Epidemiology of Schizophrenia

Definition of Schizophrenia

Schizophrenia is a severe, chronic mental health disorder characterized by a variety of symptoms that affect mental state, emotions, and behaviors. The disorder requires lifelong management, even when symptoms are not evident. According to the *Diagnostic and Statistical Manual of Mental Disorders, 5th edition* (DSM-5), the diagnostic criteria for schizophrenia include the persistence of 2 or more active-phase symptoms, each lasting for a significant portion of at least a 1-month period. At least 1 of these symptoms must be delusions, hallucinations, or disorganized speech. In addition, grossly disorganized or catatonic behavior and negative symptoms (eg, diminished emotional expression) may hallmark schizophrenia. To meet the diagnostic criteria for schizophrenia, patients must also exhibit an inability to function at work, have trouble with interpersonal relationships, or have difficulty providing self-care for a time period of at least 6 months, including 1 month of active-phase symptoms. The 6-month period may also include periods of residual symptoms, and during these residual periods, only negative symptoms may be apparent. Schizophrenia is one of multiple disorders that fall under a broader category known as schizophrenia spectrum disorders (SSDs). Subjects with SSDs other than schizophrenia may be included as subjects in some studies of treatments used for schizophrenia. Examples of other SSDs include schizoaffective disorder and other psychotic disorders.

Incidence and Prevalence

The World Health Organization estimates that schizophrenia affects more than 21 million persons worldwide. Estimates within the United States vary, but schizophrenia is believed to affect between 0.6% and 1.9% of the total population. One claims analysis suggests the annual prevalence of diagnosed disease to be 5.1 per 1000 lives in the United States. In addition, the Schizophrenia and Related Disorders Alliance of America estimates that as many as 3.5 million individuals in the United States have received a diagnosis of schizophrenia. The incidence is generally believed to be fairly equal between men and women, although men tend to initially...
Theories of Pathophysiology

Etiology and Pathophysiology of Schizophrenia

Etiology

Genetic factors are believed to play a critical role in the development of schizophrenia, with studies suggesting that the actual risk for the disorder is approximately 10% for a first-degree relative versus 3% for a second-degree relative. The risk of 1 monozygotic twin having the disorder is estimated at 48% if the other twin had schizophrenia, with a risk of between 12% and 14% in dizygotic twins. If both of a child’s parents have schizophrenia, they have about a 40% risk of bearing a child with the disorder. A genetic basis for schizophrenia is also supported by data showing that siblings with the disorder experience symptom onset at the same age.

In addition to these genetic influences, obstetric complications including bleeding during pregnancy, emergency cesarean delivery, low birthweight, and fetal asphyxia have been associated with schizophrenia later in life. In addition, there has been some focus on a link to fetal disturbances in the second trimester, which is the critical period for fetal neurodevelopment. Maternal infections and excessive stress levels during this time have been associated with the development of schizophrenia in the offspring.

Environmental factors have also been studied in relation to the disorder, but overall research suggests that schizophrenia might be better viewed as one of a group of clinical outcomes related to genetically or environmentally induced disruption to the developing fetal brain. There is a need for future epidemiologic studies surrounding the effects of environmental exposures before a true link to schizophrenia can be established.

