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A Managed Care Review of Schizophrenia: Evaluating Unmet Medical Needs, New Treatments, and Health Economics

HIGHLIGHTS

Supplement to *The American Journal of Managed Care®*

A Managed Care Review of Schizophrenia: Evaluating Unmet Medical Needs, New Treatments, and Health Economics

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Intended Audience

Managed care payers, pharmacy directors, pharmacy benefit managers, specialty pharmacy directors, and any other pharmacist and/or healthcare professional interested in the scientific advances in schizophrenia.

Activity Overview

Schizophrenia is a complex disease that represents a significant economic burden for patients, providers, and the healthcare system. Nonadherence is of particular importance, as nonadherent patients with schizophrenia struggle with disease awareness, homelessness, unemployment, and a poor quality of life. Comorbidities as a result of medication use and disease manifestations necessitate comprehensive care by the healthcare team. As the understanding of schizophrenia management evolves, there is a need for managed care professionals, pharmacists, and payers to evaluate the role of various drug utilization strategies to improve outcomes.

Statement of Educational Need

Patients with schizophrenia present unique challenges to providers, caregivers, and the healthcare system due to the nature of their disease, which exacerbates physical comorbidities and resistance to medication adherence. Although many therapies have become available to patients, there are still a number of unmet medical needs within this challenging disease state. Unwanted adverse effects of current treatment options contribute to development of comorbid conditions such as obesity, diabetes, and dyslipidemia. Additionally, nonadherence remains a treatment challenge for patients with schizophrenia and has root in a variety of medication-, patient-, disease-, and environmental-related factors, and its high rate contributes substantially to morbidity, mortality, and economic burden.

Novel therapeutic antipsychotic agents may mitigate some issues associated with nonadherence—including improved safety profiles and fewer adverse effects—but in the meantime, managed care professionals have a responsibility to implement clinical protocols and stepwise formularies to promote professional guidelines and encourage medication adherence among patients with schizophrenia. Continuing professional education will improve managed care professionals' and pharmacists' competency in managing patients with schizophrenia through greater insight into current management challenges and the emerging treatment options.

Educational Objectives

Upon completion of this activity, participants will be able to:

- Examine the pathophysiology and clinical presentation associated with schizophrenia.
- Characterize common comorbidities, adherence challenges, and areas of unmet need within schizophrenia treatment.
- Explore emerging therapies in the management of schizophrenia, including the mechanisms of action, safety and efficacy data, and unique characteristics of each.
- Explain the economic impact of schizophrenia and describe the role of formulary and disease management protocols in improving health outcomes for patients with schizophrenia.

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OVERVIEW

Through this supplement to *The American Journal of Managed Care®*, managed care professionals will identify comorbidities and adherence challenges associated with schizophrenia treatment and appraise therapies in development with the potential to improve health outcomes in this patient population.

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REPORT

Unmet Medical Needs and Other Challenges in the Treatment of Patients With Schizophrenia

Lisa W. Goldstone, PharmD, MS, BCPS, BCPP

ABSTRACT

Schizophrenia is a chronic mental health disorder hallmarked by a variety of symptoms impacting mental state, emotions, and behaviors, including delusions, hallucinations, disorganized speech, grossly disorganized or catatonic behavior, negative symptoms, and cognitive impairment. Schizophrenia leaves patients with the inability to function appropriately in their daily lives, including at work, in relationships, and even with self-care. The exact cause of this disorder has yet to be elucidated; however, multiple factors, including genetic susceptibility and environmental influences, have been implicated in its development. Patients with schizophrenia frequently demonstrate medication nonadherence and have multiple concurrent comorbidities that lead to increased morbidity and mortality. Schizophrenia is estimated to affect more than 21 million individuals globally, and while many therapies have become available for management, the disorder still presents unique challenges to providers, caregivers, and the healthcare system. Unmet medical needs remain for this complex disease state, and research is ongoing to address these needs and improve the overall health and outcomes of patients living with schizophrenia.

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For author information and disclosures, see end of text.

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.[1] The disorder requires lifelong management, even when symptoms are not evident.[2] 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.[1,3] 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.[1]

Incidence and Prevalence

The World Health Organization estimates that schizophrenia affects more than 21 million persons worldwide.[4] Estimates within the United States vary, but schizophrenia is believed to affect between 0.6% and 1.9% of the total population.[5,6] One claims analysis suggests the annual prevalence of diagnosed disease to be 5.1 per 1000 lives in the United States.[6,7] 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.[8] The incidence is generally believed to be fairly equal between men and women, although men tend to initially

experience symptoms earlier, in their early twenties, compared with women, who experience symptom onset most often in their late twenties or early thirties.[1,6] More recent data estimate that, per every 100,000 individuals, 15 men and 10 women receive a diagnosis of schizophrenia annually with a point prevalence of 4.6 per 1000 and an approximate lifetime risk for schizophrenia of 0.7%.[5,9]

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.[6,10] A genetic basis for schizophrenia is also supported by data showing that siblings with the disorder experience symptom onset at the same age.[6,11]

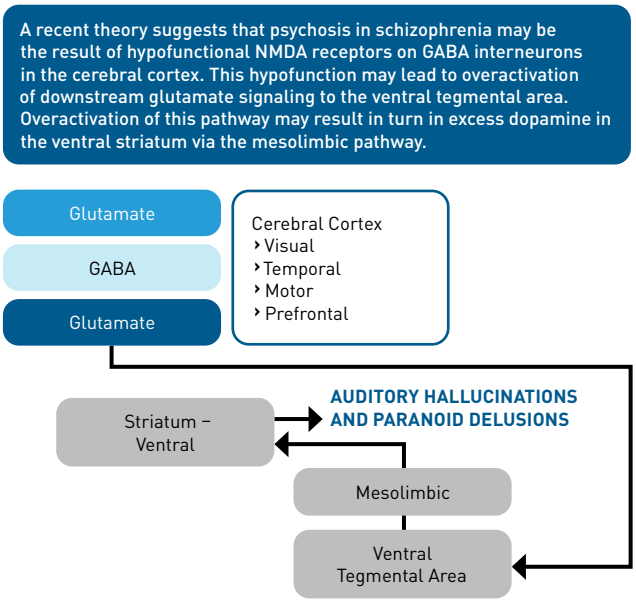
In addition to these genetic influences, obstetric complications including bleeding during pregnancy, emergency cesarean delivery, low birthweight, and fetal asphyxia have been associated with schizophrenia later in life. In addition, there has been some focus on a link to fetal disturbances in the second 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.[6,12] 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.[9]

Theories of Pathophysiology

Research into the pathophysiology of schizophrenia now focuses on multiple neural networks of psychosis, including dopamine, serotonin, and glutamate.[13] 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.[14,15] 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).[15] 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**[13]). Overaction of glutamate signaling is thought to lead to excessive stimulation of the mesolimbic dopamine pathway, resulting in an increased incidence of auditory hallucinations and paranoid delusions. In addition, excess glutamate signaling, especially in the visual centers of the cerebral cortex, is believed to be linked to visual hallucinations.[13]

Increased interest in the role of serotonin in schizophrenia came with the recognition that dual serotonin–dopamine antagonists, such as clozapine and risperidone, had beneficial antipsychotic effects in ameliorating both positive and negative symptoms associated with schizophrenia.[16,17] Excess serotonin and increased activation of 5-HT_{2A} receptors lead to downstream release of glutamate,

FIGURE 1. Proposed Glutamate Pathophysiology of Schizophrenia[13]



GABA indicates γ-aminobutyric acid; NMDA, N-methyl-D-aspartate.

Stahl SM. Beyond the dopamine hypothesis of schizophrenia to three neural networks of psychosis: dopamine, serotonin, and glutamate. *CNS Spectr.* 2018;23(3):187-191, reproduced with permission.

