other drugs associated with QT prolongation [2, 12, 17, 19, 244, 246–249]

Psychotropics	*Antiarrhythmics*
Bupropion	Amiodarone
Citalopram	Bretylium
Escitalopram	Disopyramide
Fluoxetine	Dofetilide
Lithium	Ibutilide
Sertraline	Procainamide
Trazodone	Quinidine
Tricyclic antidepressants	Sotalol
Venlafaxine	*Others*
Antibiotics	Amantadine
Clarithromycin	Cyclosporin
Co-trimoxazole	Diphenhydramine
Erythromycin	Domperidone
Fluoroquinolones	Hydroxyzine
Antimalarials	Methadone
Chloroquine	Nicardipine
Mefloquine	Ondansetron
Quinine	Tamoxifen
	Terfenadine

Table 12.3 Antipsychotic medications and commonly used enzyme inhibitors [2, 12, 244, 250]

Cytochrome P(CYP)450 enzyme	Substrate	Inhibitor
CYP1A2	Clozapine	Ciprofloxacin
	Haloperidol	Fluvoxamine
		Grapefruit juice
CYP2D6	Butyrophenones (e.g. haloperidol)	Beta-blockers (e.g. propanolol)
	Phenothiazines (e.g. chlorpromazine, thioridazine)	Bupropion
	Thioxanthines (e.g. flupentixol)	Fluoxetine
	Clozapine	Haloperidol
	Risperidone	Paroxetine
	Sertindole	Phenothiazines
	Zuclopenthixol	Quinidine
		Tricyclic antidepressants
CYP3A4	Risperidone	Grapefruit juice
	Quetiapine	HIV proteases inhibitors (e.g. indinavir, ritonavir)
	Pimozide	Itraconazole
		Ketoconazole
		Macrolide antibiotics (e.g. clarithromycin)
		Nefazodone

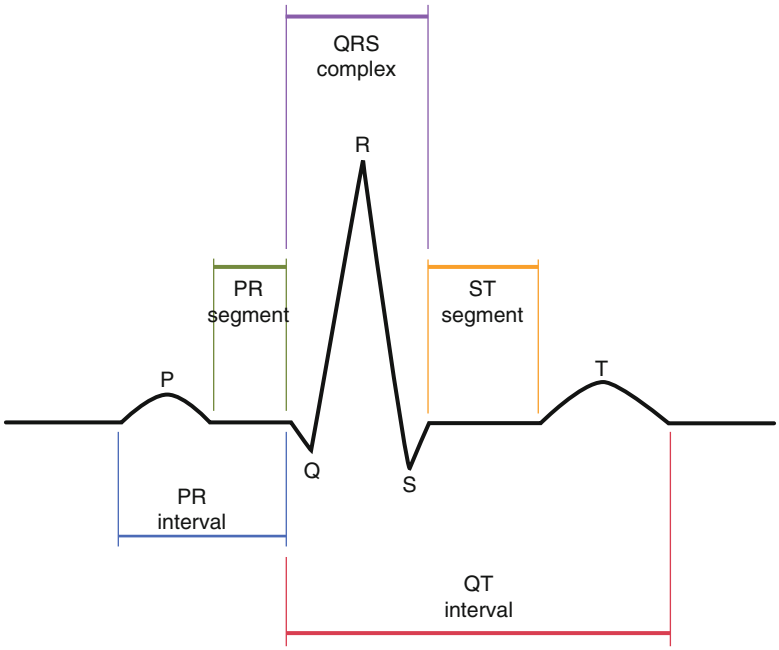

Fig. 12.1 QT interval

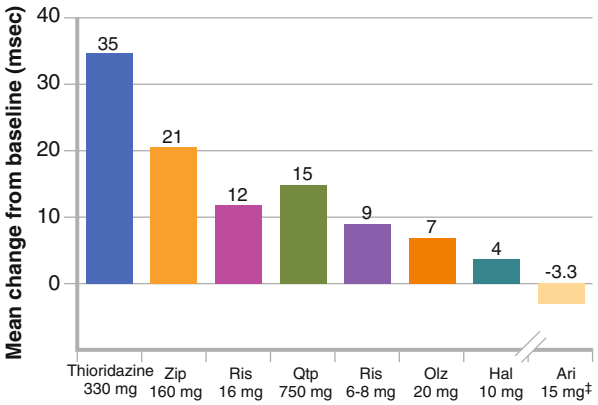

Fig. 12.2 Mean change from baseline in QTc for antipsychotics. Bazett's correction. Study 054 as presented to FDA; 2000 [257]. Proposed USPI data for aripiprazole. Data on file Bristol-Myers Squibb

The evidence is strongest for QTc durations greater than 500 ms and for QTc increases from baseline greater than 60 ms [12, 13].

Antipsychotics prolong the QT interval by blocking the HERG potassium ion channels in cardiomyocytes [13, 19–22]. TdP is a ventricular arrhythmia characterized by a gradual change in the amplitude and twisting of the QRS complex around the isoelectric line. Although usually spontaneously reversible, it can cause palpitations, dizziness, syncope, and sudden death [1, 13].

Risks of Different Antipsychotics

All antipsychotics can increase the QT interval. Thioridazine, pimozide, ziprasidone, droperidol, and intravenous haloperidol pose the greatest risks [19, 21, 23–25]. Increases in QTc duration with thioridazine and ziprasidone are approximately 25 and 10 ms more than other antipsychotics (Fig. 12.2). Nearly all cases of clinically significant intravenous haloperidol-related QTc prolongation occur in intensive care settings, with concomitant risk factors and with cumulative doses more than 2 mg. Such effects with haloperidol may be seen for up to 8 h after the last dose [16, 26, 27].

The Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) study found that 3 % of patients receiving risperidone and quetiapine developed QTc prolongation [28]. In a study of 61 patients treated with clozapine, QTc duration over 500 ms was seen in two patients and occurred in a dose-dependent fashion [29]. Paliperidone may cause minor prolongation in QTc, approximately 7 and 12 ms more than placebo at doses of 4 and 8 mg/day, respectively [30–32]. Iloperidone can increase QTc approximately 9 ms at doses of 8 and 12 mg twice/day and 15 ms at a dose of 24 mg/day [33]. Asenapine and lurasidone may cause smaller increases in QTc, approximately 2–5 ms

for asenapine (5–20 mg/day) and 5 ms for lurasidone (40, 120 mg/day) [34, 35]. Aripipazole generally has even less of an effect on QTc. Hence, all these agents are associated with a lower QT prolongation than ziprasidone.

Guidelines for Prevention and Treatment

Given the risk of sudden death from antipsychotic medications, *physicians should screen for risk factors associated with QTc prolongation*, *TdP*, *and sudden cardiac death before prescribing antipsychotics* (see Table 12.1). Inquiry should be made about a personal or family (e.g., long QT syndrome) history of cardiac disease, recurrent syncope, or sudden cardiac death [1, 2, 17]. An ECG should be obtained at baseline and after initiating treatment if a patient has any of these risk factors. Combining antipsychotics with medications which also prolong the QTc interval or inhibit cytochrome P450 enzymes should be avoided in these patients (Tables 12.2 and 12.3) [1, 22].

Once treatment is initiated, an ECG should be repeated in patients who develop syncope or dizziness, especially in the context of diarrhea, emesis, electrolyte imbalance, antidiuretic medications, or concurrent medications that prolong QTc or inhibit specific cytochrome P450 enzymes [1, 17, 36]. If QTc prolongation or cardiac arrhythmia develop, dose reduction or switching to lower risk medications and consultation with a cardiologist are appropriate.

Movement Disorders

Definition, Significance, Patient Risk Factors, and Mechanisms

Antipsychotics cause a variety of movement disorders or extrapyramidal symptoms (EPS) which negatively influence quality of life in patients with schizophrenia [37]. There are four major movement disorders associated with antipsychotic use: acute dystonia, akathisia, parkinsonism, and tardive dyskinesia (TD).

Acute dystonia is characterized by sustained contraction of voluntary muscles leading to abnormal postures and pain. The contraction may last from minutes to hours [38]. The most commonly affected site is the head and neck area, although any body part can be involved. Presentations include oculogyric crisis, laryngeal dystonia, blepharospasm, trismus, and torticollis [39]. Ninety-five percent of all cases appear within the first 4 days of starting or increasing the dose of antipsychotic [40]. The prevalence is widely variable, ranging from 2.3 to 94 % [39]. Patient risk factors include younger age, male sex, use of cocaine, and a previous history of acute dystonia [40].

Akathisia consists of a subjective and an objective component. Subjectively, patients complain of inner restlessness. Objectively, akathisia manifests as increased

Table 12.4 Differential diagnoses of akathisia [41, 207, 251]

Agitation related to psychotic symptoms or mood symptoms
Anxiety
Restless legs syndrome
Tardive dyskinesia
Antipsychotic dysphoria
Drug withdrawal syndromes (e.g., opiates, cannabis)
Neurological disorders (e.g., Parkinson's disease, Huntington's disease)
Organic disorders (e.g., delirium, head injury, hypoglycemia, encephalitis)

motor activity described as complex, semipurposeful, repetitive movements reflecting their urge to move [39, 41]. For example, patients may constantly pace up and down, rock from foot to foot, frequently shift their body position in the chair, or repeatedly stand and sit. Akathisia is divided into subtypes depending on timing of onset. *Acute akathisia* develops soon after starting or increasing the dose of antipsychotic. It typically appears within the first 2 weeks and 90 % of cases occur within the first 10 weeks of initiating therapy [39]. *Tardive akathisia* develops after longer term use of an antipsychotic. *Withdrawal akathisia* refers to symptoms which occur after discontinuation or dose decrease usually within 6 weeks. The diagnosis of akathisia may be difficult to make because it can be caused by a number of disorders (Table 12.4). The incidence of akathisia varies from 21 to 75 % and its prevalence from 20 to 35 % [41]. There appear to be no patient specific risk factors for akathisia.

Parkinsonism consists of bradykinesia, rigidity, tremor, and postural instability. It is characterized by slowness and interruption of the normal flow of movement [38, 39]. Features include decreased facial expression, decreased arm swing, reduced volume and articulation of speech, and difficulty initiating movement. *Rigidity* is characterized by an increase in resting muscle tone and manifests as cogwheel and lead-pipe rigidity. *Tremor* appears at rest and resolves with movement. The tremor has a low frequency, wide amplitude, and typically affects the hands. *Postural instability* refers to impairment of righting reflexes and manifests as swaying backwards when rising from a chair, standing, or turning. Parkinsonism usually develops within the first 72 h of treatment with an antipsychotic and usually resolves after discontinuation of the offending drug. Its natural course is unknown if the drug is continued [39]. The prevalence of antipsychotic-induced parkinsonism during treatment with first generation antipsychotics (FGAs) varies between 50 and 75 % [42]. Risk factors include older age, female sex, history of antipsychotic-induced EPS, and Alzheimer's disease [42].

Tardive dyskinesia (TD) is characterized by involuntary writhing or purposeless, irregular movements. The most common type is *orofacial* and involves the oral-buccal areas. It consists of involuntary movements of the tongue, jaw, lips or face, such as tongue protrusion, lip smacking, and chewing [43]. Other less common presentations include *limb-truncal* movements, such as writhing movements of the fingers;

Table 12.5 Differential diagnoses of TD [43]

Ill-fitting dentures or dental problems
Stereotypies and mannerisms in schizophrenia
Tics
Akathisia
Neurological disorders (e.g., Wilson's disease, Huntington's disease, Syndenham's chorea)

head nodding and pelvis thrusting; and *respiratory* movements of the muscles and/or the diaphragm, such as fast irregular breathing pattern and dyskinetic movement of the abdomen. TD develops after months to years of treatment with an antipsychotic. It is aggravated by anxiety and volitional motor activity and disappears during sleep. TD is potentially irreversible. The mortality rates in patients with TD are approximately 2.5 times higher than patients without TD [44]. Differential diagnosis of TD includes a number of disorders (Table 12.5). The annualized incidence of TD is 3.9 % for second generation antipsychotics (SGAs) and 5.5 % for FGAs. Prevalence is 13.1 % for SGAs and 32.4 % for FGAs [45]. The incidence increases linearly at about 5 % per year for the first 5 years of FGA exposure [46, 47].

The main risk factors are older age, history of antipsychotic-induced EPS, and nonwhite race [48]. Other reported risk factors include brain damage or dementia, major affective disorder, treatment with anticholinergics, LAI antipsychotic formulations, prolactin-related sexual disturbances, and substance abuse [47–51]. There is evidence both for and against female sex, diabetes mellitus, antipsychotic dose, positive symptoms, and negative symptoms acting as additional risk factors [47–49, 51, 52].

Common Mechanisms

Efforts to explain EPS focus on the observed lower incidence with SGAs. One hypothesis is the high ratio of serotonergic (5-HT_{2A}) to dopaminergic (D_2) blockade. Since serotonin inhibits dopamine transmission, blocking serotonin receptors might increase dopamine release to an extent that some of the D_2 blockade is reversed, thereby reducing EPS [53]. SGAs block 5-HT_{2A} in addition to D_2 receptors. Neuroimaging studies show that clinical response occurs with D_2 occupancy rates around 65 % and EPS with occupancy rates around 78 %, indicating that, for a given antipsychotic, dose is important [54]. Other models include the "fast dissociation hypothesis" which postulates that SGAs bind to the D_2 receptor long enough to cause antipsychotic effects, but not long enough to cause EPS [55].

The pathophysiology of TD is uncertain, but two hypotheses have held sway for many years. The "dopamine supersensitivity hypothesis" states that long-term D_2 receptor blockade in the striatal area induces an up-regulation of receptor activity which causes dyskinetic symptoms [43, 53]. The "neurotoxicity hypothesis" states that antipsychotics increase dopamine metabolism, thereby releasing neurotoxic free radicals leading to damage of its receptors [53].

Risks of Different Antipsychotics

High potency FGAs (e.g. haloperidol) induce more EPS than low potency FGAs (e.g. chlorpromazine). SGAs induce fewer EPS than high potency FGAs, even when the latter are prescribed at low doses. Some SGAs (clozapine, olanzapine, and risperidone) have fewer EPS than low potency FGAs [56]. Among the SGAs, risperidone induces more EPS; quetiapine induces fewer EPS; and olanzapine induces fewer EPS than ziprasidone and aripiprazole [57].

Guidelines for Prevention and Treatment

Management of antipsychotic-induced EPS depends on their type and severity. In patients at high risk for **acute dystonia** (e.g., young males), prophylaxis with oral anticholinergic medications such as benztropine (1 mg two or three times daily) or trihexyphenidyl (5 mg one to two times daily) for the first week of treatment can reduce the incidence [39]. Anticholinergics are the treatment of choice for acute dystonia and are given orally or parenterally depending on the setting and severity of symptoms. Parenteral treatment such as diphenhydramine (50 mg) or benztropine (1–2 mg) can be repeated in 30 min if response is not sufficient. Other diagnoses (e.g., catatonia, tardive dystonia, or hypocalcemia) should be considered if the dystonia does not respond to repeated injections. Parenteral treatment is typically followed by oral anticholinergics for at least a few days to prevent recurrence.

Management of **acute akathisia** includes switching or decreasing the dose of antipsychotic. Pharmacological treatment for akathisia includes propranolol (starting at 10 mg three times daily and increasing every few days to a maximum of 90–120 mg/day) [41]. Blood pressure and heart rate should be closely monitored during dose titration. Limited evidence shows that benzodiazepines are also useful for treatment of akathisia [58]. There are a few double-blind, randomized controlled trials supporting the use of anticholinergics for akathisia. The quality of these trials is limited, however, due to their small sample sizes and concomitant benzodiazepine treatment [59–62]. Several agents, including mirtazapine, mianserin, cyproheptadine, zolmitriptan, trazodone, clonidine, and vitamin B6 are reported to be helpful in small, double-blind trials ($n<30$) [63–75]. Presently the most convincing evidence is for mirtazapine (15 mg/day).

In patients at high risk for antipsychotic-induced or preexisting **parkinsonism**, starting or switching to low potency FGAs or SGAs is appropriate when clinically feasible. The use of anticholinergics to prevent EPS is controversial. Anticholinergic prophylaxis may benefit certain high-risk patients such as younger males receiving treatment with high potency antipsychotics and a previous history of EPS. Generally, however, they are not beneficial for routine prophylactic use in most patients [76, 77]. There are several strategies to manage antipsychotic-induced parkinsonism. These include dose reduction, switching to a medication with lower EPS risk or adding antiparkinsonian agents. Dose reduction and medication switching should be considered before using an antiparkinsonian drug, because these medications have their own adverse effects. The most common medications used to treat

antipsychotic-induced parkinsonism are anticholinergics such as benztropine (1–6 mg/day) or trihexyphenidyl (5–15 mg/day). These agents, however, can cause a number of adverse effects including cognitive impairment, delirium, blurred vision, dry mouth, tachycardia, urinary retention, and constipation. There is also a potential for anticholinergic abuse, a worsening of TD, and drug-induced psychosis [42, 78]. These effects are particularly concerning in the elderly. If prescribed for this age group, their use should be reviewed every 3 months and slowly tapered (to avoid cholinergic rebound and re-emergence of EPS) when patients are psychiatrically stable and have undetectable EPS [77, 78]. Limited evidence shows that amantadine (100–400 mg/day) is comparable to anticholinergic medications but has fewer cognitive and peripheral adverse effects. It may, however, carry a greater risk for aggravating psychosis [79–81].

