Rationale for Adjunctive Treatment Targeting Multiple Mechanisms in Schizophrenia

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Abstract

Importance: Schizophrenia is a complex syndrome with taxing symptoms and for which treatment challenges remain. Current dopamine D_2 receptor–blocking antipsychotics have well-known limitations, including ineffectively treating across all symptom domains and generating common side effects such as motor disturbances, weight gain, and metabolic dysfunction. New approaches are sorely needed to address the continued unmet treatment needs for individuals living with schizophrenia.

Observations: Although current antipsychotic drugs indicated for the treatment of schizophrenia interact with various neurotransmitter receptors, they all commonly act as dopamine D_2 receptor antagonists or partial agonists. While antipsychotics primarily relieve positive symptoms, residual positive symptoms are still common, and management of negative symptoms and cognitive impairment remains an unmet need. Problematic side effects are common with current agents and can contribute to nonadherence. In addition to alterations in dopaminergic pathways, increasing evidence indicates that the pathophysiology of schizophrenia also includes dysfunction in other neurotransmitter systems including glutamate, acetylcholine, serotonin, and γ-aminobutyric acid. While the pathophysiology of schizophrenia is complex, treatments with novel pharmacologic actions that target these systems are of interest as adjunctive treatment for individuals with schizophrenia.

Conclusion and Relevance: An unmet need exists for effective treatment of all the core symptoms of schizophrenia. Novel antipsychotics with a nondopaminergic mechanism of action may be useful candidates for antipsychotic adjunctive treatment in people with schizophrenia who are showing inadequate responses, treatment resistance, or low tolerance to dopamine D_2 receptor–blocking antipsychotics.

J Clin Psychiatry 2024;85(3):23nr15240

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Schizophrenia is a complex and chronic syndrome that affects approximately 24 million people worldwide[1] and remains associated with considerable disability,[1] premature mortality,[2] and significant economic burden.[3] The primary symptom domains of schizophrenia include positive symptoms such as hallucinations and delusions, negative symptoms such as social withdrawal, and cognitive dysfunction. Approved treatments for schizophrenia are limited in their efficacy across symptom domains and are associated with side effects including motor symptoms, somnolence/sedation, weight gain, hormonal abnormalities, and metabolic dysregulation.[4] When an individual living with schizophrenia does not have an adequate response to treatment, alternative strategies are often employed, including dose increases, switching to another antipsychotic drug, or combination with a second psychotropic medication, such as antipsychotics, antidepressants, anxiolytics, stimulants, and mood stabilizers.[5–7] There are currently no approved pharmacologic combinations for the treatment of schizophrenia.

While the classical dopamine hypothesis of psychosis has been an enduring theory in schizophrenia, this hypothesis has been refined, with additional neurotransmitter systems implicated in the pathophysiology of schizophrenia.[8] In addition to dopaminergic dysfunction, alterations in glutamate, γ-aminobutyric acid (GABA), serotonin, and acetylcholine neurotransmitter systems have been reported.[9–13] All currently approved antipsychotics are dopamine D_2 receptor antagonists or partial agonists, and many bind with varying affinities to other receptors, contributing to both their efficacy and side effect profiles.[9,14] To date, strong evidence is lacking to support the combination of an antipsychotic drug with a second psychotropic medication for improved symptom reduction.[7] Novel pharmacologic approaches are profoundly needed.

This article reviews existing pharmacologic treatments for schizophrenia and investigational antipsychotic and psychotropic agents with novel, non-D_2 receptor mechanisms of action, with a focus on

Clinical Points

- Currently available antipsychotics act as D_2 receptor antagonists/partial agonists, which may lack effectiveness for some individuals with schizophrenia.
- Treatments combining multiple mechanisms of action hold promise in addressing some of the unmet treatment needs in schizophrenia.
- Novel agents without direct D_2 receptor blocking may be useful to augment current antipsychotics' effects in individuals with inadequate response/intolerance to current schizophrenia treatment.

adjunctive or cotreatments for schizophrenia. In this article, the term "adjunctive treatment" is used to describe a therapy given to enhance the main or current treatment to maximize its effectiveness. This term is used interchangeably with similar terms such as "augmentation," "add-on," "combination treatment," or "cotreatment" to reflect the term used in the cited literature. It is acknowledged that these terms are not necessarily synonymous in meaning and may, in some instances, denote 2 cotreatments given together to enhance the effectiveness of either given alone.