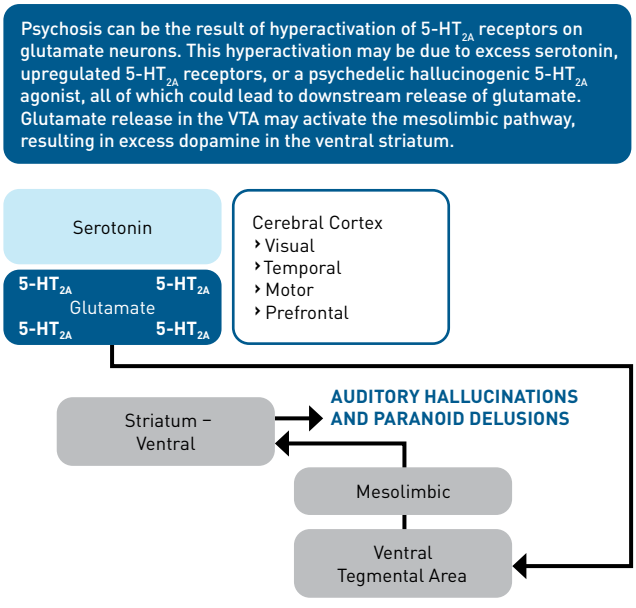
activating the mesolimbic dopamine pathway as part of a chain reaction, leading to positive symptoms such as delusions and hallucinations.[13] A strategy of focusing on targets in the serotonin hypothesis would potentially reduce extrapyramidal effects as well as improve negative symptoms and cognitive impairments associated with schizophrenia (**Figure 2**[13]).[17]

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.[9,18] 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).[19] Although positive symptoms can be successfully treated with antipsychotic agents, negative symptoms are more difficult to manage.[20] This is especially critical because approximately 20% to 40% of patients with schizophrenia exhibit persistent negative symptoms.[20,21] 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.[22] Finally, patients with schizophrenia may exhibit notable cognitive impairment, performing more poorly than patients without the disease over a diverse range of cognitive functions.[9,23] 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.[18] Evidence suggests substantial cognitive heterogeneity in schizophrenia, with potential genetic or other basis for this yet to be elucidated.[23] 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.[9]

FIGURE 2. Role of Serotonin in the Pathophysiology of Schizophrenia[13]



VTA indicates ventral tegmental area.

Stahl SM. Beyond the dopamine hypothesis of schizophrenia to three neural networks of psychosis: dopamine, serotonin, and glutamate. *CNS Spectr.* 2018;23(3):187-191, reproduced with permission.

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**[24]). Some common comorbidities in individuals with schizophrenia include[24]:

- 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 unhealthy lifestyle and also the use of antipsychotic agents, especially second-generation antipsychotics.[25] The presence of MetS in a patient with schizophrenia can have a critical influence on future morbidity and mortality. One study by Mitchell et al attempted to assess the prevalence and predictors of MetS in patients with schizophrenia and related disorders. 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 (**Table 1**[26]). 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.[26]

Sexual Function/Dysfunction

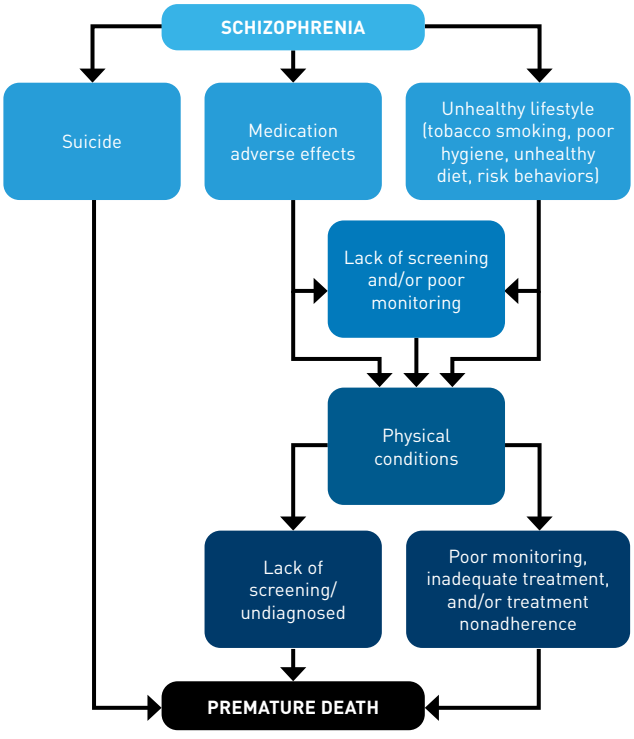
Data surrounding sexual dysfunction in patients with schizophrenia tend to be limited, and most patients show sexual interest similar to the general population. Available evidence demonstrates that psychiatric symptoms, institutionalization, and antipsychotic therapy can contribute to impaired sexual 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 α_1-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.[27]

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.[28] 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.[29] 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

FIGURE 3. Multifactorial Aspects of Schizophrenia Leading to Premature Death[24]



Adapted from: World Federation for Mental Health. World Mental Health Day 2014: living with schizophrenia. World Health Organization website. who.int/mental_health/world-mental-health-day/paper_wfmh.pdf.

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.[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.[30]

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.[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.[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 vocation, peer group inclusion, sense of hopelessness, beliefs about symptoms and the influence of street drugs on them, and, importantly, 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.[34]

TABLE 1. Rates of MetS in Patients With Schizophrenia According to Therapy Received[26]

Antipsychotic Agent	Percentage of Patients With MetS
Clozapine	51.9%
Olanzapine	28.2%
Risperidone	27.9%
No antipsychotic therapy	20.2%

MetS indicates metabolic syndrome.
Adapted from: Mitchell AJ, Vancampfort D, Sweers K, van Winkel R, Yu W, De Hert M. Prevalence of metabolic syndrome and metabolic abnormalities in schizophrenia and related disorders – a systematic review and meta-analysis. *Schizophr Bull.* 2013;39(2):306-318.

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.[35,36] Preventing relapse is an important therapeutic goal, along with increasing adaptive functioning, because patients may not return to their baseline level of adapative functioning after relapse.[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.[37,38] General findings from studies have approximated nonadherence rates in schizophrenia to range from 37% to 74%.[6] Nonadherence to therapy is often the culprit behind exacerbations in psychopathology, symptom relapse, and rehospitalization, and it is also a problem that is likely preventable.[39,40] Nonadherence to therapy results in poor health and economic outcomes, including increased hospitalization rates and subsequent greater resource usage.[41]

Reasons for nonadherence to pharmacotherapy vary significantly 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 nonadherent 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**[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.[38,40] 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.[42] Provider factors include a low level of therapeutic alliance with the patient and poor education of patients and caregivers.[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.[42] 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.[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.[38,42] 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.[40,43] Because AEs are common with antipsychotic agents, patients should receive regular follow-up that includes monitoring for AEs with interventions as approriate.[42]

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%.[42,44] Another study found that 77% of symptoms recurred within 1 year of medication discontinuation and more than 90% recurred within 2 years.[37,38] 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.[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.[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.[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.

TABLE 2. Risk Factors for Medication Nonadherence in Persons With Schizophrenia[40]

Patient-related risk factors	
Sociodemographic factors	• Younger and older patients • Male
General clinical factors	• Illicit drug or alcohol consumption • Previous nonadherence
Psychopathologic symptoms	• Impaired insight • Cognitive deficiency • Delusion of persecution, poisoning, or grandeur • Psychotic symptoms • Negative symptoms
Psychological factors: attitudes, beliefs, and other subjective aspects	• 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
Environmental-related risk factors	
Poor social and familial support	
Negative social perception of the disease	
Stigmatization	
Difficulty accessing healthcare services	
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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REPORT

An Update on Current Treatment Strategies and Emerging Agents for the Management of Schizophrenia

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ABSTRACT

Schizophrenia is a chronic neuropsychiatric disorder that has a significant impact on the functioning and quality of life of individuals affected by the disease. It affects 0.6% to 1.9% of individuals within the United States, and currently there is no cure. Guidelines recommend a combined treatment approach with both pharmacologic agents and psychological interventions for first-episode psychosis, acute exacerbations, and relapse prevention. Presently, multiple agents are available for the treatment of schizophrenia; however, the majority do not address negative symptoms and cognitive dysfunction, with many patients having debilitating residual symptoms, difficulties with adherence, and drug-related adverse effects. To address these concerns, new research evaluating investigational therapies has been undertaken to examine novel treatment strategies. This review summarizes the schizophrenia treatment guidelines, current treatment strategies, and emerging agents for the management of schizophrenia.

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For author information and disclosures, see end of text.

