Reviewing Non-Dopaminergic Mechanisms for Positive and Negative Schizophrenia Symptom Management

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Schizophrenia is a chronic and debilitating mental health condition that significantly impacts quality of life and can shorten patients' lifetime by decades, with a 2.5-fold greater mortality risk than the general population.[1] It has a global prevalence of 1% and an age at onset of late adolescence/early adulthood for men and slightly later in women.[2] Schizophrenia is characterized by positive symptoms including hallucinations and delusions, negative symptoms such as anhedonia and apathy, and cognitive impairment.[2] People with schizophrenia also experience many somatic comorbidities such as metabolic disturbances, infectious diseases, cardiovascular issues, and respiratory illnesses.[3]

For decades, treatment for schizophrenia has focused on antipsychotics (APs) that reduce excess dopamine signaling to the associative striatum by blocking the dopamine D_2 receptors located there, thus addressing positive symptoms.[4] However, treatment that blocks excess dopamine signaling in the associative striatum also blocks dopamine signaling in the dorsal striatum, creating movement disorders such as drug-induced Parkinsonism.[5] Second-generation APs, or atypical APs, have a lower propensity to cause drug-induced Parkinsonism than first-generation APs.[5,6] Nonetheless, only 1 out of 3 patients respond to any of the available APs; moreover, negative and cognitive symptoms tend to persist, while side effects and long-term risks can contribute to poor outcomes.[7,8]

However, there are new understandings in how to reduce dopamine release presynaptically and selectively in the neurocircuitry that governs psychotic symptoms. These mechanisms offer a different treatment approach for patients with schizophrenia.[9]

Muscarinic agonism is one novel mechanism for treating psychosis.[10] An example of this is xanomeline, which targets muscarinic M_1 and M_4 receptors, ultimately reducing excess dopamine signaling to that specific part of the striatum thought responsible for the positive symptoms of schizophrenia and without affecting the dorsal striatum, thus avoiding motoric adverse effects.[10,11] However, due to peripheral cholinergic adverse effects, xanomeline alone is not well tolerated. A solution to this problem has been to combine xanomeline with trospium, an anticholinergic medication that does not cross the blood-brain barrier.[12] Other agents under clinical investigation that stimulate muscarinic receptors in the brain include positive allosteric modulators (PAMs) that target M_4, such as emraclidine.[13]

Another means of reducing aberrant dopamine signaling is modulation of the trace amine–associated receptor 1 (TAAR1). Trace amines have chemical structures that are similar to monoamine neurotransmitters but are expressed at very low levels in the CNS (hence "trace"), and their associated receptors reside intracellularly. Importantly, trace amine–associated receptors, particularly TAAR1, have been implicated in models of schizophrenia.[14] In TAAR1 knockout mice, abnormal dopamine signaling was observed in striatal areas associated with positive symptoms of psychosis, but not in motor regions.[14,15] In other animal models, TAAR1 agonists block the behavioral effects of stimulants and NMDA antagonists and also potentiate antipsychotic effects on amphetamine-induced hyperactivity without inducing catalepsy. They also inhibit firing rates of dorsal raphe neurons. TAAR1 agonists exhibit prometabolic functions as well.[15] Of clinical importance is that TAAR1 agonism has no deleterious effect on the motor area of the striatum.

Clinical data have borne out these two models with very encouraging results.

In a phase 2 double-blind five-week, placebo-controlled trial conducted with acutely exacerbated inpatients with schizophrenia, xanomeline-trospium (XT) showed improvements in Positive and Negative Syndrome Scale (PANSS) scores vs placebo, with

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a robust effect size.[16] XT showed no metabolic, endocrine, or motor adverse effects (AEs).[16] In 2 subsequent phase 3 clinical trials whose results await formal publication, XT was associated with similarly clinically meaningful and statistically significant improvement in PANSS scores and with a similar AE profile.[17,18] Promising results are also available for the M_4 PAM emraclidine; a phase 1B inpatient study demonstrated statistical superiority over placebo.[19] Phase 2 trials of emraclidine are being conducted, with results expected in the first half of 2024.[20]

In addition to the studies of agents that target muscarinic receptors, clinical trial data are available for an agent targeting TAAR1. Ulotaront is a TAAR1 agonist that has demonstrated efficacy in a phase 2 double-blind, four-week, placebo-controlled trial of inpatients with an acute exacerbation of schizophrenia[21] and supported by a 6-month open-label extension study.[22] Ulotaront treatment is associated with a durable antipsychotic effect, without extrapyramidal, metabolic, or sedative adverse effects, and no elevations in prolactin or prolongation of the electrocardiogram QT interval.[21,22] It has received breakthrough therapy status for further development, and phase 3 clinical trials have been recently completed, with results that should be available by the time you are reading this.

The hope is to be able to treat people with schizophrenia with agents that work well, are better tolerated, and lead to improved outcomes. Having different mechanisms of action also opens the door to rational polypharmacy and potential synergy for those patients in whom clinical response has thus far been suboptimal.

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