To minimize the risk of **tardive dyskinesia**, antipsychotics should be used at the lowest effective dose and discontinued when clinically appropriate. Although there are more than 500 randomized controlled trials evaluating over 90 different interventions to treat TD, they have not produced sufficient evidence to recommend a definite treatment [82]. If discontinuation of antipsychotics is possible, clinicians should be aware that TD may worsen initially, with the severity returning to the level before discontinuation after 6–12 weeks [43]. Discontinuation can lead to complete resolution of TD, particularly when the duration of TD is short and patients are younger than 50–60 years [43]. There are, however, no randomized controlled trials evaluating antipsychotic cessation to treat TD [83]. If discontinuation is not possible, other treatment options include dose reduction, switching to an alternate antipsychotic, and adding other agents. There are two small, double-blind, randomized controlled trials evaluating the effects of 50 and 90 % reduction in dose compared with the continuation of the current dose [83–85]. The results indicated that dose reduction was not associated with either improvement or worsening of TD [83–85]. Switching to clozapine or quetiapine may be effective [43]. Small trials demonstrate that tetrabenazine diminishes TD; however, its use is limited by cost and adverse effects such as depression, parkinsonism, and somnolence [86]. Vitamin E may protect against further deterioration but does not appear to improve symptoms of TD [87]. There is no compelling evidence supporting cholinergic medications, benzodiazepine, or calcium channel blockers for TD or for adding or withdrawing anticholinergic medications [88–91]. Finally, bilateral deep brain stimulation of the globus pallidus may be effective and relatively safe for patients with severe, disabling, treatment-resistant TD [92–94].

Hyperprolactinemia and Sexual Dysfunction

These two adverse effects are considered under a single heading because hyperprolactinemia is one of the major contributors to sexual dysfunction. It is also associated with other adverse effects, while other pharmacologic effects may also contribute to sexual dysfunction.

Hyperprolactinemia

Definition, Significance, Patient Risk Factors, and Mechanisms

Hyperprolactinemia is a common but frequently undetected adverse effect of antipsychotics. While normal serum prolactin levels vary between different laboratories, they are usually below 20 for men and 25 μg/L for women [95]. Higher levels are considered diagnostic, though during pregnancy and breast-feeding the levels can increase 10–20 times above the nonpregnant values [96, 97]. Prolactin is secreted by the lactotroph cells in the pituitary and its main physiological function is to induce milk production in mammary glands. Dopamine, via its tuberoinfundibular pathway, is the predominant inhibitory factor for prolactin secretion. Blockade of D_2 receptors on lactotroph cells removes the inhibitory effect leading to hyperprolactinemia. Antipsychotic-induced hyperprolactinemia is often, but not always, dose-related [98, 99]. Levels begin to increase a few hours after initiating antipsychotics, persist throughout treatment and, following discontinuation, return to normal range within 2–3 weeks after oral treatment and 6 months after intramuscular treatment [100, 101].

The prevalence of antipsychotic-induced hyperprolactinemia among psychiatric patients is 42 % for men and 66 % for women [102]. Direct action of prolactin causes gynecomastia in men and galactorrhea in both sexes. Gynecomastia, however, is relatively rare, occurring in 2 % of male patients [103]. High prolactin levels inhibit the hypothalamic-pituitary-gonadal axis at several levels resulting in a reduction of gonadal hormone levels (estrogen in women and testosterone in men). Symptoms of secondary hypogonadism include sexual dysfunction, menstrual abnormalities, and infertility. Forty to 50 percent of female patients with hyperprolactinemia experience menstrual abnormalities with an association between increasing prolactin level and increasing risk [102]. Long-term hypogonadism can lead to decreased bone mineral density (BMD). In one study of premenopausal women with schizophrenia who took antipsychotics for approximately 8 years, hyperprolactinemia was associated with low BMD (i.e., 62 % of those with hyperprolactinemia had a low BMD versus only 11 % of those without hyperprolactinemia) [104]. The relationship between antipsychotic use and increased risk of breast cancer is controversial. A recent well-designed study, however, concluded that women receiving prolactin-raising antipsychotics have a modest but significantly increased risk [96, 105].

Patient risk factors for hyperprolactinemia include female sex, the postpartum period, and younger age [96, 98, 102, 106]. In addition, renal and hepatic failure, hypothyroidism and pituitary tumors can increase this risk (Table 12.6).

Risks of Different Antipsychotics

FGAs and some SGAs (e.g., risperidone and paliperidone) significantly elevate prolactin levels [31, 107]. Other SGAs including clozapine, olanzapine, quetiapine,

Table 12.6 Differential diagnoses of hyperprolactinemia [96, 97, 100, 106, 107, 252]

Physiological conditions	*Medications*
Pregnancy	Antidepressants (TCAs, MAOIs, SSRIs)
Lactation	Antihypertensive (verapamil, methyldopa, reserpine)
Sleep	Antiemetics (metoclopramide, domperidone)
Stress	H2 receptor blockers (ranitidine, cimetidine)
Exercise	Hormones (estrogens, oral contraceptives, protirelin, antiandrogens)
Sexual activity	Others (opiates, cocaine, protease inhibitors)
Breast stimulation	
Pituitary diseases	*Endocrine diseases*
Prolactinoma	Cushing's disease
Adenomas	Polycystic ovarian disease
Empty sella syndrome	Acromegaly
Pituitary stalk section	Primary hypothyroidism
Lymphoid hypophysitis	
Hypothalamic diseases	*Miscellaneous*
Hypothalamic tumors	Cirrhosis
Hypothalamic sarcoidosis	Chronic renal failure
Postencephalitis	Chest wall lesions (trauma, tumors, herpes zoster)
	Ectopic production of prolactin (small-cell bronchial carcinoma)

ziprasidone, and aripiprazole are rarely implicated [107]. A recent review indicates that aripiprazole can lower prolactin levels an average of 74.3 %, even in psychotic patients with prolactinoma [108].

Guidelines for Prevention and Treatment

Screening for hyperprolactinemia is not routinely done [100]. A serum prolactin level should be obtained, however, if a patient presents with related symptoms. A single measurement of serum prolactin at any time of the day without excessive venipuncture stress is sufficient to establish the diagnosis. A level above the upper limit of normal (e.g., 20 μg/L for men and 25 μg/L for women; 1 μg/L = 21.2 mIU/L) confirms the diagnosis [95, 97]. A prolactin level above 250 μg/L usually indicates a prolactinoma and above 500 μg/L indicates a macroprolactinoma, though risperidone and some phenothiazines are linked to elevations above 200 μg/L in patients without evidence of adenoma [97]. If highly elevated prolactin levels do not return to normal following discontinuation, magnetic resonance imaging (MRI), or computed tomography (CT) of the hypothalamic-pituitary area should be obtained to exclude a mass lesion [107].

The first step in treatment of antipsychotic-induced hyperprolactinemia is to determine if the patient is significantly symptomatic. Reassurance may be sufficient for a woman with normal menses who has only some non-bothersome galactorrhea, whereas more active treatment is required when significant symptoms (e.g., bothersome galactorrhea, decreased libido, amenorrhea, and osteoporosis) occur [97, 107]. If a patient is symptomatic and requires continuation of an antipsychotic,

switching to aripiprazole can lower prolactin levels and resolve symptoms of antipsychotic-induced hyperprolactinemia [108]. Switching to another prolactin-sparing agent is also effective [96, 97, 107]. In the unlikely event that none of these are clinically effective, adjunctive treatment with a D_2 receptor agonist such as bromocriptine (5.0–7.5 mg/day) or cabergoline (0.125–0.250 mg/day) may help [96, 107]. Bromocriptine, however, can cause a psychotic relapse, postural hypotension, gastrointestinal symptoms, and vasospasm of the fingers and toes. A recent meta-analysis found that cabergoline was superior in normalizing prolactin levels and restoring gonadal function; better tolerated with fewer adverse events compared with bromocriptine; and effective in patients resistant to bromocriptine [97, 109]. If estrogen or testosterone levels are decreased, these hormones can be supplemented. With osteoporosis, a bisphosphonate should be considered [107].

Sexual Dysfunction

Definition, Significance, Patient Risk Factors, and Mechanisms

Sexual dysfunction is a distressing adverse effect, not surprisingly associated with poorer adherence [110]. A large, international study found that sexual dysfunction affected approximately 50 % of both male and female antipsychotic-medicated patients [111]. Another study reported that the rates of sexual dysfunction in an outpatient schizophrenia clinic resembled those in a specialized sexual dysfunction clinic [112]. Women appear 15 times more likely and men 4 times more likely to complain of sexual dysfunction compared with gender-matched healthy controls [112]. Despite the high prevalence, sexual dysfunction is typically discounted by psychiatrists [111, 113].

Other factors which contribute to sexual dysfunction in patients with schizophrenia include their psychopathology; social sequelae of the illness; medical illnesses; and alcohol abuse [96]. Antipsychotic dose is correlated with sexual dysfunction, while other risk factors include low potency FGAs, polypharmacy, severity of illness, and depot FGAs in women [113, 114].

Antipsychotics may affect sexual function via dopaminergic, histaminergic, cholinergic, and α-adrenergic receptor actions leading to diminished motivation and reward, increased sedation, and reduced performance [96]. The role of prolactin in sexual dysfunction is not entirely clear, though its incidence largely parallels the classification into prolactin-raising and prolactin-sparing antipsychotics [112, 115, 116].

Risks of Different Antipsychotics

Quetiapine, ziprasidone, perphenazine, and aripiprazole are associated with relatively low total sexual dysfunction rates (16–27 %), whereas olanzapine, risperidone, haloperidol, clozapine, and thioridazine are associated with relatively high rates (40–60 %) [117]. Aripiprazole is associated with the lowest rates for each

aspect of sexual dysfunction. The liability of antipsychotics for phase-specific sexual dysfunction, including *desire*, *arousal, and orgasmic dysfunction* are about the same as for total sexual dysfunction [117]. More variability is demonstrated by clozapine, however, which is associated with relatively low rates of arousal and orgasmic dysfunction, and haloperidol which is associated with relatively low rates of orgasmic dysfunction [117].

Guidelines for Prevention and Treatment

Management of antipsychotic-induced sexual dysfunction includes decreasing the dose, switching to a medication with lower risk, and adding medication to specifically target these symptoms. Dose reduction should be beneficial, but has not been clearly established. Switching to aripiprazole is the most studied strategy [118]. Aripiprazole can improve sexual function and lower prolactin levels compared with olanzapine, quetiapine, or risperidone [119]. A randomized, placebo-controlled trial in male patients with antipsychotic-induced erectile dysfunction reported that sildenafil (25 or 50 mg/day) significantly improved the number of adequate erections, satisfactory sexual intercourse, and the duration of erections [120]. Another study of sildenafil for treatment of psychotropic-induced sexual dysfunction in psychiatric patients reported significant improvements in all domains for both men and women [121].

Metabolic Syndrome

The metabolic syndrome is discussed in greater detail in Chap. 10. We focus primarily on the contribution of antipsychotic medications.

Definition, Significance, Patient Risk Factors, and Mechanisms

The metabolic syndrome is a cluster of risk factors which increase the likelihood of developing type 2 diabetes mellitus and cardiovascular disease (Table 12.7). As a result, the average life expectancy for patients with schizophrenia is 10–25 years shorter than the general population. Overall, the prevalence of and the mortality from cardiovascular disease is two- to three-fold higher for patients with schizophrenia than the general population [122, 123].

In addition to generic disease-based factors, personal and family history of obesity, diabetes, dyslipidemia, hypertension, or cardiovascular disease contribute to the risk of developing or aggravating preexisting metabolic syndrome. Some patient risk factors, however, appear counter-intuitive. Thus, a significant predictor of antipsychotic-induced weight gain appears to be lower baseline body mass index

Table 12.7 Metabolic syndrome criteria [253–255]

Risk factor	IDF (central obesity plus ≥2 other factors)	ATP III (≥3 factors)
Waist circumference (*cm*)		
Men	≥94 for Europids ≥90 for South Asians and Chinese	>102 for Europids
Women	≥80 for Europids ≥80 for South Asians and Chinese	>88 for Europids
Triglycerides (mg/dL)	≥150	≥150
HDL cholesterol (*mg/dL*)		
Men	<40	<40
Women	<50	<50
Blood pressure (mmHg)	≥130/85	≥130/85
Fasting plasma glucose (mg/dL)	≥100	≥100[a]

IDF International Diabetes Federation, *ATP* adult treatment protocol
[a]Originally ≥110

(BMI) [124]. Other predictors include younger age, nonwhite ethnic background, tendency to overeat in time of stress, cannabis use, and first episode psychosis [125].

Antipsychotics increase the risk of the metabolic syndrome through various mechanisms [125, 126]. They cause weight gain via activity at histamine H_1, serotonin 5-HT_{2C}, serotonin 5-HT_{2A}, muscarinic M_3, and adrenergic receptors [127]. They alter insulin and glucose metabolism by decreasing pancreatic *B*-cell responsiveness via effects on the 5-HT_{1A} receptor and suppressing skeletal muscle glucose uptake via 5-HT_{2A} receptor effects [128]. In addition, some antipsychotics may act on adipocytes to alter insulin action, lipogenesis, and lipolysis leading to lipid accumulation [129].

Risks of Different Antipsychotics

The incidence of metabolic syndrome and the individual contributory risk factors vary markedly across agents. Specifically, the risk of the metabolic syndrome is highest with clozapine and olanzapine; moderate with quetiapine, risperidone paliperidone, iloperidone, and asenapine; and low with aripiprazole, ziprasidone, lurasidone, haloperidol, and perphenazine [130, 131]. Related adverse effects are commonly seen in the first 3 months of exposure to olanzapine [132]. The development of metabolic risk factors is predicted by clozapine and olanzapine plasma concentrations [133]. Patients, however, may present early in the course of treatment with life-threatening diabetic ketoacidosis (DKA) even before other symptoms such as weight gain occur (Chap. 10) [134].

Weight gain is a major risk factor and occurs most with clozapine and olanzapine and least with aripiprazole and ziprasidone [124, 130, 135, 136]. Weight gain appears to be dose-related with clozapine and olanzapine, averaging about 1.5 lbs per month, particularly in the first months of treatment. The time period over which

weight continues to accumulate varies among drugs. For example, weight gain continues beyond the first year with clozapine but stabilizes at about 9 months with olanzapine and haloperidol [124].

Clozapine and olanzapine are associated with the highest risk of **insulin resistance**, whereas ziprasidone and amisulpride are associated with the lowest risk [28, 137–140]. Quetiapine, risperidone, haloperidol, and perphenazine also have negative effects on glucose regulation [28, 137, 138]. Changes in glucose regulation are usually seen within 6 weeks of initiating treatment with antipsychotics [138]. An average change in blood glucose of about 14 mg/dL and glycosylated hemoglobin of about 0.40 % occurs in patients treated with olanzapine within 18 months [28]. In contrast, ziprasidone and amisulpride can improve glycemic parameters, including glycosylated hemoglobin and fasting blood glucose over 6 months [28, 139, 140].

The risk of antipsychotic-induced **dyslipidemia** is greatest with olanzapine and least with ziprasidone and aripiprazole [28, 137, 140–147]. Clozapine, quetiapine, haloperidol, and perphenazine may induce dyslipidemia, whereas an association between risperidone and dyslipidemia is controversial [28, 137, 143, 148]. Dyslipidemia associated with olanzapine tends to be dose-related [149]. Olanzapine can increase total cholesterol an average of 10–30 mg/dL and triglycerides an average of approximately 30 mg/dL within 8 weeks of initiating treatment [137, 141, 149]. In this context, ziprasidone and aripiprazole can improve lipid parameters, including total cholesterol, triglycerides, low-density lipoprotein, and high-density lipoprotein [28, 140, 142, 145–147].

Guidelines for Prevention and Treatment

Given the serious health risks associated with the metabolic syndrome, patients taking antipsychotics should receive baseline screening and ongoing monitoring [150]. Consensus guidelines developed jointly by the American Diabetes Association, American Psychiatric Association, American Association of Clinical Endocrinologists, and North American Association for the Study of Obesity recommend screening for and monitoring of metabolic risk factors as follows:

- Personal and family history of obesity, diabetes, dyslipidemia, hypertension, or cardiovascular disease at baseline
- Weight and height (BMI for adults and BMI percentile for children and adolescents) at baseline, every 4 weeks during the first 12 weeks and quarterly thereafter
- Waist circumference (at the level of the umbilicus) at baseline and then annually
- Blood pressure at baseline, at 12 weeks and then annually
- Fasting plasma glucose at baseline, at 12 weeks and then annually
- Fasting lipid profile at baseline, at 12 weeks and then every 5 years

These guidelines also emphasize educating patients, family members, and caregivers about the signs and symptoms of diabetes and DKA, and referring patients with metabolic dysregulation to appropriate healthcare professionals [150].

Management of patients who gain weight or develop metabolic dysregulation during treatment with antipsychotic medications includes non-pharmacological and pharmacological interventions. *Non-pharmacological interventions* are effective in preventing and treating antipsychotic-induced weight gain and other metabolic risk factors for metabolic syndrome [151, 152]. The interventions include dietary counseling, increasing energy-consuming activities, behavioral therapy, and smoking cessation [153–156]. *Pharmacological interventions* may include switching to another agent with a lower risk or which can reverse weight gain and metabolic dysregulation [136, 150]. There is strong evidence for switching to aripiprazole and ziprasidone, while adding aripiprazole to clozapine also reverses weight gain [145, 157–163]. Current best evidence indicates metformin at doses of 750 and 1,000 mg in divided doses for 12 weeks to prevent and reverse antipsychotic-induced weight gain and insulin resistance (see Chap. 10 for additional information about management) [164–168].