Introduction

Schizophrenia is a chronic neuropsychiatric disorder affecting an estimated 3.5 million individuals in the United States.[1] It is characterized by a combination of positive symptoms (eg, hallucinations, delusions, disorganized thoughts or speech, and bizarre behaviors), negative symptoms (lack of motivation, drive, enjoyment, social interactions), cognitive dysfunction (affecting attention, memory, executive functioning, social interactions), and motor disturbances that can lead to functional impairment and poor health-related quality of life (QOL).[2]

At present, there is no cure for schizophrenia, and treatment guidelines recommend a combined approach with pharmacologic agents and psychological interventions for first-episode psychosis, acute exacerbations, and prevention of relapse of psychosis.[3] Multiple agents are currently available for the treatment of schizophrenia; however, many fall short of their therapeutic goals, as adherence, cognitive dysfunction, negative symptoms, residual positive symptoms, and adverse effects (AEs) remain a challenge for many patients.[2]

Currently available antipsychotics, which are thought to work primarily via modulation of dopamine, largely target positive symptoms.[4] As a result, many patients are left with residual negative and cognitive symptoms.[4] To address these gaps in therapy, new research combined with an increased understanding of the etiology and pathophysiology of schizophrenia is leading to the development of novel agents with the goal of improving schizophrenia management. The purpose of this review is to discuss schizophrenia treatment guidelines and summarize current treatment strategies and emerging agents for the management of schizophrenia.

Schizophrenia Treatment Guidelines

The most recently published schizophrenia treatment guidelines from the American Psychiatric Association (APA) were released in 2004.[3] These treatment guidelines recommend that the selection of pharmacotherapy be individualized based on patient characteristics and preference. Second-generation antipsychotics (SGAs) are recommended as first-line treatment for acute schizophrenia

symptom management (although first-generation antipsychotics [FGAs] may be appropriate for some patients).[3] In 2009, the APA released a guideline watch[5] for practitioners, which highlighted key clinical trials that had been published between 2002 and 2009.[6-11] Most recently, in May 2019, the APA released a draft of updated guidelines for the treatment of schizophrenia in adults.[12] The updated proposed guidelines indicate that antipsychotic medication for the treatment of schizophrenia is only one component of the overall treatment paradigm. Further, decision making regarding choice of treatment should include the patient whenever possible. Developing a therapeutic alliance is important to the overall success of the treatment plan, particularly to address distressing symptoms of schizophrenia and unwanted AEs from pharmacotherapy. As patients with schizophrenia often have attentional and cognitive impairments during acute exacerbations, it is important for healthcare professionals to revisit target symptoms and unwanted AEs from drug treatment on multiple occasions to adjust treatment over time.[12] The final version of the updated practice guidelines is expected to be released in summer 2020.

The goals of therapy for acute treatment of schizophrenia are to reduce the acute symptoms and return the patient back to their baseline level of functioning.[12] Once maintenance therapy is initiated, the goal is to prevent the recurrence of symptoms, optimize functioning, and improve QOL. Due to the heterogeneity of clinical trial designs and lack of head-to-head comparisons, the draft guidelines do not offer an evidence-based list or algorithmic approach for antipsychotic selection. The draft guidelines acknowledge that there may be clinically meaningful distinctions in response and tolerability among the various antipsychotic medications; however, no definitive evidence exists of consistent superior efficacy, with the exception of clozapine for treatment-resistant schizophrenia.[12]

Therefore, the antipsychotic is usually chosen based on patient preference, response to past treatment, tolerability, AE profile, presence of comorbid conditions, drug–drug interactions, drug pharmacokinetics, and drug formulation availability and access. The APA recommends SGAs as first-line treatment of schizophrenia, excluding clozapine due to its AE profile.[12] SGAs are preferred over FGAs because they are less often associated with extrapyramidal side effects (EPS), although SGAs are more often associated with metabolic AEs (eg, weight gain, hyperlipidemia, and diabetes mellitus).[12] Combination therapy or treatment with clozapine is reserved for patients who have a partial or poor response to standard treatment with SGAs.

Response to pharmacologic therapy varies widely among patients with schizophrenia, with many having a poor or partial response. Approximately 10% to 30% of individuals with schizophrenia experience a limited benefit from antipsychotic treatment.[13] Moreover, some studies have shown that 30% of individuals with schizophrenia experience improvement but still have some persistent psychotic or residual symptoms that affect their functioning and QOL.[14] Furthermore, acute treatment of schizophrenia is complicated by the delay between initiation of treatment and therapeutic response. It can take between 2 and 4 weeks to show an initial response and up to 6 months or longer for the full therapeutic effect.[12]

Pharmacologic Treatment of Schizophrenia

Prompt, effective pharmacologic treatment of individuals with schizophrenia within the first 5 years after their initial episode is crucial due to pathophysiologic changes occurring in the brain during this time.[3] The acute treatment of schizophrenia focuses on reducing psychotic symptoms while minimizing AEs.[13] After a patient is stabilized, maintenance therapy is continued to help prevent relapse, increase socialization, and improve self-care and mood.[3] The incidence of relapse in schizophrenia is significantly higher among those who do not receive maintenance therapy compared with those who do (60%-80% vs 18%-32%, respectively).[3,15,16]

While used as first-line agents, SGAs have an increased risk of metabolic AEs, with some carrying a greater potential risk than others, and this must be considered when selecting a therapy for schizophrenia management.[13] FGAs are efficacious in reducing positive symptoms, such as hallucinations, uncooperativeness, hostility, and paranoid ideations, along with fostering improvement in thought disorganization and blunted affect.[3] The use of these agents is complicated by the severity of EPS, which typically precludes their use as first-line agents.[3] Additionally, clozapine has shown efficacy as a second-line option in patients with a poor or partial response to other agents.[17] Clozapine is distinguished by its greater efficacy in treating positive symptoms in patients with treatment-resistant schizophrenia and by the relative absence of EPS.[3] The use of clozapine is precluded by several rare but serious and potentially fatal AEs that require close monitoring. These include severe neutropenia or agranulocytosis and cardiac complications, such as myocarditis or cardiomyopathy.[13]

First- and Second-Generation Antipsychotic AE Overview

Early in the course of treatment with antipsychotics, common AEs include sedation, orthostatic changes in blood pressure, and anticholinergic AEs such as dry mouth, constipation, and difficulty with urination.[12] Prolongation of the QTc interval can also be a concern because of the potential for life-threatening torsades de pointes.[12]

Acute EPS

Akathisia is the most common EPS seen in patients treated with antipsychotics.[13] It presents as restless movements, and patients may describe a sense of inner restlessness. Drug-induced parkinsonism may also be experienced by patients and can manifest as tremors, rigidity, impaired gait, and psychomotor retardation. Similarly,

drug-induced dystonia presents with involuntary muscle contractions that result in contorted positions of body parts such as the neck, jaw, or arms.[13] To alleviate acute EPS, healthcare professionals can decrease the dose of antipsychotic medication or switch to an alternative agent with fewer EPS. Anticholinergic medications (eg, benztropine) can be added to the current regimen to address acute dystonia or pseudoparkinsonism; however, they can cause additional AEs such as dry mouth, blurred vision, and constipation.[13] Benzodiazepines or β-blockers, such as propranolol, may be prescribed to help manage akathisia.[12,13]

Tardive Dyskinesia (TD)

TD is defined by abnormal movements that emerge after months or years of treatment with an antipsychotic medication.[18] The movements are usually slow and athetoid or rapid choreiform jerks; both types of movements commonly manifest in the mouth, face, jaw, tongue, hands, or feet.[13] The strategy for managing TD is to lower the dose of the antipsychotic drug or to change to quetiapine or clozapine, which are associated with a lower risk of TD symptoms than other antipsychotic drugs.[18] Additionally, vesicular monoamine transporter 2 inhibitors may be used to help manage symptoms of TD.[19]

Neuroleptic Malignant Syndrome (NMS)

NMS is a rare but potentially life-threatening AE typically seen within the first month of antipsychotic treatment. It is characterized by a classic triad of rigidity, hyperthermia, and sympathetic nervous system lability, including hypertension and tachycardia.[12] Antipsychotic medication should be immediately discontinued in patients experiencing NMS, and supportive care to maintain hydration and manage autonomic symptoms should be initiated.[12]

Metabolic AEs

Metabolic AEs of antipsychotic medication include weight gain, elevations in lipid levels, and insulin resistance, all of which increase the risk of diabetes and cardiovascular disease.[12,13] It has been recommended that patients with schizophrenia receive regular monitoring of weight, glucose, and lipid levels.[13,20] Some antipsychotics carry a greater risk than others, and switching to a medication with lower metabolic risk may be helpful if a patient experiences metabolic AEs. If changing the antipsychotic drug is not possible, and lifestyle interventions are not effective, adding metformin to the patient's medications may be helpful in reducing the metabolic effects, but limited data support its efficacy for this off-label indication.[13,21]

Hyperprolactinemia

Prolactin levels can also become elevated as a result of treatment with antipsychotic medications. The increased prolactin may result in galactorrhea and menstrual disturbances in women and sexual dysfunction and gynecomastia in men, which can contribute to medication nonadherence.[13] Long-term effects of hyperprolactinemia may include an increased risk of osteoporosis and breast or endometrial cancer.[12] Switching to a medication with a lower risk for hyperprolactinemia may be advisable if patients are affected by elevations in prolactin.[22]

Novel Treatment Strategies and Emerging Agents for Schizophrenia

Approximately 30% of individuals with schizophrenia are considered resistant to currently available drug therapies. Furthermore, 80% to 90% of individuals will experience a relapse at some point in the course of their illness, often related to nonadherence to maintenance therapy.[23] Market research analysis has identified several gaps in pharmacologic therapy for schizophrenia, which include a need for agents that improve cognition, are capable of treating negative symptoms, improve treatment-resistant schizophrenia, have improved AE profiles, and improve adherence.[23] Novel therapies that attempt to fill these treatment gaps have recently been approved or are currently being researched and will be discussed in more detail here.

