The Emerging Treatment Landscape in Schizophrenia

Dawn I. Velligan, PhD,[a] and Sanjai Rao, MD[b]

The incomplete efficacy and tolerability profiles of therapies used to treat schizophrenia necessitate the development of superior alternatives, particularly for patients experiencing negative symptoms and cognitive impairment. Currently, there are a minimum of 6 investigational agents that have entered late-stage development, and each operates through a non-dopaminergic mechanism of action.[1]

Among the promising agents in phase 3 clinical development is ulotaront—a first-in-class trace amine-associated receptor 1 (TAAR1) agonist with 5-HT_{1A} receptor activity. Mechanistically, TAAR1 is a G-protein–coupled receptor that appears to modulate dopaminergic, serotonergic, and glutamatergic signaling when activated by endogenous trace amines.[2] In an open-label extension of the SEP-363856 phase 2 clinical trial, investigators evaluated the long-term efficacy and tolerability of ulotaront in patients with schizophrenia at doses of 25, 50, and 75 mg daily.[3] After 26 weeks, 67% of participants receiving ulotaront completed treatment, which exceeds 26-week completion rates observed in long-term studies of atypical antipsychotics (39%–65%). Investigators additionally observed significant improvements in a broad array of symptom measures, including Positive and Negative Syndrome Scale (PANSS) positive, negative, and general psychopathology subscales. Notably, rates of extrapyramidal-related adverse events were low, as were the frequency of metabolic effects and changes in body weight.[3]

Already indicated in the treatment of Parkinson's disease psychosis, the selective 5-HT_{2A} inverse agonist and antagonist pimavanserin is undergoing investigation in patients with schizophrenia. In the 26-week, phase 2 ADVANCE study, researchers assessed the ability of pimavanserin 20 mg daily to alleviate negative symptoms of schizophrenia in adult patients aged between 18 and 55 years.[4] Participants receiving pimavanserin demonstrated a reduction in negative symptoms versus those assigned placebo, but the effect size was modest and requires validation. Treatment-related adverse events, encouragingly, were similar between the pimavanserin treatment arms (40%) and placebo (35%).[4]

Like pimavanserin, roluperidone exhibits activity against the 5-HT_{2A} receptor. In a placebo-controlled, multinational trial, researchers noted that roluperidone at a dose of 64 mg/d improved PANSS-derived Negative Symptom Factor scores relative to placebo, although the magnitude of symptom reduction missed statistical significance.[5] More data are required to confirm the utility of roluperidone, whose associated New Drug Application with the US Food and Drug Administration was rejected in October 2022.[6]

Findings from the phase 3 EMERGENT-2 trial suggest that xanomeline-trospium effectively treats positive and negative symptoms seen in patients with schizophrenia.[7] In the trial, the combination regimen met its primary endpoint of a statistically significant and clinically meaningful drop on the PANSS (9.6 points) over a period of 5 weeks. Additionally, investigators found that xanomeline-trospium achieved its key secondary endpoints of reducing hallucinations and social isolation. Although the incidence of treatment-related adverse events was greater among participants randomized to xanomeline-trospium (75%) compared with placebo (58%), overall discontinuation rates were similar between the two treatment arms. Weight gain and extrapyramidal symptoms were also absent among patients receiving the novel treatment combination.[7]

To address the cognitive impairment associated with schizophrenia, clinicians may soon gain an option in the form of iclepertin. Biologically, iclepertin is a potent, selective, orally administered glycine transporter-1 (GlyT1) inhibitor that has shown therapeutic potential. In a phase 2, double-blind, placebo-controlled trial, researchers evaluated iclepertin as an add-on therapy at doses of 2, 5, 10, and 25 mg over 12 weeks against placebo in patients with schizophrenia.[8] Change from baseline in MATRICS Consensus Cognitive Battery composite T-score at week 12 served as the trial's primary endpoint. At 12 weeks, study investigators observed a non-flat dose-response relationship between iclepertin and cognitive improvement. Although rates of gastrointestinal-related side effects were higher among participants receiving GlyT1 therapy versus placebo, adverse events leading to premature discontinuation occurred at low frequencies across all treatment groups (< 2%).[8] A trio of confirmatory phase 3 trials—CONNEX-1, CONNEX-2, and CONNEX-3—are ongoing to assess

[a]Division of Schizophrenia and Related Disorders, Department of Psychiatry and Behavioral Sciences, The University of Texas Health Science Center at San Antonio, San Antonio, Texas

[b]University of California San Diego and VA San Diego Healthcare System, San Diego, California

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the magnitude of cognitive improvement over 26 weeks in patients with schizophrenia.[9–11] If validated, iclepertin can fill longstanding gaps in treatment for patients experiencing cognitive impairment.[12]

The next generation of treatments in schizophrenia is poised to transform existing therapeutic paradigms and substantially improve outcomes for patients. To maximize gains from these novel agents expanding the treatment landscape, clinicians should work closely with patients to determine the most appropriate choice for long-term management. This therapeutic alliance can help ensure that patients achieve the greatest outcome possible from continued pharmacotherapy.

Patient Perspective

"I have been working for a year at my job and am doing well. I still have symptoms but weather the storm and am doing fairly well. I don't work full-time though but am able to pay my bills and for my food. I am doing OK and am grateful for the medication. . . . Without medication, I was homeless and severely symptomatic. I learned from my experience of homelessness that I need to be on medication at all costs. I also realized I would rather work than do nothing. So, since I want to work, I need to take my medication. . . . I know that being compliant is key for my survival and independence."[13]

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