Advanced Age

While the risk of most adverse effects reviewed above increases with age, there are particular concerns for the elderly, especially those with dementia. Interestingly, these risks do not seem to vary as much across different antipsychotics for elderly patients with and without schizophrenia and hence risks of different medications are integrated into the first section below. In some cases, risks are clearly elevated in those with dementia versus age-matched controls, but this question remains unresolved for many adverse effects.

Definition, Significance, Patient Risk Factors, and Mechanisms

An older (or elderly) person is defined as a chronological age of 65 years or more, particularly in Western countries [169]. Antipsychotics are commonly used to treat both behavioral and psychological symptoms in elderly patients, particularly those with dementia. In the USA, an average of 620,000 elderly patients receive an antipsychotic annually [170]. Frequently reported diagnoses among those patients are dementia (26 %), anxiety (20 %), and schizophrenia (7 %) [170].

Antipsychotics increase the risk of *death* (1.2–1.6 times) in elderly patients with dementia versus those without dementia [171]. The risk is similar when comparing FGAs and SGAs, and no specific medication is proven safer [171]. Patient risk factors for death include older age, male sex, severity of dementia, and functional impairment [171]. Recent meta-analyses reported that the risk of *cerebrovascular events* is 1.3–2 times higher in those with dementia and the risk is similar for FGAs and SGAs, particularly at higher doses. Risk factors include older age, vascular

dementia, atrial fibrillation, hypertension, a history of previous stroke, and concurrent use of anticoagulants [171, 172]. As noted above, the elderly receiving antipsychotics are at increased risk for *cardiac arrhythmias* and the association with dementia is not known [17]. Antipsychotics increase the risk of *falls and hip fractures* in the elderly [173–176]. Evidence about the differential risk between FGAs and SGAs is inconclusive [177]. The risk increases within 1 week after exposure to FGAs or SGAs but stabilizes at a higher level with exposure beyond 12 weeks [176]. An antipsychotic increases the risks of both hospital- and community-acquired *pneumonia* in the elderly with or without dementia and is highest during the first week [176, 178–180]. Data comparing the liability between FGAs and SGAs are conflictual [176, 178–180]. A few studies also report an association between antipsychotics and an increased risk of *venous thromboembolism* (VTE) in elder patients either with or without dementia; however, a recent study could not replicate the findings [181–183].

The Clinical Antipsychotic Trials of Intervention Effectiveness-Alzheimer's Disease (CATIE-AD) study found that SGAs had an adverse effect on weight, but surprisingly no effect on glucose levels, total cholesterol, or triglyceride in patients with schizophrenia and dementia [184]. Other studies confirm no association between antipsychotics and diabetes in the elderly [185–188]. Of note, the risk of developing antipsychotic-induced movement disorders in patients with dementia is similar for FGAs and SGAs [189, 190].

Mechanisms regarding increased sensitivity to antipsychotics in the elderly are not fully understood. They may involve age-related changes in peripheral and central pharmacokinetics and pharmacodynamics. Specifically, plasma levels in elderly patients are higher for a given dose; permeability of the blood–brain barrier increases with aging; and age-related decreases in endogenous dopamine levels and receptors result in higher susceptibility to clinical/adverse effects for a given level of occupancy [191].

Guidelines for Prevention and Treatment

Given the increased mortality and morbidity among elderly patients treated with antipsychotics, clinicians should consider non-pharmacological approaches (e.g., by modifying the environment, improving communication, and optimizing social contacts) before prescribing these agents [192]. Antipsychotics should be especially avoided in elderly patients with risk factors for cerebrovascular adverse effects including vascular dementia, hypertension, atrial fibrillation, or a history of stroke [171, 172]. If necessary, these medications should be started at a low dose, increased slowly, and maintained at the minimally effective dose [193]. The need for continued medications should be reviewed regularly to avoid unnecessary exposure and patients should be monitored regularly for hypotension, sedation, and EPS [193].

Clozapine

Clozapine is a very effective antipsychotic, frequently the treatment of choice for patients who are treatment-resistant or suicidal [194]. It is, however, associated with a number of serious adverse effects (i.e., the United States Food and Drug Administration (FDA) insert includes five boxed warnings). We review this agent's serious adverse effects, more common but less serious adverse effects and their management by organ system. In addition, we review evidence about the safety of rechallenge after an adverse effect has occurred.

Hematologic Adverse Effects

Clozapine has a range of adverse effects on blood components, particularly neutropenia and agranulocytosis [195]. Neutropenia is defined as a neutrophil count (ANC) less than 1,500/mm^3 or a white blood cell (WBC) count less than 3,000/mm^3. Agranulocytosis is defined as ANC less than 500/mm^3 or WBC less than 1,000 mm^3. The risk of developing neutropenia and agranulocytosis from clozapine is 3 % and 0.8 %, respectively. *The mortality rate due to clozapine-induced agranulocytosis is 3–4 %* of identified cases under the blood monitoring system with clozapine [196]. The risk of developing agranulocytosis is higher during the first 18 weeks of treatment and decreases thereafter (Table 12.8). Guidelines require the WBC to be monitored weekly for the first 18 weeks in the UK (6 months in the USA), then every other week to the end of the first year and every 4 weeks thereafter. The blood monitoring system is highly effective in reducing both the incidence of clozapine-related agranulocytosis and its associated mortality [197]. Agranulocytosis related to clozapine is an idiosyncratic (type B) reaction which is not dose-related [198]. Patient risk factors include older age, female sex, and its combination with other medications known to cause neutropenia or agranulocytosis (e.g., carbamazepine). If a patient develops an abnormal WBC or ANC during treatment, the recommendation according to the US clozapine monitoring system is shown in Table 12.9.

A recent review ($n = 112$) reported that 70 % of patients who developed neutropenia were successfully rechallenged with clozapine. Of the remaining 30 %, 44 % of those patients went on to develop agranulocytosis during their second exposure

Table 12.8 Incidence of clozapine-induced agranulocytosis [196]

Duration of clozapine treatment (weeks)	Incidence (per 1,000 patient-years)
0–18	7.77
18–52	0.83
>52	0.37

Table 12.9 Clozapine monitoring guideline [256]

Values	Actions
WBC ≥ 3,500/mm^3 and ANC ≥ 2,000/mm^3	Initiate therapy
WBC < 3,500/mm^3 and/or ANC < 2,000/mm^3	Monitor twice weekly until WBC > 3,500/mm^3 and ANC > 2,000/mm^3
WBC < 3,000/mm^3 and/or ANC < 1,500/mm^3	1. Temporarily discontinue therapy 2. Monitor daily until WBC > 3,000/mm^3 and ANC > 1,500/mm^3 3. After that monitor twice weekly until WBC > 3,500/mm^3 and ANC > 2,000/mm^3 and then rechallenge may be considered 4. If rechallenged, monitor weekly for 1 year before returning to the usual monitoring schedule of 2 weeks for 6 months and then every 4 weeks thereafter
WBC < 2,000/mm^3 and/or ANC < 1,000/mm^3	1. Permanently discontinue therapy 2. Monitor until normal and for at least 4 weeks from day of discontinuation as follows – Daily until WBC > 3,000/mm^3 and ANC > 1,500/mm^3 – Twice weekly until WBC > 3,500/mm^3 and ANC > 2,000/mm^3 – Weekly after WBC > 3,500/mm^3

to clozapine [199]. Of the 15 patients who developed agranulocytosis, 80 % failed rechallenge [199]. Therefore, clozapine rechallenge should not be considered in patients with previous agranulocytosis, and it should be undertaken carefully in patients with neutropenia only when other treatment options are not viable [194, 195, 199, 200].

Lithium, filgrastim, granulocyte colony-stimulating factor (G-CSF), and granulocyte-macrophage colony-stimulating factor (GM-CSF) may be useful in managing neutropenia and agranulocystosis [201]. Lithium can increase WBC counts approximately 2.0×10^9/L with a serum concentration of at least 0.4 mmol/L [202]. Lithium may also increase WBC counts for both patients with low baseline counts and those who develop neutropenia after treated with clozapine [195]. In addition, GM-CSF and G-CSF may shorten the duration of clozapine-induced agranulocytosis [202].

Cardiovascular Adverse Effects

Common cardiovascular effects include tachycardia (25 %), postural hypotension (9 %), and hypertension (4 %) [194]. Tachycardia is attributable to the anticholinergic activity of clozapine, elevated plasma norepinephrine levels, and hypotension [197]. Tachycardia may be transient and related to rapidity of titration [197]. Reducing the dose or adding a beta-blocker can help if it persists [194]. Postural hypotension is related to the alpha-adrenergic antagonistic properties of clozapine, usually transient and occurs at the beginning of treatment [197]. It is also influenced by the rate and magnitude of clozapine dose titration. While tolerance often develops,

it can persist and limit dose escalation. Isolated episodes of hypertension may also occur early in the course of treatment and are related to the rapidity of titration.

Clozapine-related myocarditis and cardiomyopathy are less common but potentially fatal. Myocarditis usually develops within 1 month of clozapine initiation and presents with fever (48 %), dyspnea (35 %), "flu-like illness" (30 %), chest pain (22 %), and fatigue (17 %) [203, 204]. The mechanism of clozapine-induced myocarditis is unclear; however, it may be related to an IgE-mediated hypersensitivity and a direct toxic effect on cardiac muscle followed by inflammatory infiltrates [205]. Factors associated with an increased risk of clozapine-induced myocarditis include high cumulative doses of clozapine (more than 920 mg) during days 1–9; concomitant use of sodium valproate; and increasing age [206]. Cardiomyopathy arises less acutely [194]. The most common type is dilated cardiomyopathy which often presents with symptoms of congestive heart failure [203].

Given that major cardiovascular adverse effects can occur within the first month, it is reasonable to perform an ECG at baseline and 2 and 4 weeks after starting treatment [203]. Clozapine should be titrated slowly and concomitant sodium valproate avoided [206]. If myocarditis is suspected, clozapine should be discontinued immediately. Clozapine rechallenge after myocarditis may be successful with a slower dose titration [206, 207].

Neurological Adverse Effects

Common neurological effects of clozapine include sedation (39 %), dizziness (19 %), and syncope (6 %) with tolerance usually developing [194]. Sedation is often mild, transient, and restricted to the initial treatment period [197]. It can be minimized by giving the majority of the dose at bedtime and avoiding concomitant central nervous system depressants. Nevertheless, since chronic sedation is an important issue, stimulants and stimulant-like drugs (e.g., dextroamphetamine, monafidil, methylphenidate, L-dopa) can potentially ameliorate it in some cases. There is limited, conflicting evidence, however, supporting their efficacy and they may worsen psychoses or induce movement disorders [208]. Two small, double-blind controlled trials reported no benefit with modanifil for treatment of clozapine-induced sedation [209, 210].

Clozapine can lower the seizure threshold and induce various types of episodes. The most common type is a generalized, tonic-clonic seizure, while myoclonic and atonic seizures occur less frequently [211]. Clozapine-induced seizures are dose-related with a 1 % risk at doses less than 300 mg/day; 2.7 % at 300–600 mg/day; and 4.4 % at more than 600 mg/day [211]. Plasma clozapine levels and screening EEGs are of limited value in predicting and diagnosing seizures [211]. Treatment for the first clozapine-induced seizure includes reducing the dose and eliminating other risk factors. If a second seizure occurs, an anticonvulsant should be initiated. Recommended anticonvulsants are valproate, lamotrigine, and gabapentin, while carbamazepine should be avoided because like clozapine it may cause bone marrow suppression [211].

Gastrointestinal Adverse Effects

The most common gastrointestinal effect of clozapine is constipation (14 %) [194]. Other less common effects include nausea, vomiting, bloating, heartburn, and abdominal pain. The mechanisms of these adverse effects may relate to the anticholinergic effects and 5-HT_3 receptors antagonism of clozapine [197, 212]. These effects can be managed with a high fiber diet, adequate hydration, and the use of bulk laxatives and stool softeners [197]. Since clozapine may induce gastrointestinal hypomotility (including dysphagia, ileus, intestinal obstruction, bowel ischemia, and megacolon) which may lead to a fatal outcome, prophylactic treatment with a stool softener is important.

Hypersalivation

Hypersalivation (31 %) is common, occurs early in treatment and is more profound during sleep [194]. Hypersalivation may result in parotitis, skin irritation, skin infection, aspiration pneumonia, and sleep disturbances. Further, it can be stigmatizing and lead to discontinuation of therapy [213, 214]. The pathophysiology of clozapine-induced hypersalivation is poorly understood with proposed mechanisms including an increase in salivary flow via adrenergic $alpha_2$ antagonism and muscarinic M_4 agonism, a decrease in laryngeal peristalsis or inhibition of the swallowing reflex [214]. Antimuscarinic agents are widely used to treat clozapine-induced hypersalivation but the data supporting their use is weak. Glycopyrrolate demonstrated promise in an initial study [215]. Lowering the dose and a slower dose titration may also help.

Thermoregulatory Adverse Effects

Fever occurs in 4–13 % of patients treated with clozapine [194]. This may be due to host defense mechanisms mediated by cytokines [208]. It occurs early in treatment and is usually benign (seldom rises above 38 °C or 100 °F), transient (a few days), and responds to antipyretics [194, 208]. If fever is high or persistent, other serious conditions including underlying infection, myocarditis, agranulocytosis, and NMS should be ruled out.

Other Serious Adverse Effects

The following adverse effects are relatively rare but serious and therefore are discussed separately.

Neuroleptic Malignant Syndrome

NMS is an uncommon, idiosyncratic, life-threatening adverse effect of antipsychotics characterized by fever, severe muscle rigidity, autonomic instability, and mental status changes. Although its incidence has decreased from 3 % in the past to 0.01–0.02 % at present, it can still cause significant morbidity and mortality [216]. An international consensus study and DSM-5 diagnostic features emphasize the following criteria [217, 218]:

- Recent dopamine antagonist exposure
- Hyperthermia ($T > 100.4$ °F or >38.0 °C on at least two occasions measured orally)
- Generalized muscle rigidity (except clozapine)
- Mental status alterations (delirium, altered consciousness ranging from stupor to coma)
- Creatine kinase elevation (≥4 times the upper limit of normal)
- Autonomic nervous system instability manifested by tachycardia (rate >25 % above baseline), blood pressure elevation (systolic or diastolic ≥25 % above baseline) or fluctuation (≥20 mmHg diastolic change or ≥25 % mmHg systolic change within 24 h), and tachypnea (rate >50 % above baseline)
- A negative work-up for other causes

NMS usually occurs 1 to 2 weeks after initiation or a dose increase of antipsychotic. Fever usually exceeds 38 °C but occasionally can exceed 41 °C [219]. The clinical profile of SGA-induced NMS is similar to FGA-induced NMS with the exception of clozapine which presents with less rigidity [220].

Possible risk factors include higher doses and more rapid rates of antipsychotic dose titration; acute IM antipsychotic exposure; psychomotor agitation; dehydration; physical restraints; iron deficiency; history of NMS; and concomitant lithium administration [216, 219]. NMS can occur with FGAs and SGAs, and any difference in liability between the two classes is not established [221]. High potency FGAs are, however, associated with a greater risk compared with low potency FGAs [222]. The pathophysiology of NMS remains unknown. Two popular hypotheses include a central hypodopaminergic state resulting from dopamine D2 receptor antagonism and sympathoadrenal hyperactivity [216].

The most important management step is discontinuation of the antipsychotic. NMS is a self-limiting condition which usually resolves within 1–2 weeks after discontinuation of the causative agent and supportive care [219]. Supportive care includes fluid replacement; fever reduction; monitoring and correction of electrolyte abnormalities; and monitoring for complications including cardio-respiratory failure, renal failure, aspiration pneumonia, and coagulopathies [216]. Pharmacological treatment of NMS includes benzodiazepines; dopaminergic agents such as bromocriptine and amantadine; and dantrolene. Lorazepam (1–2 mg IM or IV every 4–6 h) may ameliorate symptoms and reduce time to recovery in patients with NMS, particularly in those with milder and primarily catatonic symptoms [216]. Bromocriptine (2.5–5 mg orally two or three times daily) and amantadine (200–400 mg orally in divided dose)

may reverse the parkinsonism in NMS, as well as reduce time to recovery and mortality rates. Bromocriptine can, however, worsen psychosis and produce hypotension [216]. Dantrolene (1–2.5 mg/kg followed by 1 mg/kg every 6 h) may be useful in NMS presenting with extremely high fever, rigidity, and hypermetabolism. Although these medications are widely used to treat NMS, there is no definitive evidence supporting their efficacy [216, 223]. Electroconvulsive therapy (ECT) (six to ten treatments with bilateral electrode placement) is another option for NMS which is relatively safe and appears effective, even after failed pharmacological trials [224]. It can improve the underlying psychiatric disorder as well. A review of published cases reported a 10 % mortality rate in the patients with NMS who received ECT or those who received specific drug treatments (including amantadine, bromocriptine, L-dopa, and dantrolene) compared with 21 % in those who received no specific treatment [225]. ECT is considered the preferred treatment in severe NMS, for patients presenting with underlying psychotic depression or catatonia and for patients in which lethal catatonia cannot be ruled out. Data supporting its efficacy, however, are limited to a few reviews of published cases [224, 225].

Rechallenge with an antipsychotic after NMS is associated with 30–50 % risk of recurrence [219]. If an antipsychotic is required, low potency FGAs or SGAs are preferred and should be titrated slowly with the lowest possible dose starting no earlier than 2 weeks after NMS resolution.