New Formulation Approved: Asenapine Transdermal System

Asenapine transdermal system is the only transdermal medication approved for the treatment of schizophrenia, achieving approval in October 2019.[24] Approval was based on efficacy data from trials with sublingual asenapine as well as a 6-week, fixed-dose, randomized, double-blind, placebo-controlled study in 616 adults with schizophrenia.[24,25] Patients were randomized to a dose of asenapine 3.8 mg/24 hours, 7.6 mg/24 hours, or placebo. The primary end point was a change in PANSS total score from baseline to week 6. Both doses of asenapine transdermal were statistically superior to placebo in the primary end point with a least squares mean change of −22.1 for asenapine 3.8 mg/24 hours and -20.4 for asenapine 7.6 mg/24 hours compared with approximately 15.5 with placebo ($P < .01$ for both). Changes in the key secondary end point, CGI-S, were also statistically significant for both doses.[25,26] The most commonly observed AEs were EPS, application-site reactions, and weight gain.[25]

Transdermal delivery systems may have benefits over other formulations, such as the ability to visually confirm medication adherence and possible improved tolerability. In particular, AEs such as the hypoesthesia and dysgeusia associated with sublingual asenapine could be avoided by utilizing the transdermal patch.[26] A release date for this product has not yet been confirmed.

New Agent Approved: Lumateperone Tosylate (ITI-007)

Lumateperone is a selective serotonin (5-HT) 5-HT_{2A} receptor antagonist that received approval in December 2019 for the treatment

of schizophrenia in adults. It has been investigated in acute or residual schizophrenia, bipolar depression, and other neurologic and psychiatric conditions.[4] Lumateperone has a unique mechanism of action that targets 3 neurotransmitter pathways through modulation of dopamine D_1 and D_2 receptors and glutamate (NMDA) receptor subunit epsilon-2, also known as N-methyl D-aspartate receptor subtype 2B (GLuN2B), via downstream dopamine D_1 receptors and through AMPA currents via the mTOR protein pathway.[4,27,28]

Lumateperone was investigated in two phase 3 randomized controlled trials in individuals with acute exacerbations of schizophrenia diagnosed via the *Diagnostic and Statistical Manual of Mental Disorders,* 5th edition criteria. The first phase 3 trial (n = 450), called ITI-007-301, was a multicenter, randomized, double-blind, fixed-dose, placebo-controlled trial.[29] Participants were randomized (1:1:1) to either lumateperone 60 mg, lumateperone 40 mg, or placebo once daily in the morning for 4 weeks. Lumateperone 60 mg/day demonstrated statistically significant superiority in the change in the Positive and Negative Syndrome Scale (PANSS) total score versus placebo, with a least squares mean change from baseline on the PANSS total score of −14.5 points versus −10.3 points with placebo (P = .022). Furthermore, significant antipsychotic efficacy was observed as early as week 1 with lumateperone 60 mg and maintained throughout the entire study. No statistically significant changes emerged in EPS, body weight, lipids, glucose, or prolactin.[29] The most common AEs were somnolence, with 17.3% versus 4.0% with lumateperone and placebo, respectively; mild sedation (12.0% vs 5.4%); and fatigue (5.3% vs 1.3%).[29]

The second phase 3 trial, ITI-007-302, was a multicenter, randomized, double-blind, fixed-dose, placebo- and active-controlled inpatient study conducted in 696 patients.[30] Participants were randomized (1:1:1:1) to either lumateperone 60 or 20 mg, risperidone 4 mg as the active control, or placebo once daily in the morning for 6 weeks.[27] Neither dose of lumateperone separated from placebo, whereas risperidone did. However, a greater placebo effect occurred in this trial when compared with other lumateperone trials, making the results potentially less reliable.[4,27]

Agents Under Development

Olanzapine/Samidorphan (ALKS 3831)

Olanzapine/samidorphan is a combination therapy that includes a fixed dose of samidorphan (a μ-opioid receptor antagonist) and olanzapine.[31] The intended purpose of this combination therapy is to help reduce the olanzapine-associated weight gain and adverse metabolic effects with samidorphan while maintaining the established therapeutic effect of olanzapine in the treatment of schizophrenia.[23,31]

Olanzapine/samidorphan was evaluated in two phase 3 studies. ENLIGHTEN-1 was a double-blind, randomized trial that evaluated the efficacy, safety, and tolerability of olanzapine/samidorphan compared with olanzapine alone and placebo over 4 weeks in 403 patients experiencing an acute exacerbation of schizophrenia.[32] Individuals were randomized 1:1:1 to receive either a bilayer fixed-dose tablet of 10 mg samidorphan combined with either 10 or 20 mg of olanzapine, olanzapine 10 or 20 mg daily as monotherapy, or placebo. The olanzapine/samidorphan arm showed statistically significant reductions from baseline in PANSS scores compared with placebo (P <.001) using a mixed model with repeated measurements. Olanzapine also demonstrated similar improvements from baseline PANSS scores compared with placebo (P = .004). A key secondary end point of improvement on the Clinical Global Impression–Severity of illness (CGI-S) scale was also observed with olanzapine/samidorphan compared with placebo (P = .002). All participants who completed the double-blind portion of ENLIGHTEN-1 were eligible to continue in an open-label, long-term safety, tolerability, and durability-of-effect study in which participants would receive olanzapine/samidorphan for an additional 12 months.[33]

ENLIGHTEN-2 was a multicenter, randomized, double-blind, phase 3 trial that evaluated the weight gain profile of olanzapine/samidorphan compared with olanzapine over 6 months in patients with stable schizophrenia.[34] Participants with stable schizophrenia (n = 561) were randomized (1:1) to receive either olanzapine/samidorphan or olanzapine. The study had 2 primary end points: (1) percent change from baseline in body weight at 6 months, and (2) the proportion of participants with 10% or more weight gain from baseline at 6 months. A key secondary end point evaluated the proportion of patients with 7% or more weight gain from baseline at 6 months. ENLIGHTEN-2 met both co-primary end points with patients in the olanzapine treatment group having a 57% higher mean percent weight change at 6 months compared with the olanzapine/samidorphan treatment group (6.59% olanzapine vs 4.21% olanzapine/samidorphan; P = .003).[34,35] Also, patients in the olanzapine treatment group had nearly twice the risk of gaining 10% or more of their baseline body weight at 6 months compared with the olanzapine/samidorphan treatment group (29.8% olanzapine vs 17.8% olanzapine/samidorphan; P = .003).[34] Similarly, patients in the olanzapine treatment group had approximately twice the risk of gaining 7% or more of their baseline body weight at 6 months compared with olanzapine/samidorphan (42.7% olanzapine vs 27.5% olanzapine/samidorphan; P = .001). Safety was also evaluated in ENLIGHTEN-2; overall, 62.4% of olanzapine/samidorphan participants completed the study compared with 63.8% of olanzapine participants. The most common AEs reported for olanzapine/samidorphan were weight gain, somnolence, and dry mouth compared with olanzapine, which were weight gain, somnolence, and increased appetite. Serious AEs were observed in 2.5% of the olanzapine treatment group and 3.6% of the olanzapine/samidorphan treatment group during the 6-month trial period.[34] A new drug application was approved, and the drug has a Prescription Drug User Fee Act date of November 15, 2020.[35,36]