LIMITATIONS OF CURRENT ANTIPSYCHOTIC MEDICATIONS

Current antipsychotic medications address positive symptoms of schizophrenia without clear evidence of efficacy in controlling primary negative or cognitive symptoms, except for cariprazine and amisulpride in low doses.[15] No or partial responses to antipsychotics are common. An analysis of 16 randomized, controlled trials showed that 67% of individuals with acute exacerbation of schizophrenia had ≤50% reduction in overall symptoms, and 20% had no reduction at all.[16] Approximately 24%–30% of people with schizophrenia have treatment-resistant schizophrenia,[17–19] defined as failure to respond to ≥2 trials of adequate dose and duration of antipsychotic medications.[20] Further, up to 60% of people with treatment-resistant schizophrenia do not respond to clozapine,[21] the only antipsychotic agent specifically indicated for this condition.[22] Even when psychosis responds to the antipsychotic used and positive symptoms are reduced extensively, the overall therapeutic effect is usually not a cure or complete remission. Manifestations of the illness are persistent, especially those related to negative symptoms and cognitive impairments. Residual symptoms are also associated with higher relapse rates.[23,24]

Antipsychotics are associated with increased risks of extrapyramidal symptoms (EPS) including antipsychotic drug–induced parkinsonism, akathisia, and rescue use of antiparkinson medications, as well as weight gain, metabolic side effects, and elevated serum prolactin levels.[25–29] Among these side effects, EPS and increased prolactin are attributable to D_2 receptor blockade.[30] In general, antipsychotics with relatively lower D_2 antagonism and higher 5-hydroxytryptamine 2A (5-HT_{2A}) receptor antagonism tend to carry a lower risk of EPS and prolactin elevation, but a greater risk of weight gain.[31] Studies in individuals taking typical and atypical antipsychotics reported prevalence rates ranging from approximately 20%–35% for antipsychotic-induced parkinsonism and tardive dyskinesia.[32] A systematic review and meta-analysis of 15 studies that included users of typical and/or atypical antipsychotics found overall pooled prevalence of approximately 20%, 11%, and 7% for antipsychotic drug-induced parkinsonism, akathisia, and tardive dyskinesia, respectively.[33] Unfavorable side effects of antipsychotics also contribute to treatment discontinuation, poor compliance, and subsequent relapse.[34,35] A systematic review of 39 studies found an estimated nonadherence rate of 40%–50% in individuals with schizophrenia.[36] Approximately 75% of people with schizophrenia stopped the first antipsychotic prescribed during the first 18 months of treatment.[37]

Both negative and cognitive symptoms are common in most individuals with schizophrenia and are associated with functional impairment.[38–40] Primary negative symptoms are intrinsic to the underlying pathophysiology and present throughout the course of the disease, while secondary negative symptoms are thought to be related to other factors such as positive symptoms, side effects of medications including certain antipsychotics, other comorbidities, social deprivation, and substance abuse; the 2 types can be clinically indistinguishable.[41] While antipsychotics can reduce negative symptoms in individuals with schizophrenia and exacerbations of psychosis, it is unclear whether their effects are on primary or secondary negative symptoms.[41] A meta-analysis revealed that amisulpride was the only antipsychotic drug to improve primary negative symptoms with evidence from placebo-controlled trials, while drugs like olanzapine and zotepine did not outperform placebo, and cariprazine was the only antipsychotic that was clearly better than another antipsychotic (risperidone) in this regard.[15] Commonly prescribed antipsychotic medications for schizophrenia have limited cognitive benefits.[42] Meta-analyses found only mild neurocognitive improvements for certain atypical antipsychotics, mainly compared to haloperidol, and the effect sizes were generally small.[43–46] Moreover, neurocognitive improvements may be the result of improvements in secondary factors such as EPS.[47,48]

ADJUNCTIVE AND COMBINATION TREATMENT STRATEGIES

Combining multiple antipsychotic medications or adding a nonantipsychotic agent to an antipsychotic agent is a common practice for addressing inadequate responses to antipsychotic monotherapy. The goal is to improve general or selective symptoms, functional outcome, and/or tolerability.[6,49]

Inherent challenges exist to demonstrate the superiority of combinations vs monotherapy. A comprehensive, systematic overview of 29 meta-analyses for 42 combinations (mostly antipsychotic/nonantipsychotic combinations) showed significantly more benefit with some strategies versus their antipsychotic monotherapy controls in positive or negative symptoms.[7] Fourteen agents, including certain antidepressants, antioxidants, and mood stabilizers, combined with antipsychotics were found superior to controls for total symptom reductions, while all clozapine augmentation strategies did not outperform controls.[7] However, the effect sizes of the pooled interventions were inversely correlated with the quality of the studies included in the meta-analyses, lowering the confidence in recommending any of the combination strategies.[7]

Results from a meta-analysis showed that augmentation of a current antipsychotic with a different antipsychotic appeared to be more effective than monotherapy in overall symptom reduction in open-label or low-quality studies, but not in double-blind, high-quality studies.[50] In a meta-analysis of clozapine augmentation studies, only aripiprazole among the 10 add-on antipsychotics analyzed exhibited a greater effect vs placebo in reducing total psychosis,[51] consistent with the real-world data that clozapine augmented with aripiprazole reduces rehospitalization risks compared with clozapine alone.[52] However, the effect of the clozapine/aripiprazole combination on total psychosis was not statistically different when poor-quality studies were excluded from the meta-analysis.[51] It was speculated that the treatment response resulting from D_2 receptor blockade may already be maximized with clozapine, and therefore, adding a second dopamine blocker would provide limited benefit,[53] although clozapine at clinical doses was shown to only transiently occupy 47%–72% of D_2 receptors without saturating the receptors.[54–56] Preliminary data from a small pilot study suggest that clozapine augmentation with cariprazine, which has partial D_2/D_3 receptor agonism, may improve overall, negative, and cognition symptoms.[57] The positive effects of cariprazine were hypothesized to be related to its unique pharmacodynamic profile of partial agonism at D_3/D_2 receptors and 5-HT_{1A} receptors along with antagonism of 5-HT_{2A} and 5-HT_{2B} receptors.[57,58] Further evaluations in large, randomized controlled studies are needed to confirm these effects. A meta-analysis of 2 randomized controlled trials with head-to-head comparisons of augmentation with another antipsychotic versus switching to a new antipsychotic found no significant differences between the 2 strategies in controlling total, positive, or negative symptoms.[59] Overall, current evidence remains inconclusive to show the superior efficacy of antipsychotic combinations compared with monotherapies. This is especially notable considering that most studies included in these meta-analyses had small sample sizes, which can cause potential biases in meta-analysis as smaller studies tend to overestimate treatment effects.[60]