Venous Thromboembolism

VTE, manifesting as deep vein thrombosis (DVT) and pulmonary embolism (PE), is a serious and potentially fatal medical condition [226]. Patients with DVT usually complain of calf or thigh pain, leg swelling or redness whereas patients with PE present with dyspnea, chest pain, and syncope [226]. Treatment with antipsychotics is associated with an increased risk of VTE [227]. The use of SGAs (particularly clozapine) and low potency FGAs is associated with a higher risk compared with high potency FGAs, with the risk higher among new users [227–230]. The underlying mechanisms for antipsychotic-related VTE are unknown. Proposed mechanisms include antipsychotic-induced weight gain and immobility which are recognized risk factors of VTE; enhanced platelet aggregation by FGAs; increased antiphospholipid antibodies; and hyperhomocysteinemia [227, 231]. The impact of changing antipsychotics to prevent VTE has not been investigated. Antipsychotics with lower risk of VTE should be considered in patients with a personal or family history of VTE [231].

Acute Laryngeal Dystonia

While acute laryngeal dystonia is a rare reaction to antipsychotics, immediate attention is required to prevent death. Laryngeal dystonia usually occurs at the beginning of antipsychotic treatment or a few days after an increase in dose. It presents with

dyspnea, laryngeal stridor, extreme distress, and dystonic reactions in other parts of the body [232]. The patient's hands characteristically grab his/her throat. Immediate attention is frequently required to save the patient's life. Differential diagnosis includes acute anaphylaxis, tardive laryngeal dystonia, airway obstruction, and respiratory dyskinesia [232]. The risk factors for this dystonia include male sex and younger age [232]. All FGAs can cause acute laryngeal dystonia [232]. Only a few cases with SGAs are reported and all were receiving ziprasidone [233, 234]. Acute laryngeal dystonia responds well to parenteral anticholinergics.

Hepatotoxicity

Up to 50 % of patients treated with SGAs have idiosyncratic, asymptomatic liver enzyme elevations [235]. Hepatotoxicity usually occurs in the early weeks of treatment and is reversible [236, 237]. Some reported risk factors include high daily doses, high plasma concentrations, older age, alcoholism, obesity, and antecedent hepatic disorders like Gilbert syndrome [237, 238]. Elevation in liver enzymes is more frequent with clozapine and olanzapine than with risperidone and quetiapine [236, 239]. There is insufficient data about the degree of liver enzyme elevation which should lead to discontinuation or reduction in dose. Discontinuation is clearly indicated, however, if patients have clinical symptoms related to the hepatotoxicity or if enzyme levels exceed three times the upper limit of normal [239, 240].

EPS and Respiratory Distress in Newborns

All antipsychotics may cause EPS and withdrawal symptoms in newborns whose mothers are treated with these agents during the third trimester of pregnancy. A search of the FDA Adverse Event Reporting System database identified 69 cases of neonatal EPS or withdrawal from antipsychotics [241]. Symptoms may include agitation, hypertonia, hypotonia, tremor, somnolence, respiratory distress, and feeding disorder which may occur anytime from birth to 1 month postpartum. The severity of symptoms varies with some neonates recovering within hours or days without specific treatment, while others require intensive care unit support and prolonged hospitalization. Phenobarbital and benzodiazepines may help in treating these withdrawal symptoms.

Conclusion

Apart from EPS which is more common with FGAs, all antipsychotics have similar adverse effects. The severity of the adverse effects, however, varies widely within each class. Adverse effects have a considerable negative impact on quality of life and undermine adherence to treatment. Because efficacy does not differ

substantially among these agents with the exception of clozapine, selection of a specific antipsychotic should involve consideration of tolerability and safety, patient risk factors and preferences. Subsequent to starting medication, regular monitoring for adverse effects is crucial to prevent or ameliorate their negative impact and to a reevaluation of the risk–benefit ratio should they arise.

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Part IV
Management of Schizophrenia and Its Long-Term Complications

Chapter 13
Long-Term Pharmacological Management of Schizophrenia

Stephen R. Marder

Introduction

Patients with schizophrenia generally reach a stable clinical state after treatment for an acute episode. For some individuals, this is characterized by the elimination of all symptoms. For most patients, however, some positive symptoms will persist along with impaired cognition and possibly negative symptoms. Patients may also be burdened by impaired mood—particularly depression—and anxiety. Problems with substance use may also interfere with a full recovery.

Until recently, most clinicians viewed relapse prevention as the main goal of pharmacology during long-term treatment. Effective relapse prevention reduced the need for psychiatric hospitalization and allowed patients to live in their communities. Preventing relapse, however, was often insufficient as a treatment goal. Long-term studies suggested that unrelapsed patients were usually unable to meet their educational and vocational goals or to fulfill their family responsibilities. This observation, as well as the views of schizophrenia patients and their advocates, led to a reevaluation of the role of long-term treatment and the concept of recovery.

The term recovery can have different meanings in an illness such as schizophrenia. We use the definition from the Presidents New Freedom Commission on Mental Health. They define it as "… the process in which people are able to live, work, learn, and participate fully in their communities. For some individuals, recovery is the ability to live a fulfilling and productive life despite a disability." It should be noted that recovery is a process rather than a well-defined state. Its conceptualization also emphasizes the importance of the patient setting his or her own goals. Recovery-oriented programs are built on individuals' strengths and support their ability to

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P.G. Janicak et al. (eds.), *Schizophrenia: Recent Advances in Diagnosis and Treatment*,
DOI 10.1007/978-1-4939-0656-7_13,

manage the challenges in their lives. In this chapter and Chap. 14, we emphasize the roles for both drugs and non-pharmacological treatments to help patients meet their own recovery goals.

Antipsychotic Medications and Long-Term Treatment

Antipsychotic medications are effective in decreasing the risk of psychotic relapse. This is demonstrated in a large number of clinical trials in which patients who are stable on their medication either stay on an antipsychotic or are switched to placebo. Taken together, these studies find that those who continue on medication are less likely to have a relapse of their psychosis [1, 2]. In the first year following drug discontinuation (i.e., those switched to placebo), about two-thirds of patients relapsed in contrast to only about a quarter who remained on an antipsychotic. There is also a suggestion from the Leucht et al. meta-analysis that the second-generation antipsychotics (SGAs) may have a small advantage over older medications [2]. This may be attributable to better adherence due to the milder adverse effects of these newer drugs.

Antipsychotics do more than just prevent psychotic relapse. Thus, when relapses occur in patients receiving an antipsychotic they tend to be less severe than those occurring in patients off drugs. For example, those on an antipsychotic are less likely to require involuntary hospitalization and less likely to make suicide attempts [3].

These findings support the clinical recommendation that patients with schizophrenia should remain on their medication after they recover from an episode of acute psychosis. Patients who are stable for years with minimal symptoms will often ask whether there is a need to continue on their antipsychotic. Studies which attempted to discontinue medications in these patients, however, found that they had similar rates of relapse as other stable phase patients [4]. In a sense, these individuals may be deriving the greatest benefit from an antipsychotic.

Relapse Prevention and Recovery

Although preventing relapse in schizophrenia with antipsychotic medication does not by itself lead to recovery, there is evidence that it is an important component. This was noted by Hogarty and coworkers who compared long-acting and oral fluphenazine combined with a type of social therapy or a control condition [5]. They found that patients who received long-acting fluphenazine derived the most benefit from social therapy. Thus, it appears that remaining stable (or unrelapsed) is a necessary condition for deriving benefit from such treatments. A subsequent study found that patients who were more symptomatic tended to have greater impaired work skills and derived less benefit from vocational programs [6]. This area of research supports the importance of continuing antipsychotic medication for patients involved in psychosocial treatments or rehabilitation.

Medication Adherence During Long-Term Treatment

Medication nonadherence is relatively common and the most frequent cause of relapse in schizophrenia [7]. A Veterans Affairs study found that 61 % of patients had adherence problems at some time during a 4-year period [8]. There is also evidence that nonadherence is associated with a worse functional outcome [9]. As a result, managing nonadherence and improving partial adherence are important components of long-term treatment.

Managing nonadherence requires being aware of when it is occurring. There is evidence that clinicians tend to underestimate the levels of nonadherence in their patients which may result from the reluctance of many to admit to their provider that they are not following directions. Barry Blackwell suggests an approach to this dilemma [10]. Asking patients if they are taking their medications may elicit a defensive response if they believe the provider will be critical. By contrast, inquiring about the difficulties of taking medication once or more a day in a manner that is not judgmental may provide an opportunity for patients to discuss their attitudes about taking antipsychotics. This may provide further opportunities for clinicians to educate about the role of these drugs in stable patients.

Long-Acting Injectable Antipsychotics

Long-acting injectable (LAI) antipsychotics are administered intramuscularly every 2–4 weeks. Possible advantages include:

- *Assuring drug delivery* in patients who are unreliable pill takers or are drug reluctant
- Providing a *mechanism for monitoring adherence* with injections
- Treating patients with *lower and more stable plasma concentrations* than oral medications

Regarding the last point, LAIs have a different pharmacokinetic profile compared with oral compounds. Patients who receive an oral drug usually reach peak plasma concentration shortly after ingestion which is then followed by a gradual elimination. In contrast, patients who receive an LAI agent will usually have a relatively steady release of the drug from the injection site [11]. There may, however, be some exceptions. For example, paliperidone palmitate will usually be released shortly after an injection [12]. Nevertheless, LAIs generally have a lower peak plasma concentration which can reduce adverse effects.

Effectiveness of LAI Versus Oral Antipsychotics

A number of studies comparing the effectiveness of LAI and oral antipsychotics have generated inconsistent results. Large naturalistic trials with diverse populations usually find advantages for LAIs in relapse prevention. For example, a recent study

from Finland followed 2,588 consecutive patients hospitalized for a first episode of schizophrenia [13]. LAI antipsychotics were associated with a lower risk of re-hospitalization compared with oral antipsychotics (HR = 0.36, 95 % CI = 0.17–0.75). Controlled trials, however, are less clear with a recent meta-analysis (ten trials; 1,700 patients) finding only modest advantages for LAIs [14]. The difference between the naturalistic and controlled trials may be explained by the types of individuals who are included. Thus, patients who are willing to cooperate with a controlled trial which involves a long-acting condition may not be the subjects most likely to derive a differential benefit from a treatment that assures drug delivery.

Certain patients are more likely to benefit from LAIs. They include those who are unreliable in taking pills, as well as those who have a history of repeated psychotic episodes which occur after medication nonadherence. As mentioned earlier, there is also evidence that patients receiving LAIs may derive greater benefit from psychosocial treatments. Clinicians often reserve LAIs for patients who have an established history of nonadherence and are reluctant to prescribe these medications early in the illness. There is evidence, however, that LAIs may help patients who are recovering from an initial episode because even brief periods of nonadherence can have negative consequences [15]. In a study of recent onset patients, those treated with LAI risperidone had better cognitive outcomes and, notably, avoided the losses in white matter associated with oral risperidone [16].

Switching from an Oral to an LAI Antipsychotic

Clinicians who switch patients from an oral antipsychotic should consider a number of important characteristics of LAIs [17]. The most important is that LAIs are 100 % bioavailable, whereas the availability of an oral antipsychotic is usually limited by drug metabolism, absorption in the gut, and variable adherence by the patient. As a result, simple conversion formulas for calculating the LAI dose requirements based on the oral drug dose may be inaccurate. Therefore, LAIs should be prescribed at relatively conservative doses. In addition, it often takes three or more months for patients to reach a steady state plasma level after starting an LAI agent. This problem is addressed by continuing patients on an oral drug for the first several weeks after starting the LAI. This may not be necessary, however, for patients who are treated with paliperidone palmitate or olanzapine pamoate, since there is a more rapid release of these agents during the first days of treatment.

Selecting an LAI Antipsychotic

There is no data indicating that the available LAIs differ in their effectiveness or their tendency to cause extrapyramidal side effects (EPS). As noted in Table 13.1, there are differences in the intervals between injections and the convenience of

Table 13.1 Long-acting injectable antipsychotic medications

Agent	Dose range (mg)	Injection interval	Available doses	Comments
Fluphenazine decanoate	12.5–100	2–4 weeks	25 mg/mL vials	z-Track injection in gluteal or deltoid
Haloperidol decanoate	50–200	4 weeks	50 or 100 mg/mL vials	z-Track injection in gluteal or deltoid
Risperidone microspheres	12.5–50	2 weeks	12.5, 25, 37.5 or 50 mg	Requires storage in a refrigerator
Paliperidone palmitate	39–234	4 weeks	39, 78, 117, 156, or 234 mg	Higher plasma concentrations with deltoid injections
Olanzapine pamoate	150–405	2–4 weeks	210, 300 or 405 mg	Patients should be observed for 3 h after each injection for postinjection delirium sedation. Requires gluteal injection
Aripipirazole monohydrate	300 or 400	4 weeks	300 or 400 mg	Requires suspension in sterile water prior to injection

giving injections. The adverse effects of each LAI agent, however, are similar to their corresponding oral agent. In addition, the newer LAI agents are likely to be more costly.

Olanzapine Pamoate

This agent is a microcrystalline salt of pamoic acid and olanzapine suspended in an aqueous solution [18]. Once injected the constituents slowly dissociate into their separate components. The peak plasma concentration is reached 3 or 4 days following a single injection. This indicates there may be a sufficient release of olanzapine during the first days to provide therapeutic plasma levels. As a result, patients with acute schizophrenia may not need oral supplementation. The half-life of olanzapine pamoate (OP) is about 30 days and steady state is reached in about 12 weeks [19].

OP is associated with a risk of postinjection delirium/sedation syndrome (PDSS) which consists of severe sedation, delirium, and confusion, with some individuals having lost consciousness as a result. Most of these symptoms occur within an hour of the OP injection and resemble an overdose of olanzapine. A case analysis based on all eight olanzapine LAI clinical trials identified this syndrome in approximately 0.07 % of injections or 1.4 % of patients [20]. Because of the concerns about this syndrome, OP is only available through a system which requires registration of the patient, the prescriber, the facility, and the pharmacy. Further, patients who receive OP must be observed for a PDSS in a medical setting by a healthcare professional for 3 h after each injection. In the absence of direct comparison between LAI agents, it is unclear if this risk differs among the various agents.

The efficacy of OP for acute schizophrenia was evaluated in a placebo-controlled, 8-week trial which compared 210 mg every 2 weeks; 300 mg every 2 weeks; 405 mg

every 4 weeks; and placebo. All three active treatment groups showed greater improvement on the PANSS total score compared with the placebo group (all p values ≤ 0.001) [21]. Similar to the oral olanzapine, there was clinically significant weight gain and changes on some lipid parameters. The effectiveness of OP in preventing relapse was also evaluated in a 24-week trial [22]. This study randomized patients on a stable oral dose of olanzapine to the LAI formulation at 150 mg every 2 weeks, 300 mg every 2 weeks, 45 mg every 4 weeks, 405 mg every 4 weeks, or to remain on the stabilized oral dose. The LAI 45 mg dose every 4 weeks was considered as a subtherapeutic control arm. Based on the changes in the PANSS total score, all three standard doses of OP were superior to the 45 mg dose ($p < 0.001$) and similar to the oral condition in protecting patients against psychotic exacerbations. There were no clinically significant differences in general safety between the LAI doses and oral formulation. Two patients experienced the PDSS.

Paliperidone Palmitate

This agent is an ester in an aqueous suspension [12]. Given the very low solubility, it is slowly absorbed at the injection site where it is hydrolyzed by muscle esterases, releasing paliperidone into the circulation. The release begins on the first day, but the maximum plasma concentration is not reached for about 2 weeks. As a result, this formulation has antipsychotic activity on the first day following administration. A higher maximum plasma concentration is reached when the drug is injected into the deltoid rather than the gluteal muscle. Therefore, if a clinician is starting a patient on paliperidone palmitate (PP) without a cross titration from an oral antipsychotic, deltoid administration may be preferred. On the other hand, if minimal adverse effects are a priority, gluteal administration may have advantages.

The effectiveness of PP for treating acute schizophrenia was evaluated in a placebo-controlled trial which compared injections of two doses of PP (50 or 100 mg equivalents) or placebo on days 1, 8, and 36 [23]. Both active drug doses were more effective than placebo ($p \leq 0.001$). Safety measures indicated PP was well tolerated. In a second 13-week trial, three fixed doses of PP (25, 50, and 100 mg equivalents) were compared with placebo [24]. Based on change in the PANSS total score, all PP doses were superior to placebo (25 and 50 mg, $p \leq 0.02$; 100 mg, $p \leq 0.001$). The active drug was generally well tolerated both locally and systemically. The effectiveness of PP for maintenance therapy was demonstrated in a trial which randomized stable patients to continue on active drug or a placebo injection [25]. PP was more effective than placebo for delaying relapse ($p \leq 0.001$). A Cochrane review noted that PP was more effective than placebo, comparable to risperidone LAI and has similar adverse effects to oral risperidone and paliperidone including weight gain, elevated prolactin and tachycardia [26].

Risperidone Microspheres

This agent is an aqueous suspension of risperidone contained in microspheres of a biodegradable copolymer [27]. After injections, the copolymer is degraded within the muscle, releasing risperidone. This begins about 3 weeks after the first injection and steady state is usually reached after the fourth injection. Because of the delayed release of risperidone, patients should continue to receive the oral formulation or another oral antipsychotic during the transition. In their review, Harrison and Goa concluded that risperidone microspheres (RM) (25 or 50 mg every 2 weeks) was superior to placebo and comparable to oral risperidone (2–6 mg/day) in two, 12-week, double-blind trials [27]. Further, symptom improvement in stable patients was significant in two non-comparative multicentral trials (25 or 50 mg over 12 months [28]; or 25, 37.5 of 50 mg over 12 weeks [29]). There was generally a low incidence of injection site pain and a similar adverse effect profile to oral risperidone.