Paliperidone

Long-acting injectable (LAI) antipsychotics with a longer duration of action are under development to improve adherence in patients with schizophrenia. Currently, once-monthly and trimonthly intramuscular injectable formulations of paliperidone are available.[37] The manufacturer is currently conducting a phase 3 trial for a formulation of paliperidone palmitate that can be administered every 6 months. There are currently 841 patients enrolled in the 3-part study, which consists of a screening, maintenance, and double-blind phase, with a primary end point of time to relapse. In the double-blind phase, patients will receive either paliperidone every 3 months or paliperidone every 6 months. The study is estimated to be completed in August 2020.[38]

Pimavanserin

Pimavanserin is a 5-HT_{2A} inverse agonist currently approved for the treatment of psychosis associated with Parkinson disease. Pimavanserin was investigated in the phase 3 ENHANCE trial as an adjunct to antipsychotic treatment in patients with residual positive symptoms.[39] The addition of pimavanserin showed a consistent trend of improving psychotic symptoms; however, the results for the primary end point, change in PANSS total score from baseline, did not achieve statistical significance (P = .0940). Pimavanserin was well tolerated and demonstrated similar AEs compared with placebo (40.4% vs 36.9%, respectively). The most common AEs (≥5%) were headache, somnolence, and insomnia. Also, no statistically significant differences in vital signs, weight, metabolic profile, or EPS emerged, compared with placebo. Just 1% of patients in each arm reported serious AEs, and discontinuation was low at 2.5% for pimavanserin and 0% for placebo. Although pimavanserin did not achieve statistical significance in the primary end point, there were significant changes in secondary end points that measured negative symptom improvement.[40] Pimavanserin is currently in phase 2 development for its utility as an adjunct in managing negative symptoms of schizophrenia. The primary end point being studied is the change in Negative Symptom Assessment-16 (NSA-16) total score from baseline to week 26.[41] Topline results of the study showed a statistically significant improvement in NSA-16 score as compared with placebo (–10.4 vs –8.5; P = .0043).[42] Further results have not yet been published.

Risperidone in situ Microparticle (ISM)

ISM is a technological advancement that allows for the release of drugs based on in situ formulation of biodegradable matrices after the administration of a liquid carrier. ISM allows for therapeutic blood levels of LAI antipsychotic to be achieved without coadministration of initial oral antipsychotics, loading doses, or booster injections, potentially improving adherence.[4] Topline results for PRISMA-3, a phase 3, multicenter, randomized, placebo-controlled study of risperidone ISM, were recently released.[43] This study evaluated once-monthly intramuscular risperidone ISM in 438 patients with acutely exacerbated schizophrenia. Results showed that both the 75-mg and 100-mg once-monthly doses demonstrated statistically significant improvements (P <.0001) compared with placebo injections in the PANSS and CGI at 12 weeks.[43] Complete results have not yet been published.

Roluperidone (MIN-101)

Roluperidone is a cyclic amide derivative developed to target the negative symptoms of and cognitive dysfunction in schizophrenia. The agent is an antagonist of σ-2 and 5-HT_{2A} and has a low affinity for dopaminergic, muscarinic, cholinergic, and histaminergic receptors.[44,45] A phase 3, randomized, double-blind, placebo-controlled, parallel-group trial evaluating the efficacy and safety of roluperidone in 501 adult patients with negative symptoms of schizophrenia is currently underway.[46] The primary objective is to evaluate the efficacy of 32 mg/day and 64 mg/day of roluperidone compared with placebo over 12 weeks via change in PANSS Marder negative symptoms factor score. The estimated study completion date is January 2021, and top-line results are expected to be reported in the second quarter of 2020.[46]

Trace Amine-Associated Receptor 1 (TAAR-1) Agonists

TAAR-1 is a G-protein–coupled receptor found in the central nervous system, olfactory epithelium, and various other tissues.[4] The TAAR-1 receptor is activated via endogenous trace amines that are structurally similar to monoaminergic neurotransmitters. Agonists of the TAAR-1 receptor include amphetamine and methamphetamine. Furthermore, the TAAR-1 receptor seems to respond the most to dopamine, followed by glutamine, compared with tryptamine, norepinephrine, and serotonin.[4] As a result of these features, TAAR-1 agonists are being targeted for treatment of schizophrenia.[47,48] Two TAAR-1 agonists are currently in development: SEP-363856 and R05263397.[47,49]

In May 2019, SEP-363856 received breakthrough designation from the FDA as a novel agent for the treatment of schizophrenia.[50] Breakthrough status was granted based on the pivotal phase 2 data, along with data from a 2018 six-month open-label extension study (SEP361-202) that evaluated safety and tolerability. The phase 2 trial was a randomized, double-blind, placebo-controlled, flexible-dose study that took place over 4 weeks in 245 hospitalized patients. Participants received either SEP-363856 (50 mg/day or 75 mg/day) or placebo. SEP-363856 met its primary end point with a statistically significant and clinically meaningful improvement in the PANSS compared with placebo at week 4 (–17.2 vs –9.7; P = .001; effect size, 0.45). Additionally, there were clinically significant improvements in secondary end points, including CGI-S score, PANSS positive subscale score, PANSS negative subscale score, and

PANSS general psychopathology subscale score. The most common AEs were somnolence, agitation, nausea, diarrhea, and dyspepsia for SEP-363856. Other concerns such as change in body weight, blood glucose, lipids, and prolactin levels were comparable with placebo.[51] In September 2019, the Developing Innovative Approaches for Mental Disorders (DIAMOND) phase 3 trial program was initiated to demonstrate the safety, efficacy, and tolerability of SEP-363856.[52] The phase 3 program will include 4 trials (DIAMOND 1-4) and enroll more than 1000 adolescents and adults with schizophrenia; it has a target completion date of 2022.[52]

Conclusions

Schizophrenia affects a small percentage of patients within the United States; however, its effect on physical function and QOL is significant. Currently approved pharmacologic agents focus mainly on modulating dopamine, leaving patients with schizophrenia to cope with considerable residual symptoms. Suboptimal treatment, significant AEs, and challenges related to nonadherence create a need for new agents to better manage schizophrenia. To address these concerns, many investigational agents are being researched to improve overall treatment, negative symptoms, cognitive dysfunction, adherence, antipsychotic AE profiles, and residual and/or treatment-resistant schizophrenia. New treatment strategies, such as modulators of serotonin and glutamate, agonists of TAAR-1, and antagonists of σ-2, and new dosage forms that aid in adherence have the potential to improve the lives and outcomes of individuals with schizophrenia. ■

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REPORT

Schizophrenia: Opportunities to Improve Outcomes and Reduce Economic Burden Through Managed Care

Curtis Wander, PharmD, BCPS

Economic Impact of Schizophrenia

Direct and Indirect Costs

Schizophrenia represents a significant economic burden for patients, payers, and society, and the total costs related to the illness appear to be disproportionate to the disease prevalence. A study published in 2016 elucidated current medical costs, including both direct and indirect costs of schizophrenia in the United States.[1] Using the prevalence rate of 1.1% from 2013, the study estimated the number of patients diagnosed with schizophrenia in the United States to be 3.5 million, which translated to an annual economic burden of approximately $155.7 billion. Direct healthcare costs amounted to $37.7 billion, or 24% of the total cost, and included medication use, outpatient and inpatient services, emergency department (ED) visits, long-term care utilization, and other medical services. Of the drivers of direct healthcare costs, inpatient visits and medications were found to be the largest contributors to spending, accounting for 10% and 6% of the total cost, respectively. Indirect costs were estimated at $117.3 billion and contributed to 76% of the total economic cost. Of the drivers of indirect costs related to schizophrenia, high unemployment rates and caregiver burden were found to be the largest contributors to spending, accounting for 38% and 34% of the total cost, respectively. Based on the findings from the study, the total average annual cost per patient diagnosed with schizophrenia was estimated to be $44,773.[1]

Medicare and Commercially Insured Costs of Care Estimates

A study by Feldman et al compared the cost of care for 2 groups of Medicare beneficiaries: those who were diagnosed with nonschizoaffective schizophrenia in a sample collected from 2003 to 2007, and the general Medicare population, for whom cost estimates were determined from 2001 to 2009.[2] Medicare patients with diagnosed schizophrenia had a cost of care that was approximately 80% higher than the general Medicare population per year in 2010 dollars. Overall, more than 50% of the annual cost was due to psychiatric and medical hospitalizations, occurring in approximately 30% of the patients with schizophrenia.[2]

ABSTRACT

Schizophrenia is a complicated chronic disease affecting approximately 3.5 million people in the United States, and its annual healthcare costs exceed $155 billion. People living with schizophrenia often experience a reduced quality of life (QOL) and are more likely to be homeless, unemployed, or living in poverty compared with the general population. Life expectancy for patients with schizophrenia is 15 to 20 years below the average and is complicated by numerous comorbidities, such as weight gain, increased cardiovascular risk, and changes in mood and cognition. Treatment nonadherence can increase the risk of relapse, rehospitalization, and self-harm, leading to a reduced QOL and increased economic burden. Managed care professionals are positioned to improve adherence and outcomes through various drug utilization strategies. Clinicians may also empower patients with schizophrenia through shared decision making and the creation of a therapeutic alliance. Careful monitoring of medication-related adverse effects and offering potential medication alternatives and routes of administration when indicated may also improve adherence to treatment regimens, resulting in improved outcomes and reduced healthcare costs.