Antidepressants, anxiolytics, mood stabilizers, and antioxidants have been studied as adjunctive therapies with antipsychotics.[5,61] Results from meta-analyses suggest the beneficial effects of adjunctive antidepressants (eg, selective serotonin reuptake inhibitors) on reducing negative or depressive symptoms are small,[62,63] particularly for people with chronic schizophrenia.[64] A comparative, real-world effectiveness study showed that adjunctive antidepressants were associated with lower risks of psychiatric hospitalization and emergency department visits compared with alternative antipsychotic therapy, while poorer outcomes were observed for adjunctive benzodiazepines and mood stabilizers.[65] However, data from 2 earlier meta-analyses did not provide support for the effectiveness of adjunctive antidepressants.[66,67] Despite mixed findings, these combination strategies are common in clinical practice. Real-world data from Europe showed that in outpatient treatment, 8%–23%, 7%–19%, and 22%–37% of individuals with schizophrenia who took antipsychotics received adjunctive antidepressants, mood stabilizers, and anxiolytics, respectively.[68] A nationwide register-based study among individuals with schizophrenia in inpatient or specialized outpatient care in Finland and Sweden found a rate of 25%–30% for adjunctive antidepressants, 17%–18% for adjunctive mood stabilizers, and 22–33% for adjunctive benzodiazepines and related drugs.[69]

Positive effects with adjunctive anti-inflammatory agents or azapirones have been reported.[70,71] A systematic review and meta-analysis of 7 randomized, controlled studies showed that adjunctive N-acetylcysteine versus placebo reduced total and negative schizophrenia symptoms after 24 weeks of treatment and improved the cognitive domain of working memory.[72] However, the absolute changes may be too small to be clinically meaningful.[73] In a more recent, randomized, placebo-controlled study in people with treatment-resistant schizophrenia who were taking clozapine, no significant benefits were observed in negative symptoms or cognition function at any time point over 1 year of treatment with adjunctive N-acetylcysteine.[74]

Augmenting cognitive remediation therapy with novel medications has also been studied in individuals with

schizophrenia. Amphetamine[75,76] and memantine[77] were found to enhance auditory discrimination and learning in cognitive training for schizophrenia. When combined with auditory cognitive remediation, D-serine improved plasticity compared with placebo.[78] However, no significant effects on cognitive performance were observed for D-serine,[79] PF-03463275,[80] and iclepertin,[81] when these agents were combined with computerized cognitive training compared with training alone.

Concerns exist regarding the potential exacerbation of D_2 receptor blocking–related adverse effects with concurrent use of multiple antipsychotics. Combinations of multiple antipsychotics have been reported to cause more side effects than monotherapies, particularly antipsychotic drug-induced parkinsonism, rescue anticholinergic use, and hyperprolactinemia.[82] An overall greater total dose of antipsychotics can contribute to the increased risk of side effects.[82,83] Antipsychotic combinations may also have detrimental effects on cognition,[82] although a causal relationship has not been definitively established.[84] However, less insomnia was seen when combining 2 D_2 receptor antagonists compared with monotherapy.[50] Adjunctive aripiprazole, a D_2 receptor partial agonist, was also found to lower prolactin levels and reduce body weight.[50,85]

While augmentation of clozapine with other agents has been recommended for clozapine-refractory schizophrenia by the Treatment Response and Resistance in Psychosis Working Group,[86] current treatment guidelines lack direction for other augmentation strategies. The National Institute for Health and Care Excellence guideline recommends against the regular combined use of antipsychotic medications except for short periods of time such as when changing medication.[87] The American Psychiatric Association practice guidelines suggest augmentation approaches for individuals showing no or partial response to antipsychotics, although a trial of clozapine should not be delayed.[88] Combining multiple antipsychotics for refractory schizophrenia is possible by the Royal Australian and New Zealand College of Psychiatrists guidelines, but careful monitoring is required due to potentially increased side effects, hospitalization, and mortality.[89]