Aripiprazole Monohydrate

This agent consists of lyophilized particles containing aripiprazole which are suspended in sterile water just prior to injection. The aripiprazole particles are slowly absorbed with a time to maximum plasma concentration of about 5–7 days and a mean terminal elimination half-life of 29.9 days for the 300 mg dose and 46.5 days for the 400 mg dose. Since steady state is reached after four injections, the patient's oral antipsychotic should be continued for at least 2 weeks [30].

The effectiveness of aripiprazole monohydrate (AM) was demonstrated in a 52-week, Phase 3, multicenter, randomized, double-blind study [31, 32]. Stable patients ($n = 403$) were randomly assigned to either 400 mg of LAI aripiprazole or placebo. The time to impending relapse was significantly delayed compared with placebo in both the interim and final analysis ($p \leq 0.001$). The most common adverse effects with AM were insomnia, tremor, and headache. The discontinuation rates were less in the AM group compared with placebo (i.e., 24.9 % versus 54.5 %).

Haloperidol and Fluphenazine Decanoate

These formulations are produced by combining the antipsychotic with a fatty acid (decanoic acid) administered in sesame oil. The esterified antipsychotic is gradually absorbed by the oil and hydrolyzed by tissue esterases. Since the drug release for both is delayed, neither decanoate is appropriate for acute treatment. The effectiveness of both LAIs for relapse prevention is supported by multiple trials and meta-analyses [33–37].

Conclusion

Antipsychotic medications play a critical but limited role in helping patients to achieve recovery. They are effective in decreasing the likelihood that patients who are stable will experience a relapse of their psychosis, as well as minimizing the severity if a relapse does occur. This is an essential component, since remaining stable is a necessary element if patients are to benefit from the psychosocial treatment and rehabilitation methods described in Chap. 14.

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Chapter 14
Psychosocial Rehabilitation and Psychotherapy Approaches

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Abbreviations

ACT	Assertive Community Treatment
BFT	Behavioral family therapy
CAT	Cognitive adaptation training

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P.G. Janicak et al. (eds.), *Schizophrenia: Recent Advances in Diagnosis and Treatment*,
DOI 10.1007/978-1-4939-0656-7_14,

CBT	Cognitive behavioral therapy
CBTp	Cognitive behavioral therapy for psychosis
CR	Cognitive remediation
CRT	Cognitive remediation therapy
ICM	Intensive Case Management
IPS	Individual placement and support
IPT	Integrated psychological therapy
MFG	Multifamily group treatment
NET	Neurocognitive enhancement therapy
PORT	Patient outcomes research team
RCT	Randomized controlled trials
SAMSHA	Substance abuse and mental health services administration
SCIT	Social cognition interaction training
SCST	Social cognition skills training
SE	Supported employment
SMI	Severe mental illness
TAR	Training in affect recognition
TAU	Treatment as usual
TCL	Training in community living
ToM	Theory of mind
VA	Veterans administration

Introduction

Despite advances in pharmacological approaches to the treatment of people with schizophrenia, it has become clear that medications alone are not sufficient to adaptively function in the community. Even with optimal pharmacological treatment, many affected individuals do not achieve a full remission of psychotic symptoms. In addition to the long-standing challenges associated with treating psychotic symptoms, the treatment of schizophrenia has recently shifted fundamentally from a focus on management and stabilization of psychotic symptoms to the much broader and more ambitious goal of achieving functional recovery. The burning question for the field is whether or not having a severe mental illness, with or without a complete remission of symptoms, necessarily places a limit on the ability to attain a personally meaningful and productive life.

A recovery orientation to psychiatric illness holds that individuals are more than the sum of their symptoms and that recovery involves "a redefinition of one's illness as only one aspect of a multidimensional sense of self, capable of identifying, choosing, and pursuing personally meaningful goals and aspirations." [1] All formal definitions of recovery include criteria to address symptom stability or freedom from psychiatric hospitalization plus some criteria for normalization of social and work/school functioning over a prescribed period of time (e.g., 2–5 years) [2–5].

Recovery-oriented treatments in schizophrenia require identifying and addressing the determinants of poor functioning. Although psychotic symptoms are generally poor predictors of functioning in community dwelling outpatients (although the topic is open to debate), other factors, particularly the cognitive impairments that are so common among people with schizophrenia, are strongly associated with functional outcome and are increasingly addressed in psychosocial treatments [6]. Indeed, psychosocial treatments that enable people with schizophrenia to cope with the disabling aspects of their illness and achieve personal goals are widely regarded as a necessary complement to somatic treatments.

In this chapter, we provide an overview of evidence-based approaches to the psychosocial treatment of people with schizophrenia. Available approaches can be broadly categorized into *rehabilitation*, which includes skills training, assertive community treatment (ACT), cognitive remediation (CR), social cognition training, supported employment (SE), and peer-implemented services, and *psychotherapy*, which includes family-based therapy and cognitive behavioral therapy (CBT). Some of these approaches have existed for many decades (e.g., ACT, skills training, family-based therapy) whereas others have emerged in the past decade or so (e.g., social cognition training). As summarized in Table 14.1, the eight treatment approaches covered in this review also differ on several other dimensions, including treatment targets, format, and duration. For each approach, we provide a brief background on its development, describe the main intervention methods, and summarize results on efficacy. We conclude by discussing the current state of psychosocial treatments and discuss implementation and dissemination obstacles that impede broader service delivery.

Rehabilitation

Skills Training

Background

The idea of *skills training* as an approach to psychiatric or psychological treatment has been integral to the evolution of modern CBT in general, and to psychiatric rehabilitation for schizophrenia in particular (e.g., [7, 8]). In the 1960s "assertiveness" was first identified as a particular set of behavioral abilities, whose acquisition through "assertiveness training" reduces the emotional and behavioral difficulties associated with anxiety, depression, and related clinical presentations [9]. American psychologist Andrew Salter and South African psychiatrist Joseph Wolpe are generally credited for introducing "assertiveness training" as a psychotherapy technique. Perhaps because both were Pavlovian behaviorists, "skills training" did not take on its contemporary meaning until the 1970s, after the cognitive revolution transformed psychology, and *social learning theory* achieved paradigmatic status [10].

Table 14.1 Summary of psychosocial treatment approaches

	Treatment target(s)	Format	Duration	Training and set up	PORT recommended
Rehabilitation					
Skills training	Social skills, symptom and medication management skills, recreation and leisure skills, basic conversation skills, social problem solving ability, workplace fundamentals	Individual + group	3–6 month modules	Training can take up to 6 months; treatment can be provided by any mental health team member; treatment manuals for specific treatment targets widely available	Yes
Assertive community treatment	Prevention of relapse and rehospitalizations; lengthening community tenure	Multidisciplinary treatment team	12 months or longer	Team members often have necessary skill sets (e.g., case management) prior to implementing the shared team infrastructure, which can take 6 months to establish	Yes
Supported employment	Competitive employment	Employment specialist	Indefinite	Approximately 6 months to train employment specialists and achieve "good" fidelity levels in most programs	Yes
Cognitive remediation	Neurocognitive abilities (attention, memory, reasoning and problem solving, auditory and visual perception)	Individual or group	Dosing and hours of training varies considerably across programs; 3–12 months	Varies between approaches; for strictly computer-based training, requirements are minimal; more integrated programs require longer training for group bridging elements	Needing further empirical support
Social cognition training	Social cognitive abilities (emotion processing, social cue perception, attributional bias, empathy, Theory of Mind)	Group	3 months	3–6 months of training for group leaders	Not yet considered

Peer-implemented services	Weight management, substance use prevention, and illness management have been targeted in peer-delivered educational services; employment rate and job tenure are targets in supported employment	Individual or group	Tied to services implemented	Varies widely depending on role	Needing further empirical support
Psychotherapy					
Family-based therapy	Prevention of relapse through improving family skills and recovery attitudes	Single family or multifamily groups	6–24 months	6 months including initial training and consultation on going cases	Yes
Cognitive behavioral therapy for psychosis	Treatment-resistant psychotic symptoms, negative symptoms	Individual or group	6–12 months	6–9 months including initial training and consultation on ongoing cases	Yes

In social learning theory, a "skill" became any assemblage of behavioral, cognitive, psychophysiological and/or psychomotor processes or abilities, whether elemental or complex, that is acquired, organized, activated, and performed by a person for an instrumental purpose. In this climate, "assertiveness skills" quickly expanded to include "social skills," and the skill concept soon became applicable to virtually every domain of personal and social functioning. Two landmark applications appeared in 1975, one the original assertiveness concept for neurosis and the other a broader "personal effectiveness" social skills concept for schizophrenia [11, 12]. Today, the versatility of the skills training concept complements the functional, pragmatic imperatives of psychiatric rehabilitation. Virtually any deficit or functional failure associated with schizophrenia could potentially be targeted as a measurable "skill to be learned." Psychiatric disorders may compromise normal developmental acquisition of skills, and may cause skills to be lost, but they do not prohibit acquisition or reacquisition under special skills training conditions.

Description of Treatment

In psychiatric applications, "skills training" is nearly coterminous with "social skills training." This makes sense conceptually—in social learning theory, all skills are "social" skills. However, this terminology can cause confusion. For pragmatic if not conceptual reasons, "social skills" have differentiated into major subcategories of interpersonal, independent living, and illness/wellness management and recovery skills.

Interpersonal skills training focuses on dyadic interactions, from the relatively basic skills involved in simple conversation to more advanced relationship building and intimacy. It relies heavily on structured role-play and practice, conducted in small groups, to acquire (or reacquire) skills needed for a wide variety of common interpersonal situations. A variety of comprehensive clinical manuals (e.g., a guide for social skills training) and packaged materials for training basic to advanced skills (e.g., basic conversational skills, symptom management, workplace fundamentals) are commercially available [13, 14]. It can be administered in either a closed format involving a specific number of group sessions (usually 2–3 per week for 2–3 months) or an open format involving rotation of participants in and out without a uniform "start" or "end" point. The former appears most in controlled research, while the latter is more practical in real-world settings.

Independent living skills training includes basic personal hygiene and self-care, wardrobe maintenance, housekeeping, meal planning and preparation, personal financial management, and use of public resources (e.g., for transportation, recreation). Living skill modalities project basic social skills training techniques into natural settings, usually in a "personal life coach" format suitable for use by (specifically trained) case managers and community support personnel [15–17].

Illness/wellness/recovery skills are what a person uses to manage the illness process itself and generally promote health. They range from simple and concrete, e.g., adhering to a medication regimen, to more complex, e.g., stress management, psychophysiological self-regulation, and the skills used by many people to maintain general health and reduce stress, from yoga to good nutrition [18]. *Coping skills*

is also a highly structured and evidence-based skills training modality within the illnesss/wellness/recovery subcategory [19]. As the recovery concept has evolved, abilities for identifying and systematically pursuing personal desires, life goals, frustrations, and barriers are increasingly addressed in skills training packages.

Tailoring skills training for targeted subgroups has been an important area of advancement. Targeted subgroups include older people with schizophrenia and people early in the course of the illness [20–23]. Skills training is used broadly, crossing national and ethnic boundaries [14, 17, 22, 24–27].

Results on Efficacy

In outcome research on skills training for schizophrenia, "social skills training" has been by far the most common rubric, but pragmatically any modality can only address a subset of skills. Two main issues arise in interpreting treatment outcome research in this area. First, the methodological rigor varies substantially across studies. As in the early years of psychotherapy research, it was initially difficult to compare studies that used different versions of "social skills training." Similarly, overuse of "Treatment As Usual" (TAU, usually case management and medication) as a control condition limited interpretation of differential outcome. These methodological challenges were eventually met through more active comparison conditions (e.g., supportive or occupational therapy) and by the sheer volume of studies. The second issue is that the outcome domain that would be expected to change as a result of participation in social skills training programs has been a topic of some debate [28, 29]. Although the focus of treatment in social skills training programs is developing social and independent living skills, a number of studies, particularly from the earlier literature, examined symptom exacerbation and relapse as the primary outcome. These areas represent a more distal target and can be influenced by a number of factors.

Findings indicate that people with schizophrenia can acquire a variety of precisely defined social and independent living skills through the type of structured behavioral training used in skills training. In the Kurtz and Mueser meta-analysis of 22 social skills training studies that included 1,521 individual subjects, the results revealed a large effect size for acquisition of social skills knowledge ($d = 1.20$), a moderate effect size on social and daily living skills performance-based assessments in the clinic ($d = 0.52$), a moderate effect size for community functioning ($d = 0.52$), and a small effect size for reduction of symptoms and relapse ($d = 0.23$) [30]. The few studies that have included follow-up data have shown retention of acquired skills for up to 1-year post-training.

Efforts to facilitate generalization of acquired skills in the clinic to community functioning are an important and necessary focus of this rehabilitation approach. Do the skills acquired and demonstrated under the structure of a classroom setting under a trainer's supervision and guidance generalize to other settings with other people? Traditionally, homework assignments have been used to facilitate generalization. More recent strategies include having trainers work directly with consumers in the community where they can practice newly learned skills in real-world settings (e.g.,

coffee shop) or the enlistment of family members to help facilitate the transfer of skills. Skills training programs that have used a more direct approach have shown better generalization compared to those using homework assignments [15, 16, 31, 32].

Summary and Future Directions

Skills training approaches have a well-established history in the psychosocial treatment of schizophrenia and have been extensively employed internationally. Several recent trends and advances in skills training are expected to continue in the coming years. First, efforts are underway to integrate skills training with other psychosocial interventions and psychotherapies, such as CR and CBT [33, 34]. Second, there is interest in extending skills training beyond conventional targets to such areas as emotion regulation and work-related skills [35]. Money management is an oft-neglected skill area, but one critical to independent living for adults with schizophrenia, and may have particular relevance for homeless individuals with severe mental illness. This area may be another target for future efforts [36, 37]. Finally, an important new treatment area, social cognition training, is largely based on a skills training model. Given its putative importance for facilitating recovery along with the rapid growth of investigative interest in social cognition and schizophrenia, this training approach is treated separately and appears later in this chapter.

Assertive Community Treatment

Background

With the advent of effective antipsychotic medication and the deinstitutionalization movement in the 1960s and 1970s, it was hoped that most individuals with schizophrenia and other debilitating psychiatric illnesses would be able to live satisfying lives in the community and that the need for psychiatric hospitalizations would be reduced. The US Community Mental Health Centers Act of 1964 established funding for local outpatient facilities where consumers, even those with limited financial resources, could access outpatient psychiatric treatment, case management, and counseling. However, it was not immediately clear how to best offer and coordinate these office-based services to support community tenure. While it was considered possible that many individuals would only need low intensity services, it also appeared likely that more intensive outpatient services might be needed by those who had high levels of persisting symptoms, had a history of long or frequent hospitalizations, or were currently exacerbated.

In the early 1970s, a group of mental health clinicians in Madison, Wisconsin developed an intensive outpatient mental healthcare program, the *Training in Community Living* (TCL), which focused on providing team-based community-housed mental health services as an alternative for individuals seeking an inpatient hospital admission. TCL served as the foundation for ACT. It was grounded in

several principles that have now become core ACT tenets, including meeting consumers' physical and material needs as well as their mental health needs, teaching coping skills, promoting consumer motivation, avoiding dependent relationships, supporting and educating community members who care for or interact with consumers, providing community-based services, focusing on treatment engagement and retention, and assuring consumers do not fall through "service gaps" if additional services are needed. In a 14-month randomized controlled trial (RCT) comparing TCL to regular care in 135 individuals presenting for hospitalization, TCL participants spent less time in the hospital, more time in sheltered employment (rather than being unemployed), had more trusting relationships and higher self-esteem, and reported less symptomatology than those in the traditional care group [38]. However, most of these advantages were lost once TCL support ended, highlighting the importance of long-term community support. The TCL program findings attracted national notice and served as the catalyst for the further development of intensive community support programs such as ACT, which were refined throughout the 1980s and early 1990s [39]. ACT was manualized and is now a component of the SAMHSA evidence-based toolkit initiative (http://store.samhsa.gov/product/Assertive-Community-Treatment-ACT-Evidence-Based-Practices-EBP-KIT/SMA08-434) [40].

Description of Treatment

In many ways, ACT can be understood more as a way to organize interdisciplinary services rather than as a unique psychosocial intervention. The specific content guiding interactions with consumers is less defined, and a concern has been raised that learning principles and specific evidence-based practices have not been fully integrated into the model [16]. Many organizational features are central to how ACT teams are comprised and function, and there are now several ACT fidelity scales [41–43]. Core program features, as operationalized on the ACT fidelity scale in the SAMHSA kit, include the team comprising interdisciplinary members with a small caseload (consumer:provider ratio of 10 or less) which functions as a group (rather than several independent clinicians) and meets frequently (usually daily) to review cases [43]. The team should be stable and fully staffed, overseen by a supervisor who also provides direct services, and include at least one psychiatrist and two nurses for 100 consumers, and substance abuse and vocational specialists. The caseload across the team should be large enough to support the full complement of diverse clinicians necessary to meet the comprehensive needs of consumers. The team should have well-articulated admission criteria, and have an entry pace that assures consumers are easily incorporated. ACT staff should be involved in decisions to hospitalize and discharge consumers when they may need more intensive inpatient services, and should offer 24-h crisis services in house. Services should be time unlimited and both the intensity and frequency of weekly contact should be high between staff members and consumers.

