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Authors

Correll, Christoph
Meyer, Jonathan

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LEADING ARTICLE

Increased Metabolic Potential, Efficacy, and Safety of Emerging Treatments in Schizophrenia

Jonathan M. Meyer[1] · **Christoph U. Correll**[2,3,4]

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Abstract
Patients with schizophrenia experience a broad range of detrimental health outcomes resulting from illness severity, heterogeneity of disease, lifestyle behaviors, and adverse effects of antipsychotics. Because of these various factors, patients with schizophrenia have a much higher risk of cardiometabolic abnormalities than people without psychiatric illness. Although exposure to many antipsychotics increases cardiometabolic risk factors, mortality is higher in patients who are not treated versus those who are treated with antipsychotics. This indicates both direct and indirect benefits of adequately treated illness, as well as the need for beneficial medications that result in fewer cardiometabolic risk factors and comorbidities. The aim of the current narrative review was to outline the association between cardiometabolic dysfunction and schizophrenia, as well as discuss the confluence of factors that increase cardiometabolic risk in this patient population. An increased understanding of the pathophysiology of schizophrenia has guided discovery of novel treatments that do not directly target dopamine and that not only do not add, but may potentially minimize relevant cardiometabolic burden for these patients. Key discoveries that have advanced the understanding of the neural circuitry and pathophysiology of schizophrenia now provide possible pathways toward the development of new and effective treatments that may mitigate the risk of metabolic dysfunction in these patients. Novel targets and preclinical and clinical data on emerging treatments, such as glycine transport inhibitors, nicotinic and muscarinic receptor agonists, and trace amine-associated receptor-1 agonists, offer promise toward relevant therapeutic advancements. Numerous areas of investigation currently exist with the potential to considerably progress our knowledge and treatment of schizophrenia.

1 Cardiometabolic Dysfunction and Schizophrenia

For every patient with schizophrenia, risk/benefit decisions that balance a number of medication-related concerns (e.g., metabolic, neurological, endocrine adverse effects) are important drivers of antipsychotic choice. Patients with schizophrenia are at higher risk for cardiometabolic

Key Points

Patients with schizophrenia are at higher risk for cardiometabolic abnormalities, such as hypertension, type 2 diabetes, obesity, and metabolic syndrome; current antipsychotics, which directly act on D_2 receptors to modulate dopamine, may increase these risks.

Recent advances in the understanding of the pathophysiology of schizophrenia, including the role of numerous nondopaminergic neurotransmitters, has guided discovery of novel treatments that do not directly target dopamine receptors and that also minimize cardiometabolic burden for these patients.

Novel medications are beginning to emerge that have the propensity to considerably advance the treatment of schizophrenia and reduce patients' cardiometabolic burden.

✉ Jonathan M. Meyer
jmmeyer@health.ucsd.edu

1 Department of Psychiatry, University of California San Diego, La Jolla, CA, USA

2 Department of Psychiatry, The Zucker Hillside Hospital, Northwell Health, Glen Oaks, NY, USA

3 Department of Psychiatry and Molecular Medicine, Donald and Barbara Zucker School of Medicine at Hofstra/Northwell, Hempstead, NY, USA

4 Department of Child and Adolescent Psychiatry, Charité Universitätsmedizin, Berlin, Germany

abnormalities, such as hypertension, type 2 diabetes, obesity, and metabolic syndrome, due to a combination of lifestyle factors, illness severity, genetics/epigenetics, and adverse effects of psychiatric medications, especially antipsychotics [1–6]. A retrospective database study of over 55,000 US patients with schizophrenia found that ~ 66% had at least one cardiometabolic comorbidity and ~ 40% had two or more [7]. These comorbidities have a significant impact on quality of life and life span, with affected patients having a reduced life expectancy of 10–25 years compared with the general population, largely due to the two-fold increase in standard mortality rates for cardiovascular disease [2, 3, 7–9]. A recent meta-analysis of 135 studies has shown all-cause mortality was increased by 2.5-fold in people with schizophrenia versus any nonschizophrenia control group, with the largest risk observed in first-episode and incident, or earlier-phase, schizophrenia versus the general population [10].