RATIONALE FOR TARGETING MULTIPLE NEUROTRANSMITTER SYSTEMS

Increasing evidence suggests that the pharmacologic actions of current antipsychotics, all of which share the ability to block the D_2 receptor, are insufficient to adequately control all symptoms of schizophrenia for all individuals. Postmortem and neuroimaging studies revealed differences in dopamine neurotransmission between treatment-responsive and treatment-resistant schizophrenia.[90–93] Based on these findings, 2 subtypes of schizophrenia were hypothesized, one with increased dopamine synthesis and release capacity in the striatum (hyperdopaminergic) and the other with unaltered dopaminergic function (normodopaminergic), with the latter type likely involving nondopaminergic mechanisms.[94] Given that all current antipsychotics are D_2 receptor blockers, a sizable subgroup of people with schizophrenia with little dopaminergic pathophysiology would not be expected to respond well to current antipsychotic treatments.[94,95] Moreover, positive symptoms of schizophrenia are associated with dopamine hyperactivity in the striatum, and negative and cognitive symptoms have been hypothesized to be associated with reduced cortical dopamine signaling.[10,96,97] Current antipsychotic drugs acting as D_2 receptor functional antagonists could therefore actually impair cognition and secondarily increase negative symptoms. This is supported by evidence that administration of antipsychotics can induce negative symptoms and cognitive dysfunction in healthy volunteers[98,99] and increase or cause secondary negative symptoms in people with schizophrenia.[30]

Therapies combining complementary mechanisms have been shown to provide more clinical benefits than monotherapy when treating diseases with diverse mechanisms, such as diabetes, hypertension, and cancer.[100–102] Similarly, targeting multiple mechanisms in schizophrenia may improve treatment effects. Perturbations in acetylcholine, glutamate, GABA, and serotonin neurotransmitter systems have been implicated in schizophrenia and may contribute to negative and cognitive symptoms.[38,97] Treatments targeting these nondopaminergic pathways may produce beneficial effects on these symptom domains. The rationale for adjunctive therapy with multiple antipsychotics targeting different mechanisms also stems from the observation that high-efficacy antipsychotic drugs, particularly clozapine, have complex actions with pleiotropic effects on multiple neurotransmitter systems. Compared with other antipsychotics, clozapine is more effective in controlling overall and secondary negative symptoms,[27,103] although no clear difference was found between olanzapine and clozapine.[104,105] Clozapine is also associated with lower risks of EPS, hospitalization, and all-cause discontinuation.[106] While not the first-line drug of choice due to its safety profile, clozapine is the only antipsychotic drug approved by the US Food and Drug Administration (FDA) for treatment-resistant schizophrenia.[22] The superior efficacy of clozapine has been postulated to be attributable to its low D_2 receptor occupancy, rapid dissociation from D_2 receptors, a higher affinity ratio for 5-HT_{2A} versus D_2 receptors, and high D_4 receptor affinity.[107] The ability of clozapine to interact with other receptors, including the muscarinic (M_1, M_2, M_3, and M_5), histamine, and α_1-adrenergic receptors

may also contribute to its superior efficacy.[107] Additionally, clozapine's effects on glycine transport inhibition[108] and glutamatergic modulation,[109,110] as well as the M_1 and M_4 agonism attributable to norclozapine,[109] may be involved in its unique efficacy.

Advantages of combining traditional antipsychotic agents with a nondopaminergic agent have been reported. For example, adjunctive sodium benzoate, a D-amino acid oxidase (DAAO) inhibitor that indirectly enhances *N*-methyl-D-aspartate (NMDA) receptor functions, was shown to improve a variety of symptom domains and cognitive function when added to an ongoing antipsychotic medication.[111,112] Improvements in several domains of cognition were also observed for combinations of antipsychotics with acetylcholinesterase inhibitors.[113] Taken together, these data suggest that individuals suffering from schizophrenia very likely have complex and heterogeneous pathophysiology. There is hope that they may demonstrate more favorable outcomes when treated with pharmacologic approaches that go beyond D_2 receptor blockade.

NOVEL PSYCHOTROPIC AGENTS THAT DO NOT BLOCK DOPAMINE RECEPTORS

Considerable efforts have been dedicated to the research and development of non-D_2 agents for schizophrenia over the past 20 years,[114] although none of these new agents has received FDA approval, with some being unsuccessful in phase 3 programs. For instance, encenicline, a selective partial α7 nicotinic receptor agonist, demonstrated only limited cognitive effects when added to stable antipsychotics in 2 large phase 3 trials.[115] Three phase 3 studies evaluating adjunctive bitopertin, a glycine transporter 1 (GlyT1) inhibitor, missed their primary efficacy end point of significant improvement in negative symptoms.[116] Pomaglumetad methionil, a mGlu2/3 receptor agonist, failed to show greater improvement in psychotic symptoms compared with placebo in its pivotal, phase 2 study,[117] nor did it demonstrate superiority over aripiprazole in a phase 3 study.[118] However, there is continued interest in the development of novel, nondopaminergic psychotropics for people with schizophrenia who do not respond to approved antipsychotics properly. Several new agents are currently at their later stage of clinical development (Table 1).[119]