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Cost comparison studies have also been conducted in commercially insured patients. A study by Fitch et al evaluated the average cost per patient per month (PPPM) for patients with diagnosed schizophrenia compared with a demographically adjusted population without schizophrenia.[3] On average, the total claim cost per patient with schizophrenia was more than 4 times the average total claim cost for a demographically adjusted population without schizophrenia. In a breakdown of cost, the PPPM cost for patients with diagnosed schizophrenia was $1806, with 42% used for inpatient resources, 33% for outpatient resources, and 25% for prescription medications. Authors also determined that PPPM costs are highest in the month of diagnosis, labeled as the index month, with an average of $6601 owing mainly to the high cost of inpatient care.[3]

Additionally, a retrospective claims-based study published in 2018 by Huang et al investigated healthcare resource utilization (HRU) and costs of care in young adults aged 18 to 64 years with diagnosed schizophrenia.[4] The study included 9889 patients and compared them with a control cohort of patients who did not have schizophrenia. Additionally, younger adults with schizophrenia aged 18 to 35 years were compared with older adults aged 36 to 64 years, also diagnosed with schizophrenia. Those aged 18 to 35 years with schizophrenia had significantly lower rates of comorbid conditions but significantly higher rates of depressive disorders, anxiety, dipolar disorder, attention-deficit/hyperactivity disorder, and personality disorder as compared with the older group. Total costs of care were also significantly higher for younger patients with schizophrenia as compared with the older group ($22,578 vs $28,857; P <.0001). When compared with controls who did not have schizophrenia, patients with schizophrenia had higher all-cause HRU (inpatient admissions, outpatient office visits, ED visits, pharmacy visits) as compared with controls. HRU costs per patient per year (PPPY) were also significantly higher for patients with schizophrenia compared with those who did not have a diagnosis of schizophrenia ($22,338 vs $7332; P <.0001).[4]

Cost of Treatment Resistance

Treatment resistance has been broadly defined in previous studies as when 2 or more adequate trials of an antipsychotic therapy have been administered for 4 or more weeks at appropriate doses, and they fail to elicit a response.[5,6] Up to 30% of patients with chronic schizophrenia meet these criteria for treatment-resistant schizophrenia.[7] Patients with treatment-resistant schizophrenia face a disease burden that includes a reduced quality of life (QOL), presence of disease-associated and treatment-associated adverse effects (AEs), increased medical costs, increased rates of serious comorbidities, and increased suicide risk compared with patients who are not considered treatment resistant. Annual costs associated with treatment resistance range from $66,360 to $163,795, or 3- to 11-fold higher than the annual cost of patients with schizophrenia that is not considered treatment resistant. Although estimates in the literature vary, treatment resistance in schizophrenia conservatively adds more than $34 billion in annual direct medical costs as a result of HRU, including hospitalizations and outpatient costs.[8]

QOL in Schizophrenia

Patients diagnosed with schizophrenia experience a reduced QOL that is multifactorial. Some contributors to reduced QOL include homelessness, unemployment, and poverty.[9] Unemployment rates have been reported to be as high as 80% to 90% in this population and pose an ongoing challenge.[10] Nearly 50% of patients have long-term psychiatric problems and approximately 20% have chronic symptoms and disability.[10] QOL measures have been shown to aid in predicting likelihood of relapse in patients with schizophrenia. In a study by Boyer et al (n = 1024), relapse was defined by the following criteria: (1) hospitalization due to worsening of psychotic symptoms or of such magnitude that hospitalization appeared imminent; (2) a re-emergence of florid psychotic symptoms such as delusions, hallucinations, or bizarre behavior; or (3) a thought disorder lasting 7 days or longer. Results of the study showed that a higher QOL score predicts a lower rate of relapse at 24 months (hazard ratio [HR], 0.82; 95% CI, 0.74-0.91; P <.001] for the SF36-Physical Composite Score; (HR, 0.88; 95% CI, 0.81-0.96; P = .002] for the SF36-Mental Composite Score).[11] With the evidence showing that reduced QOL results from many different disease aspects, it is important to address areas of reduced QOL in order to limit the chances of relapse.

Nonpharmacologic interventions, such as exercise, may improve QOL and be beneficial for patients with schizophrenia. A meta-analysis conducted in the Netherlands evaluated the relationship between physical fitness and functionality in 1109 patients with schizophrenia.[12] Studies in patients with schizophrenia in which effects of exercise were assessed were pooled and compared with a control group who did not exercise. The meta-analysis findings were that exercise improved clinical symptoms, QOL scores, symptoms of depression, and global functioning. Exercise was superior to control conditions in improving total symptom severity; positive, negative, and general symptoms; QOL scores; global functioning; and depressive symptoms. Yoga, specifically, was found to have a positive effect on cognition, but more research is needed to elucidate this connection. Physical exercise, including aerobic exercise and yoga, should be considered as a potential adjunct to pharmacologic treatment to improve overall well-being in patients with schizophrenia.[12]

Morbidity and Mortality

A diagnosis of schizophrenia has been associated with a reduced life expectancy of 10 to 20 years as well as an increased risk of premature mortality. One meta-analysis evaluating more than 1 million participants found that increased morbidity and mortality

for patients with schizophrenia is related to social factors such as alcohol or tobacco use,[13] while another meta-analysis[14] demonstrated the increased rates of metabolic syndrome were partly attributable to the medications themselves. Patients with severe mental illness, including schizophrenia, are often heavy smokers, and healthcare professionals are uniquely equipped to assess smoking status and offer support in smoking cessation.[15]

Patients with schizophrenia are at an increased risk for several comorbid conditions, such as dementia, liver disease, AIDS, heart failure, and type 2 diabetes. Cardiovascular (CV) morbidity and mortality in schizophrenia often occur before age 50 years. In a meta-analysis, the schizophrenia mortality rate (2.5) was at least as high as in individuals with heavy smoking status (RR, 2.4-2.7).[16] Further, the main causes of death in patients with schizophrenia are suicide, cancer, and CV disease.[17] Suicide in patients with schizophrenia is estimated to be more than 12 times greater (median standardized MR, 12.86) than in the general population.[18] Depression is another common comorbid illness in patients with schizophrenia. In a study of 2228 participants, almost 40% of patients with schizophrenia were deemed to have depression.[19] Over the course of the 3-year study period, the cohort with depression was more likely to use mental health services, present safety concerns, have greater substance use, and report lower overall QOL (**Table**).[19]

A US study evaluating the risk of premature death in adult Medicaid patients with mental illness from 2001 to 2007 found that adults with schizophrenia die at approximately 3.5 times the rate of the general population (standardized MR, 3.7; 95% CI, 3.7-3.7).[20] Deaths were attributed to several comorbid illnesses, with CV disease representing the highest mortality rate (403.2 per 100,000 person-years) and a standardized MR of 3.6 (95% CI, 3.5-3.6). Various cancers were also evaluated; lung cancer was found to have the highest mortality rate (74.8 per 100,000 person-years) and a standardized MR of 2.4 (95% CI, 2.4-2.5) in this patient population. Other comorbidities contributing to mortality include chronic obstructive pulmonary disease (standardized MR, 9.9; 95% CI, 9.6-10.2) as well as influenza and pneumonia (standardized MR, 7.0; 95% CI, 6.7-7.4).[20]

Substance Use in Schizophrenia

Substance use can have a negative effect on QOL and impact disease progression in patients with schizophrenia. Substance use has been linked to higher conversion rates from schizotypal disorder to schizophrenia. More specifically, cannabis, amphetamine, and opioid use disorders may be associated with conversion. In one study, 2539 participants with schizotypal disorder were identified and followed over several decades.[21] After 2 years, 16.3% of participants experienced conversion to schizophrenia. After 20 years, the conversion rate was 33.1% (95% CI, 29.3%-37.3%) overall, 58.2% (95% CI, 44.8%-72.2%) among those with cannabis use disorders, and 47.0% (95% CI, 35.3%-60.2%) among those with alcohol use disorder compared with 30.6% (95% CI, 27.7%-34.5%) in those without substance use disorders.[21]

