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A New Treatment Paradigm: Targeting Trace Amine-Associated Receptor 1 (TAAR1) in Schizophrenia
John M. Kane, MD

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John M. Kane, MD
Professor and Chairman, Department of Psychiatry, The Donald and Barbara Zucker School of Medicine at Hofstra/Northwell, Hempstead, New York

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Target Audience
The audience for this educational initiative is psychiatrists, advanced practice psychiatric clinicians, and other mental health professionals who care for people with schizophrenia.

Activity Description
Antipsychotics fail to control symptoms for approximately one-third of patients with schizophrenia. In addition, they frequently cause adverse effects that may cause patients to abandon treatment or experience long-term health consequences. Recently, promising clinical data have emerged for a novel class of drugs with an entirely new mechanism for treating schizophrenia: The trace amine–associated receptor 1 (TAAR1) agonists. An additional treatment option for schizophrenia could dramatically improve the prospects for patients who cannot achieve recovery with existing antipsychotics or experience safety or tolerability issues. In this supplement, John M. Kane, MD, reviews the data available for TAAR1 agonists, so that if and when they are approved for the treatment of schizophrenia, clinicians will be ready to use them to optimize patients' outcomes. Topics covered include unmet needs in schizophrenia care, the mechanism of action of TAAR1 agonists versus traditional antipsychotics, preclinical and clinical data for TAAR1 agonists, and potential uses of TAAR1 agonists if approved.

Learning Goal/Purpose

The goal of this supplement is to enhance clinicians' knowledge of unmet needs in schizophrenia care; the rationale for investigating the use of TAAR1 agonists to fill these needs; and the biologic, preclinical, and clinical data currently available on the use of TAAR1 agonists to treat schizophrenia.

Learning Objectives
On completion of this activity, the learner will be better able to:
- Identify current major areas of unmet need among patients with schizophrenia
- Describe the mechanism of action by which TAAR1 agonists con trol schizophrenia symptoms
- Evaluate clinical data on the use of TAAR1 agonists to treat schizo phrenia

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A New Treatment Paradigm

Targeting Trace Amine-Associated Receptor 1 (TAAR1) in Schizophrenia

John M. Kane, MD

Abstract: All currently available antipsychotics work via essentially the same mechanism: by antagonizing the dopamine D_2 receptor. However, schizophrenia is an extremely heterogeneous condition, and antipsychotics do not adequately control symptoms for all patients. Negative and cognitive symptoms are especially difficult to manage with existing medications. Therefore, antipsychotic agents with novel mechanisms of action are urgently needed. Recently, a phase 2 clinical trial and extension study demonstrated that, relative to placebo, the trace amine–associated receptor 1 (TAAR1) agonist ulotaront was effective at controlling the positive, negative, and cognitive symptoms of schizophrenia. In addition, ulotaront seems to lack the weight gain, metabolic issues, and extrapyramidal symptoms associated with traditional antipsychotics. This agent is currently undergoing multiple phase 3 trials for the treatment of schizophrenia. Another TAAR1 agonist, ralmitaront, is being investigated for the treatment of schizophrenia and schizoaffective disorders. Two phase 2 clinical trials are underway, evaluating ralmitaront both as a monotherapy and an add-on therapy to traditional antipsychotics. In this supplement, we review the biologic, preclinical, and clinical data available for TAAR1 agonists, so that if and when they are approved for the treatment of schizophrenia, psychiatry specialists will be ready to use them to optimize patient outcomes. We also briefly review other emerging therapies in late-stage development for the treatment of schizophrenia.

Key Words: TAAR1, TAAR1 agonist, ulotaront, ralmitaront, schizophrenia

(*J Clin Psychopharmacol* 2022;42: S1–S13)

LEARNING OBJECTIVES

On completion of this activity, the learner will be better able to:

- Identify current major areas of unmet need among patients with schizophrenia
- Describe the mechanism of action by which TAAR1 agonists control schizophrenia symptoms
- Evaluate clinical data on the use of TAAR1 agonists to treat schizophrenia

Among adults in the prime of their lives, schizophrenia is one of the top 25 causes of disease burden around the world.[1] Unfortunately, the toolkit we have to fight this disorder remains similar to the one available in the 1950s, when the first antipsychotic was discovered. Today, all antipsychotics work via essentially the same mechanism: by antagonizing the dopamine D_2 receptor. Although this mechanism is able to control the positive symptoms of schizophrenia for many patients, substantial unmet needs remain. Studies have shown that schizophrenia is an extremely heterogeneous condition in terms of symptoms,[2–4] brain structure and chemistry,[5–7] and the genetic and epigenetic variants that confer risk.[4,8,9] It is unsurprising that a single class of medications is not effective for all patients and all symptoms.

In fact, antipsychotics fail to control symptoms for approximately one third of patients with schizophrenia.[10] In addition, they frequently cause adverse effects that may result in patients abandoning treatment.[11] In one trial of nearly 1500 patients with schizophrenia randomized to take various antipsychotics, nearly 75% discontinued the medication that they had been assigned within 18 months because of lack of effectiveness, intolerable adverse effects, or other reasons.[12] In the context of this trial, they were offered another antipsychotic; however, in real life, many patients simply stop taking their medication.

Our inability to effectively manage schizophrenia for so many patients has consequences for them, their families, the health care system, and society. Only approximately 14% to 50% of patients with schizophrenia achieve recovery, depending on the definition used.[13] Recovery depends on many factors, of which effective medication is just one.[14] However, effective medication is an essential tool in controlling the symptoms of this debilitating disorder.

Because of the limitations of our current care options, the life expectancy of patients living with schizophrenia in North America is approximately 14 years shorter than that of the general population.[15] One contributor to this much shorter life expectancy is the rate of suicide among patients with schizophrenia, which is 4.5 times the US population average; among patients 18 to 34 years of age, it is a stunning 10 times the population average.[16] At a broader level, in 2020, the economic burden of schizophrenia in the United States was estimated to be $281.6 billion annually, reflecting both direct costs (eg, health care, supportive housing, the criminal justice system) and indirect costs (eg, nonemployment, caregiver burden, and caregiver unpaid wages).[17] Clearly, new medications are urgently needed.

Recently, promising clinical data have emerged for a novel class of drugs with an entirely new mechanism for treating schizophrenia: the trace amine–associated receptor 1 (TAAR1) agonists. An additional treatment option for schizophrenia could dramatically improve the prospects of patients who cannot achieve recovery with existing antipsychotics. However, clinicians who care for patients with schizophrenia may be skeptical of potential new treatments, for good reason. Promising preclinical data have raised the field's hopes about new agents many times, only for the results of late-stage clinical trials to dash them. Examples of past disappointments are varied, including a glutamate receptor agonist,[18] an α-7 nicotinic receptor agonist,[19] a phosphodiesterase 10A inhibitor,[20] and a glycine reuptake inhibitor.[21]

Given the strong performance of the TAAR1 agonist ulotaront in a recent phase 2 clinical trial,[22–24] as well as the existence of ralmitaront, another TAAR1 agonist being investigated in clinical trials, there is good reason to believe that these novel agents may hold greater promise than previous approaches. Here, we review the biologic, preclinical, and clinical data available for TAAR1 agonists, so that if and when they are approved for the treatment of schizophrenia, psychiatry specialists will be ready

From the Department of Psychiatry, The Donald and Barbara Zucker School of Medicine at Hofstra/Northwell, Hempstead, New York.

Address correspondence to: John M. Kane, MD, Professor and Chairman Department of Psychiatry, The Donald and Barbara Zucker School of Medicine at Hofstra/Northwell, Hempstead, New York (e-mail: Kane2@northwell.edu).

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to use them to optimize patient outcomes. We also briefly review other emerging therapies in late-stage development for the treatment of schizophrenia.

UNMET NEEDS IN SCHIZOPHRENIA: LIMITATIONS OF CURRENT ANTIPSYCHOTIC MEDICATIONS

The first antipsychotic, chlorpromazine, was introduced in 1952.[25] Although antipsychotics revolutionized the treatment of schizophrenia, the limitations of this class of medications were evident as early as the 1960s.[25] Schizophrenia is a multifaceted disorder that consists of positive, negative, and cognitive symptoms (Fig. 1).[26,27] Whereas the intensity of positive symptoms tends to come and go over a patient's life course, negative and cognitive symptoms tend to be ever present (Fig. 2).[26,28] Recovery from schizophrenia necessitates control of all 3 types of symptoms. However, available antipsychotics tend to control only positive symptoms.[25]

Positive Symptoms

Positive schizophrenia symptoms can be considered an excess or distortion of normal functions.[26] Examples include delusions, hallucinations, and disorganized behavior. Although antipsychotics offer substantial relief from positive symptoms for many patients with schizophrenia, up to one third of individuals exhibit treatment resistance, typically defined as the persistence of symptoms despite 2 or more trials of antipsychotics of adequate dose and duration, with documented adherence.[10,29]

Multiple hypotheses have been proposed to explain why some individuals experience treatment resistance.[10,30] One hypothesis is that these patients develop dopamine supersensitivity, caused by the upregulation of dopamine receptors, from past antipsychotic treatment. This supersensitivity would prevent the dopamine receptor blockade by which antipsychotics work. Another hypothesis is that patients with treatment-resistant schizophrenia have normal dopaminergic function, and alterations in other neurotransmitter systems—such as the glutamatergic system—are responsible for their disorder. The dopamine-focused mechanism of action of antipsychotics would not help control symptoms in these patients. Such hypotheses are not mutually exclusive; treatment resistance may be caused by different mechanisms in different patients.[10,30]

Currently, clozapine is the only evidence-based therapy for treatment-resistant schizophrenia that is approved by the Food and Drug Administration (FDA). Despite its well-established efficacy for managing positive symptoms in treatment-resistant schizophrenia,[30] as well as improving quality of life and functioning,[31] its association with cardiometabolic, hematologic, and other adverse effects limits its use.[25,32] Although research suggests that clozapine can be used safely when dietary, clinical, and therapeutic monitoring is in place,[33] it can be challenging for clinicians to provide such monitoring in everyday practice.[34] Many healthcare providers also remain wary of using this agent because of the risk of severe adverse effects.[34,35] Finally, some patients with treatment-resistant schizophrenia fail to respond to clozapine, or are unwilling to take it.[30] As a result, clozapine is underused, although many patients have a favorable experience taking it.[36–38] For these reasons, agents with attractive safety profiles that could be used to treat patients who do not respond to existing antipsychotics would represent a major advance for the field.