While clinicians can control the iatrogenic contribution to cardiometabolic risk through judicious prescribing of lower cardiometabolic risk antipsychotics, such as aripiprazole, brexpiprazole, cariprazine, lumateperone, lurasidone, and ziprasidone, behavioral and environmental mechanisms associated with schizophrenia play a significant role in the development and presence of many comorbid conditions [2, 5, 6, 11–13]. Compared with demographically matched peers and patients without major psychiatric disorders, individuals with serious mental illnesses such as schizophrenia and bipolar disorder have higher rates of smoking, sedentary lifestyles, poor dietary habits, substance use, and medication nonadherence; moreover, these risk factors are often inadequately addressed because of lower rates of somatic healthcare access and utilization, a confluence of factors that increase the risk of cardiometabolic dysfunction [5, 14].

From a biological perspective, both schizophrenia and cardiometabolic diseases are highly heritable, with genetics accounting for at least 80% of the pathophysiology in schizophrenia [15, 16]. Investigating biological/genetic mechanisms underlying these conditions can be tricky because of the added interplay of behavioral- and treatment-based causes. However, evidence has suggested that polygenic and pleiotropic effects of genes/gene loci may regulate both schizophrenia and cardiometabolic diseases as well as the effects of medications, especially antipsychotics, on the risk for weight gain and cardiometabolic morbidity/mortality [2, 4, 5, 17–20]. Clinical evidence that the risk for cardiometabolic abnormalities may be inherent in serious mental disorders has been shown in metabolic studies of treatment-naïve patients with schizophrenia in whom dysfunctional glucose homeostasis, hypothalamic–pituitary–adrenal axis hyperactivity, autonomic nervous system dysfunction, increased levels of systemic inflammatory markers, and lipid abnormalities have all been demonstrable prior to antipsychotic exposure [4, 5, 21]. Recent analyses of possible genetic overlap between cardiometabolic traits and schizophrenia have found tentative polygenic associations between schizophrenia and abnormalities in glucose metabolism, adverse adipokine profile, increased waist-to-hip ratio, and visceral adipose tissue [18].

The implicit disease-related, behavioral, and biological factors that lead to cardiometabolic abnormalities in schizophrenia are exacerbated even more by the adverse metabolic effects of antipsychotic medications necessary to treat the primary disorder. Second-generation antipsychotic drugs (SGAs) are the standard of care for schizophrenia; however, many of the earliest agents in this class were associated with significant adverse metabolic and cardiovascular effects, such as weight gain, dyslipidemia, coronary heart disease, stroke, and glucose dysregulation [1, 2, 12, 22]. Olanzapine and especially clozapine have been associated with high levels of metabolic disruption but have also largely been considered among the most efficacious at preventing relapse in schizophrenia [23, 24]. For patients with treatment-resistant schizophrenia in particular, no viable alternatives to clozapine exist, and clinicians must assiduously monitor metabolic parameters during clozapine treatment. Literature exploring the use of metformin and glucagon-like peptide 1 (GLP-1) agonists to help mitigate clozapine's metabolic risks provide evidence that these options are effective and well tolerated [25, 26]. Yet not all patients with schizophrenia are treatment resistant, and newer SGAs may have lower metabolic risks compared with older agents [12, 22]. A large network meta-analysis of over 100 controlled trials noted marked differences in metabolic adverse effects seen across all antipsychotics in the acute treatment of schizophrenia, indicating the need for individualized treatment based on the patient's risk of metabolic complications (Fig. 1) [12].