Targeting the Glutamate Receptors

Glutamatergic dysfunction is implicated in the pathophysiology of schizophrenia,[10,11] so there is great interest in investigating the therapeutic potential of glutamatergic compounds. However, most of these compounds (eg, mGlu2/3 receptor agonists, riluzole, and memantine) have failed to demonstrate definitive efficacy on positive, negative, or cognitive symptoms.[38,117] Results from meta-analyses suggest that NMDA receptor–enhancing agents have little to negligible effect on improving overall cognition when added to antipsychotics.[120,121] However, adjunctive NMDA receptor modulators as a group exhibited a small effect on negative symptoms,[122] and adjunctive NMDA receptor coagonists, such as glycine, D-serine, and D-alanine, have been reported to improve both positive and negative symptoms in some but not in all studies.[123–127] In addition, a review of current findings suggests that indirect modulators of the NMDA receptor glycine modulatory site, such as GlyT1 inhibitors or DAAO inhibitors, may offer more benefits, at least on cognition, than direct modulators.[128]

Iclepertin (BI 425809) is a GlyT1 inhibitor that indirectly potentiates glutamate acting on the NMDA receptor, resulting in normalization of the NMDA receptor–mediated cortical excitatory-inhibitory imbalance.[129] A phase 2, randomized controlled study showed significantly greater improvement in cognition with oral, adjunctive iclepertin vs placebo.[130] The treatment was well tolerated, with similar incidence of adverse events (AEs) across treatment groups and low frequencies of serious AEs and AE-related study discontinuations.[130] Several phase 3 trials are ongoing to further investigate the efficacy and safety of adjunctive iclepertin in treating impaired cognition and daily functioning associated with schizophrenia (Table 1).[129]

Luvadaxistat (TAK-831 or NBI-1065844) is a DAAO inhibitor that increases the synaptic levels of the glutamate coagonist D-serine, thereby indirectly modulating the NMDA receptor activity.[131] A small, phase 2a, randomized controlled, crossover study did not demonstrate any effect of adjunctive luvadaxistat at an oral, daily dose of 50-mg or 500-mg on learning as assessed with eyeblink conditioning (primary end point). However, the 50-mg dose improved or showed a trend toward improving mismatch negativity (MMN) and auditory steady-state responses, which are the neurocircuitry biomarkers implicated in NMDA receptor function and schizophrenia.[131] Luvadaxistat was well tolerated in the study with mild, nontreatment-related AEs.[131] The phase 2, randomized controlled, INTERACT study showed that 12 weeks of treatment with luvadaxistat added to current antipsychotics did not improve negative symptoms of schizophrenia (primary end point) in adults with schizophrenia.[132] However, INTERACT met its secondary end points of improving cognitive function,[132] and luvadaxistat is being further investigated for the treatment of cognitive impairment in schizophrenia (Table 1).

Evenamide is a highly selective, voltage-gated sodium channel blocker that normalizes excessive glutamate release due to NMDA receptor hypofunction.[133] In a pilot, phase 2, open-label trial, evenamide added to an ongoing antipsychotic was shown to improve the overall symptoms

Table 1.

Novel, Investigational Antipsychotic and Psychotropic Agents With a Nondopaminergic Mechanism of Action Currently Being Studied for Schizophrenia Treatment

Compound	Receptor targets	Therapy type	Current efficacy results	Ongoing clinical trials
Glutamatergic				
Iclepertin (BI 425809)	GlyT1 inhibitor	Adjunctive for CIAS	Positive results on cognitive functions (NCT02832037) Negative results on cognitive functions (NCT03859973)	Phase 3: • NCT04846868 (CONNEX-1; RCT) • NCT04846881 (CONNEX-2; RCT) • NCT04860830 (CONNEX-3; RCT) • NCT05211947 (OLE)
Luvadaxistat (TAK-831/NBI-1065844)	DAAO inhibitor	Adjunctive for CIAS	Negative results on EBC; positive results on MMN; a trend toward improvement in ASSR (NCT03359785)	Phase 3: • NCT05182476 (ERUDITE; RCT + OLE)
		Adjunctive for negative symptoms	Negative results on negative symptoms; positive results on cognitive functions (NCT03382639 [INTERACT])	
Evenamide	Voltage-gated sodium channel blocker	Adjunctive	Positive results on overall symptoms (Study 014/015)	A phase 3 study in patients with TRS has been planned
Muscarinic acetylcholinergic				
KarXT (xanomeline + trospium chloride)	Muscarinic M_1 and M_4 receptor agonist	Monotherapy	Positive results on overall, positive, and negative symptoms, and cognitive functions (NCT03697252 [EMERGENT-1]) Positive results on overall symptoms (NCT04659161 [EMERGENT-2])	Phase 3: • NCT04820309 (EMERGENT-5; OL) • NCT04659174 (EMERGENT-4; OLE) • NCT05919823 (UNITE-001; RCT + OLE)
		Adjunctive		Phase 3: • NCT05145413 (ARISE; RCT) • NCT05304767 (OLE)
Emraclidine (CVL-231)	Muscarinic M_4 receptor PAM	Monotherapy	Positive results on overall symptoms (NCT04136873)	Phase 2: • NCT05227703 (RCT) • NCT05227690 (RCT) • NCT05443724 (OL)
Serotonergic and others				
Pimavanserin	5-HT_{2A} receptor inverse agonist and antagonist	Adjunctive for negative symptoms	Positive results on negative symptoms (NCT02970305 [ADVANCE]) Negative results on overall symptoms; a trend toward improvement in negative symptoms (NCT02970292 [ENHANCE]) Negative results on negative symptoms (NCT04531982 [ADVANCE-2])	Phase 3: • NCT04531982 (ADVANCE-2; RCT) • NCT03121586 (OLE)
Roluperidone (MIN-101)	σ_2, 5-HT_{2A}, and α_1-adrenergic receptor antagonist	Monotherapy	Positive results on negative symptoms, cognitive performance, and social functioning (phase 2b) Negative results on negative symptoms (NCT03397134)	NDA filed for the treatment of negative symptoms of schizophrenia and rejected by the FDA
Ulotaront (SEP-363856)	TAAR1 and 5-HT_{1A} receptor agonist	Monotherapy	Positive results on overall symptoms (NCT02969382; NCT02970929) Negative topline results on overall symptoms (NCT04072354 [DIAMOND 1]; NCT04092686 [DIAMOND 2])	Phase 3: • NCT04072354 (DIAMOND 1; RCT) • NCT04092686 (DIAMOND 2; RCT) • NCT05628103 (OL) • NCT04109950 (OLE) • NCT05359081 (OL) • NCT05741528 (OLE) Phase 2/3: • NCT04825860 (RCT + OLE) Phase 1: • NCT05848700 (RCT) • NCT05463770 (OL) • NCT05402111 (randomized, OL) • NCT05542264 (randomized)