In addition to failing to control positive symptoms in patients with treatment-resistant schizophrenia, available antipsychotics fail to prevent relapse for a sizable proportion of patients. One study found that 1 in 5 patients with first-episode schizophrenia who initially responded well to antipsychotic treatment experienced breakthrough psychotic symptoms over a 2-year period, even when a long-acting injectable (LAI) antipsychotic was used to ensure adherence.[39] Although the breakthrough symptoms tended to be less severe than first-episode symptoms, the patients' treatment response was poorer. Similarly, a meta-analysis of 19 LAI trials found that 1 of 5 patients relapsed over a period of roughly 9 months.[40] Among patients who did not initially achieve symptom remission while taking their LAI, this figure was 1 in 3. Because every relapse makes remission harder to achieve,[41] failure to prevent relapse has serious ramifications for a patient's life-long disease trajectory.

To treat patients experiencing treatment-resistant schizophrenia or breakthrough symptoms, clinicians may try increasing the dose of their antipsychotic or augmenting it with another antipsychotic.[30] Unfortunately, although increasing the dose of an antipsychotic may improve its effectiveness, it also makes a patient more likely to experience a range of adverse effects, including weight gain, parkinsonism, hyperprolactinemia, and neurocognitive impairment.[42] Similarly, with regard to treatment-resistant schizophrenia, there is little evidence that 2 antipsychotics are more beneficial than one antipsychotic, and adding another antipsychotic to a patient's treatment plan increases the chance they will experience adverse effects.[30,41] Clearly, the limited tools available hamper clinicians' ability to manage patients' positive symptoms.

Negative Symptoms

Negative schizophrenia symptoms involve a reduction in or absence of normal behaviors related to motivation, interest, and expression.[26] Examples include avolition, anhedonia, asociality, blunted affect, and alogia. Negative symptoms are not typically

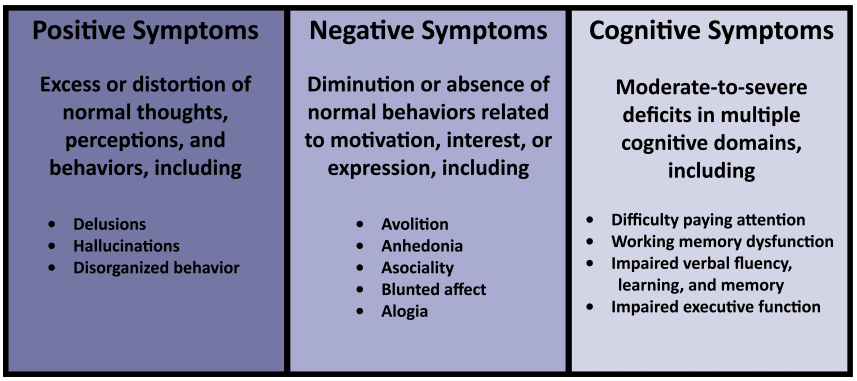

FIGURE 1. Patients with schizophrenia experience 3 core types of symptoms: positive, negative, and cognitive. However, currently available antipsychotics primarily control positive symptoms. Adapted from Correll and Schooler[26] (2020) and Bowie and Harvey[27] (2006).

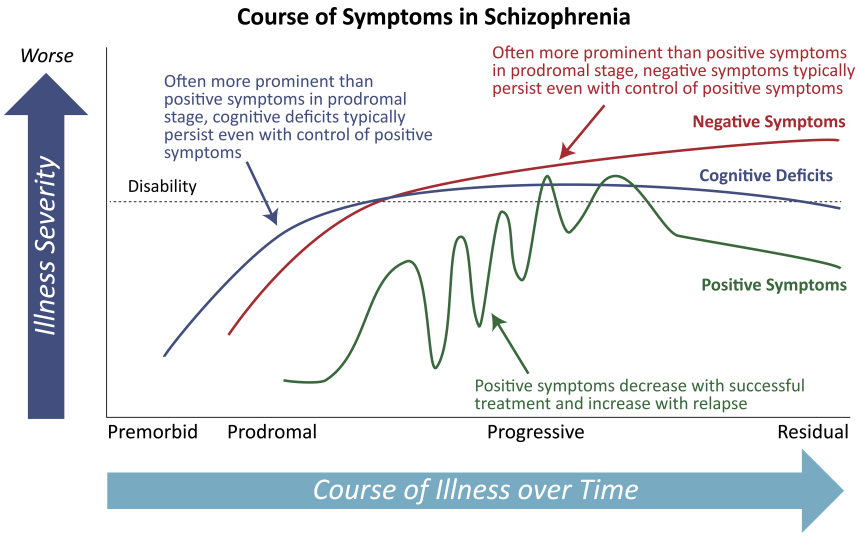

FIGURE 2. Schematic of different types of symptoms over the life course of a typical patient with schizophrenia. Adapted from Correll and Schooler[26] (2020) and Millan et al[28] (2014).

the reason that patients with schizophrenia receive clinical care, and patients often lack insight into their negative symptoms.[26] As a result, it is easy for clinicians to give patients' negative symptoms less attention than their positive symptoms. However, negative symptoms are extremely common and have an outsized impact on patients' lives.

Among patients experiencing a first psychotic episode, 90% experience at least 1 negative symptom.[26] Negative symptoms severe enough to require treatment occur in up to 60% of patients with schizophrenia.[26] Research shows that negative symptoms are a better predictor of quality of life and functional outcomes than are positive symptoms.[43]

As mentioned previously, negative symptoms do not respond well to currently available antipsychotics.[26] In some cases, clinicians try to address negative symptoms by prescribing antidepressants in addition to antipsychotics. However, the evidence supporting this practice is lacking, and adding another medication makes a patient's regimen more complex—and potentially problematic.[41] Therapies that address schizophrenia's negative symptoms are sorely needed.

Cognitive Impairment

Cognitive symptoms of schizophrenia include impaired attention, working memory, verbal fluency, and executive functioning.[27] Like negative symptoms, cognitive symptoms are extremely common in schizophrenia, occurring in roughly 80% of patients.[44] They too are a better predictor of functional outcomes than positive symptoms.[45] In fact, neurocognitive ability has been found to be the best predictor of everyday life skills among patients with schizophrenia.[46] Because currently available antipsychotics fail to meaningfully address the cognitive impairment present in schizophrenia, it remains difficult for patients to achieve recovery.

Adverse Effects

The adverse effects associated with antipsychotics are well known and include weight gain, prolactin elevation, and extrapyramidal symptoms (EPS), among others. Many of these adverse effects are associated with excessive D_2 receptor occupancy, so they are directly related to available antipsychotics' mechanisms of action.[47] In

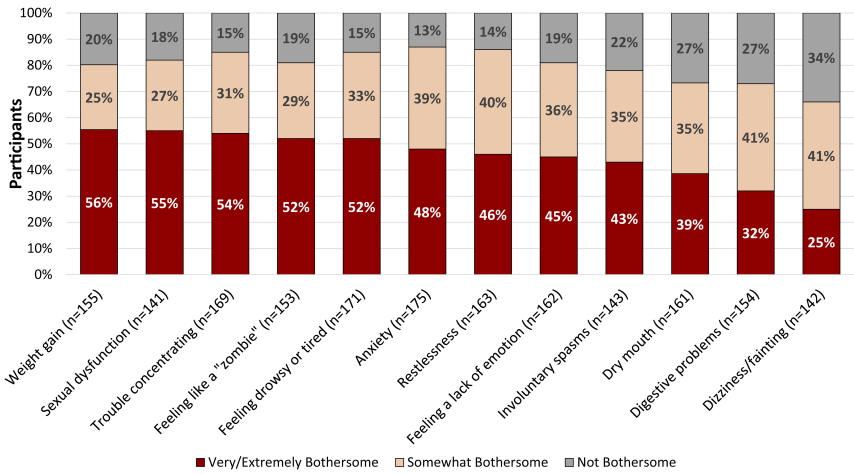

FIGURE 3. Bothersomeness of the adverse effects of antipsychotics, as rated in a survey of 200 patients with schizophrenia.[11] *Patient Preference and Adherence* 2020;14:2043–2054. Originally published by and used with permission from Dove Medical Press Ltd.

a recent survey of 200 individuals with schizophrenia who were taking antipsychotics, the adverse effects considered most bothersome were weight gain, sexual dysfunction, and trouble concentrating (Fig. 3).[11] Although 92% of patients surveyed said that antipsychotics improved their symptoms, more than one quarter (27%) reported that antipsychotics did more harm than good.

Given the prevalence of adverse effects, it is not surprising that many patients stop taking their antipsychotics (Fig. 4).[41] In the survey mentioned previously, of the 56% of respondents who reported stopping their medication at some point, 65% reported doing so because of adverse effects.[11] The adverse effects that most often led to treatment discontinuation were also among those most frequently rated "extremely bothersome": feeling like a zombie, feeling drowsy/tired, and weight gain. The single biggest risk factor for relapse in schizophrenia is medication nonadherence, and with every successive relapse, remission becomes harder to achieve.[41] The adverse effect profile of current antipsychotics is a major contributor to both treatment discontinuation and failure to achieve remission.

Even among patients who are able to take their antipsychotics consistently, concerns about serious adverse effects such as tardive dyskinesia and cardiometabolic disease remain. Indeed, cardiovascular disorder and diabetes are among the leading causes of morbidity and mortality in individuals with schizophrenia[48,49] and are major drivers of the lifetime costs associated with the disorder.[50]

In individuals with schizophrenia, long-term treatment with antipsychotics is associated with lower overall mortality rates than no long-term treatment,[14] even from cardiovascular disease.[51] This may be because individuals with schizophrenia experience a higher risk of cardiovascular mortality independent of antipsychotic use,[52] and antipsychotics improve their ability to manage comorbidities. Comorbidities are quite common; for example, in a study of 404 patients with first-episode psychosis, 57% had dyslipidemia, 15% had prediabetes, 13% had metabolic syndrome, 10% had high blood pressure, 3% had diabetes, and many were overweight and smoked.[41] By stabilizing patients' schizophrenia symptoms with medication, clinicians can help lay the foundation for treatment of their other chronic health conditions. However, schizophrenia therapies with a more favorable cardiometabolic profile would further improve patients' health.