Theories of Pathophysiology

Research into the pathophysiology of schizophrenia now focuses on multiple neural networks of psychosis, including dopamine, serotonin, and glutamate. The pathophysiologic basis for schizophrenia was initially thought to be primarily related to the dysregulation of the dopaminergic system. As a result, therapies were designed to target the dopamine pathway in the central nervous system. The original dopamine hypothesis stated that symptoms of schizophrenia were caused by hyperactive dopamine transmission; however, that theory has been questioned over time. More recently, a revised dopamine hypothesis has been proposed and focuses on hyperactive dopamine transmission in the mesolimbic areas and hypoactive dopamine transmission in the prefrontal cortex (mesocortical system) in patients with schizophrenia. Based on this revised hypothesis, increased dopaminergic activity in the mesolimbic areas is responsible for the positive symptoms associated with schizophrenia (ie, delusions, hallucinations); decreased dopaminergic activity in the prefrontal cortex is responsible for the negative symptoms associated with schizophrenia (ie, anhedonia, cognitive dysfunction). However, overall evidence accumulated over time found that the dopamine hypothesis was an oversimplification of the pathophysiology of schizophrenia. Increasing evidence shows that the pathophysiology of schizophrenia is likely related to complex dysfunctions in multiple pathways and involves several neurotransmitters, including dopamine, glutamate, serotonin, and γ-aminobutyric acid (GABA). Glutamate has been found to play an important role in the pathophysiology of schizophrenia (Figure 1).

A recent theory suggests that psychosis in schizophrenia may be the result of hypofunctional NMDA receptors on GABA interneurons in the cerebral cortex. This hypofunction may lead to overactivation of downstream glutamate signaling to the ventral tegmental area. Overactivation of this pathway may result in turn in excess dopamine in the ventral striatum via the mesolimbic pathway.

FIGURE 1. Proposed Glutamate Pathophysiology of Schizophrenia

<table>
<thead>
<tr>
<th>Glutamate</th>
<th>Cerebral Cortex</th>
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<tbody>
<tr>
<td></td>
<td>• Visual</td>
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<tr>
<td></td>
<td>• Temporal</td>
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<td></td>
<td>• Motor</td>
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<td>• Prefrontal</td>
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GABA indicates γ-aminobutyric acid, NMDA, N-methyl-D-aspartate.
activating the mesolimbic dopamine pathway as part of a chain reaction, leading to positive symptoms such as delusions and hallucinations. A strategy of focusing on targets in the serotonin hypothesis would potentially reduce extrapyramidal effects as well as improve negative symptoms and cognitive impairments associated with schizophrenia (Figure 2) .

Clinical Presentation of Schizophrenia

Signs and Symptoms

The core features of schizophrenia center on positive and negative symptoms and cognitive impairment. Positive symptoms describe psychosis in which the patient loses contact with reality. These include delusions and hallucinations, disorganized thinking and/or behavior, or catatonia. Negative symptoms encompass disruptions to normal emotions and behaviors and may include a flat affect, impaired motivation, reduction in spontaneous speech, social withdrawal, and difficulty starting and sustaining activities, along with reduced feelings of pleasure in the activities of daily living. Patients with persistent and clinically significant negative symptoms have been found to have the poorest clinical outcomes in schizophrenia and experience diminished quality of life (QOL). Although positive symptoms can be successfully treated with antipsychotic agents, negative symptoms are more difficult to manage. This is especially critical because approximately 20% to 40% of patients with schizophrenia exhibit persistent negative symptoms. As an example, data from a study of a sample of 7500 patients indicated that 41% of these patients had at least 2 or more negative symptoms. Those with 2 or more negative symptoms were 24% more likely to experience mental health hospital admission for their symptoms and had a 58% higher risk of admission within the following 12 months. Negative symptoms across the participant sample were associated with a greater likelihood of hospital admission, longer inpatient duration, and increased likelihood of readmission post discharge. Finally, patients with schizophrenia may exhibit notable cognitive impairment, performing more poorly than patients without the disease over a diverse range of cognitive functions. These cognitive deficits include poor ability to comprehend information and assess it for decision making, lack of focus or inability to pay attention, and problems with working memory. Evidence suggests substantial cognitive heterogeneity in schizophrenia, with potential genetic or other basis for this yet to be elucidated. In general, positive symptoms of schizophrenia tend to occur in a relapsing/remitting fashion, although some patients experience residual longer-term psychoses. Negative and cognitive symptoms tend to be more chronic and impact patient social functioning in the long term.