Impact of Medication-Related AEs

Antipsychotics are considered effective for both acute and maintenance management of schizophrenia, but numerous AEs, including weight gain, metabolic disturbances, hyperprolactinemia, impaired

TABLE. Functional Outcomes Variables for Cohorts Without and With Depression at Enrollment and Across the 3-Year Study[19]

	Assessed at Enrollment		3-Year Outcomes	
Outcome[a]	No depression	Depression	No depression	Depression
HRU				
Emergency psychiatric services	5.4	15.3	4.1	12.4
ED visits	15.5	24.2	7.4	14.5
Psychiatrist contacts (mean)	3.8	4.9	3.3	4.0
Safety to self and others				
Violent behavior	3.3	12.4	3.5	10.3
Arrested or jailed	5.6	8.6	3.8	6.2
Victim of crime	8.2	15.7	6.7	14.5
Suicidal ideations	4.6	33.3	4.3	30.1
Suicide attempts	0.7	6.0	0.7	4.7
Substance use	25.2	32.2	21.4	28.8
QOL, overall (mean)	64.9	52.9	64.3	52.3

ED indicates emergency department; HRU, healthcare resource utilization; QOL, quality of life.
[a]Figures are percentages unless otherwise noted.
Adapted from: Conley RR, Ascher-Svanum H, Zhu B, Faries DE, Kinon BJ. The burden of depressive symptoms in the long-term treatment of patients with schizophrenia. *Schizophr Res.* 2007;90(1-3):186-197. doi: 10.1016/j.schres.2006.09.027.

cognition, extrapyramidal symptoms, sedation, QTc prolongation, and sexual dysfunction have been well documented.[22-26] Antipsychotic polypharmacy increases the frequency of AEs, and a longer duration of treatment translates to greater severity of AEs.[26] Second-generation antipsychotics (SGAs), especially clozapine and olanzapine, may contribute to weight gain in patients with schizophrenia by stimulating higher caloric intake and lowering energy expenditures. Behavioral intervention recommendations have been made for the management of weight gain and obesity in patients with schizophrenia through caloric intake reduction, dietary restructuring, and moderate-intensity physical activity.[27]

Dyslipidemia may occur in patients with schizophrenia as a consequence of medication use and poor dietary and lifestyle habits.[28] The degree of effect on lipid levels varies for each antipsychotic; Yogaratnam et al evaluated several SGAs and determined that clozapine, olanzapine, and quetiapine were more likely to increase triglyceride levels and olanzapine and quetiapine were more likely to increase total cholesterol levels. Alternatively, risperidone, aripiprazole, and ziprasidone were associated with either minimal effects or decreases in cholesterol and triglyceride levels.[29] Treatment for schizophrenia should be individualized for patients, and management of potential medication AEs, such as dyslipidemia, should be part of an integrated care team approach. Given the numerous AEs related to SGAs, careful screening and monitoring of blood glucose, cholesterol, and weight are of the utmost priority in identifying and preventing metabolic syndrome. Managed care professionals and the care teams are positioned to help provide management of potential AEs and improve QOL for patients with schizophrenia through case management and medication therapy management programs.

Impact of Negative Symptoms in Schizophrenia

Negative symptoms and cognitive impairment associated with schizophrenia tend to be chronic and are associated with long-term effects on social function. This is in contrast with positive symptoms, which tend to relapse and remit, although some patients experience residual long-term positive symptoms.[10] Negative symptoms contribute to poor functional outcomes, including reduced interpersonal relations, instrumental role functioning, and use of common objects and activities.[30] None of the currently approved agents specifically target negative symptoms of schizophrenia.

Impact of Medication Nonadherence

Nonadherence is a challenge in schizophrenia and can occur due to various factors, such as social isolation, disease stigma, and substance abuse. In addition, the symptoms of the illness itself may cause a lack of disease awareness, depression, and cognitive impairment, making medication adherence more difficult. From a societal perspective, many patients face challenges in accessing much needed mental health services, which also can be fragmented and difficult to navigate.[31] Managed care formularies should be designed in such a manner to ensure there is adequate access to therapy and to limit the barrier of medication coverage.

In the setting of nonadherence, patients previously in remission may experience relapse, and those with existing symptoms may experience symptom persistence. Nonadherence leads to increases in both patient and service costs. For patients, nonadherence may manifest in several ways, including impaired functioning, decreased QOL, self-neglect, self-harm, vulnerability, aggression, and substance misuse. A study conducted in the United States estimated the cost of rehospitalization due to antipsychotic medication nonadherence at about $1.5 billion per year.[32] Unrecognized nonadherence may result in unnecessary medication changes for patients or a misdiagnosis of treatment resistance.[31] Improving medication adherence can reduce hospitalizations, rehospitalizations, and hospital length of stay. Initiatives and strategies to improve adherence have the potential to improve outcomes in this population.[33,34]

Strategies to Improve Management and Outcomes

Reducing Medication-Related AEs

Although all medications can cause AEs, clinicians are charged with carefully selecting the most appropriate treatment option for each individual patient to achieve the best possible outcome. Practical strategies to improve patient care include shared decision making, regularly assessing adherence, selecting manageable regimens, and providing adequate counseling regarding possible AEs and expected therapeutic benefit. To mitigate AEs, clinicians can use the following techniques[31]:

- Titrate doses gradually.
- Set realistic expectations for patients if AEs might resolve with time.
- Use a checklist of possible AEs for patients to complete.
- Alter the timing of administration.
- Conduct a dose reduction with shared decision making regarding potential for relapse.
- Offer treatment options to address an AE.
- Switch to an alternative antipsychotic medication.

Shared Decision Making and the Therapeutic Alliance

Shared decision making involves the patient in all aspects of disease treatment and management. It is one way to empower patients with severe mental illness such as schizophrenia to self-manage their illness and actively participate in their healthcare. In a study by Delman et al, young patients with severe mental illness who actively participated in treatment decisions demonstrated reduced

symptoms, improved self-esteem, increased service satisfaction, and improved treatment adherence.[35] Use of patient preferences through a discrete choice experiment, which helps to define stated preferences, is one way to improve patient understanding of risks and benefits and involve patients in the selection of their treatment.[36] More research is needed to identify and develop tools to improve shared decision making. Taking patient-specific factors into consideration and working with the patient to understand various treatment options can help avoid excessive HRU and unnecessary stress for the patient.

Improving Adherence and Comorbidity Management

When SGAs were introduced as a replacement for first-generation antipsychotics, cost was a concern as most new brand-only agents initially cost 10 to 100 times more than older medication options.[37] The strategy for cost containment included initiating step therapy, allowing exceptions with prior authorization, and giving preference to generic drugs with low risk of AEs.[37] Ideally, in addition to cost, policies and utilization management strategies should take into account safety, efficacy, outcomes, and health indicators. As new treatments enter the market, the opportunity to evaluate HRU and healthcare costs for various treatment options materializes. Support services, such as electronic reminders via text messages and telephones, cognitive–behavioral and motivational strategies, and financial incentives, may also be used to address medication adherence; however, these have mixed results and should be tailored to specific patient needs.[38]

FIGURE. The STAY Initiative[41]

1	Recognizing that most patients with schizophrenia are at risk of partial adherence/nonadherence at some time during the course of their illness
2	The benefits of good therapeutic alliance and nonjudgmental atmosphere for identifying potential adherence issues
3	Tailored treatment plans to meet an individual's needs, including the most suitable route of delivery of antipsychotic medication
4	Involving family/key persons in care and psychoeducation of the patient, assuming the patient agrees to this
5	Ensuring optimal effectiveness of care
6	Ensuring continuity in the care of patients with schizophrenia

STAY indicates Six principles to improve Treatment Adherence in Your patient.