Although cardiometabolic disease burden in patients with schizophrenia is related to high mortality and lower quality of life, the presence of cardiometabolic risk factors is also associated with poor psychiatric outcomes [27–29]. A prospective, population-based study of first-episode patients ($N = 1230$) demonstrated that both no exposure and high exposure to antipsychotic medications (all dispensed antipsychotics included except lithium) led to a higher risk of cardiovascular mortality versus low or moderate exposure, indicating the need for adequate dosing [30]. While exposure to antipsychotics increases cardiometabolic risk factors that can increase the risk of cardiovascular death, use of antipsychotics has been associated with a decreased risk of all-cause cardiovascular mortality versus no antipsychotic treatment in patients with schizophrenia [10, 31]. This seemingly paradoxical effect of antipsychotics on cardiovascular morbidity and mortality is likely due to better adherence to secondary and tertiary preventive interventions when appropriately

treated with antipsychotics [32]. Not surprisingly, all-cause mortality is also higher in patients with schizophrenia not treated with antipsychotics compared with those receiving treatment, indicating that adequate treatment of the psychiatric disorder is crucial to minimizing natural and unnatural causes of death (e.g., suicide, accidents) [2, 30, 33].

The reduction of cardiometabolic risk in these patients relies on an understanding of how these increases in risk occur. Antipsychotic-related weight gain is one pathway to cardiometabolic dysfunction, and in first- and second-generation antipsychotics, there is a strong correlation between weight gain and H_1 affinity, especially H_1 blockade in the posterior hypothalamus [34, 35]. Antipsychotics that show the highest clinically relevant antagonism of H_1 receptors at therapeutic doses stimulate hypothalamic processes that lead to increased appetite and metabolic disruptions [35, 36].

However, there is evidence for weight-independent mechanisms that also underly antipsychotic-related adverse cardiometabolic effects. Mechanisms implicated in these weight-independent effects include muscarinic receptor antagonism based on the role of muscarinic receptors in energy homeostasis and antipsychotic-induced metabolic adverse effects, especially M_3 [12]. Various genes for histaminergic, serotonergic, adrenergic, and dopaminergic pathways have also been implicated in antipsychotic-induced weight gain and other metabolic disruptions [34, 36, 37]. For example, evidence suggests that polymorphisms in 5-HT_{2a} and 5-HT_{2C} receptors are associated with various types of metabolic dysfunction, such as obesity, glucose intolerance, and insulin resistance [35]. Serotonin receptors are commonly modulated by many antipsychotics and, therefore, may be another mechanism by which drug-induced metabolic dysfunction occurs.

The cardiometabolic adverse effects of D_2-receptor-binding antipsychotics (antagonists and partial agonists) may partly be due to the impact of D_2 binding on the ability of pancreatic beta cells to accurately sense glucose levels, resulting in hyperinsulinemia [38]. In addition, preclinical studies have demonstrated that selective D_2/D_3-blockade enhances insulin secretion, loss of D_2-receptors results in glucose intolerance, and administration of haloperidol or olanzapine impairs central glucose effectiveness; however, it is worth acknowledging that the human data are less well developed [39, 40]. These drug-induced effects compound the difficulties in a population that is already predisposed to metabolic comorbidities due to genetic and lifestyle factors [4, 7, 21, 41]. Although SGA tolerability profiles have improved since oral risperidone was approved in the USA in 1993, a broadened understanding of the pathophysiology of schizophrenia has elicited exploration of agents with novel mechanisms that target glutamate, serotonin, acetylcholine, or GABA, and that do not directly target dopamine. These not only have