Common Comorbidities and Unmet Medical Needs Associated With Schizophrenia

Patients with schizophrenia are between 2 and 2.5 times more likely to die early than people without the disorder, representing a 10- to 25-year mortality gap. Psychiatric comorbidities often found in patients with schizophrenia include generalized anxiety disorder, depressive disorders, obsessive-compulsive disorder, and panic disorder. Many of these disease states can exacerbate symptoms of schizophrenia and lead to increased morbidity and mortality in this patient population, including an increased risk of suicide about 5% higher than in the general population. Patients with serious mental illness, including schizophrenia, can experience a substantial variety of complications due to their disease and other common physical and social issues that result in significant morbidity and mortality (Figure 3). Some common comorbidities in individuals with schizophrenia include:

- Cardiovascular and obstetric complications in women
- Overweight
- Diabetes
- Hyperlipidemia
- Dental problems
- Impaired lung function
- Osteoporosis
- Pain sensitivity
- Sexual dysfunction
- Infectious diseases (HIV, hepatitis, and tuberculosis)
Cardiometabolic Risk Factors/Metabolic Syndrome

Patients with psychiatric disorders, including schizophrenia, are more likely to develop obesity, type 2 diabetes, hypertension, dyslipidemia, and metabolic syndrome (MetS). The incidence of MetS has been linked to an unhealthy lifestyle and also the use of antipsychotic agents, especially second-generation antipsychotics. The presence of MetS in a patient with schizophrenia can have a critical influence on future morbidity and mortality. A meta-analysis of 126 analyses in 77 publications found that the overall rate of MetS was 32.5%, with only minor differences surrounding treatment setting, country of origin, gender, and utilized definitions of MetS. Illness duration was the strongest predictor identified, and older age had a moderate effect. Rates of MetS differed with use of different antipsychotic agents. Overall, the investigators concluded that patients with schizophrenia should be considered a high-risk group for MetS and metabolic abnormalities and should receive regular monitoring and treatment, if indicated, for any cardiometabolic risk factors.

Sexual Function/Dysfunction

Data surrounding sexual dysfunction in patients with schizophrenia tend to be limited, and most patients show sexual interest similar to the general population. Available evidence demonstrates that psychiatric symptoms, institutionalization, and antipsychotic therapy can contribute to impaired sexual functioning. Social and interpersonal impairments can impede the ability of a patient to develop a stable sexual relationship, although women with schizophrenia have been found to have better social outcomes, longer-lasting sexual relationships, and more children than their male counterparts. Overall, the use of antipsychotic drugs is a significant factor in sexual functioning issues. Medications affect patients differently, with higher frequencies of sexual dysfunction linked to risperidone and first-generation antipsychotics versus lower levels of sexual dysfunction for clozapine, olanzapine, quetiapine, and aripiprazole. Postsynaptic dopamine antagonism, prolactin elevation, and α₁-receptor blockade have been hypothesized as the key culprits in the pathogenesis of antipsychotic-induced sexual dysfunction. Psychosocial strategies to treat sexual dysfunction related to pharmacotherapy should emphasize patient education and relationship counseling. Pharmacologic strategies, after weighing benefit versus risk, may include lowering the dose of the associated agent, switching to a prolactin-sparing drug, and potentially adding a dopamine agonist, aripiprazole, or a phosphodiesterase-5 inhibitor, although evidence to prove benefit with these therapies remains to be fully delineated.

Tobacco/Illicit Drug Use

A very high prevalence of tobacco use exists among patients with schizophrenia; it is estimated to be 3 times that of the general population, and the disparity is increasing. Patients with schizophrenia die on average 10 to 15 years earlier than their counterparts without the disorder, and smoking is the largest preventable cause for these deaths. Meta-analysis data have also shown that smokers have an approximately 2-fold increased risk of incident schizophrenia or psychosis, even after adjustment for any related confounding factors. One analysis by Scott et al assessed 8 studies linking tobacco smoking and psychosis, of which 6 demonstrated a statistically significant positive association between smoking and SSDs. Data showed a consistent association with both a dose–response relationship and a moderate to large size of effect. More recently, data assessing smoking in schizophrenia have shown that daily tobacco use is associated with an increased risk of psychotic illness and an earlier age of onset for psychosis. Additional data have shown that smoking was statistically significant, with an inverse association with a patient’s total Repeatable Battery for the Assessment of Neuropsychological Status cognitive score (coefficient, −0.282; P < .001) and with attempts at suicide (OR, 2.25; P = .047). In addition, smoking at baseline was found to be the strongest predictor of subsequent natural cause mortality (RR, 2.29; P < .001), contradicting the concept that tobacco cessation...
is a low healthcare priority to address in this population because products containing nicotine are used as a form of self-medication by patients with schizophrenia.\textsuperscript{30} Data have shown that patients with schizophrenia find smoking cessation difficult, with almost 40% reporting quit attempts but just 4% with verified abstinence at 6 months post initial attempt at quitting. Further efforts toward smoking cessation are needed in patients with schizophrenia, including counseling, smoking cessation pharmacotherapy, and assistance toward weight management and increasing physical activity to better promote smoking abstinence.\textsuperscript{10}

Illicit substance use is common in patients with schizophrenia, with approximately 27.5% of this population using illicit substances. The prevalence of a comorbid substance use disorder (SUD) in patients with schizophrenia is approximately 41.7%. The rates of SUD have not changed over time, indicating that SUD is difficult to treat in patients with schizophrenia.\textsuperscript{31} Self-reported features that have been identified for drug misuse in these patients include achievement of intoxication, enhancement of ability to socialize, self-medication for both the positive and negative symptoms of schizophrenia, and relief of dysphoric mood. In addition, cannabis has been associated with precipitating schizophrenia in vulnerable persons, with cannabis use doubling the risk of developing psychosis in these populations.\textsuperscript{32-34} One small study by Asher and Gask asked patients with schizophrenia to describe the history of their use of illicit “street” drugs. The data demonstrated 5 reasons for continuing this drug use, specifically an identity-defining voca-
tion, peer group inclusion, sense of hopelessness, beliefs about symptoms and the influence of street drugs on them, and, import-
tantly, viewing these drugs as equivalent to using antipsychotic agents. Street drugs were used to relieve anxiety in patients who were hearing voices as part of their psychosis, with some patients hoping the illicit substances would help them focus on these voices and essentially outwit their perceived enemies. Methods are needed to better assess patients with schizophrenia who are using illicit drugs to better tailor management of comorbid SUD to the individual patients and optimize outcomes.\textsuperscript{14}

<table>
<thead>
<tr>
<th>TABLE 1. Rates of MetS in Patients With Schizophrenia According to Therapy Received\textsuperscript{26}</th>
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<tbody>
<tr>
<td><strong>Antipsychotic Agent</strong></td>
</tr>
<tr>
<td>-------------------------</td>
</tr>
<tr>
<td>Clozapine</td>
</tr>
<tr>
<td>Olanzapine</td>
</tr>
<tr>
<td>Risperidone</td>
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<tr>
<td>No antipsychotic therapy</td>
</tr>
</tbody>
</table>

MetS indicates metabolic syndrome.

Examining Nonadherence to Therapy for Schizophrenia
The Challenge of Nonadherence in Persons With Schizophrenia

Treatment with antipsychotic agents has been proven to reduce disease severity in patients with serious mental illnesses. In a meta-analysis of 65 clinical trials involving 6493 patients with schizophrenia whose disease was stabilized by these medications, results demonstrated that antipsychotic therapy significantly reduced rates of relapse.\textsuperscript{35,36} Preventing relapse is an important therapeutic goal, along with increasing adaptive functioning, because patients may not return to their baseline level of adaptive functioning after relapse.\textsuperscript{6,11} Although first-line antipsychotic therapy is estimated to be effective in up to 80% of patients with schizophrenia, it is estimated that approximately 50% of patients with schizophrenia who respond well to pharmacotherapy are nonadherent to their treatment regimens.\textsuperscript{37,38} General findings from studies have approximated nonadherence rates in schizophrenia to range from 37% to 74%.\textsuperscript{4} Nonadherence to therapy is often the culprit behind exacerbations in psychopathology, symptom relapse, and rehos-
pitalization, and it is also a problem that is likely preventable.\textsuperscript{39,40} Nonadherence to therapy results in poor health and economic outcomes, including increased hospitalization rates and subsequent greater resource usage.\textsuperscript{38}

Reasons for nonadherence to pharmacotherapy vary signifi-
cantly among patients. Some may refuse to take a medication due to lack of acceptance of the need for treatment, whereas others may accept and recognize the need for medication but are nonad-
herent due to reasons such as forgetfulness or financial constraints. Nonadherence in patients with schizophrenia is a combination of patient-, environmental-, clinician-, and treatment-related factors (Table 2\textsuperscript{40}). For example, some of the patient-related and environmental factors associated with nonadherence to antipsychotics for schizophrenia include newly started treatment, younger or older age of treatment onset, substance misuse, poor social and familial support, and the stigmatization that comes with a schizophrenia diagnosis.\textsuperscript{39,41} Disease-related concerns may also impact patient adherence to therapy, as patients with cognitive impairment often have poor insight regarding their serious mental illness; those with psychotic symptoms may feel that taking their medication will cause danger or harm.\textsuperscript{42} Provider factors include a low level of therapeutic alliance with the patient and poor education of patients and caregivers.\textsuperscript{38,40} Results of a meta-analysis showed that clinician communication was positively correlated with patient adherence. The risk of nonadherence is 19% higher for patients whose clinician communicated poorly as compared with patients whose clinician communicated well.\textsuperscript{43} Medication-related factors include drug ineffectiveness against persistent symptoms, fear of adverse effects (AEs), and complex treatment regimens. Both positive and
negative symptoms can affect a patient’s attitude toward taking medications and can lead to nonadherence.\textsuperscript{40}

**Medication AEs Impact Adherence**

Medication AEs from antipsychotics negatively impact adherence among patients with schizophrenia. Antipsychotics are associated with a range of AEs, including extrapyramidal symptoms, sedation, elevated prolactin levels, weight gain, and cognitive impairment. Many AEs are dose-related, and severity may vary by specific agent.\textsuperscript{36,42}

Overall, the occurrence of past or current AEs has been associated with less favorable attitudes (\(P < .005\)) on the part of patients toward their pharmacologic treatment and decreased adherence (\(P < .001\)). These patients tended to doubt medication effectiveness and were less likely to encourage others to use the agent in case of need. Nonadherence was primarily affected by negative general and effectiveness attitudes toward antipsychotics and a patient’s previous or current experience with antipsychotic AEs.\textsuperscript{40,41} Because AEs are common with antipsychotic agents, patients should receive regular follow-up that includes monitoring for AEs with interventions as appropriate.\textsuperscript{41}

**Consequences of Nonadherence**

Medication nonadherence is associated with an increased risk of relapse, rehospitalization, self-harm, and lower QOL. Although a small proportion of patients with schizophrenia experience a single episode and make a full recovery, for most patients, schizophrenia is a chronic condition. The relapse rate is high, with a 5-year follow-up study demonstrating a cumulative first relapse rate of 82\% and a second relapse rate of 78\%.\textsuperscript{32,44} Another study found that 77\% of symptoms recurred within 1 year of medication discontinuation and more than 90\% recurred within 2 years.\textsuperscript{47,48} A 3-year prospective observational study conducted in the United States found links between antipsychotic nonadherence and multiple negative consequences, including increased psychiatric hospitalizations and emergency department care, higher rates of substance misuse, and a higher incidence of violent behavior and arrests.\textsuperscript{42,45} It should be noted that the vast majority of persons with schizophrenia are not violent and are more likely to be victims, rather than perpetrators, of violent acts.\textsuperscript{46}

Although maintenance therapy with antipsychotic treatment does not eliminate the possibility of relapse, it significantly reduces the risk. A meta-analysis of 65 trials showed that patients stable on antipsychotic medication had a reduced rate of relapse after 1 year (27\% vs 64\%; RR, 0.40; 95\% CI, 0.33-0.49). Moreover, those patients were less likely to be admitted to the hospital and had a more significant success rate with treatment compared with those patients who received a placebo. In addition, some evidence indicated that treated patients experienced improved QOL and demonstrated fewer acts of aggression. The advantages of pharmacotherapy must be weighed against associated AEs; however, data strongly indicate that antipsychotic maintenance therapy benefits patients with schizophrenia.\textsuperscript{35,42}

**Conclusions**

Schizophrenia is a disorder that negatively impacts affected patients with symptoms that include delusions, hallucinations, disorganized speech, and grossly disorganized or catatonic behavior, along with negative symptoms and substantial cognitive impairment.

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**TABLE 2. Risk Factors for Medication Nonadherence in Persons With Schizophrenia\textsuperscript{40}**

<table>
<thead>
<tr>
<th>Patient-related risk factors</th>
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<tbody>
<tr>
<td>Sociodemographic factors</td>
<td>Younger and older patients, Male</td>
</tr>
<tr>
<td>General clinical factors</td>
<td>Illicit drug or alcohol consumption, Previous nonadherence</td>
</tr>
<tr>
<td>Psychopathologic symptoms</td>
<td>Impaired insight, Cognitive deficiency, Delusion of persecution, poisoning, or grandeur, Psychotic symptoms, Negative symptoms</td>
</tr>
<tr>
<td>Psychological factors: attitudes, beliefs, and other subjective aspects</td>
<td>Negative attitude toward the treatment, Negative subjective response to treatment, Regarding the disease as mild and/or perceived minor benefit from treatment, Shame or stigmatization associated with the medication or the disease</td>
</tr>
<tr>
<td>Environmental-related risk factors</td>
<td>Poor social and familial support, Negative social perception of the disease, Stigmatization, Difficulty accessing healthcare services</td>
</tr>
</tbody>
</table>

**Physician-related risk factors**

- Poor relationship with the therapist
- Poor psychoeducation and information to patients and relatives
- Poor contact with the therapist
- Inadequate planning of the postdischarge period

**Treatment-related risk factors**

- Ineffectiveness against persistent symptoms (psychotic and negative symptoms)
- Fear of adverse effects
- Complex medication schedule
- Poorer adherence to oral than to intramuscular treatments

Whereas the exact etiology and pathophysiology of the disorder have yet to be elucidated, a combination of genetic and environmental factors place patients at risk for schizophrenia and its symptoms and consequences. Multiple comorbidities are associated with schizophrenia, complicating the optimal management of patients and potentially limiting positive outcomes. In addition, adherence to recommended antipsychotic therapy for the disorder is often suboptimal and affected by a host of patient-, environment-, clinician-, and treatment-related risk factors for nonadherence. With so many potential challenges to patient management, data surrounding best practices in schizophrenia management must continue to evolve, providing more information and options for patients and clinicians that may improve outcomes and QOL for those affected by this common and serious mental health disorder.

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25. Ascher-Svanum H, Faries DE, Zhu B, Ernst FR, Swartz MS, Swanson JW. Medication adherence and nonadherence. With so many potential challenges to patient management, data surrounding best practices in schizophrenia management must continue to evolve, providing more information and options for patients and clinicians that may improve outcomes and QOL for those affected by this common and serious mental health disorder.

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