ACT programs are widely available in the USA, especially for targeted populations such as high service users. Much of the current scientific work in this area involves integrating more recovery-oriented techniques and philosophies into the ACT model [44]. ACT was developed prior to the wider acceptance of the principles

of the consumer recovery movement such as person-driven care [45]. The program has been criticized for being intrusive, coercive, and grounded in an outdated medical model of psychiatric illness [46]. More recently, several efforts have been made to incorporate more recovery-oriented practices into ACT, such as including consumer (peer) providers and broadening the relevant outcome domains to include ones of particular value to consumers (e.g., graduating out of the ACT program) but not integral to the initial conceptualization of the model [47, 48].

Results on Efficacy

Extensive controlled research on the ACT model has been conducted over the past 35 years; it has been summarized in several review articles and meta-analyses. Mueser et al.'s early review of 32 RCTs and 36 quasi-experimental studies on ACT and Intensive Care Management (ICM) found that these models reduced time in the hospital and improved housing stability, especially among consumers who are high service users, but had moderate effects on improving symptomatology and quality of life [49]. Most studies in their review suggested little effect of ACT and ICM on social functioning, arrests and time spent in jail, or vocational functioning.

A Cochrane meta-analysis supported the Mueser et al. conclusions and found that ACT participants were also more likely to remain in contact with services [50]. ACT reduced the cost of hospital care, but did not have a clear advantage over standard care when other costs were taken into account. A subsequent meta-analysis by Ziguras and Stuart of 44 controlled studies on ACT and clinical case management found that traditional clinical and assertive types of case management were more effective than usual care with regard to family burden, family satisfaction with services, and cost of care [51]. The total number of admissions and the proportion of consumers hospitalized were reduced in ACT compared to traditional case management; ACT also had an advantage compared to traditional case management in the number of hospital days.

Coldwell and Bender conducted a meta-analysis on RCTs and observational studies investigating the benefits of ACT for *homeless* individuals with severe mental illness [52]. They found that those receiving ACT achieved greater reductions in homelessness and greater improvements in psychiatric symptom severity compared with standard case management treatments. In contrast to the findings described above, hospitalization outcomes were not significantly different between the two groups.

Summary and Future Directions

ACT has permitted many individuals with the most severe course of schizophrenia to remain living in the community. Two sets of recent ACT findings have drawn notice. First, the primary established benefit of participation in ACT has been a reduction in hospitalization. However, with the decline in psychiatric hospitalization overall, this benefit has become increasingly limited to individuals with a high rate of baseline hospitalizations and not the larger consumer population [53, 54].

Thus, more recent work in the field has been directed at assessing the benefits of ACT in specialized populations, such as individuals with severe mental illness and concurrent forensic issues, and consumers in a first episode [55–57]. Second, the benefits of ACT in comparison to standard care have been harder to establish in Europe, although there have been some positive findings [58–60]. Several reasons for the contrasting results in the USA and Europe include variations in how the ACT model has been operationalized, differences in basic medical and social services systems (e.g., a greater availability of home-based care in Europe) that may duplicate or obscure condition differences, or the fact that the European studies have been conducted in the context of decreasing rates of psychiatric hospitalization [61]. With changing patterns of psychiatric hospitalizations, and the broader availability of community support in general mental health, it seems clear that further work clarifying for whom the more intensive ACT program is best suited will be especially valuable. Adaptations of the model to incorporate recovery principles and consumer empowerment would be especially timely.

Supported Employment

Background

The benefits and significance of employment for people with severe mental illness are well established. Work provides opportunities for socialization and independence, is associated with reduced levels of psychotic symptoms and re-hospitalization, and is associated with enhanced quality of life and social functioning [62]. Unfortunately, obtaining and holding a job remains a substantial challenge for many people with severe mental illness [63, 64]. Estimates of unemployment range from 65 to 90 % with the highest rates associated with schizophrenia. These figures are particularly striking in light of evidence that approximately 70 % of individuals with severe mental illness report that they would like to have a job.

A number of factors can interfere with efforts to obtain and maintain employment [65]. These include cognitive impairments that interfere with performance of work tasks, positive symptom exacerbations resulting in hospitalization and job absence, social interaction difficulties with co-workers and supervisors, motivational difficulties, stigma from employers, and the fear of losing disability benefits. A variety of vocational rehabilitation approaches have been tested over the past several decades. Initially, sheltered employment or job clubs were commonly utilized, but these services did not typically provide or lead to competitive employment. Subsequently, there was debate about the superiority of two main approaches—the "train-place" model, which moves through a stepwise process involving prejob screening, assessment of job-readiness, training, transitional job placement, and ultimately placement in competitive employment, or the "place-train" model. Research now consistently supports the latter approach. An example of the place-train model is supported employment (SE), which involves rapid job search with ongoing follow-along vocational and mental health support but bypasses extensive prevocational training [66].

Description of Treatment

SE programs provide people with disabilities support in finding and maintaining employment. The most widely used model of SE, Individual Placement and Support (IPS), was first introduced in the mid-1990s and is now implemented in over 250 programs throughout the USA and Europe [67]. Two key elements of IPS include rapid job search and integration of SE services with delivery of clinical services provided by the consumer's mental health treatment team [68]. A major shift from previous employment-related interventions was the focus on job placement regardless of "job readiness."

The IPS model is based on the following set of principles: (a) zero exclusion criteria (i.e., IPS is appropriate for anyone wanting to work), (b) including work rehabilitation as an integral component of mental health treatment, (c) competitive employment as the primary goal, (d) rapid job search that is based on consumer preferences, and (e) continuous follow-along support which is community-based and provided by an employment specialist [67]. The focus is on obtaining community-based competitive jobs that pay at least minimum wage and are available to anyone who wishes to apply for them. A strong emphasis is placed on matching the job with the consumer's abilities and interests. Employment specialists actively facilitate job acquisition, establishing working relationships with community employers to optimize a good job match.

SE programs are found in a wide variety of service contexts in the USA and internationally. Common settings include community mental health centers, community rehabilitation programs, clubhouses, and psychiatric rehabilitation centers. IPS has also been evaluated in some consumer subgroups including those receiving Social Security Disability Insurance benefits, younger adults with a recent onset of psychosis, and middle-aged and older adults [69–71].

One recent trend in research settings has been to augment IPS programs with psychosocial interventions that target key barriers to job placement and retention. For example, motivational interviewing has been used as a complementary intervention to help engage consumers who are in early stages of commitment to employment [71]. A few studies have also integrated elements of social skills training and cognitive rehabilitation within the context of IPS [72]. In a new area of research, there have been efforts to extend IPS to address educational goals, particularly those with a relatively recent onset [73, 74].

Results on Efficacy

Research clearly supports the efficacy of SE. Five major reviews and meta-analyses all found that SE led to significantly greater employment rates than alternative approaches with effect sizes ranging from 0.43 to 0.79 [75–79]. A recent meta-analysis of 11 RCTs including high-fidelity IPS programs found that 61 % of IPS participants obtained a competitive job compared with 23 % of participants in alternative vocational rehabilitation conditions [79]. About two-thirds of IPS

participants who obtained competitive employment worked 20 h or more per week; the average time to employment was 138 days for IPS participants compared with 206 days for controls. These findings are similar to those from a multisite RCT involving 312 consumers from six European centers [80]. Studies augmenting standard IPS with additional interventions have yielded promising results as well. Initial studies suggest that consumers receiving SE plus either skills training or cognitive rehabilitation showed better outcomes than those receiving SE alone [72].

Despite clear support for the efficacy of SE, a few caveats from these reviews should be noted. Among consumers who enroll in high-fidelity SE programs, approximately 1/3 are unsuccessful in finding a competitive job. These numbers increase to approximately 55 % when examining IPS programs more broadly. For those who do obtain employment, job tenure is typically brief lasting approximately 6–8 months (11–12 months in high-fidelity programs). Also, earnings are typically quite modest, and unsatisfactory job terminations are not uncommon. Consumer variables have been examined to help understand who is most likely to benefit from SE. Better work history predicted higher job attainment (though not retention) and receiving disability benefits predicted lower job retention (though not attainment) [81]. A large range of clinical and demographic variables, including substance abuse, educational background, disability income, hospitalization history, and symptomatology, showed no relation to employment outcome. Hence, benefits from IPS appear to extend to a broad range of consumers.

Summary and Future Directions

Employment is a critical element of recovery and there is now substantial support for the efficacy of SE on job acquisition. However, the findings on job tenure are more modest, particularly when one considers the median length of employment for SMI individuals compared to national averages of individuals in comparable jobs at the same age level (3–5 years; US Bureau of Labor Statistics) [82]. Efforts to integrate IPS with other psychosocial interventions may target job tenure more directly (e.g., augmenting IPS with cognitive rehabilitation and/or social cognition training). Lastly, an area likely to see continued growth is supported education.

Cognitive Remediation

Background

In the past 40 years numerous CR programs have been developed and evaluated. This approach is motivated by the substantial evidence that neurocognitive impairments are core features of schizophrenia [83]. Schizophrenia is associated with a range of cognitive impairments, which include attention, learning and memory, working memory, speed of processing, and reasoning and problem

solving among others. Furthermore, neurocognitive deficits show consistent relations to community functioning, instrumental living skills, and rehabilitation outcome [83, 84].

Description of Treatment

Recent reviews indicate that there are as many as 14 CR approaches, although arguably they have more similarities than differences. Across modalities, the aim of CR is to improve community functioning, although some argue that improvement in cognition alone is a worthwhile goal and treatment endpoint [85]. Among the various CR approaches, a broad distinction can be made between cognition-enhancing and compensatory approaches. Cognition-enhancing approaches aim to improve cognitive functioning through stimulation of impaired areas of cognition (e.g., working memory). Originally, this approach was based on the assumption that cognitive impairment could be restored through activation and repetitive exercise. More recently, this approach is based on discoveries that support the brain's neuroplasticity, referring to the brain's lifelong capacity for physical and functional change. These approaches directly target cognitive impairment as a means by which to improve functioning. In contrast, compensatory approaches aim to bypass or "compensate" for cognitive impairments by devising training methods that emphasize recruitment of relatively intact cognitive processes or reduce the burden on affected ones often by establishing supports or prosthetic aids in the environment. These approaches directly target functional deficits but with consideration of the cognitive impairments which limit or impede the ability to carry out those functions.

Among cognition-enhancing approaches, the most common method is "drill and practice" which involves the use of repetitive practice or training in increasingly difficult cognitive exercises. Exercises may be titrated to the individual's level, so that they are neither too challenging nor too easy. Difficulty level is increased in a stepwise manner as performance improves. Drill-and-practice exercises are frequently computerized although they can be administered by using paper-and-pencil exercises. These interventions have been used in isolation or in the context of multifaceted packages that include complementary psychosocial interventions.

There are two primary approaches to drill-and-practice CR. "Bottom-up" approaches are based on the assumption that there is a basic deficit in the ability to discriminate signal from noise in auditory and visual processing. This basic deficit is theorized to be the cause of higher-level cognitive impairments (i.e., planning, problem solving, memory, attention), and is targeted through high intensity training exercises. Software developed by PositScience is one commonly used approach that targets auditory and visual processing in computerized training sessions, typically administered daily over a period of several weeks totaling 50–100 h [86, 87]. "Top-down" approaches target higher-order cognitive functions (i.e., attention, memory, and executive functioning) through complex, consciously effortful exercises that place demands on multiple cognitive abilities. Top-down approaches involving

computer-based training share similar methods with bottom-up approaches. The primary difference is the target of training. Both involve standardized computer-based curricula that utilize intense and repetitive practice and a lengthy duration of training with defined levels of mastery. Examples of top-down approaches include Neuropsychological Educational Approach to Remediation (NEAR), Neurocognitive Enhancement Therapy (NET) and CogPack [33, 88, 89]. These comprehensive programs involve training exercises across a broad range of cognitive functions, including attention and concentration, psychomotor speed, learning and memory, and executive functions. Both of these programs have been used in the context of multifaceted treatment programs that incorporate vocational rehabilitation.

In addition to drill and practice, strategy coaching has been used to teach individuals to apply new cognitive techniques learned through training exercises to areas of real-world functioning. For example, cognitive remediation therapy (CRT) is an individualized 40-h program that uses drill and practice to enhance working memory, planning, and problem solving along with an emphasis on strategy coaching [90]. The strategy coaching component relies on the therapist's emphasis on and discussion of the relevance of new cognitive skills to community functioning. For example, a therapist may provide coaching about how to use recently acquired memory (e.g., list learning) and categorization skills (e.g., sorting by taxonomic category) while grocery shopping. Therapists continuously encourage participants to reflect on how the trained cognitive skills might be used in a number of real-world settings [91].

In contrast to cognition-enhancing approaches, compensatory approaches focus on compensatory strategies to reduce overall cognitive load and minimize the functional impairment caused by specific cognitive deficits [92, 93]. The most common compensatory approaches are ones that manipulate environmental demands and errorless learning. Environmental adaptation involves using cues to direct the consumer's attention and thereby augment performance on goal-oriented tasks. An example of this type of approach is Cognitive Adaptation Training (CAT), a manualized treatment in which a caregiver or mental health provider tailors environmental supports to the needs of each individual to increase behaviors such as medication adherence and self-care skills [93]. Commonly used environmental supports in the consumer's home environment may include pill containers with alarms to facilitate medication adherence, and activity checklists to provide reminders about clinic appointments [94].

Errorless learning is a separate approach that compensates for difficulties associated with error commission and concomitant filtering of relevant from irrelevant information observed in schizophrenia. Training involves preventing (or minimizing to the extent possible) the commission of errors during the learning of a new skill or behavior. Training proceeds stepwise in a hierarchical manner beginning with the most basic, simple task components to the eventual integration of all complex aspects, enabling the participant to master the task without making mistakes in the process [95–98]. In errorless learning, the need to self-correct is bypassed, and processing burden is believed to predominantly shift from explicit to implicit memory processes, of which selected components are relatively intact in schizophrenia. Errorless learning has been used in a variety of settings to facilitate acquisition of work and social skills.

Results on Efficacy

Several meta-analyses and review papers have summarized CR approaches [29, 99–105]. Recently, Wykes and colleagues conducted a comprehensive meta-analysis including 40 RCTs of drill-and-practice or drill plus strategy coaching interventions [105]. Results were wholly consistent with a previously published meta-analysis finding small to medium mean effect sizes for improvements on cognitive measures that were not directly involved in training exercises [104]. Recent evidence also documents changes in brain systems targeted by drill-and-practice interventions [106].

With regard to generalization to improvements in functional outcome, an important factor is whether CR is administered alone or in conjunction with other psychosocial rehabilitation approaches. Research consistently shows the effects of drill-and-practice interventions on functional outcome are largely moderated by whether they are administered along with adjunctive psychosocial rehabilitation. Across 26 studies involving 1,151 consumers the mean effect size for improvement in functional outcome was 0.36 [104]. However, when only studies with adjunctive psychosocial rehabilitation were included, the effect size rose to 0.47; studies that did not include additional psychosocial rehabilitation interventions had a mean effect size of 0.05.

Although substantially fewer randomized clinical studies have evaluated compensatory interventions, they have also been found to show significant treatment benefits. A series of studies indicate that CAT improves medication adherence and community functioning, and decreases symptom relapse rates [93, 107]. Similarly, errorless learning is associated with improvements in performance on entry-level job tasks, social problem-solving ability, and assigned job tasks at a community mental health setting, with gains maintained up to 3 months later without further intervention [96, 108, 109].

Summary and Future Directions

Research on CR has substantially expanded in concert with growing awareness of the impact of neurocognitive impairments on functioning. Evidence indicates that drill-and-practice interventions lead to improvements in functioning when implemented in conjunction with more comprehensive psychosocial rehabilitation approaches (e.g., skills training, SE). Also, strategy coaching appears to lead to better community functioning than drill-and-practice alone. Compensatory approaches, though less extensively studied, also show potential for improving specifically targeted areas of functioning. Medalia and Saperstein recently provided suggestions for continued development and evaluation of CR [110]. Suggestions included (a) measuring outcomes in terms of consumers' personal goals (as opposed to standard competency and capacity measures) and (b) expanding CR to include problem-solving and planning skills to facilitate the use of improved cognitive abilities in the service of daily living activities.

Social Cognition Training

Background

Research into the social aspect of cognition in schizophrenia is relatively new but has expanded rapidly over the past decade. Social cognition refers to cognitive processes that are involved in perceiving and understanding social situations, particularly the behaviors, emotions, and intentions of other people. Schizophrenia is associated with impairment in several domains of social cognition, with a mean overall effect size of 0.69 compared to healthy controls [111, 112]. Importantly, social cognition deficits show stronger relations to community functioning than neurocognition or clinical symptoms [113–115]. These findings have generated interest in intervening at the level of social cognition as a means of improving functioning. Early evidence indicates that social cognition impairments are amenable to psychosocial intervention.

Description of Treatment

Social cognition domains include emotion perception (facial affect identification), social perception, social knowledge, Theory of Mind (ToM), attributional bias, and empathy [116]. Social cognition interventions commonly follow the skills training model. Training is conducted in group format, and incorporates didactic skills training and experiential role-play and rehearsal. Standard behavioral techniques, such as modeling, shaping, providing behavioral cues/prompts, and repetition, under a rich schedule of positive social reinforcement, are intrinsic to social cognition training. Participants are trained on perceiving, identifying, interpreting, and responding to social cues and affective information. Training proceeds from simple to complex exercises, with later stages incorporating ambiguous and emotionally evocative stimuli to mimic real-life interpersonal situations (e.g., beginning with happy and sad faces and progressing to fear, anger, disgust, and shame-inducing situations). A distinction can be made between targeted treatments, which focus on one or more social cognitive domains, and broad-based treatments, which include social cognitive training exercises within multifaceted treatment programs.

Early efforts involving targeted treatments focused on emotion perception. There were several short-term interventions (1–5 sessions) that trained participants to use effective face-scanning techniques and repetition and coaching to identify the forehead, eye, and mouth movements that are characteristic of various emotions [117–120]. An example of an emotion-focused intervention is Training in Affect Recognition (TAR), a 12-session manualized approach consisting of three segments: identifying prototypical components of basic emotions, integrating facial cues to form quick decisions about affect, and applying the learned information to the processing of ambiguous facial expressions [121–123]. Training consists of practice with computerized stimuli as well as learning compensatory strategies such as verbalization and self-instruction.

As research in this area progressed, more comprehensive programs that address multiple social cognition domains were developed. These programs included 20 or more sessions and targeted emotion perception, ToM, and social perception, with some addressing higher-order social cognitive processes such as attributional style and deception as well. For example, Social Cognition Interaction Training (SCIT) is a manualized, group-based, 20–24 session treatment, targeting affect recognition, attributional style, and ToM [124]. It is divided into three discrete sections: identifying and understanding basic emotions and paranoia, learning strategies to avoid the tendency to "jump to conclusions" in social situations, and applying newly acquired social cognitive skills to real-life situations. Another approach, Social Cognition Skills Training (SCST), combines and augments elements of SCIT and TAR to address emotion recognition, social cue perception, attributional bias, and ToM (e.g., distinguishing among sarcasm, white lies, and sincerity) [125, 126].

Social cognition has also been included as a target of intervention in broad-based treatments that concomitantly address other areas, such as nonsocial cognition and employment. For example, cognitive enhancement therapy (CET) uses a group skills training format to address social information processing, emphasizing accurate social context appreciation and perspective-taking, in addition to a rigorous program of computerized neurocognition training administered to consumer dyads [127]. Similarly, integrated psychological therapy (IPT) includes a 21-session social and emotion perception module that is embedded within a broader group-based neurocognition training intervention [128]. IPT contains five subprograms, administered sequentially, totaling approximately 8–12 months of biweekly group sessions that target neurocognition, social cognition, and social skills. Conceptually, these programs view neurocognition training as a necessary prerequisite to training on higher cognitive functions such as social cognition and social skills.

Results on Efficacy

Early evidence supports the efficacy of social cognition training, at least on selected, most commonly lower level areas of processing [129–131]. Horan and colleagues concluded that social cognition is responsive to systematic intervention, but stressed the importance of expanding beyond emotion perception and developing interventions for more complex areas such as conveying empathy and detecting sarcasm and hostility. Kurtz and Richardson's meta-analysis included 19 RCTs and found medium to large treatment effect sizes for performance on measures of affect recognition, medium effect sizes for ToM, and no clinically meaningful effects for social perception or attributional bias. Six studies assessed generalization to functional or institutional outcome and revealed an overall mean effect size of 0.78.

Although the early results of social cognition training efforts are promising, caveats include the relatively small samples in most studies, inclusion of inpatient and outpatient studies (effects were much larger in inpatients), large variability in intervention methods and outcome measures, and minimal consideration of the durability of training effects. In addition, a challenge in interpreting these studies has been the difficulty in determining how much, if any, treatment benefits are

associated with social cognition exercises per se rather than general improvements in nonsocial cognition, particularly in broad-based treatments that include CR. The few studies that have directly addressed this issue suggest that gains in social cognition are not necessarily dependent on improvements in neurocognition, challenging the notion that neurocognition training is a prerequisite building block for achieving gains in social cognition [126, 132].

Summary and Future Directions

Although social cognition is a relatively new area for treatment development, emerging evidence suggests efficacy of training for selected areas of social cognition (typically lower-order skills), and there is some evidence that these gains may confer improvements in real-world functioning. Much work remains to be done in further refining these training intervention programs, identifying the most potent and efficient training methods, improving their effects on higher-order social cognitive domains, and demonstrating both durability and generalization to community functioning. A separate issue particularly germane to social cognition is the need to develop or refine psychometrically sound assessment measures that can be used across treatment trials. Such efforts are currently underway [133].

Peer-Implemented Services

Background

Peer support and peer-provided services are a rapidly expanding component of the psychosocial recovery and rehabilitation toolbox. Peer providers are individuals who have achieved functional recovery from a mental disorder, continue to receive mental health services themselves, and are employed by mental health programs to work alongside professionally prepared staff members [134]. The peer movement is based on the premise that persons with lived experience can offer support, respect, shared responsibility, guidance, and wisdom that cannot be offered by a professional [135]. The peer support approach to psychosocial rehabilitation includes consumer-run programs as well as the employment of peers within traditional mental health services. The peer-services approach has its roots in the recovery movement, becoming more widely accepted and supported by the Supreme Court and the President's New Freedom Commission on Mental Health in the late 1990s [136].

Description of Treatment

Consumer-run programs are prevalent across the USA, although the majority of these are support groups and self-help organizations. A 2002 national study found that of the 7,467 groups, organizations, and services run by and for mental health

consumers, 1,133 (15.2 %) were identified as consumer-operated services [136]. Consumer-operated services include drop-in centers, mutual support groups, peer educator and advocacy programs, multi-service agencies with benefits counseling and case-management, peer phone services, and specialized supportive services focusing on crisis respite, employment, and housing [137].

Within traditional mental health services, roles for peer providers have also grown exponentially in the past 10 years. Peer provider roles include case manager aides, community aides that connect hospitalized consumers to continuing outpatient services, counselors and advocates, outreach workers, providers of self-help educational services, and vocational counselors [138]. Formal training for peer specialists is a central component of effective peer-provided services. Certified Peer Specialists (also called Peer Support Specialists) are employed in numerous capacities, which most frequently include serving on ACT teams, in peer-support programs, as counselors and advocates in psychiatric inpatient facilities, and as group leaders or providers of one-on-one services in community mental health systems of care [139].

Results on Efficacy

The majority of published research has focused on the roles of peers in traditional mental health service settings. Qualitative and non-controlled studies on the use of peers as Peer Support Specialists and case management aides indicate comparable benefits for individuals with SMI receiving services from peer vs. non-peer providers [140–143]. Research also indicates working as a Peer Support Specialist confers benefits for the peer-provider, with improvements in job satisfaction as well as decreased need for mental health services [144–146]. The few RCT published in this area have shown positive results. Consumers who received services from peers serving as assistants to case managers resulted in increased service engagement and improvements in the level of social participation and quality of life [147, 148]. Furthermore, recent studies show that peer-led educational training on mental illness self-management led to reduced levels of depression and anxiety, increased self-perceived recovery, and increased empowerment, self-esteem, and self-advocacy-assertiveness [149–151]. These results suggest that not only do objective measures of clinical symptoms and autonomy improve as a result of peer-led services, so too do more subjective measures of empowerment and self-efficacy.

To illustrate an example of peers as implementers of rehabilitation services, we describe a recently conducted community-based study of IPS SE in which three peers were trained to assume the role of employment specialists [134]. As noted earlier in this chapter, IPS emphasizes an integrative, collaborative working relationship among clinicians, employment specialists, employers, and consumers with the aim of helping the consumer attain his/her vocational goals. The duties of an employment specialist under this model are multifaceted, requiring comprehensive vocational assessments of each consumer, initiating a rapid job or school search, and continued monitoring, support and problem solving after job or school placement. The results from this study showed that peers could be trained to implement

evidence-based practices with a modest degree of fidelity. Importantly, the peer-implemented program yielded employment rates over the span of the study comparable to other IPS SE programs in the region. Of note, all three peer employment specialists received promotions within the county department of mental health and remain with the program 5 years later.

Summary and Future Directions

Peer-providers are an important and promising addition to recovery-oriented services for adults with schizophrenia and other forms of SMI. The three main roles for peers are leading self-help/support groups, running consumer-operated programs, and working as trained peer-providers in traditional services. A new role deserving further examination is the use of peers as implementers of evidence-based practices. Peer-provided services are not only cost-effective—they also create roles and responsibilities for people in recovery from mental illness, and may augment the benefits attained through traditional rehabilitation services. Although the involvement of peers in service delivery has progressed substantially in recent years, there remain few RCTs to document the efficacy of their involvement in treatment and rehabilitation services.

Psychotherapy

Family-Based Services

Background

There is a large and robust literature supporting the benefits of family therapy in reducing relapses and hospital readmissions for adolescents and adults with schizophrenia [152, 153]. The impetus for much of this work was the finding that the family environment played a significant role in influencing outcomes after a hospitalization, with consumers whose relatives expressed high levels of critical comments and/or report high levels of self-sacrificing behavior at the time of a symptom exacerbation (i.e., who are "high" in expressed emotion) having a significantly greater likelihood of relapse within the subsequent 9 months [154, 155]. An additional rationale for these interventions emanates from the recognition that schizophrenia can be especially debilitating, and relatives often assume responsibility for caring for their ill loved ones for extended periods of time [156, 157]. Interventions designed to increase coping skills of consumers and supportive behaviors of relatives simultaneously can be particularly efficient in improving outcomes.

Family involvement in mental health services for those individuals with SMI is associated with greater treatment retention and increased consumer satisfaction [158]. Increasing evidence confirms that many SMI individuals *want* their family

involved in their care [159, 160]. In fact, family involvement in care to support recovery from SMI is a core principle in the President's New Freedom Commission on Mental Health, which states that "*services and treatments must be consumer and family centered*." Furthermore, the SAMHSA working definition of recovery articulates two guiding principles of special relevance to consumers in mental health treatment and their loved ones: "*Recovery is supported through relationships and social networks*," and "*Recovery involves individual*, *family*, *and community strengths and responsibility*."

Description of Treatment

A range of family-based interventions has been found to be effective in reducing relapse in schizophrenia. Most of these interventions are cognitive behavioral; they share a number of core components, including illness education, development of a relapse prevention plan, and formal problem-solving skills training, but they vary on several dimensions including duration, the presence of consumers in the family sessions, single vs. multifamily group modality, and relative emphasis on formal behavioral rehearsal as a key component of the treatment [161]. The interventions are designed to be embedded in a comprehensive treatment program and are open to a wide range of relatives, including partners, parents, adult children, siblings, and non-kin supporters. Although in practice these interventions are used with individuals in almost any phase of illness, in the research trials described below the interventions were usually begun either during or immediately after a symptomatic exacerbation, with the outcome of interest being delay or elimination of subsequent relapse.

The two most widely implemented and studied family programs in schizophrenia are Behavioral Family Therapy (BFT) and Multifamily Group (MFG) Treatment [162–164]. BFT is offered to single families; typically, 20–25 one-hour conjoint sessions are conducted across 9–12 months on a declining contact basis, with monthly boosters offered in year two. After orientation and an assessment with each participant, the active intervention begins with education on the psychiatric illness—symptoms, causes, etiology, prognosis, and treatment—to promote recovery attitudes and attainable expectations in both the consumer and relatives. Following this education, participants are provided with several sessions of instruction on communication skills and problems solving. BFT incorporates many behavioral techniques—modeling, shaping, prompting, positive reinforcement, and programmed generalization—to help relatives compensate for consumer attentional difficulties and to assure that family members together can successfully address stressors and achieve goals to improve outcomes with the illness. BFT was developed as a home-based program, but a subsequent trial comparing BFT to customary care in 41 military veterans with schizophrenia substantiated the efficacy of offering BFT in the clinic [162, 165].

There has been considerable interest in determining whether family interventions conducted with *groups* of relatives may confer more benefits than those conducted

with single families, because groups offer more opportunities to obtain social support and normalize responses to the development of a psychiatric illness in a loved one. MFG includes many of the components of the single family intervention discussed above, including active engagement, illness education (typically, an extended educational workshop), and problem solving. In contrast to the BFT, MFG deemphasizes formal behavioral rehearsal and programmed generalization and does not include a unique communication skills component; significant attention is directed at strengthening social bonds among participants. Both consumers and relatives typically attend biweekly MFG meetings. A typical course of treatment would be at least a year.

Results on Efficacy

Several meta-analyses on the impact of family interventions sharing the features described above for schizophrenia have been conducted, with positive results. Pitschel-Walz et al. compared the impact of family interventions to customary care on symptom relapse and reported a mean effect size of 0.19 for first year outcomes and 0.25 for second year outcomes, with treatments lasting less than 3 months having smaller mean effect sizes than longer treatments (0.14 vs. 0.30) [166]. Individual and group treatments had comparable results. Pfammatter et al. compared family interventions to standard care and reported an effect size of 0.42 for relapse rates and 0.22 for rehospitalizations from 6 to 12 months post-study entry, and 0.51 for a reduction in rehospitalizations at 18–24 months [167]. Other meta-analyses on 1-year results reported similar positive findings [168, 169].

Matching interventions to the specific characteristics of consumers and their families is an understudied area. Many published family intervention studies are insufficiently powered to test whether subgroups of participants benefit differentially. There are a few studies that have attempted to examine the issue of differential benefit more directly [170]. Unfortunately, the guidance accruing from these studies to assist consumers, families, and professionals in family-based treatment planning is limited and sometimes contradictory. At this point, it seems the most prudent course of action would be to allow consumer and relative preference drive the choice of modality.

Summary and Future Directions

Several decades of research document the efficacy of family interventions for reducing symptom relapses and rehospitalizations. The benefits of involving relatives in care and providing education and problem-solving training are widely supported in psychosocial intervention studies for schizophrenia. Further, the President's New Freedom Commission on Mental Health highlights the importance of services and treatments being family centered. Unfortunately, implementation is the significant challenge, and innovative strategies are needed to improve access and uptake. To address these

challenges, recent efforts have moved to explore the feasibility and efficacy of Internet-based services. Making family-based therapies more personalized and tailored to the characteristics of individual consumers and their family members is an area requiring further investigation.

Cognitive Behavior Therapy

Background

The premise of CBT is that cognition, the process of acquiring information and forming beliefs, can influence feelings and behavior. Through CBT, individuals learn to identify and modify thoughts, misinterpretations of experiences, and thinking patterns that contribute to maladaptive behavior or distressing feelings. CBT for psychosis (CBTp) developed out of work by Aaron T. Beck as early as the 1950s. Since then, CBT has been widely used to treat mood and anxiety disorders, but the use of CBT to treat psychotic disorders was not as readily accepted, due to skepticism that SMI could be successfully treated through psychotherapy [171]. Although Beck published a case report describing the use of CBT to treat a consumer with a paranoid delusion in 1952 [172], followed by additional reports in the 1970s [173, 174], it was not until the 1990s that controlled trials of CBTp started to emerge, primarily in the United Kingdom.

Description of Treatment

CBTp includes a range of approaches with a variety of treatment elements [175, 176]. Core elements of CBTp include the collaborative identification of target problems or symptoms, development of specific cognitive and behavioral strategies to cope with these problems or symptoms, and testing of key beliefs that maintain delusional thinking and distressing beliefs about voices. Other elements may include a collaborative understanding of the nature of the illness, identification of factors exacerbating symptoms, and problem solving to reduce relapse and achieve recovery goals.

CBTp assumes: (a) hallucinations and delusions are not fixed and can be modified as a target for intervention; (b) situational factors can exacerbate or ameliorate psychotic symptoms; and (c) the content of psychotic symptoms can be meaningful when placed in the context of the individual's prior experiences and beliefs [177]. A primary goal of CBTp is to help consumers become more cognitively flexible, change the way they evaluate their symptoms and thoughts, and consider alternative explanations for psychotic experiences (e.g., objective distancing and reappraisal of psychotic symptoms by examining evidence). Exercises and homework assignments (e.g., thought records and experiments) are used to examine the evidence for and against thoughts and interpretations of events and symptoms. For example, an experiment involving an activity that exacerbates (e.g., imagining a stressor) or

ameliorates (e.g., humming) hallucinations might be conducted to challenge beliefs about the power or control of voices to reduce distress or compliance with command hallucinations. By re-evaluating evidence and considering alternative explanations for psychotic experiences, positive symptom severity, distress, and dysfunction may be reduced in CBTp.

The majority of CBTp approaches have focused on reducing positive symptom severity in people with schizophrenia who have persistent psychotic symptoms despite adequate pharmacotherapy. Although positive symptoms remain the most common treatment target, more recent trials have targeted other outcomes. For example, CBTp interventions have been bundled with other approaches, like social skills training for functioning [34], anxiety interventions for social phobia [178, 179], and motivational interviewing for substance use [180]. CBTp has also been modified to specifically target negative symptoms with some success [181, 182].

Results on Efficacy

Significant improvements in symptoms and other outcomes have been consistently found in clinical trials of CBTp in schizophrenia, with medium or large effects found relative to standard care and small effects found relative to other active psychosocial treatments. Benefits have been found for severity of positive, negative, and overall symptoms, as well as depression, suicidality, social functioning, and social anxiety [171, 175, 183–187]. In a meta-analysis by Wykes et al. [175], effect sizes for a variety of outcomes were remarkably similar to the effect size for positive symptoms (typically the primary treatment target; $d=0.37$), including social anxiety ($d=0.35$), negative symptoms ($d=0.44$), mood ($d=0.36$), and functioning ($d=0.38$). There is also preliminary evidence that CBTp is effective as part of an early intervention approach in recent onset schizophrenia [188, 189], as well as a possible approach to preventing psychosis in prodromal/high-risk populations [190], with more than 50 % reduction in risk of developing psychosis found in a meta-analysis of seven trials of people who were receiving CBTp and not taking antipsychotic medication [191].