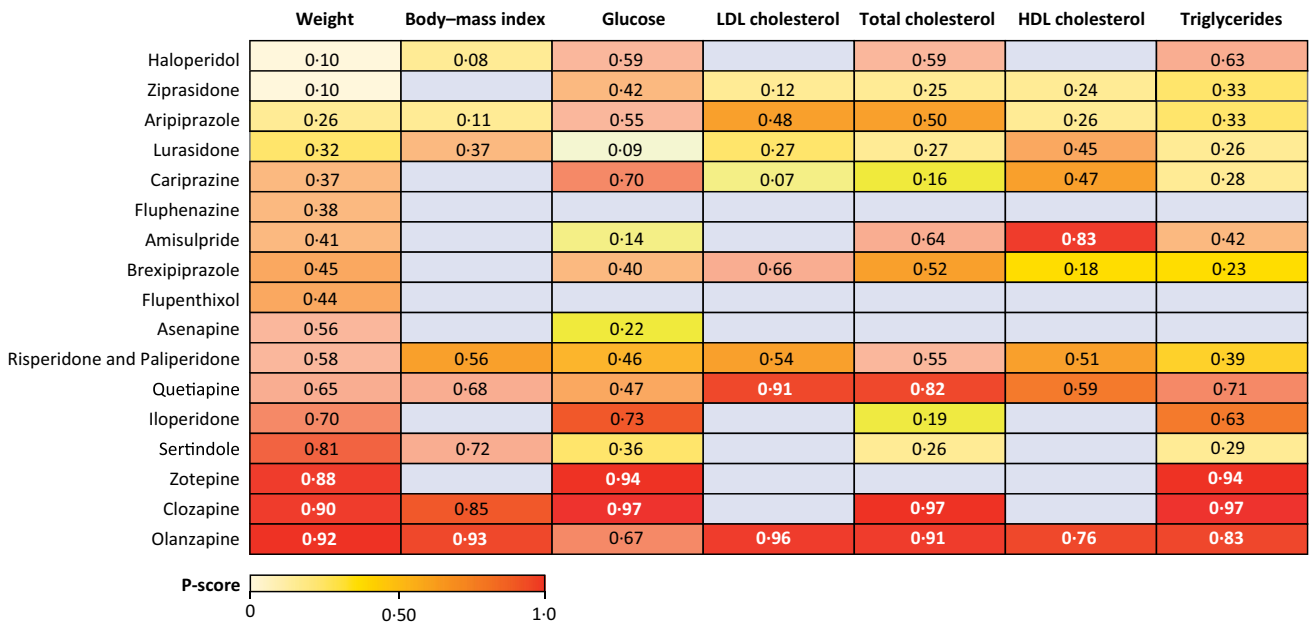


Fig. 1 Heat map of antipsychotic drugs ranked according to associated degree of alteration in bodyweight, body mass index, and metabolic parameters [12]. Reused from Pillinger et al., *Lancet Psychiatry* (under Creative Commons license CC BY). Numbers reflect the P-scores, which rank antipsychotics on a continuous scale from 0 to 1. A higher P-score indicates a greater increase in the metabolic parameter, with the exception of HDL cholesterol, for which a higher P-score indicates a smaller increase. Gray squares indicate that data were not available. *HDL* high-density lipoprotein, *LDL* low-density lipoprotein

the propensity to minimize cardiometabolic burden, but they may also radically reshape concerns about dopamine D_2-related adverse effects as the price to pay for adequate management of the positive symptoms of schizophrenia. A deeper understanding of the neural circuitry and pathophysiology of schizophrenia through further study and new approaches to discovery of treatments would be a critical step in unveiling these novel mechanisms.

2 Neural Circuitry and Pathophysiology of Schizophrenia

For years, the main treatment paradigm for schizophrenia has been postsynaptic dopamine D_2 receptor blockade. This has been standard of care since the discovery of chlorpromazine's antipsychotic properties and the synthesis of other first-generation antipsychotics (FGAs) using animal behavioral assays [42]. Key discoveries confirming dopamine's involvement included the realization that medications with dopamine D_2 blockade were beneficial for positive symptoms and that exposure to dopamine agonists led to psychotomimetic effects [41, 43, 44]. D_2-receptor-binding antipsychotics (antagonists and partial agonists) can, as discussed, have cardiometabolic adverse effects, which only compound the difficulties in a population who are already predisposed to these comorbidities [4, 7, 21, 41]. At the same time, although D_2 receptor blockade is effective in reducing positive symptoms, ~ 30% of patients are treatment resistant and respond very poorly, if at all, to nonclozapine antipsychotics. Moreover, current antipsychotics provide only modest improvements in negative symptoms and cognitive function [45, 46]. Thus, the reduction of cardiometabolic risk in these patients is only one of many reasons that treatments with new mechanisms of action are needed.