Abbreviations: 5-HT_{1A} = 5-hydroxytryptamine 1A receptor, 5-HT_{2A} = 5-hydroxytryptamine 2A receptor, ASSR = auditory steady-state responses, CIAS = cognitive impairment associated with schizophrenia, DAAO = D-amino acid oxidase, EBC = eyeblink conditioning, FDA = Food and Drug Administration, GlyT1 = glycine transporter 1, MMN = mismatch negativity, NDA = new drug application, OL = open label, OLE = open-label extension, PAM = positive allosteric modulator, RCT = randomized controlled trial, TRS = treatment-resistant schizophrenia, TAAR1 = trace amine–associated receptor 1.

of schizophrenia from baseline to 6 weeks, 6 months, and 1 year, with favorable tolerability, in people with treatment-resistant schizophrenia.[133] Evenamide also demonstrated progressively increasing efficacy as assessed with the Clinical Global Impression (CGI)-Severity and CGI-Change scales.[133] No clinically important weight gains, metabolic syndrome, or EPS were noted in the study.[133] A phase 3, randomized controlled study has been planned to further evaluate evenamide in treatment-resistant schizophrenia (Table 1).[134]

Targeting the Muscarinic Acetylcholine Receptors

KarXT (xanomeline and trospium chloride) is an oral, investigational treatment that combines xanomeline, a dual M_1 and M_4 preferring muscarinic acetylcholine receptor agonist, with trospium chloride, a peripherally restricted pan-muscarinic acetylcholine receptor antagonist.[135] Xanomeline was initially developed to treat the cognitive symptoms of Alzheimer disease but unexpectedly demonstrated efficacy in reducing and preventing psychosis symptoms (eg, delusions and hallucinations) in people with Alzheimer disease.[136] A later, proof-of-concept, phase 2 trial demonstrated antipsychotic-like effects of xanomeline in people with schizophrenia or schizoaffective disorder.[137] However, further clinical development of xanomeline was hampered by its significant peripheral cholinergic side effects.[138] The addition of trospium chloride to xanomeline reduces the incidence of these cholinergic AEs in healthy volunteers, making the development of the combination, KarXT, for schizophrenia possible.[139] In the phase 2, randomized controlled, EMERGENT-1 trial, KarXT significantly improved overall, positive, and negative symptoms vs placebo in people with acute exacerbations of schizophrenia.[135] Post hoc analyses from EMERGENT-1 also revealed cognitive improvement with KarXT that was independent of the improvement in positive symptoms in participants with baseline clinical cognitive impairment.[140] Procholinergic (nausea or vomiting) or anticholinergic (dry mouth or constipation) AEs occurred early in treatment and were transient in nature.[141] Incidence of weight gain and EPS was similar with KarXT and placebo, and no clinically meaningful changes in metabolic parameters were observed.[135,141] The randomized, placebo-controlled, phase 3, EMERGENT-2 trial further demonstrated the efficacy of KarXT, which significantly reduced the Positive and Negative Syndrome Scale (PANSS) total score versus placebo in acutely psychotic hospitalized adults with schizophrenia after 5 weeks of treatment (primary end point).[142] Frequencies of treatment-emergent EPS, akathisia, weight gain, and somnolence were similar across treatment groups.[142] KarXT is being further investigated as a monotherapy and as an adjunctive therapy for schizophrenia in several other ongoing phase 3 studies (Table 1).