Currently, clinicians are limited in their ability to satisfactorily manage antipsychotics' adverse effects. One obvious response to an adverse effect is to reduce the dose of a patient's antipsychotic, especially once their symptoms have been stabilized. However, a recent meta-analysis showed that reducing the dose below the standard range recommended for acute stabilization is associated with an increased risk of relapse and medication discontinuation.[53] Relative to a standard dose, a low dose (50%–99% of the standard dose) increases the risk of relapse by 44%, and a very low dose (<50% of the standard dose) increases the risk by 72%. Moreover, in this study, adverse effect outcomes—including intolerability-related discontinuations—differed little among the dose groups. Thus, dose reductions below the standard range do not seem to be a safe or effective way to respond to adverse effects.

Older adults (those 65 years and older) seem to be especially vulnerable to elevated mortality rates and cardiopulmonary arrest when taking antipsychotics.[54] As the proportion of older adults in the United States and many other countries rises over time,[55] the toll that antipsychotics take on cardiopulmonary health will increase at the population level. This makes the search for new, safer schizophrenia therapies urgent.

Recovery

The criteria for functional recovery from schizophrenia typically include symptom remission, vocational function, independent living, and meaningful peer relationships for more than 2 years.[41] The adverse effect profiles and limited effectiveness of current antipsychotics have contributed to the relatively low percentage of patients who achieve recovery. Long-term treatment for schizophrenia is characterized by recurrent cycles in which antipsychotics are interrupted and then reintroduced, which is not conducive to recovery.[56] Patients and clinicians report that the top 2 reasons for discontinuing antipsychotics are lack of effectiveness and adverse effects.[57] Even in Finland, where issues of insurance coverage and treatment access are less problematic than in the United States, participants in a national cohort study experienced a median of 6 treatment interruptions during 8 years of follow-up.[56] More effective, tolerable, and safe treatment options could help increase the proportion of patients with schizophrenia who are able to achieve recovery.

THE NEW BIOLOGY OF TAAR1 AGONISTS: EMERGING AGENTS FOR THE TREATMENT OF SCHIZOPHRENIA

Schizophrenia is a multifaceted disorder that affects multiple interconnected brain pathways, including the dopaminergic, glutamatergic, and serotoninergic systems.[58] Despite the nuanced neurobiology underlying schizophrenia, as well as the wide spectrum of symptoms, available antipsychotics work almost exclusively by antagonizing D_2 receptors, which results in dopamine blockade.[59] Many atypical antipsychotics also possess serotonin 5-hydroxytryptamine 2A receptor (5-HT_{2A}) activity.[59]

The limited effectiveness of current antipsychotics suggests that some cases of schizophrenia are caused by dysfunction outside the D_2 dopaminergic system.[60] It is notable that some patients with treatment-resistant schizophrenia respond to clozapine, which is unique among typical antipsychotics for its affinity for the D_4 dopamine receptor, as well as its action at serotonergic, noradrenergic, and glutamatergic receptors.[61,62] Given the inability of currently available antipsychotics to control symptoms for many patients with schizophrenia, agents with entirely novel mechanisms of action are likely required, especially to control negative and cognitive symptoms.

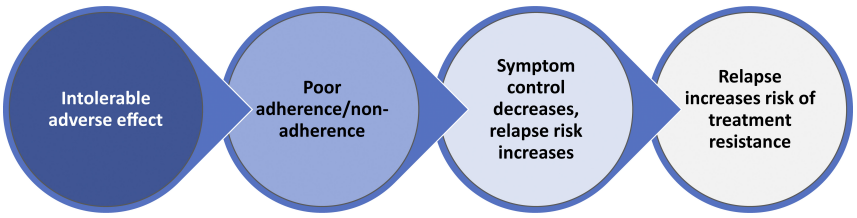

FIGURE 4. Risks associated with the adverse events caused by antipsychotics. Adapted from Harvey and Kane[41] (2021).

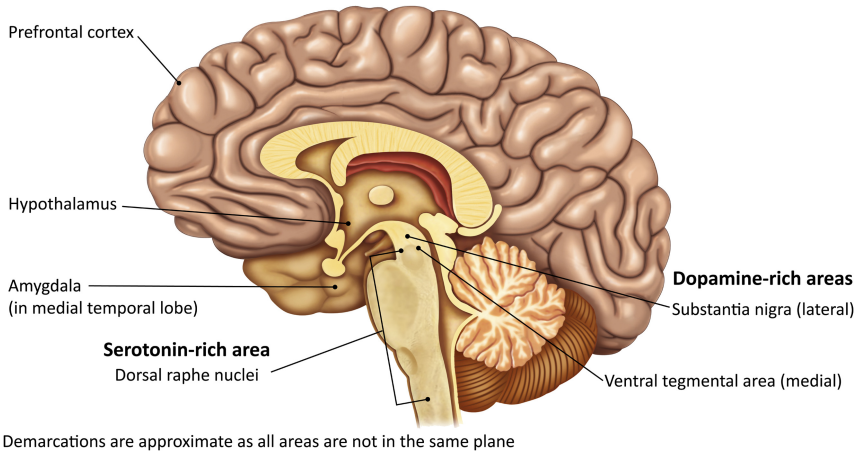

FIGURE 5. Key regions of TAAR1 expression in the brain that are associated with schizophrenia pathophysiology. Trace amine–associated receptor 1 is found in dopamine-rich regions, such as the ventral tegmental area and substantia nigra, and serotonin-rich regions, such as the dorsal raphe nucleus. Adapted from Nair et al[63] (2022).

Trace amine–associated receptor 1 agonists have emerged as a novel class of potential schizophrenia therapies. Trace amine–associated receptor 1 is a G-protein–coupled receptor expressed in various dopamine-rich regions of the brain that are associated with schizophrenia (Fig. 5.)[63,64] Initial evidence suggests both intracellular and membrane localization for TAAR1.[64] Preclinical data show that TAAR1 affects central nervous system function and behavior, possibly through its influence on the monoamine system, which encompasses dopamine, noradrenaline, and serotonin signaling; it also has effects on the glutamatergic system.[64] Trace amine–associated receptor 1 seems to act as an internal rheostat, maintaining neurotransmission within healthy physiologic limits.[65] Specifically, it is believed to function in regulating reward circuits, cognitive processes, mood states, glucose levels, and body weight,[65] all of which are disrupted in schizophrenia.

The rationale for investigating TAAR1 agonists as schizophrenia therapies is supported by several lines of evidence. First, by activating TAAR1, TAAR1 agonists seem to modulate the signaling of multiple neurotransmitter systems, including the dopaminergic, serotonergic, and glutamatergic systems, that are dysregulated in schizophrenia.[59,64,66] Second, genetic variants in the *TAAR* genes, including *TAAR1*, have been linked to schizophrenia.[67] This suggests that targeting TAAR1 could modify the symptoms of schizophrenia. Finally, agents that do not block postsynaptic D_2 receptors are unlikely to contribute to the development of important adverse effects associated with current antipsychotics, such as hyperprolactinemia and EPS.[68]

Although TAAR1 agonists do not directly antagonize D_2 receptors, as current antipsychotics do, they do act at multiple points in the dopaminergic signaling system. Preclinical research shows

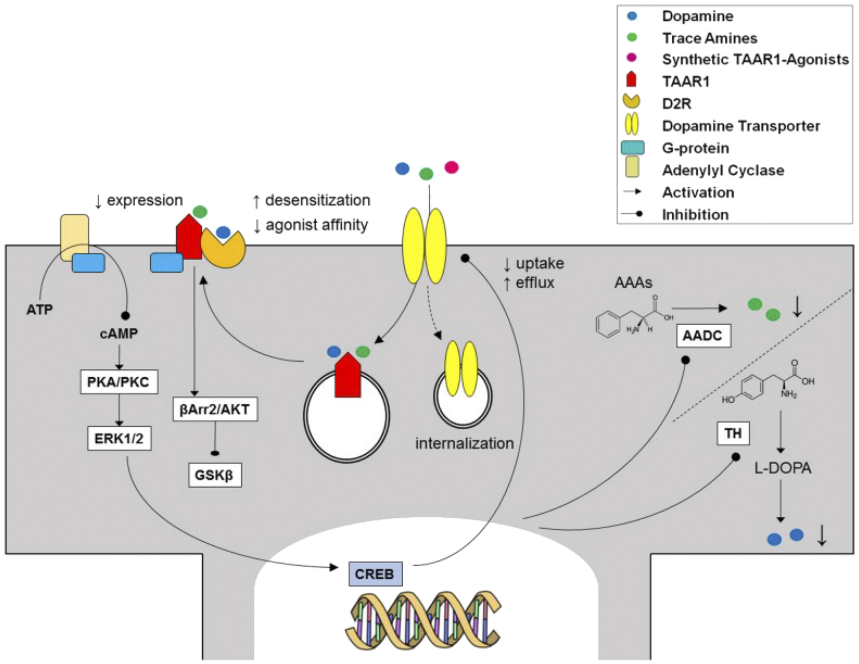

FIGURE 6. Effects of TAAR1 on the dopaminergic system. Figure reprinted from Rutigliano et al[64] (2018, CC-BY 4.0).

that when bound by an agonist, TAAR1 forms heterodimers with D_2 dopamine receptors on presynaptic and postsynaptic neurons, altering the way that these receptors function (Fig. 6).[64,69,70] Dopamine efflux then occurs through the D_2 receptors, reducing dopamine levels within presynaptic neurons.[71] Simultaneously, dopamine transporters are internalized, decreasing dopamine uptake and the rate at which dopaminergic neurons fire.[64,69,71] This action of TAAR1 agonists at the presynaptic level represents a novel approach to managing schizophrenia, given that current antipsychotics function primarily at the postsynaptic level by blocking dopamine receptors from binding dopamine released into the synaptic cleft.

Trace amine–associated receptor 1 agonists do more than alter dopamine release by presynaptic neurons. They also decrease postsynaptic dopamine activity via the β-arrestin-2–dependent Akt/glycogen synthase kinase-3 pathway (Fig. 6).[69] This pathway governs dopamine-mediated behaviors and is implicated in schizophrenia.[69] Furthermore, TAAR1 agonists reduce the firing of serotonergic neurons and increase transmission through glutamatergic neurons[66]—all potentially important processes for controlling schizophrenia symptoms.