One driver for the development of SGAs was to utilize the model of clozapine, with high levels of 5-HT_{2A} antagonism and low levels of D_2 blockade, to mitigate extrapyramidal adverse effects commonly seen with FGAs. The unique efficacy of clozapine, despite low levels of postsynaptic D_2 receptor occupancy, was the first hint that other neurotransmitter systems, such as acetylcholine, glutamate, and serotonin, are involved in antipsychotic response and, by extension, may underlie the pathophysiology of schizophrenia [41, 47]. The glutamate hypofunction hypothesis evolved based on observational and experimental studies noting that exposure to *N*-methyl-D-aspartate (NMDA) antagonists, such as phencyclidine, ketamine, and MK-801, induces psychosis, social withdrawal (a behavioral analog of negative symptoms), and cognitive dysfunction, which are the three core features of schizophrenia. Further research suggested that changes in cortico-limbic NMDA receptor-mediated neuronal transmission modulates downstream dopaminergic transmission via excitation of the striatal structures associated with positive psychosis symptoms [41, 45]. Serotonergic-mediated modulation of this circuitry involves serotonergic input from the raphe nucleus to the ventral tegmental area (VTA), which results in increased dopaminergic output to the striatum (Fig. 2) [48, 49]. The raphe nucleus also innervates the cortex, which could lead to hyperstimulation of cortical glutamate and possibly the hallucinations and delusions associated with psychosis [48]. The epithalamus comprises the dorsal portion of the diencephalon and includes the pineal gland, habenular nuclei, and the tracts that connect these structures [50, 51]. The epithalamus plays a crucial role for the dorsal diencephalic conduction system by conveying information from the limbic forebrain to the limbic midbrain [51, 52]. Signals from the pineal body regulate secretion of melatonin and pituitary hormones, with effects on energy conservation and utilization [53]. The medial habenular nucleus, which projects to structures such as the interpeduncular nucleus, pineal gland, and other midbrain structures, and the lateral habenular nucleus, which descends to GABAergic and dopaminergic neurons in the VTA, are involved in reward, cognitive flexibility, and emotion [50, 54–58]. These nuclei have been shown to have reduced volume and altered functional connectivity in patients with schizophrenia, suggesting a role in the pathogenesis of the disorder [54]. It has been suggested that the habenular nuclei may also control dopaminergic neurons in the VTA, such that excitation of the lateral habenular nucleus activates GABAergic neurons in the VTA resulting in an inhibition of dopaminergic transmission [54]. Thus, there are numerous pathways using various neurotransmitters that may alter regulation of the midbrain dopamine system in patients with schizophrenia.

Cross-sectional neuroimaging studies have suggested that poorer therapeutic responsiveness to D_2-receptor modulation is associated with normal striatal dopamine synthesis but elevated anterior cingulate cortex (ACC) and striatal glutamate levels, which may indicate that, in some patients, increased glutamate in certain brain regions determines the level of efficacy of D_2 blockade [59]. Further, a meta-analysis of 59 studies found that, compared with controls, patients with schizophrenia had excess glutamatergic transmission in several areas of the limbic system, suggesting that compounds that reduce glutamate, directly or indirectly, may offer therapeutic potential [60].