Emraclidine (CVL-231) is an oral, brain-penetrant, highly selective positive allosteric modulator of the muscarinic M_4 receptor.[143] A two-part, phase 1b trial evaluated the safety, tolerability, and pharmacology of multiple ascending doses of emraclidine monotherapy in people with schizophrenia.[143] The study demonstrated a favorable safety profile and potential antipsychotic activities of emraclidine without need for dose titration.[143] Both the 30-mg (daily) and 20-mg (twice daily) doses significantly improved overall symptoms, and the 30-mg dose also significantly improved the CGI-Severity score.[143] No treatment effects on EPS were noted, gastrointestinal AEs were infrequent, and emraclidine-associated increases in heart rate and blood pressure were modest and transient.[143] Emraclidine is currently in phase 2 of clinical development as monotherapy (Table 1).

Different from KarXT, emraclidine selectively stimulates the M_4 receptor and therefore may reduce peripheral side effects, such as increased gastrointestinal motility and increased secretions associated with peripheral M_1 receptor stimulation.[144] Dosing schedules are different for the 2 agents. Flexible dosing (twice daily) is used for KarXT and could complicate efficacy evaluation and affect patient adherence compared with the constant dosing (daily) used for emraclidine.

Targeting the Serotonin and Other Neurotransmitter Receptors

Pimavanserin is an oral, selective inverse agonist and antagonist of 5-HT_{2A}[145] approved for the treatment of hallucinations and delusions associated with Parkinson disease.[146] The activity of pimavanserin for the treatment of schizophrenia was tested in 2 randomized controlled trials.[147–149] In the phase 2, ADVANCE study, adjunctive pimavanserin significantly improved negative symptoms compared with placebo in people with predominant negative symptoms of schizophrenia who were receiving a background antipsychotic medication; the treatment was well tolerated, with no clinically significant differences in vital signs, body weight, and EPS between the 2 treatment groups.[148] Higher pimavanserin exposure was associated with improved response, without increasing the incidence of key AEs, such as anxiety, headache, insomnia, and somnolence.[147] In the phase 3, ENHANCE study in adult outpatients with schizophrenia and an inadequate response to their ongoing antipsychotics, adjunctive pimavanserin failed to demonstrate an improvement in the PANSS total score (primary end point) but did show a trend toward improvement in negative symptoms.[149] Pimavanserin was well tolerated in the study, with a low rate of serious AEs and AE-related discontinuations.[149] However, adjunctive pimavanserin did not demonstrate significant improvement in negative symptoms of schizophrenia (primary end point) compared with adjunctive placebo in the phase 3, randomized controlled ADVANCE-2

study[150] (Table 1), and further development of pimavanserin has been stopped.

Roluperidone (MIN-101) is an oral antagonist of σ_2 and 5-HT_{2A} receptors; it also binds to α_1-adrenergic receptors but has no or low binding affinity for dopaminergic, muscarinic, cholinergic, and histaminergic receptors.[151] Improvements in negative symptoms, cognitive performance, and social functioning with roluperidone monotherapy were observed in individuals with stable positive and concurrent negative symptoms of schizophrenia in a phase 2b, randomized controlled trial.[151–154] No changes in vital signs, laboratory values, and EPS ratings were observed in the study and changes in body weight were small.[151] A larger, phase 3 trial failed to demonstrate statistical significance on the primary outcome of negative symptom improvement of the low (32-mg/day) and high (64-mg/day) roluperidone doses as planned, although the higher dose did demonstrate nominally statistically significant improvement vs placebo in the modified intent-to-treat population.[155] Similarly as in the phase 2b trial, roluperidone was not associated with notable changes in weight, plasma prolactin, and EPS ratings.[155] Open-label extension studies of the 2 trials demonstrated sustained effects of roluperidone up to 40 weeks on negative symptoms and social functioning.[156] The new drug application for roluperidone for the treatment of negative symptoms in schizophrenia was filed last year but was recently rejected by the FDA.[157]

Ulotaront (SEP-363856) is an oral agonist of trace amine–associated receptor 1 (TAAR1) and 5-HT_{1A} receptors that has no binding affinity for D_2 or 5-HT_{2A} receptor.[158] Ulotaront monotherapy was shown to improve total symptoms of schizophrenia compared with placebo in people with an acute exacerbation of schizophrenia in a 4-week, phase 2, randomized controlled trial,[159] and the improvement persisted during the subsequent 26-week, open-label extension study.[160] Ulotaront was generally well tolerated; the incidence rates of AEs related to EPS, metabolic syndrome, and serum prolactin levels were similar across treatment groups during the placebo-controlled phase[159] and remained minimal during the extension phase.[160] A relatively high completion rate (67%) was observed in the extension study.[160] Moreover, preclinical evidence suggests that ulotaront can reduce weight gain associated with common antipsychotics, such as olanzapine.[161] Further investigations on the efficacy and safety of ulotaront for the treatment of schizophrenia are ongoing (Table 1). However, recent results from the phase 3, randomized controlled, DIAMOND 1 and DIAMOND 2 trials showed no significant improvement in overall symptoms with ulotaront versus placebo in acutely psychotic adults with schizophrenia, although the high response to placebo in the 2 trials may possibly obscure a significant drug effect.[162]

PERSONALIZED TREATMENT

Schizophrenia is a highly heterogeneous disease, and significant interindividual differences likely exist in clinical characteristics and underlying pathophysiology.[90,93,163–165] Response to antipsychotic medications varies considerably across individuals with schizophrenia.[17,21,166] By tailoring the treatment to the clinical, or ideally biological, characteristics of each individual, a personalized approach could optimize the treatment response. As part of the approach, identifying biomarkers that are predictive of antipsychotic drug outcomes could markedly facilitate informed selection of treatment for individuals with schizophrenia.[167,168]

Pharmacogenetic studies have identified a number of genetic variants that are associated with antipsychotic efficacy and side effects, such as antipsychotic-induced weight gain, metabolic syndrome, risk of tardive dyskinesia, antipsychotic-related prolactin levels, and clozapine-induced agranulocytosis.[167,169,170] In particular, dose reductions for aripiprazole and clozapine are recommended by the FDA for the *CYP2D6* poor metabolizers who carry nonfunctioning variants of the cytochrome P450 2D6 enzyme to prevent potential drug-associated AEs caused by increasing drug exposure.[22,171] However, the clinical relevance of these identified genetic markers may be limited due to their small effect sizes and the need for them to be validated in large, well-designed studies.[167,169]

Electroencephalography (EEG) features have been linked to antipsychotic treatment responses[172] and can serve as a useful research tool for studying the treatment effect of an antipsychotic agent. One of the EEG-based biomarkers is MMN. In the recent phase 2a study of luvadaxistat, MMN responses to treatment aligned with the cognitive improvement produced by luvadaxistat at the same dose in the parallel, INTERACT study, suggesting the potential of MMN as a predictive biomarker for antipsychotic effects.[131] With the potential establishment of procholinergic antipsychotics for schizophrenia treatment, markers that can predict response to procholinergic vs dopaminergic agents will be useful when choosing effective treatment. Possible muscarinic deficit markers include resistance to antidopaminergic agents, visual hallucinations, severe cognitive deficits, reduced MMN, presence of antimuscarinic antibodies, and reduced M_1 receptor availability on radionucleotide imaging.[173] Additional neuroimaging, proteomic, and metabolic biomarkers have also been identified for schizophrenia.[168,174]

It is believed that biomarker testing may help stratify individuals with heterogeneous characteristics of schizophrenia into relatively more homogeneous

subgroups and aid in the selection of optimal antipsychotic treatment.[175] This may also ultimately provide a framework for a rational approach to combination treatment strategies.

CONCLUSIONS

Current antipsychotic medications are all D_2 receptor antagonists or partial agonists and are associated with suboptimal efficacy and intolerable side effects in many individuals with schizophrenia. While combinations of currently prescribed antipsychotics are commonly used to improve inadequate treatment response, evidence supporting their superior efficacy over antipsychotic monotherapies is inconclusive. It is highly likely that the etiology and pathophysiology of schizophrenia is quite heterogeneous, and thus, subsets of people with schizophrenia are likely unable to achieve optimal treatment response to the dopamine receptor–blocking agents, highlighting the need for targeting other, non-D_2 receptors. Clinical findings on investigational antipsychotic agents and innovative psychotropics that act via novel, nondopaminergic mechanisms are encouraging. If the results with these novel agents can be corroborated, they may serve as useful adjunctive or cotreatments in people with schizophrenia who do not derive sufficient benefits from current treatment strategies.

Article Information

Published Online: August 19, 2024. https://doi.org/10.4088/JCP.23nr15240

Submitted: December 29, 2023; accepted May 23, 2024.

To Cite: Kinon BJ, Leucht S, Tamminga C, et al. Rationale for adjunctive treatment targeting multiple mechanisms in schizophrenia. *J Clin Psychiatry*. 2024;85(3):23nr15240.

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Relevant Financial Relationships: Drs Kinon and **Paul** are former employees of Karuna Therapeutics. **Dr Marcus** is an employee of Bristol Myers Squibb. **Dr Leucht** has received honoraria as an advisor/consultant and/or for lectures and/or for educational material from Alkermes, Angelini, Apsen, Eisai, Gedeon Richter, Janssen, Karuna, Kynexis, Lundbeck, Medichem, Medscape, Merck Sharp and Dome, Mitsubishi, Neurotorium, Novo Nordisk, Otsuka, Recordati, Roche, Rovi, Sanofi Aventis, and Teva. **Dr Tamminga** has received honoraria as a consultant from Karuna and Kynexis and is a founding partner of Kynexis. **Dr Breier** is a consultant for Karuna, BioXcel, and Neumarker.

Funding/Support: Karuna Therapeutics, a Bristol Myers Squibb company, provided support for the medical writing assistance.

Role of the Sponsor: The Sponsor had the opportunity to review during manuscript development, but the authors had final control of the content included in the manuscript.

Acknowledgment: We thank Hui Zhang, PhD (Precise Publications); Alicia Meli, MS (Bristol Myers Squibb); and Nichole Neugebauer, PhD (Bristol Myers Squibb) for their medical writing and editorial assistance. Hui Zhang declares no conflicts of interest. Alicia Meli and Nichole Neugebauer are employees of Bristol Myers Squibb.

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