Ulotaront (SEP-363856)

Ulotaront is a TAAR1 agonist with serotonin 5-HT_{1A} agonist activity, and it is the first TAAR1 agonist to enter phase 3 trials. As such, it has been granted breakthrough therapy designation by the FDA.[72]

Pharmacology

Ulotaront was discovered during a screen for agents that lacked D_2 or serotonin 5-HT_{2A} antagonist activity while demonstrating an antipsychotic-like profile in vivo.[59] Specifically, researchers used SmartCube, an artificial intelligence–based phenotypic discovery platform, to identify ulotaront.[59,73] In the SmartCube system, after an agent is administered to a mouse, supervised machine learning algorithms assess the animal's phenotype, including locomotion, trajectory complexity, body posture and shape, and behaviors. On the basis of this automated assessment, the agent being studied is assigned a label, such as antipsychotic or antidepressant, based on the similarity of its profile to that of known drugs. This high-throughput approach allows investigators to efficiently screen large compound libraries.

In this case, screening a compound library with the SmartCube system showed a dose-dependent relationship between ulotaront treatment and antipsychotic activity in mice (Fig. 7).[59] Ulotaront also showed modest antidepressant properties. Next, receptor panel screening and functional tests showed that this agent is a TAAR1 and serotonin 5-HT_{1A} agonist. Subsequent experiments in mice, rats, and monkeys demonstrated that orally administered ulotaront has good systemic bioavailability and high brain penetrance. Finally, follow-up experiments in mice showed that ulotaront exhibits antipsychotic- and antidepressant-like activity without inducing catalepsy, indicating low potential for causing EPS in humans. These preclinical findings set the stage for studies in humans.

Clinical Trial Data

Findings from a 4-week phase 2 randomized trial comparing ulotaront to placebo in acutely ill patients with schizophrenia have been reported,[22] as well as the results of a 26-week open-label extension of this trial.[23] A total of 193 patients completed the 4-week trial, of whom 157 continued in the extension study.[23] Figure 8 shows how these studies were designed.[22,23]

With regard to efficacy, ulotaront was found to have a medium effect size (0.45, $P = 0.001$) on the Positive and Negative Syndrome

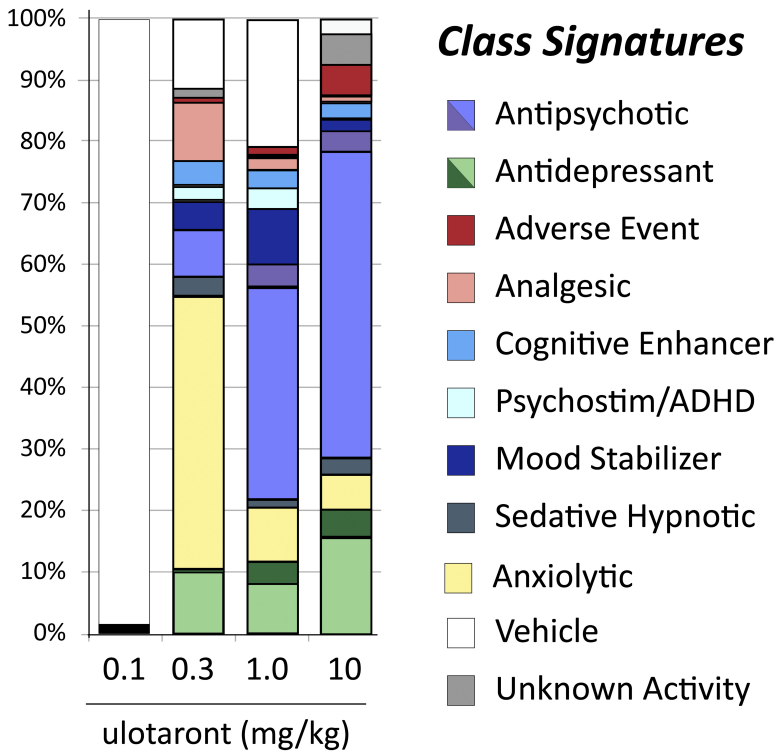

FIGURE 7. Screening a compound library in mice revealed that ulotaront exhibits dose-dependent antipsychotic properties, as well as antidepressant activity, despite lacking D_2 and serotonin 5-HT_{2A} antagonist activity. ADHD, attention-deficit/hyperactivity disorder. Adapted from Dedic et al [59] (2019) with permission from American Society for Pharmacology and Experimental Therapeutics.

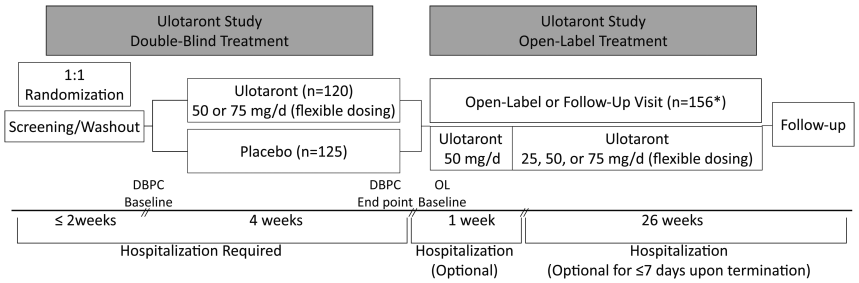

FIGURE 8. Study design for the 4-week phase 2 trial comparing ulotaront to placebo in acutely ill patients with schizophrenia, as well as its 26-week extension study. Adapted from Koblan et al[22] (2020) and Correll et al[23] (2021).

Scale (PANSS), with improvement seen for both positive and negative symptoms (Table 1).[22] Further improvement in symptoms was documented in the extension study, as measured by both PANSS score and Clinical Global Impressions Scale–severity, including for cognitive symptoms (Fig. 9).[23,24] The extension study also confirmed the effect of ulotaront on negative symptoms: significant improvements from baseline were noted using the PANSS negative subscale, Brief Negative Symptom Scale (BNSS) total score, and uncorrelated PANSS score matrix Negative Apathy/Avolition Factor and Negative-Deficit of Expression Factor scores.[23]

With regard to safety, the incidence of adverse events in the 4-week trial was roughly the same for the ulotaront and placebo groups.[22] The most common adverse events associated with ulotaront were somnolence, agitation, nausea, diarrhea, and dyspepsia. In both the 4-week trial and 26-week extension study, no significant changes in metabolic laboratory parameters or prolactin levels were found in participants taking ulotaront.[22,23] Whereas modest weight gain was documented in the ulotaront group in the 4-week trial, modest weight loss (-0.3 kg) was observed in the extension study. The incidence of EPS in the 4-week trial was similar between the ulotaront and placebo groups (3.3% and 3.2%, respectively),[22] and it remained low (3.2%) in the extension study.[23] Finally, prolactin levels decreased slightly in both the ulotaront and placebo groups in the 4-week trial, for both men and women,[22] and only 4 cases of increased prolactin (an incidence of 2.6%) were documented in the extension study.[23]

These safety data are compelling. In a comparison of randomized controlled trials, the cumulative rate of adverse events was substantially lower for ulotaront than for available antipsychotics: 23% for ulotaront versus 42% to 60% for lurasidone, quetiapine, and olanzapine.[74] To further compare the safety profiles of these agents, researchers analyzed real-world data from the US FDA Adverse Event Reporting System to identify which types of class-related adverse events are disproportionately associated with 30 atypical and typical antipsychotics. They then used clinical trial data for ulotaront and the 3 comparison atypical antipsychotics to plot the proportion of participants who experienced each type of adverse event disproportionately associated with antipsychotics. For many key adverse events associated with antipsychotics, including weight gain, diabetes, elevated fasting glucose, extrapyramidal disorder, and tardive dyskinesia, ulotaront had a superior profile (Fig. 10).[74]

Ulotaront is currently being investigated in the DIAMOND program, a collection of 4 clinical studies conducted in patients with schizophrenia. This program consists of a 6-week phase 3 placebo-controlled trial of ulotaront in adult patients with acute psychosis (NCT04092686),[75] a 6-week phase 3 placebo-controlled trial of ulotaront in adult and adolescent patients with acute psychosis (NCT04072354),[76] an open-label extension study for participants in

TABLE 1. Efficacy of Ulotaront vs Placebo* in a 4-Week, Phase 2 Randomized Trial Conducted in Acutely Ill Patients with Schizophrenia[22]

Efficacy Measure	Least-Square Mean Change From Baseline at Week 4		Least-Square Mean Difference (95% CI)
	Ulotaront 50 or 75 mg	Placebo	
Primary end point			
PANSS total score	−17.2 ± 1.7	−9.7 ± 1.6	−7.5 (−11.9 to −3.0)
Secondary end points†			
CGI-S score	−1.0 ± 0.1	−0.5 ± 0.1	−0.05 (−0.7 to −0.2)
PANSS positive subscale score	−5.5 ± 0.5	−3.9 ± 0.5	−1.7 (−3.1 to −0.3)
PANSS negative subscale score	−3.1 ± 0.4	−1.6 ± 0.4	−1.5 (2.6 to −0.4)
PANSS general psychopathology subscale score	−9.0 ± 0.9	−4.7 ± 0.8	−4.3 (−6.6 to −2.0)
BNSS total score	−7.1 ± 1.0	−2.7 ± 0.9	−4.3 (−6.8 to −1.8)
MADRS total score	−3.3 ± 0.6	−1.6 ± 0.6	−1.8 (−3.2 to −0.3)

Adapted from *New England Journal of Medicine* 2020;382(16):1497–1506. Originally published by and used with permission from the Massachusetts Medical Society.

*Mean change from baseline ± standard error.

†No inferences can be made for the secondary end points because the study did not include a plan to control for multiple comparisons.

CGI-S, Clinical Global Impressions Scale-Severity; MADRS, Montgomery-Åsberg Depression Rating Scale.

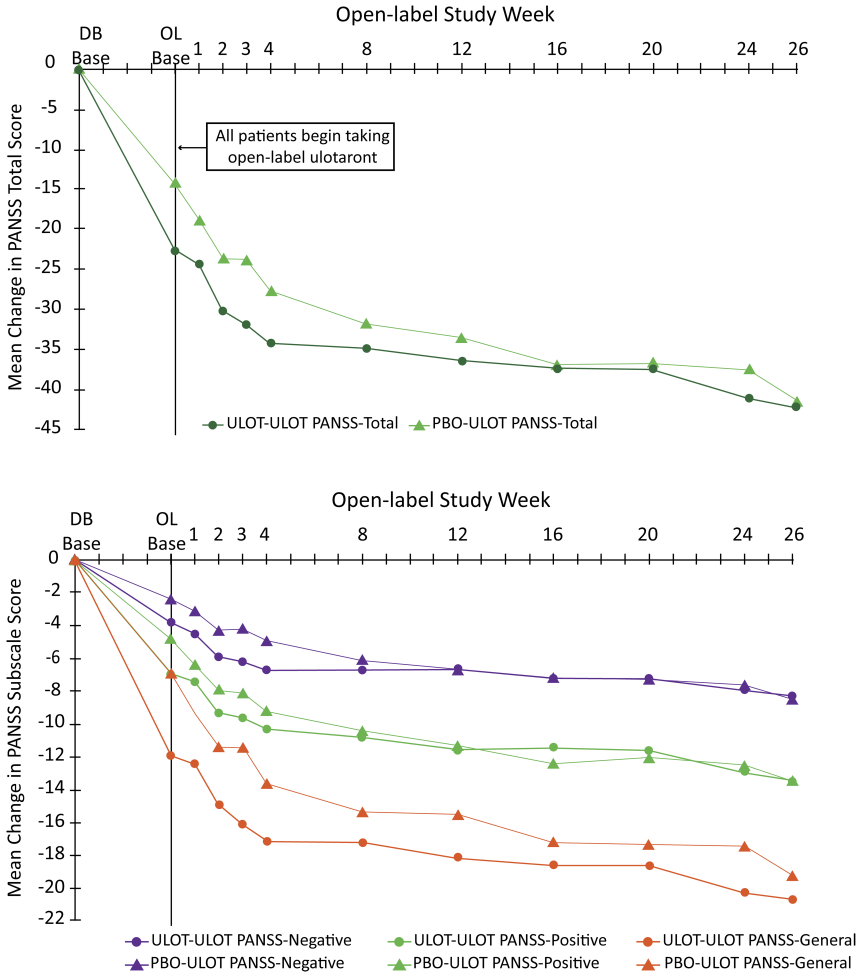

FIGURE 9. Mean change in positive and negative schizophrenia symptoms during 4 weeks of double-blind treatment with ulotaront or placebo (left portion of plots) and 26 weeks of open-label treatment with ulotaront (right portion). A, Change in PANSS total score. B, Change in PANSS subscale scores: negative, positive, and general. DB, double blind; OL, open label; PBO, placebo; ULOT, ulotaront. Adapted from Correll et al[23] (2021, CC-BY 4.0).

either 6-week trial, and a 57-week phase 3 trial comparing ulotaront to quetiapine in adults with schizophrenia (NCT04115319).[77] In addition, phase 1 trials are investigating ulotaront treatment in conjunction with an antipsychotic (NCT04038957)[78] and the effect of ulotaront on metformin transit in the body of patients with schizophrenia (NCT04865835).[79]

Ralmitaront (RO6889450)

Ralmitaront is a TAAR1 partial agonist being investigated as a potential treatment for schizophrenia and schizoaffective disorder.[70] It is currently being studied in 2 phase 2 clinical trials.

The first trial is comparing ralmitaront to placebo in patients with stable schizophrenia or schizoaffective disorder who have negative symptoms, and its primary outcome is change from baseline on the BNSS Avolition/Apathy subscore at 12 weeks (NCT03669640).[80] It also includes an arm studying ralmitaront as an add-on therapy to a patient's current antipsychotic. This trial's estimated completion date is in May 2023 (Fig. 11).[80]

The second trial is comparing ralmitaront to risperidone and placebo in patients with schizophrenia or schizoaffective disorder who are experiencing an acute exacerbation of symptoms (NCT04512066).[81] Its primary outcome is the change from baseline on the PANSS total score at week 4, and its estimated completion date is in April 2023 (Fig. 12).[81]

Potential Place of TAAR1 Agonists in Clinical Practice

Because TAAR1 agonists are only now being characterized, it remains to be seen how they might eventually be used in clinical practice. However, available data suggest that they may represent a valuable alternative to traditional antipsychotics in treating schizophrenia because they seem to target negative and cognitive symptoms as well as positive symptoms.[22–24] Because negative and cognitive symptoms are such important predictors of patients' quality of life and ability to function,[43,46] agents that can help ameliorate these symptoms could help many individuals with schizophrenia achieve recovery. In addition, because ulotaront affects 5-HT_{1A} receptors, it may have beneficial effects on mood and anxiety.[82]

Trace amine–associated receptor 1 agonists may also offer relief to patients experiencing tolerability or safety issues when taking antipsychotics. The low incidence of EPS and the lack of significant changes in weight or lipid profiles in the phase 2 ulotaront clinical trial[22,23] bolster the long-held hope that schizophrenia drugs with novel mechanisms of action would lack the adverse effect profile of antipsychotics. Researchers also hypothesize

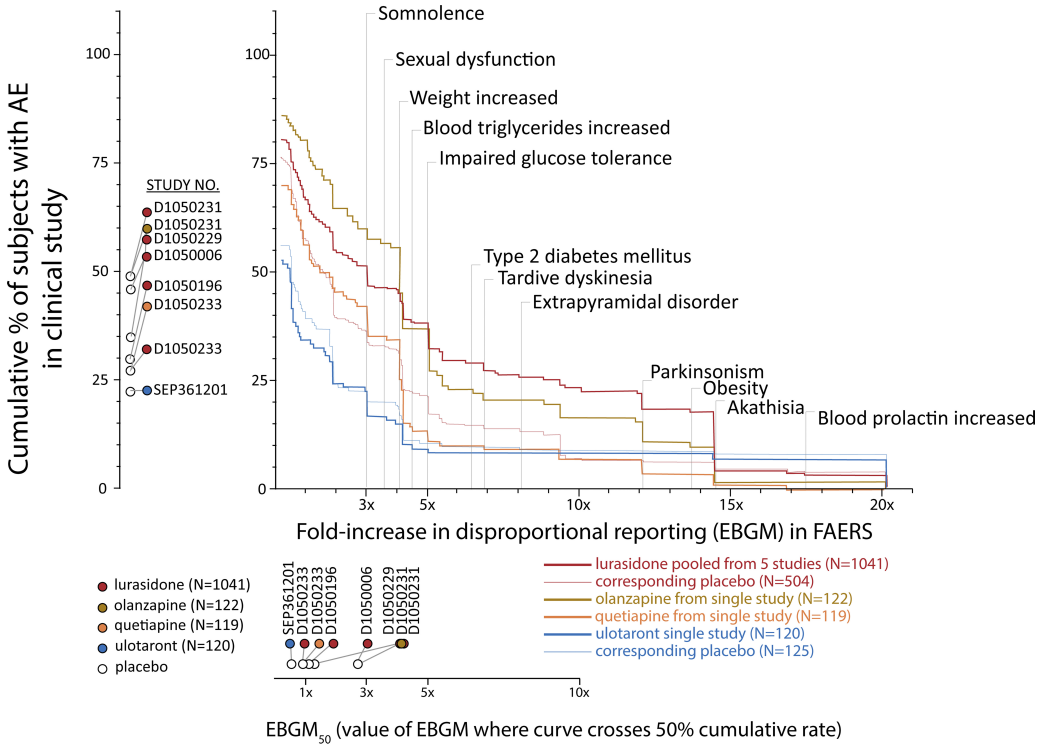

FIGURE 10. Comparison of adverse event frequency in clinical trials of ulotaront and 3 atypical antipsychotics. Cumulative percentage of individuals with schizophrenia who experienced an adverse event (y-axis) is shown in relation to disproportional reporting of that adverse event in postmarketing pharmacovigilance data reported via the US FDA Adverse Event Reporting System. Preferred terms were ranked by disproportionality analysis using the Empirical Bayes Geometric Mean (EBGM). The insets show the cumulative percentage of individuals with adverse events of 3-fold or greater disproportional reporting (left) and the $EGBM_{50}$ for individual studies (below). Adapted from Hopkins et al[74] (2021, CC-NC 4.0).

that TAAR1 agonism could be a novel strategy for managing type 2 diabetes, thanks to TAAR1's role in modulating energy metabolism and nutrient intake.[65] Trace amine–associated receptor 1 is expressed on the insulin-producing β cells of the pancreas and in the stomach and intestines.[63] Future research should clarify whether TAAR1 agonists have benefits for managing type 2 diabetes, over and beyond preventing the unfavorable weight and lipid changes associated with antipsychotics.

Finally, because TAAR1 agonists work via a novel mechanism, it is possible that they may control symptoms in patients with treatment-resistant schizophrenia. As described previously, some cases of treatment resistance may be caused by dopamine supersensitivity due to prior antipsychotic use.[10,30] Because TAAR1 agonists do not directly engage dopamine D_2 receptors, they are predicted to be less likely to cause dopamine supersensitivity.[63] Trace amine–associated receptor 1 agonists also modulate

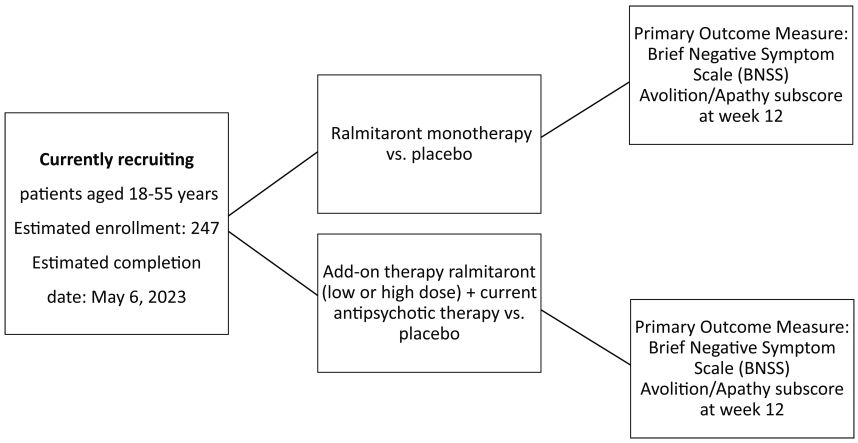

FIGURE 11. Study design for a 12-week phase 2 trial comparing ralmitaront to placebo in stable patients with schizophrenia or schizoaffective disorder (NCT03669640). Created based on information from ClinicalTrials.gov.[80]

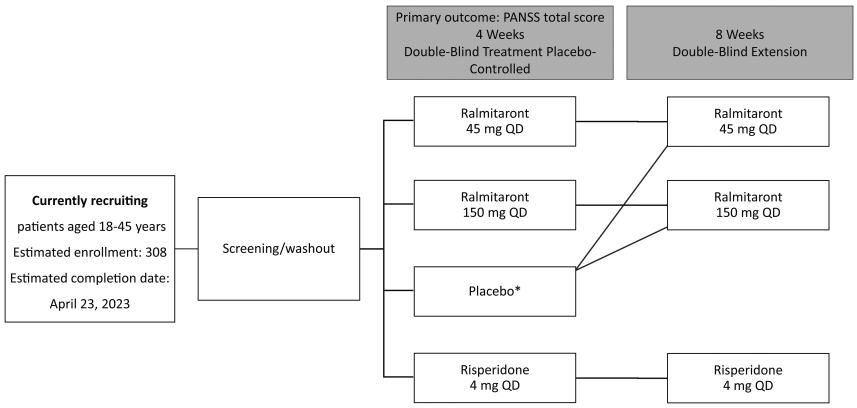

FIGURE 12. Study design for 4-week phase 2 trial comparing ralmitaront to placebo and risperidone in acutely ill patients with schizophrenia or schizoaffective disorder, as well as its 8-week extension study (NCT04512066).[81] Created based on information from ClinicalTrials.gov.

signaling of the serotonergic and glutamatergic systems,[59,66] so they may work in patients whose schizophrenia is caused by alterations outside the dopaminergic system.

ADDITIONAL EMERGING THERAPIES FOR THE TREATMENT OF SCHIZOPHRENIA

In addition to TAAR1 agonists, several other types of agents with novel mechanisms of action are being investigated for the treatment of schizophrenia. Here, we provide a brief overview of each class of emerging therapies.

Muscarinic Receptors

A variety of evidence suggests that the muscarinic cholinergic system is involved in schizophrenia.[83] Currently, a combination therapy called KarXT that targets the muscarinic system is being investigated as a schizophrenia treatment. One agent in the combination, xanomeline, is a muscarinic receptor agonist, and the other agent, trospium, is a muscarinic receptor antagonist that reduces the unwanted peripheral cholinergic effects of xanomeline.[84] A recent 5-week phase 2 trial among patients with schizophrenia showed that this combination significantly improved the PANSS total score relative to placebo, as well as the Positive Symptom and Negative Symptom subscores.[84] Treatment-emergent adverse events included constipation, nausea, dry mouth, dyspepsia, and vomiting. Phase 3 trials are currently underway to test the efficacy and safety of KarXT monotherapy in patients with stable schizophrenia (NCT04820309)[85] and in acutely psychotic hospitalized patients with schizophrenia (NCT04659161, NCT04738123).[86,87] In addition, KarXT is being investigated as an adjunct treatment to conventional antipsychotics in a phase 3 trial conducted among patients with inadequately controlled symptoms of schizophrenia (NCT05145413).[88]

Glycine Transporter 1

Blockade of glutamate neurotransmission by NMDA receptor antagonists can produce a state resembling schizophrenia; therefore, researchers have investigated whether facilitating glutamate transmission via the NMDA receptor may improve schizophrenia symptoms.[26] One strategy for enhancing glutamatergic transmission is to inhibit glycine transporter 1 and thus increase synaptic levels of glycine, a coagonist required for NMDA receptor–mediated signaling.[89] Recently, a 12-week phase 2 trial conducted among patients with schizophrenia on stable treatment found that an add-on oral glycine transporter–1 inhibitor, BI 425809, improved cognition relative to placebo, as assessed by the MATRICS Consensus Cognitive Battery overall composite *T* score.[89] The number of patients with adverse events was similar between the treatment and placebo groups, and treatment-emergent adverse events associated with BI 425809 included headache, somnolence, and gastrointestinal disorders. Phase 3 trials are now investigating the effect of adjunct treatment with BI 425809 on cognition and functional capacity in patients with schizophrenia (NCT04846868, NCT04846881, NCT04860830),[90–92] and this agent has been granted breakthrough therapy status by the FDA for the treatment of cognitive impairment associated with schizophrenia.

5-Hydroxytryptamine 2A Receptor

In addition to blocking dopamine receptors, atypical antipsychotics have a tendency to block serotonin 5-HT_{2A} receptors.[45] This has led to interest in developing agents that specifically target 5-HT_{2A} receptors, which regulate glutamatergic and dopaminergic transmission.[93] One such agent, roluperidone, is an antagonist at 5-HT_{2A}, σ_2, and α_{1A}-adrenergic receptors.[94] In a 12-week phase 3 trial conducted in patients with stable schizophrenia who had moderate-to-severe negative symptoms, roluperidone monotherapy versus placebo marginally missed statistically significant improvement for the primary end point, the PANSS-derived Negative Symptom Factor Score, in the intent-to-treat data set.[94] However, the improvement associated with roluperidone did reach statistical significance in a modified intent-to-treat data set that excluded participants from one site that had reported implausible behavioral and physiologic data. Roluperidone also displayed significant improvement relative to placebo for the secondary end point, the Personal and Social Performance Scale total score, for both the intent-to-treat and modified intent-to-treat data sets. The most common treatment-emergent adverse events associated with roluperidone were insomnia, worsening of schizophrenia symptoms, headache, anxiety, and agitation.

Another 5-HT_{2A}–targeting agent, pimavanserin, has been studied as an adjunct therapy to conventional antipsychotics. This agent is a highly selective 5-HT_{2A} inverse agonist/antagonist with no affinity for adrenergic, dopaminergic, histaminergic, or muscarinic receptors.[95] In a 6-week phase 3 trial conducted in patients with schizophrenia who displayed an inadequate response to their current antipsychotic, adding pimavanserin versus placebo did not result in statistically significant improvement for the primary end point, the PANSS total score. However, exploratory analyses revealed significant improvements in the PANSS Negative Symptoms subscale and the Marder Negative Symptom Factor score. The most common treatment-emergent adverse events associated with pimavanserin were somnolence, nausea, insomnia, headache,

and anxiety. Additional phase 3 trials are investigating the efficacy of adjunct treatment with pimavanserin on the negative symptoms of schizophrenia over 26 weeks (NCT04531982)[96] and its safety and tolerability over 52 weeks (NCT03121586).[97]

CONCLUSIONS

Since the inception of pharmacotherapy for schizophrenia, patients and clinicians have had to rely on antipsychotics that work by antagonizing the dopamine D_2 receptor. Many patients treated with antipsychotics continue to experience residual positive, negative, and/or cognitive symptoms. In addition, many patients who take antipsychotics are forced to choose between managing their schizophrenia and preserving their health and quality of life, with predictable consequences for medication adherence and relapse.

Recovery is a complex process, and it is unlikely that medication alone will be enough to allow most patients to achieve it. Although medication can help stabilize patients' symptoms, multimodal psychosocial treatments, such as cognitive behavioral therapy and family education, will probably be needed to help most patients achieve their goals.[14] However, the stability offered by medication provides the foundation that allows these complementary treatment approaches to work. Even with the limitations of available antipsychotics and psychosocial interventions, early intervention services for patients with early-phase psychosis result in significantly better outcomes, including fewer hospitalizations, lower risk of medication discontinuation, better quality of life, greater involvement in school or work, and improved symptoms and functioning.[98] Imagine how much more effective schizophrenia treatment would be if early intervention could draw on multiple therapy options, offering an unprecedented opportunity to provide personalized care.

There is reason to be optimistic that patients with schizophrenia may soon have a truly novel treatment option. Based on the clinical trial data for ulotaront,[22–24] it seems TAAR1 agonists have the potential to be both tolerable and effective, including for ameliorating negative and cognitive symptoms. Other emerging therapies include agents targeting muscarinic receptors, oral glycine transporter–1 inhibitors, and medications blocking serotonin 5-HT_{2A} receptors. The ultimate test of any novel class of treatments for schizophrenia will be its ability to prevent relapse and improve patients' disease trajectory. An agent capable of preserving patients' brain health and protecting their quality of life better than existing antipsychotics do—or even one that can manage symptoms in patients who are currently experiencing treatment resistance—would represent a true revolution in the field. Results from the phase 2 and 3 clinical trials of TAAR1 agonists that are currently underway are eagerly awaited.