Much evidence has indicated that the pathophysiology of schizophrenia involves abnormal interactions between different brain regions, many of which are glutamatergic [61]. Magnetic resonance imaging studies have shown structural

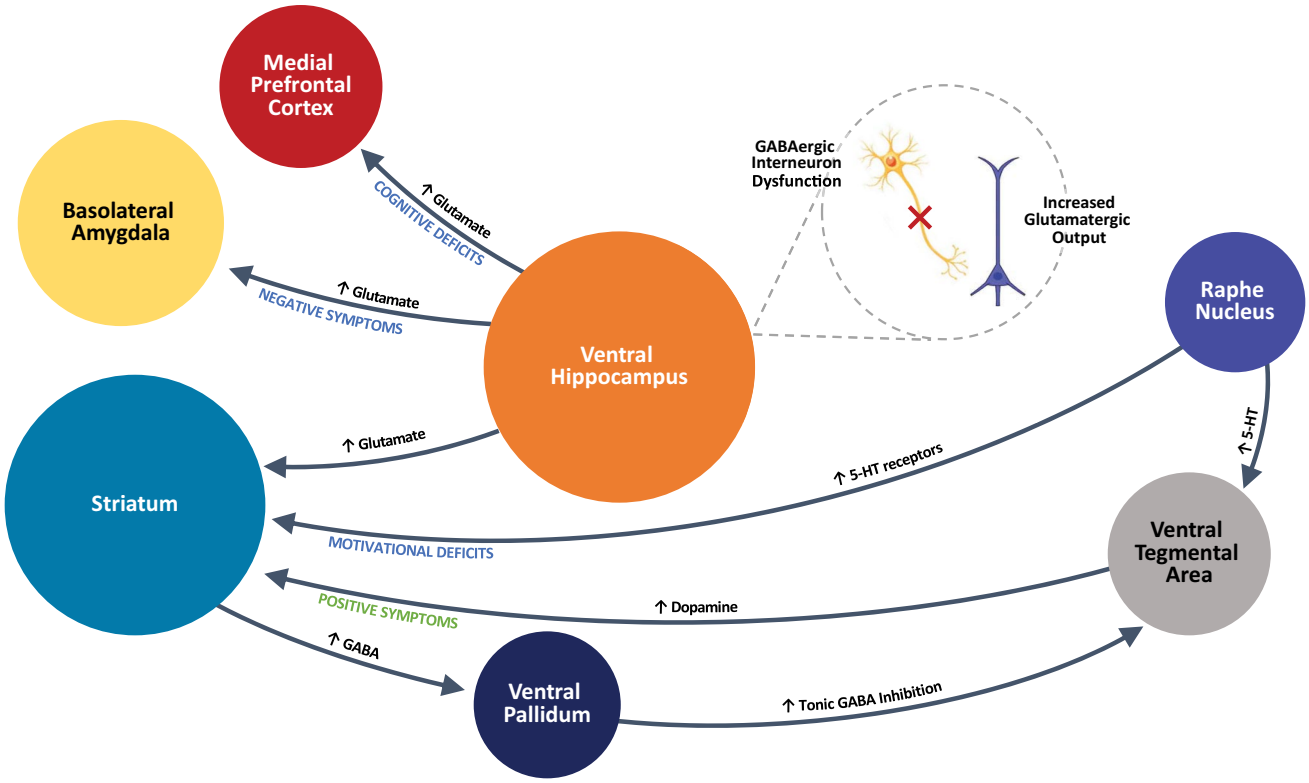


Fig. 2 Putative neurocircuitry underlying schizophrenia involving glutamate, GABA, dopamine, and serotonin transmission [41, 49]. *5-HT* serotonin, *GABA* gamma-aminobutyric acid