Long-term medication adherence in patients with schizophrenia is associated with positive outcomes, including improved clinical status, improved QOL and functioning, and reduced risk of relapse and rehospitalization.[39,40] Focusing on the importance of adherence can help patients achieve their treatment goals. The Six principles to improve Treatment Adherence in Your patient (STAY) initiative was developed and designed to address the concern of partial adherence/nonadherence of antipsychotic medication use in schizophrenia. These principles are outlined in the **Figure**.[41]

Healthcare Effectiveness Data and Information Set (HEDIS) measures were developed by the National Committee for Quality Assurance and released in 2013 to improve management of schizophrenia and help identify potential gaps in care for this population using standardized performance measures. The HEDIS measures include follow-up care after hospitalization or ED visit, diabetes and CV disease screening and monitoring, and adherence to antipsychotic medications.[42] As part of the HEDIS measures of performance where effectiveness of care can be evaluated, the measure assesses adults aged 18 to 64 years with schizophrenia enrolled in Medicaid and who were dispensed and remained on an antipsychotic medication for at least 80% of their treatment period.[43] For 2020, adherence to antipsychotics has expanded to include commercial and Medicare product lines and patients 19 years and older.[44]

In a large, prospective, noninterventional trial of more than 2000 patients with schizophrenia, authors found that medication adherence led to lower HRU and increased utilization of group therapy.[45] Psychiatric hospitalization rates were significantly lower ($P < .001$) among adherent patients; however, formulation of antipsychotic was not described.[45] Authors have also attempted to model potential direct medical cost savings, including routine care as well as inpatient and outpatient costs, if low-frequency administration (LFA) products could be developed to help guarantee adherence over longer intervals. Administration of risperidone long-acting injectable (LAI) every 3 months was estimated to reduce expensive inpatient relapses and be less costly than both monthly risperidone LAI and daily risperidone oral therapy based on the model. Further extending the interval to 6 months or 9 months resulted in additional cost savings, although the specific cost of medication therapy for LFA formulations was not part of the estimation.[46] Whereas longer-lasting products used in the model have yet to be developed, the potential for reducing expensive hospitalizations and improving relapse rates could be a significant driver in changing the management of schizophrenia, if these products are available in the future.

Role of LAI Antipsychotics

LAI antipsychotics provide a treatment option with the potential to improve adherence and overall healthcare costs. One study evaluated HRU for 435 patients with schizophrenia who were started on LAI antipsychotics.[47] A significant decrease ($P < .001$) in the number

of hospitalizations and ED visits was observed. As a breakdown, hospitalization for any reason or for psychiatric reasons decreased by 41% and 56%, respectively, and overall ED visits decreased by 40%.[47] Recent studies have also evaluated the impact of various treatment options on mortality in patients with schizophrenia. In a nationwide cohort of 29,823 patients in Sweden, researchers determined that LAI antipsychotics were associated with a 32% lower risk of all-cause mortality as compared with oral agents. Additionally, second-generation LAIs and oral aripiprazole were associated with the lowest mortality.[48]

A study by Lin et al compared the effect of initiating treatment with LAI antipsychotics versus with a broad range of oral antipsychotics by measuring healthcare costs and adherence in a Medicare database.[49] Drug costs were significantly higher (P <.001) with LAI antipsychotic use. However, inpatient and outpatient healthcare costs were significantly lower (P <.001) and medication adherence was significantly higher (P <.001) in the LAI antipsychotic group versus the oral antipsychotic group.[49] The higher cost of LAI antipsychotic medications was factored in to estimate the potential costs savings to health systems as a result of reduced schizophrenia-related hospitalizations when LAIs are used versus oral agents. Authors estimated that for every 5000 patients treated with an LAI antipsychotic, there would be a savings of more than $15 million for Medicare beneficiaries and more than $18 million annually for commercially covered patients.[49]

Researchers studying Medicaid patients with schizophrenia who started treatment with an LAI antipsychotic found significantly reduced (P <.001) overall and schizophrenia-related hospitalizations, length of stay, and hospital charges. Annual total schizophrenia-related costs were lowered by $5576 PPPY and hospital costs were lowered by $7744 PPPY after starting the LAI antipsychotic.[50] Similar results were described in a study of a commercial patient population with schizophrenia, in which researchers evaluated changes in hospitalization and costs of care from 6 months before to 6 months after initiating depot antipsychotics in patients with schizophrenia. Results in this study demonstrated a significant reduction (P <.001) in psychiatric hospitalizations, from 49.7% before depot antipsychotic use to 22.4% after initiating depot antipsychotic use. Mean hospitalization duration for psychiatric purposes was reduced from 7.3 to 4.7 days (P = .05). Depot antipsychotic use represented a significant reduction in total healthcare costs, which declined from $11,111 to $7884 ($P$ <.05); the reduction in costs for psychiatric hospitalizations from $5384 to $2538 was also significant (P <.05).[51] Evaluating total costs related to schizophrenia care represents an opportunity for payers to capture cost savings by focusing on drug utilization management strategies, including formulary options that promote adherence. These studies demonstrate the opportunity for managed care organizations to identify and engage those who begin to demonstrate nonadherence to oral therapy. Increased adherence to prescribed treatment options translates to reduced hospitalizations and improved outcomes, thereby ensuring the best chance of optimal and sustainable healthcare for patients with schizophrenia.

Conclusions

Schizophrenia is a complex chronic illness with multiple comorbidities and high mortality rates. The development of LAIs and generic medication options have significantly improved patient adherence and reduced costs for care in patients with schizophrenia. Despite these advances, schizophrenia has a high economic burden for patients and society. Providers caring for patients with schizophrenia are charged with a complicated task of ensuring individualized care while managing numerous AEs that may occur with recommended therapy. Carrying out shared decision making and careful monitoring as part of a therapeutic alliance can improve the QOL and outcomes for patients living with schizophrenia. Payers need to be aware of the difficulties that exist with managing schizophrenia and engage in strategies to ensure improved outcomes for this challenging population. ■

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POSTTEST

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Sample of Online Posttest

Choose the best answer for each of the following:

1. Which neurotransmitter causes overactivation of the mesolimbic pathway and excess dopamine release with subsequent auditory hallucinations and paranoid delusions associated with positive symptoms of schizophrenia?

A. Serotonin
B. Glutamate
C. γ-aminobutyric acid (GABA)
D. Acetylcholine

2. Which statement regarding negative symptoms in schizophrenia is CORRECT?

A. Currently available agents are effective in treating negative symptoms of schizophrenia.
B. Negative symptoms of schizophrenia include hallucinations and social withdrawal.
C. Negative symptoms are associated with increased likelihood of hospital admission.
D. SEP-363856 is being investigated for its utility in treating negative symptoms.

3. Approximately what percentage of patients with schizophrenia and related disorders also have metabolic syndrome?

A. 25%
B. 33%
C. 50%
D. 66%

4. Approximately what percentage of patients who respond well to antipsychotic agents for schizophrenia are nonadherent to therapy?

A. 20%
B. 30%
C. 40%
D. 50%

5. Which statement is accurate about comorbidities and antipsychotics in patients with schizophrenia?

A. Comorbidities are uncommon and therefore clinicians can focus solely on managing antipsychotics for patients with schizophrenia.
B. Weight gain and metabolic disturbances are due to genetic factors, and antipsychotics are not associated with these adverse effects (AEs) in patients with schizophrenia.
C. Antipsychotic polypharmacy increases the frequency of AEs, and the longer a patient uses an atypical antipsychotic, the more severe the AE, such as weight gain.
D. Clozapine, olanzapine, and quetiapine were determined to be less likely to increase blood triglyceride levels, whereas risperidone and aripiprazole were more likely to increase total cholesterol levels.

6. Which of the following agents modulates glutamate as part of its mechanism of action?

A. Roluperidone
B. Lumateperone
C. Olanzapine/samidorphan
D. Pimavanserin

7. Roluperidone is currently in development to target which of the following unmet medical needs in schizophrenia?

A. Negative symptoms
B. Weight gain
C. Nonadherence
D. Treatment resistance

8. AK is a 30-year-old woman who received a diagnosis of schizophrenia 2 years ago. She was successfully treated with olanzapine in the past but became nonadherent due to weight gain. Which emerging agent has the potential to help AK remain adherent?

A. Olanzapine/samidorphan
B. Pimavanserin
C. Roluperidone
D. Risperidone ISM

9. Which statement is accurate when describing costs of care for patients with schizophrenia?

A. The majority of direct costs are related to inpatient visits and medications.
B. Indirect costs make up less than 50% of the total cost of care.
C. The annual costs of care are estimated to be $117 million.
D. Total costs of care were found to be higher in older patients with schizophrenia as compared with younger patients.

10. All of the following are strategies to reduce healthcare resource utilization in patients with schizophrenia, EXCEPT:

A. Adding metformin to therapy to reduce risk of metabolic syndrome
B. Investigating and addressing reasons for medication nonadherence
C. Implementing careful monitoring for medication-related AEs
D. Utilizing shared decision making with the patient when making treatment decisions

NOTES

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