REFERENCES

1. GBD 2019 Diseases and Injuries Collaborators. Global burden of 369 diseases and injuries in 204 countries and territories, 1990–2019: a systematic analysis for the Global Burden of Disease Study 2019. *Lancet*. 2020;396:1204–1222.
2. Ahmed AO, Strauss GP, Buchanan RW, et al. Schizophrenia heterogeneity revisited: clinical, cognitive, and psychosocial correlates of statistically-derived negative symptoms subgroups. *J Psychiatr Res*. 2018;97:8–15.
3. Carruthers SP, Van Rheenen TE, Gurvich C, et al. Characterising the structure of cognitive heterogeneity in schizophrenia spectrum disorders. A systematic review and narrative synthesis. *Neurosci Biobehav Rev*. 2019; 107:252–278.
4. Greenwood TA, Shutes-David A, Tsuang DW. Endophenotypes in schizophrenia: digging deeper to identify genetic mechanisms. *J Psychiatr Brain Sci*. 2019;4:e190005.
5. Alnæs D, Kaufmann T, van der Meer D, et al. Brain heterogeneity in schizophrenia and its association with polygenic risk. *JAMA Psychiat*. 2019;76:739–748.
6. Cumming P, Abi-Dargham A, Gründer G. Molecular imaging of schizophrenia: neurochemical findings in a heterogeneous and evolving disorder. *Behav Brain Res*. 2021;398:113004.
7. Wolfers T, Doan NT, Kaufmann T, et al. Mapping the heterogeneous phenotype of schizophrenia and bipolar disorder using normative models. *JAMA Psychiat*. 2018;75:1146–1155.
8. Legge SE, Santoro ML, Periyasamy S, et al. Genetic architecture of schizophrenia: a review of major advancements. *Psychol Med*. 2021;51: 2168–2177.
9. Richetto J, Meyer U. Epigenetic modifications in schizophrenia and related disorders: molecular scars of environmental exposures and source of phenotypic variability. *Biol Psychiatry*. 2021;89:215–226.
10. Potkin SG, Kane JM, Correll CU, et al. The neurobiology of treatment-resistant schizophrenia: paths to antipsychotic resistance and a roadmap for future research. *NPJ Schizophr*. 2020;6:1.
11. Doane MJ, Sajatovic M, Weiden PJ, et al. Antipsychotic treatment experiences of people with schizophrenia: patient perspectives from an online survey. *Patient Prefer Adherence*. 2020;14:2043–2054.
12. Lieberman JA, Stroup TS, McEvoy JP, et al. Effectiveness of antipsychotic drugs in patients with chronic schizophrenia. *N Engl J Med*. 2005;353:1209–1223.
13. Vita A, Barlati S. Recovery from schizophrenia: is it possible? *Curr Opin Psychiatry*. 2018;31:246–255.
14. Correll CU, Rubio JM, Kane JM. What is the risk-benefit ratio of long-term antipsychotic treatment in people with schizophrenia? *World Psychiatry*. 2018;17:149–160.
15. Hjorthøj C, Stürup AE, McGrath JJ, et al. Years of potential life lost and life expectancy in schizophrenia: a systematic review and meta-analysis. *Lancet Psychiatry*. 2017;4:295–301.
16. Olfson M, Stroup TS, Huang C, et al. Suicide risk in Medicare patients with schizophrenia across the life span. *JAMA Psychiat*. 2021;78:876–885.
17. Schizophrenia & Psychosis Action Alliance. Societal costs of schizophrenia & related disorders. 2021. Available at: https://www.sczaction.org/insight-initiative/societal-costs/. Accessed May 13, 2022.
18. Downing AM, Kinon BJ, Millen BA, et al. A double-blind, placebo-controlled comparator study of LY2140023 monohydrate in patients with schizophrenia. *BMC Psychiatry*. 2014;14:351.
19. Walling D, Marder SR, Kane J, et al. Phase 2 trial of an alpha-7 nicotinic receptor agonist (TC-5619) in negative and cognitive symptoms of schizophrenia. *Schizophr Bull*. 2016;42:335–343.
20. Walling DP, Banerjee A, Dawra V, et al. Phosphodiesterase 10A inhibitor monotherapy is not an effective treatment of acute schizophrenia. *J Clin Psychopharmacol*. 2019;39:575–582.
21. Bugarski-Kirola D, Blaettler T, Arango C, et al. Bitopertin in negative symptoms of schizophrenia-results from the phase III FlashLyte and DayLyte studies. *Biol Psychiatry*. 2017;82:8–16.
22. Koblan KS, Kent J, Hopkins SC, et al. A non-D_2-receptor-binding drug for the treatment of schizophrenia. *N Engl J Med*. 2020;382:1497–1506.
23. Correll CU, Koblan KS, Hopkins SC, et al. Safety and effectiveness of ulotaront (SEP-363856) in schizophrenia: results of a 6-month, open-label extension study. *NPJ Schizophr*. 2021;7:63.
24. Milanovic S, Origala A, Dworak H, et al. Measures of cognition and social functioning in schizophrenia patients receiving SEP-363856 [SIRS abstract M208]. *Schiz Bull*. 2020;46:S215–S216.
25. Cunningham Owens D, Johnstone EC. The development of antipsychotic drugs. *Brain Neurosci Adv*. 2018;2:2398212818817498.
26. Correll CU, Schooler NR. Negative symptoms in schizophrenia: a review and clinical guide for recognition, assessment, and treatment. *Neuropsychiatr Dis Treat*. 2020;16:519–534.

27. Bowie CR, Harvey PD. Cognitive deficits and functional outcome in schizophrenia. *Neuropsychiatr Dis Treat*. 2006;2:531–536.
28. Millan MJ, Fone K, Steckler T, et al. Negative symptoms of schizophrenia: clinical characteristics, pathophysiological substrates, experimental models and prospects for improved treatment. *Eur Neuropsychopharmacol*. 2014; 24:645–692.
29. Lehman AF, Lieberman JA, Dixon LB, et al. Practice guideline for the treatment of patients with schizophrenia, second edition. *Am J Psychiatry*. 2004;161(2 suppl):1–56.
30. Kane JM, Agid O, Baldwin ML, et al. Clinical guidance on the identification and management of treatment-resistant schizophrenia. *J Clin Psychiatry*. 2019;80:18com12123.
31. Verma M, Grover S, Chakrabarti S. Effectiveness of clozapine on quality of life and functioning in patients with treatment-resistant schizophrenia. *Nord J Psychiatry*. 2021;75:135–144.
32. Masuda T, Misawa F, Takase M, et al. Association with hospitalization and all-cause discontinuation among patients with schizophrenia on clozapine vs other oral second-generation antipsychotics: a systematic review and meta-analysis of cohort studies. *JAMA Psychiat*. 2019;76: 1052–1062.
33. de Filippis R, Gaetano R, Schoretsanitis G, et al. Clozapine management in schizophrenia inpatients: a 5-year prospective observational study of its safety and tolerability profile. *Neuropsychiatr Dis Treat*. 2021;17: 2141–2150.
34. Moody BL, Eatmon CV. Perceived barriers and facilitators of clozapine use: a national survey of Veterans Affairs prescribers. *Fed Pract*. 2019;36 (suppl 6):S22–s27.
35. Okhuijsen-Pfeifer C, Cohen D, Bogers J, et al. Differences between physicians' and nurse practitioners' viewpoints on reasons for clozapine underprescription. *Brain Behav*. 2019;9:e01318.
36. Sharma S, Kopelovich SL, Janjua AU, et al. Cluster analysis of clozapine consumer perspectives and comparison to consumers on other antipsychotics. *Schizophr Bull Open*. 2021;2:sgab043.
37. Qurashi I, Stephenson P, Chu S, et al. An evaluation of subjective experiences, effects and overall satisfaction with clozapine treatment in a UK forensic service. *Ther Adv Psychopharmacol*. 2015;5:146–150.
38. Taylor D, Shapland L, Laverick G, et al. Clozapine—a survey of patient perceptions. *Psychiatr Bull*. 2000;24:450–452.
39. Emsley R, Asmal L, Rubio JM, et al. Predictors of psychosis breakthrough during 24 months of long-acting antipsychotic maintenance treatment in first episode schizophrenia. *Schizophr Res*. 2020;225:55–62.
40. Rubio JM, Schoretsanitis G, John M, et al. Psychosis relapse during treatment with long-acting injectable antipsychotics in individuals with schizophrenia-spectrum disorders: an individual participant data meta-analysis. *Lancet Psychiatry*. 2020;7:749–761.
41. Harvey PD, Kane JM. Addressing patients' unmet needs to improve outcomes in schizophrenia. *J Clin Psychiatry*. 2021;82:IC20018AH3C.
42. Yoshida K, Takeuchi H. Dose-dependent effects of antipsychotics on efficacy and adverse effects in schizophrenia. *Behav Brain Res*. 2021; 402:113098.
43. Tsapakis EM, Dimopoulou T, Tarazi FI. Clinical management of negative symptoms of schizophrenia: an update. *Pharmacol Ther*. 2015;153:135–147.
44. Carbon M, Correll CU. Thinking and acting beyond the positive: the role of the cognitive and negative symptoms in schizophrenia. *CNS Spectr*. 2014; 19(suppl 1):38–52.
45. Jones MT, Strassnig MT, Harvey PD. Emerging 5-HT receptor antagonists for the treatment of schizophrenia. *Expert Opin Emerg Drugs*. 2020;25: 189–200.
46. Mucci A, Galderisi S, Gibertoni D, et al. Factors associated with real-life functioning in persons with schizophrenia in a 4-year follow-up study of the Italian Network for Research on Psychoses. *JAMA Psychiat*. 2021;78: 550–559.
47. Findlay LJ, El-Mallakh PL, El-Mallakh RS. Cariprazine for the treatment of bipolar disorder. *Perspect Psychiatr Care*. 2017;53:148–155.
48. Liao CH, Chang CS, Wei WC, et al. Schizophrenia patients at higher risk of diabetes, hypertension and hyperlipidemia: a population-based study. *Schizophr Res*. 2011;126(1–3):110–116.
49. Lin JJ, Liang FW, Li CY, et al. Leading causes of death among decedents with mention of schizophrenia on the death certificates in the United States. *Schizophr Res*. 2018;197:116–123.
50. Kearns B, Cooper K, Cantrell A, et al. Schizophrenia treatment with second-generation antipsychotics: a multi-country comparison of the costs of cardiovascular and metabolic adverse events and weight gain. *Neuropsychiatr Dis Treat*. 2021;17:125–137.
51. Oh J, Nam H, Park S, et al. Decreased cardiovascular death in schizophrenia patients treated with antipsychotics: a Korean national cohort study. *Schizophr Res*. 2021;228:417–424.
52. Castillo-Sánchez M, Escurriola MF, Sanmartín MIF, et al. Cardiovascular disease and mortality in people with schizophrenia or antipsychotic treatment: a cohort study in primary care. *Psychiatry Res*. 2021; 306:114233.
53. Højlund M, Kemp AF, Haddad PM, et al. Standard versus reduced dose of antipsychotics for relapse prevention in multi-episode schizophrenia: a systematic review and meta-analysis of randomised controlled trials. *Lancet Psychiatry*. 2021;8:471–486.
54. Basciotta M, Zhou W, Ngo L, et al. Antipsychotics and the risk of mortality or cardiopulmonary arrest in hospitalized adults. *J Am Geriatr Soc*. 2020; 68:544–550.
55. Vespa J. The graying of America: more older adults than kids by 2035. The U.S. joins other countries with large aging populations. Available at: https://www.census.gov/library/stories/2018/03/graying-america.html. Revised October 8, 2019. Accessed May 13, 2022.
56. Rubio JM, Taipale H, Tanskanen A, et al. Long-term continuity of antipsychotic treatment for schizophrenia: a nationwide study. *Schizophr Bull*. 2021;47:1611–1620.
57. Ascher-Svanum H, Nyhuis AW, Stauffer V, et al. Reasons for discontinuation and continuation of antipsychotics in the treatment of schizophrenia from patient and clinician perspectives. *Curr Med Res Opin*. 2010;26:2403–2410.
58. Stahl SM. Beyond the dopamine hypothesis of schizophrenia to three neural networks of psychosis: dopamine, serotonin, and glutamate. *CNS Spectr*. 2018;23:187–191.
59. Dedic N, Jones PG, Hopkins SC, et al. SEP-363856, a novel psychotropic agent with a unique, non-D(2) receptor mechanism of action. *J Pharmacol Exp Ther*. 2019;371:1–14.
60. Howes OD, Kapur S. A neurobiological hypothesis for the classification of schizophrenia: type a (hyperdopaminergic) and type B (normodopaminergic). *Br J Psychiatry*. 2014;205:1–3.
61. Khokhar JY, Henricks AM, Sullivan EDK, et al. Unique effects of clozapine: a pharmacological perspective. *Adv Pharmacol*. 2018;82:137–162.
62. Cardozo T, Shmelkov E, Felsovalyi K, et al. Chemistry-based molecular signature underlying the atypia of clozapine. *Transl Psychiatry*. 2017;7:e1036.
63. Nair PC, Chalker JM, McKinnon RA, et al. Trace amine–associated receptor 1 (TAAR1): molecular and clinical insights for the treatment of schizophrenia and related comorbidities. *ACS Pharmacol Transl Sci*. 2022; 5:183–188.
64. Rutigliano G, Accorroni A, Zucchi R. The case for TAAR1 as a modulator of central nervous system function. *Front Pharmacol*. 2017;8:987.
65. Berry MD, Gainetdinov RR, Hoener MC, et al. Pharmacology of human trace amine–associated receptors: therapeutic opportunities and challenges. *Pharmacol Ther*. 2017;180:161–180.
66. Revel FG, Moreau JL, Gainetdinov RR, et al. TAAR1 activation modulates monoaminergic neurotransmission, preventing hyperdopaminergic and hypoglutamatergic activity. *Proc Natl Acad Sci U S A*. 2011;108:8485–8490.