and functional impairments of the cortico-limbic system circuit, involving the amygdala, hippocampus, cingulate cortex, and prefrontal cortex (PFC), in patients with schizophrenia [62]. In healthy individuals, emotional processing involves interaction of the ventral and dorsal systems of this circuit, with the amygdala (ventral system) functioning in emotional information assessment, and the PFC and ACC (dorsal system), regulating emotional responses [63, 64]. In patients with schizophrenia, the abnormal regulation of emotions has been associated with the amygdala and ACC as well as the dorsal lateral PFC [62]. The hippocampus is a critical glutamatergic structure for learning, memory, and integration of information, and it is also involved in emotions such as anxiety and fear. In patients with schizophrenia, disrupted interaction between the PFC and hippocampus is thought to be the cause of cognitive deficits related to working memory, while the subsequent inputs from the hippocampus to the amygdala are likely to play a significant role in positive symptoms, especially delusions [65, 66]. In addition to glutamate, other neurotransmitters of the amygdala and limbic system include GABA, norepinephrine, and serotonin, all of which may be involved in the pathophysiology of schizophrenia in these areas.

Evidence for the antipsychotic effects of serotonin blockade, specifically 5-HT_{2A} antagonism, includes the fact that clozapine is a potent 5-HT_{2A} antagonist and that pimavanserin, a selective and potent 5-HT_{2A} reverse agonist/antagonist devoid of any dopamine binding is effective for Parkinson's disease psychosis [67, 68]. Clozapine's metabolite, norclozapine, is a muscarinic agonist, and activation of muscarinic receptors through this metabolite may contribute to clozapine's unique efficacy in treatment-resistant schizophrenia. Subsequent studies with experimental compounds found that activation of hippocampal interneurons via muscarinic M_2 and M_4 autoreceptors increases inhibitory postsynaptic currents in pyramidal neurons, which could normalize excitatory–inhibitory imbalances observed in schizophrenia via attenuation of pyramidal neuron hyperactivity as well as the resultant increase in VTA dopaminergic neurotransmission [69–71]. Additionally, muscarinic acetylcholine receptor activation in striatal interneurons can reduce cholinergic tone and subsequently striatal dopamine levels, offering another possible site of targeted dopamine modulation without the risk of cardiometabolic dysfunction [41].

The changes within these numerous circuits and cascades, starting with dysfunction in cortical glutamatergic transmission and ending in increased dopamine neurotransmission in

the associative and adjacent sensorimotor striatum, are parts of the neuronal pathology seen in schizophrenia. These pathways thus offer multiple sites at which to target new treatments with greater efficacy and safety, with the broad array of targets offering various avenues of modulation. However, an ideal treatment would still need to be efficacious across a range of symptoms as well as have a safety profile that does not include the major neurologic, endocrine, and cardiometabolic adverse effects that are seen among drugs that are currently available [72].

3 Novel Targets and Emerging Treatments with Reduced Likelihood of Metabolic Disturbance

As FGAs, serotonin–dopamine antagonist and partial D_2-agonist SGAs all act directly at D_2 receptors, they all possess inherent risks for D_2-related cardiometabolic, neurologic, and endocrine-related adverse effects; however, there are varying degrees of risk [11]. One strategy to improve the benefit–risk profile of these drugs has been to use combination treatments of SGAs with drugs that may decrease the risk of cardiometabolic adverse effects. One example is a Food and Drug Administration (FDA)-approved combination treatment for schizophrenia that includes the SGA olanzapine, a D_2-receptor antagonist with additional effects on 5-HT, and samidorphan, a μ-opioid antagonist and partial κ- and δ-opioid agonist, which has been shown to reduce medication-induced weight gain and metabolic dysfunction [73]. Efficacy, as measured by the Positive and Negative Syndrome Scale (PANSS) and Clinical Global Impression Severity (CGI-S) scales, was intact, as significant reductions from baseline in both measures compared with placebo were observed, even with long-term combination treatment over 52 weeks [74]. In the 12–24 week studies designed to reduce the risk of weight gain, weight changes were consistent across trials, with data showing superiority of the olanzapine-samidorphan combination versus olanzapine [73, 75, 76]. Specifically, data indicated 37% lower weight gain and a 50% reduced likelihood of ≥ 7 and ