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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