67. Dodd S, Carvalho AF, Puri BK, et al. Trace amine–associated receptor 1 (TAAR1): a new drug target for psychiatry? *Neurosci Biobehav Rev*. 2021; 120:537–541.
68. Kapur S, Zipursky R, Jones C, et al. Relationship between dopamine D(2) occupancy, clinical response, and side effects: a double-blind PET study of first-episode schizophrenia. *Am J Psychiatry*. 2000;157:514–520.
69. Gainetdinov RR, Hoener MC, Berry MD. Trace amines and their receptors. *Pharmacol Rev*. 2018;70:549–620.
70. Dedic N, Dworak H, Zeni C, et al. Therapeutic potential of TAAR1 agonists in schizophrenia: evidence from preclinical models and clinical studies. *Int J Mol Sci*. 2021;22:13185.
71. Miller GM. The emerging role of trace amine–associated receptor 1 in the functional regulation of monoamine transporters and dopaminergic activity. *J Neurochem*. 2011;116:164–176.
72. Businesswire. Sunovion and PsychoGenics announce that SEP-363856 has received FDA breakthrough therapy designation for the treatment of people with schizophrenia. May 10, 2019. Available at: https://www.businesswire.com/news/home/20190510005212/en/Sunovion-and-PsychoGenics-Announce-that-SEP-363856-Has-Received-FDA-Breakthrough-Therapy-Designation-for-the-Treatment-of-People-with-Schizophrenia. Accessed April 12, 2022.
73. Alexandrov V, Brunner D, Hanania T, et al. High-throughput analysis of behavior for drug discovery. *Eur J Pharmacol*. 2015;750:82–89.
74. Hopkins SC, Ogirala A, Worden M, et al. Depicting safety profile of TAAR1 agonist ulotaront relative to reactions anticipated for a dopamine D2-based pharmacological class in FAERS. *Clin Drug Investig*. 2021;41: 1067–1073.
75. ClinicalTrials.gov. A clinical trial that will study the efficacy and safety of an investigational drug in acutely psychotic people with schizophrenia. NCT04092686. Available at: https://clinicaltrials.gov/ct2/show/NCT04092686. Accessed May 16, 2022.
76. ClinicalTrials.gov. A clinical trial to study the efficacy and safety of an investigational drug in acutely psychotic people with schizophrenia. NCT04072354. Available at: https://clinicaltrials.gov/ct2/show/NCT04072354. Accessed May 16, 2022.
77. ClinicalTrials.gov. A study of the long-term safety and tolerability of an investigational drug in people with schizophrenia. NCT04115319. Available at: https://clinicaltrials.gov/ct2/show/NCT04115319. Accessed May 16, 2022.
78. ClinicalTrials.gov. A clinical study to investigate the effect of an investigational drug as an added medication to an antipsychotic, in adults with schizophrenia, as measured positron emission tomography (PET) imaging. NCT04038957. Available at: https://clinicaltrials.gov/ct2/show/NCT04038957. Accessed May 16, 2022.
79. ClinicalTrials.gov. A clinical trial study to determine the effect of an investigational drug (SEP-363856) has on the way that the drug metformin travels through the body in people with schizophrenia. NCT04865835. Available at: https://clinicaltrials.gov/ct2/show/NCT04865835. Accessed May 16, 2022.
80. ClinicalTrials.gov.A study to assess the effects of RO6889450 (ralmitaront) in participants with schizophrenia or schizoaffective disorder and negative symptoms. NCT03669640. Available at: https://clinicaltrials.gov/ct2/show/NCT03669640. Accessed May 16, 2022.
81. ClinicalTrials.gov. A trial of the efficacy and the safety of RO6889450 (ralmitaront) vs placebo in patients with an acute exacerbation of schizophrenia or schizoaffective disorder. NCT04512066. Available at: https://clinicaltrials.gov/ct2/show/NCT04512066. Accessed May 16, 2022.
82. Garcia-Garcia AL, Newman-Tancredi A, Leonardo ED. 5-HT(1A) receptors in mood and anxiety: recent insights into autoreceptor versus heteroreceptor function. *Psychopharmacology (Berl)*. 2014;231:623–636.
83. Foster DJ, Bryant ZK, Conn PJ. Targeting muscarinic receptors to treat schizophrenia. *Behav Brain Res*. 2021;405:113201.
84. Brannan SK, Sawchak S, Miller AC, et al. Muscarinic cholinergic receptor agonist and peripheral antagonist for schizophrenia. *N Engl J Med*. 2021; 384:717–726.
85. ClinicalTrials.gov. An open-label study to assess the long-term safety, tolerability, and efficacy of KarXT in adult patients with schizophrenia (EMERGENT-5). NCT04820309. Available at: https://clinicaltrials.gov/ct2/show/NCT04820309. Accessed June 10, 2022.
86. ClinicalTrials.gov. A study to assess efficacy and safety of KarXT in acutely psychotic hospitalized adult patients with schizophrenia (EMERGENT-2). NCT04659161. Available at: https://clinicaltrials.gov/ct2/show/NCT04659161. Accessed June 10, 2022.
87. ClinicalTrials.gov. A study to assess efficacy and safety of KarXT in acutely psychotic hospitalized adult patients with schizophrenia (EMERGENT-3). NCT04738123. Available at: https://clinicaltrials.gov/ct2/show/NCT04738123. Accessed June 10, 2022.
88. ClinicalTrials.gov. A study to assess efficacy and safety of adjunctive KarXT in subjects with inadequately controlled symptoms of schizophrenia (ARISE). NCT05145413. Available at: https://clinicaltrials.gov/ct2/show/NCT05145413. Accessed June 10, 2022.
89. Fleischhacker WW, Podhorna J, Gröschl M, et al. Efficacy and safety of the novel glycine transporter inhibitor BI 425809 once daily in patients with schizophrenia: a double-blind, randomised, placebo-controlled phase 2 study. *Lancet Psychiatry*. 2021;8:191–201.
90. ClinicalTrials.gov. Clinical trial of BI 425809 effect on cognition and functional capacity in schizophrenia (CONNEX-1). NCT04846868. Available at: https://clinicaltrials.gov/ct2/show/NCT04846868. Accessed June 10, 2022.
91. ClinicalTrials.gov. Clinical trial of BI 425809 effect on cognition and functional capacity in schizophrenia (CONNEX-2). NCT04846881. Available at: https://clinicaltrials.gov/ct2/show/NCT04846881. Accessed June 10, 2022.
92. ClinicalTrials.gov. Clinical trial of BI 425809 effect on cognition and functional capacity in schizophrenia (CONNEX-3). NCT04860830. Available at: https://clinicaltrials.gov/ct2/show/NCT04860830. Accessed June 10, 2022.
93. Kantrowitz JT. Targeting serotonin 5-HT(2A) receptors to better treat schizophrenia: rationale and current approaches. *CNS Drugs*. 2020; 34:947–959.
94. Davidson M, Saoud J, Staner C, et al. Efficacy and safety of roluperidone for the treatment of negative symptoms of schizophrenia. *Schizophr Bull*. 2022;48:609–619.
95. Bugarski-Kirola D, Bitter I, Liu IY, et al. ENHANCE: phase 3, randomized, double-blind, placebo-controlled study of adjunctive pimavanserin for schizophrenia in patients with an inadequate response to antipsychotic treatment. *Schiz Bull Open*. 2022:sgac006.
96. ClinicalTrials.gov. Efficacy and safety of pimavanserin as adjunctive treatment for the negative symptoms of schizophrenia (ADVANCE-2). NCT04531982. Available at: https://clinicaltrials.gov/ct2/show/NCT04531982. Accessed June 10, 2022.
97. ClinicalTrials.gov. Extension study of pimavanserin for the adjunctive treatment of schizophrenia. NCT03121586. Available at: https://clinicaltrials.gov/ct2/show/NCT03121586. Accessed June 10, 2022.
98. Correll CU, Galling B, Pawar A, et al. Comparison of early intervention services vs treatment as usual for early-phase psychosis: a systematic review, meta-analysis, and meta-regression. *JAMA Psychiat*. 2018; 75:555–565.