Some meta-analyses, however, have found minimal or no benefit for CBTp when only highly controlled trials (e.g., blinded) with active psychosocial control conditions were included [192–194]. As is generally true in clinical trials, smaller effect sizes have been found for trials with more rigorous controls and active comparison groups [175, 193]. Importantly, greater benefits have been found at 6-month to 5-year follow-ups than at the end of treatment [183, 184, 187, 195] indicating that the benefits of CBTp continue to accrue over time. This finding is in contrast to many other psychotherapies and psychosocial rehabilitation interventions where there is concern over durability of treatment effects. Therefore, meta-analyses focused only on effects at the end of treatment in well-controlled trials with active control interventions fail to capture the lasting benefits associated with CBTp.

Only a few studies have examined factors that predict outcome in CBTp and results have thus far been mixed. Regarding consumer characteristics, some studies

report that better positive symptom outcomes are associated with lower delusional conviction [196, 197], greater insight [198, 199], less severe symptoms [200] (but see [196, 201]), shorter duration of illness [200–203] (but see [34, 204]), female relative to male consumers [197], and white relative to non-white consumers [205]. Greater severity of neurocognitive impairment has not been found to moderate outcome in CBT for schizophrenia, indicating that impaired neurocognition does not preclude treatment benefits [196, 206, 207].

Regarding therapy format characteristics, a meta-analysis by Wykes et al. [175] found better outcomes in CBT programs with greater behavioral emphasis, suggesting behavioral components (e.g., experiment activities to test beliefs, taking action toward recovery goal steps) are at least as important as cognitive interventions (e.g., development of a shared conceptualization of the nature of illness). They also reported no difference in outcome between studies that used individual vs. group formats. A recent meta-analysis found that therapies that were 20 sessions or longer had better outcomes than shorter approaches [184] (but see [183]). Finally, there is evidence from effectiveness trials that CBTp delivered in community mental health settings improves outcomes [201, 208, 209], and community therapists can deliver CBTp with adequate fidelity [210].

Summary and Future Directions

CBT has proven effective for a number of mental disorders, including schizophrenia. Increasingly, best practice guidelines and nationalized healthcare systems are recommending or mandating CBTp [211]. Importantly, CBT has been shown to be effective at improving a number of outcome areas with benefits observed in psychiatric symptoms, mood, anxiety, and social functioning. It also has shown strong durability with continued benefits observed long after completion of the active therapeutic intervention. Not surprisingly, the behavioral element of CBT appears to be an important element in determining treatment success. Despite its efficacy and recommended use, CBTp is largely unavailable in the USA and implementation barriers in other countries limit access to CBTp. The dissemination and implementation of evidence-based practices like CBTp into real-world clinical practice is an important focus looking forward. Additional remaining challenges include treating serious comorbidities, such as substance abuse and other conditions that limit recovery, and treating special populations, such as racial minorities, older consumers, and those at high-risk for the development of psychosis [186].

Conclusion

As the treatment of schizophrenia has shifted toward the ambitious goal of functional recovery it has become clear that psychosocial interventions are an essential component of contemporary treatment. In this chapter we reviewed eight leading

rehabilitation and psychotherapy approaches. Some are supported by extensive efficacy data whereas other more recent approaches, although promising, require further development and evaluation. In this concluding section we briefly summarize the status of these interventions as empirically based treatments recommended for best clinical practices, and consider implementation (what it takes to deliver the service) and dissemination (what it takes to deliver the service to vast numbers of consumers) issues.

Regarding the evidence base on efficacious treatments, the 2009 report from the Schizophrenia Patient Outcomes Research Team (PORT [176]) comprehensively reviewed the treatment outcome literature and, using research-based standards, recommended the following treatments: ACT, SE, CBT, skills training, and family-based services among others not reviewed in this chapter (token economy, interventions for alcohol and substance use disorders, interventions for weight management). CR and peer-delivered services were seen as areas of interest but were not recommended treatments because of lack of evidence. Social cognition training was not reviewed at that time but likely will be considered in future PORT updates given the rapid expansion of research in this area.

Unfortunately, despite the existence of well-documented evidence-based psychosocial treatments, implementation issues are a nontrivial concern for most of these interventions. They vary considerably in terms of the certification requirements for service providers, duration of treatment, and human resources needed to implement the treatments with high levels of fidelity (see Table 14.1). For example, treatments like CBT require considerable training to reach professional standards. In contrast, skills training can be led by any mental health team member and requires less extensive training to reliably implement. A separate consideration is that duration of treatment can be lengthy for many of these programs (ranging from 3 to 12 months or longer). Without sufficient staffing, lengthy treatment duration ties up staff supplying these services and limits availability to other "wait-listed" consumers.

Dissemination is an even larger problem. Surveys indicate that evidence-based practices are not broadly disseminated in the USA. Epidemiological data from the National Comorbidity Study in the 1990s found that 60 % of SMI individuals received no treatment, 25 % received inadequate treatment, and only 15 % received minimally adequate treatment [212]. Data indicate that as many as 95 % of individuals with schizophrenia receive no care or less than adequate care [213]. Furthermore, some studies indicate that quality of care may be worsening despite the development of better treatments [214–216].

What obstacles stand in the way? First, state and federal government policies play an enormous role in promoting (or curtailing) which treatment services are vs. are not made available to individuals with severe mental illness through the availability of funds. Second, in recent years smaller mental health budgets at the state and county level have created a forced prioritization of clinical and rehabilitation services with some services dropped due to lack of funds to support resources needed for these programs. Third, a related financial problem is the priority on providing services that can be billed and reimbursed (e.g., meeting Medicaid regulations for a

reimbursable clinical service). On the positive side, there is recognition of the value and need to implement evidence-based practices by state mental health authorities in most states. Interventions such as ACT, CBT, skills training, and SE can be found in most regions. Also, the Veterans Administration has sponsored an initiative to disseminate SE in VA hospitals throughout the USA. Despite these advances, consideration of methods by which to improve dissemination clearly deserves continued attention and some frameworks have been proposed. According to Drake et al. [213], "Public mental health systems need better alignment between evidence-based practices and payments, sufficient funding to create a sustainable and professional workforce, electronic medical records to monitor process and outcomes, and a systemic commitment to quality."

To conclude, our understanding of the determinants of poor functional outcome has advanced considerably in recent years. These findings have been useful in guiding the development of a number of promising new rehabilitation and psychotherapeutic approaches to address these determinants. As a whole, the field is developing therapeutic tools that show considerable promise for enabling people with schizophrenia to achieve personally meaningful goals and achieve recovery despite the challenges posed by living with a severe mental illness. As these treatment development efforts continue to move forward, we are clearly at a point where making these treatments available to all who can benefit from them needs to become a priority.

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Part V
Future Directions and Implications

Chapter 15
Conclusion

Philip G. Janicak, Stephen R. Marder, Rajiv Tandon, and Morris Goldman

Overview

The modern conceptualization of schizophrenia began in the late nineteenth century and continues to evolve. Two major initiatives exemplify this process. First, the most recent editions of the Diagnostic and Statistical Manual of Mental Disorders (DSM) and International Classification of Diseases (ICD) incorporate harmonized approaches to diagnosis which differ substantially from their predecessors. Second, major advances in our understanding of the biological basis of this disorder promise to guide future refinements in diagnosis and treatment.

This book updated the reader in four major sections:

- An overview which emphasized the evolving *nosology of schizophrenia* to better differentiate patients based on core symptom dimensions and thus improve response with more personalized treatment regimens (Chap. 2).

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P.G. Janicak et al. (eds.), *Schizophrenia: Recent Advances in Diagnosis and Treatment*,
DOI 10.1007/978-1-4939-0656-7_15,

- Updates on recent research into the *pathoetiology of schizophrenia*, focusing on barriers and progress in the identification of biological markers (e.g., genetic, neuroimaging) which will also enhance diagnosis and treatment (Chaps. 3–6).
- The *medical management of schizophrenia* which considered optimal biological strategies and raised awareness about the need to address concurrent complications due to treatment- and medical comorbidity-related complications (Chaps. 7–12).
- The *long-term management of schizophrenia* which increasingly involves the integration of both biological and psychosocial modalities. The ultimate aim is to improve symptoms and enhance functioning so that patients can achieve important personal goals and experience a better quality of life (Chaps. 13 and 14).

Diagnostic Issues in Schizophrenia

The diagnosis of schizophrenia is based on the presence of a characteristic set of symptoms associated with impairment in functioning for a period of at least 6 months and the exclusion of other causes of psychosis. Refinements in the description and criteria of schizophrenia in the DSM-5 should assist clinicians in making a more reliable diagnosis and more clearly differentiating schizophrenia from schizoaffective disorder [1]. The provision in DSM-5 of a simple scale to quantify different dimensions of psychopathology should enable measurement-based and targeted individualized treatment [2]. The dimensional approach to the heterogeneous psychopathology of schizophrenia should facilitate a better bridge to a pathoetiological diagnosis with laboratory markers in the future [3]. These diagnostic issues and the clinical implications of the changes in DSM-5 are considered in Chap. 2.

Pathophysiology of Schizophrenia

While Chaps. 3–6 summarize our current knowledge regarding the neurobiology of schizophrenia, they are largely devoted to understanding some of the limitations of previous research, as well as how current approaches address these challenges [4]. All four chapters underscore the need to clarify mechanisms to better identify biomarkers and intermediate phenotypes which serve to focus future research and treatment efforts. Chapter 3 emphasizes the general need to characterize mechanisms of brain function to better distinguish adaptive from pathological processes. Chapter 4 provides a framework for integrating diverse findings, as well as laying out some of the barriers which are now being addressed [5]. Chapter 5 provides a historical review of genetic findings in schizophrenia and summarizes the logic, strengths, and weaknesses of evolving approaches. In particular, efforts to incorporate downstream analyses and other "omics" approaches are addressed. Chapter 6 focuses on recent advances in neuroimaging and like Chap. 5 illustrates efforts to incorporate multiple modalities to better characterize the functional significance of findings and provide biomarkers of the illnesses [6].

Medical Management of Schizophrenia

The recognition and management of the earliest phases (e.g., high risk, first-episode, early-onset) of schizophrenia are critically important to favorably alter its long-term outcome. Thus, there is an increasing effort dedicated to improving the identification of at-risk individuals. This is exemplified by inclusion of *attenuated psychosis syndrome* in the DSM-5 as a condition which requires greater scrutiny and further elaboration [7]. Once reliably indentified, the next crucial question is which interventions are both reasonable (i.e., constitute a favorable risk/benefit ratio) and increase the chances of producing a clinically meaningful impact on an individual's long-term prognosis. In this context, treatment approaches include more intense monitoring for symptom evolution; managing associated symptoms (e.g., anxiety, depression, substance abuse); introducing various psychotherapeutic and psychosocial strategies; and when appropriate, employing various standard (e.g., antipsychotics) and novel (e.g., *N*-acetylcysteine, omega-3 FAs) biological therapies. In multi-episode patients, the use of antipsychotic agents remains a critical component for reducing symptoms, and allowing patients to more effectively benefit from other interventions (e.g., cognitive remediation). Optimal use of these agents during acute exacerbations and to reduce episode relapse and recurrence requires a better appreciation of drug choice and dosing strategies. Regarding the latter, we are progressing from dosing based on data from controlled trials, to plasma-level data, to imaging of dopamine receptor binding, and to the anticipated use of pharmacogenetics/pharmacogenomics to help guide clinicians in their medication strategies. Unfortunately, many obstacles preclude an optimal trial with existing antipsychotics. Thus, even when patients adequately adhere to an appropriate medication regimen their symptoms often persist, impeding recovery.

As a result, a number of strategies are presently applied to enhance the benefit of standard agents. These include:

- An adequate trial of clozapine when feasible
- Antipsychotic combinations and development of newer agents
- Novel monotherapy and adjunctive approaches

The last option often involves the repurposing of existing agents as monotherapies or augmentation strategies. The most promising of these include drugs with a novel spectrum of neuroreceptor actions including various dopamine (e.g., cariprazine), serotonin (e.g., ondansetron), glutamatergic (e.g., bitopertin), gabaergic (e.g., divalproex sodium), and cholinergic (e.g., phosphatidylcholine) agents. In addition, other promising approaches which may eventually benefit patients include the use of certain antidepressants (e.g., mirtazapine) to better manage depressive, negative, and cognitive symptoms; anti-inflammatory agents (e.g., minocycline) to improve negative and cognitive symptoms in early-onset patients; hormonal agents (e.g., estrogen compounds), especially during heightened levels of vulnerability such as the postpartum and perimenopausal periods; and neutraceuticals (e.g., omega-3 FAs, folate) to aid in normal neurodevelopment during pregnancy.

Adjunctive therapeutic modulation may also play a role in managing some of the most severe exacerbations (e.g., electroconvulsive therapy) or for resistant positive and negative symptoms (e.g., transcranial magnetic stimulation).

Medical Comorbidities

There is increasing awareness that medical comorbidities play a major role in determining the overall well-being and functionality of patients with schizophrenia. Their impact includes a substantial decrease in life expectancy due to various factors (e.g., inattention to health issues by both patients and their treatment teams). One example is the psychosis intermittent hyponatremia (PIP) syndrome associated with episodic water intoxication. This occurs in up to 10 % of chronically-ill mental patients. PIP appears related to the illness itself (e.g., schizophrenia) but hyponatremia also frequently arises from other factors (e.g., treatment with certain psychotropics such as carbamazepine). Unfortunately, these issues often go unrecognized and may lead to subtle neurological symptoms, renal and bladder problems, or even death due to severe hyponatremia. When properly diagnosed, however, recent studies support the use of clozapine or competitive vasopressin receptor 2 antagonists (i.e., vaptans) to manage this condition [8].

Medication Adverse Effects

Related to the general health issues of patients are the adverse effects associated with antipsychotics and other psychotropic agents frequently used to manage schizophrenia. In particular, antipsychotic-induced weight gain and its subsequent complications (e.g., metabolic syndrome, new-onset diabetes) contribute to much higher rates of cardiovascular disease in patients on these drugs compared with the general population. It is important for clinicians who manage these patients to monitor the modifiable risk factors for cardiovascular disease including weight, blood pressure, and lipids. In this context, recent studies support the use of metformin to prevent or reverse the weight-gain, as well as to improve BMI and lower triglyceride and hemoglobin A_{1c} levels [9]. Since this drug's impact appears to be modest, however, various psychosocial interventions (e.g., education about nutrition, caloric expenditure, portion control), behavioral self-management (e.g., goal setting, regular weigh-ins), and increased physical activity should be attempted before a trial of this agent [10].

Long-Term Management of Schizophrenia

Improving the long-term outcome in schizophrenia entails:

- Preventing recurrences of psychosis
- Improving functioning and quality of life
- Promoting improved physical health

Antipsychotic medications are effective for preventing episodes of psychosis [11]. Many patients, however, resist taking their medications and others are unreliable pill takers. As a result, successful treatment often requires strategies for assuring adequate adherence such as educating patients and family members, addressing medication side effects, and using long-acting injectable (LAI) formulations. The recent introduction of several second-generation LAIs provides new choices for patients and clinicians and should lead to greater use of this method for administering antipsychotics.

In addition to medication management, this volume emphasizes an approach to long-term management which accepts the principles of recovery [12]. According to these principles, treatment should focus on the goals of the patient. Although optimal treatment may not completely alleviate the burden of the illness, patients can often learn strategies which compensate for their impairments. This approach almost always includes combining psychosocial and pharmacological treatments. Effective psychosocial treatments include patient and family education, cognitive behavioral treatment for psychosis, social skills training, supported employment, and cognitive remediation [13].

Clinicians who manage patients with schizophrenia should also address the substantial physical health problems associated with the illness, as well as comorbidities such as substance abuse. Psychosocial treatments are effective for helping patients adapt healthier life styles with improved diets and exercise, while they also help patients address nicotine and other addictions [13]. Despite the effectiveness of these treatments, it is often difficult for patients and their families to access them. Thus, the need for resources to provide these effective and available therapies is an important social–political issue.

In the Future

Although we have made considerable progress in improving treatments and outcomes for persons with schizophrenia, substantial needs remain. Whereas a plethora of neurobiological findings in schizophrenia are described, their precise meaning is unclear and their relevance to clinical practice is limited. This is likely to change in the near future because of both methodological and conceptual advances and because of improvements in nosology, including refinement of DSM criteria and incorporation of objective measures. As neuroimaging, neurochemical and electrophysiological technologies mature, dysfunctions will become more apparent. Better integration of these data, as well as the combined use of biomarkers, may be more useful than individual markers used in isolation. Multimodal approaches (e.g., combining fMRI with ERP data) may be more useful than individual ones. Better delineation of endophenotypic markers and susceptibility genes are likely to yield better animal models for further hypothesis testing. Larger, multisite studies will also improve statistical power to confirm/refute the tantalizing observations currently limited by small sample sizes. The future holds much promise for more effective, better individualized treatments with greater opportunities for recovery in individuals with schizophrenia.

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P.G. Janicak et al. (eds.), *Schizophrenia: Recent Advances in Diagnosis and Treatment*,
DOI 10.1007/978-1-4939-0656-7,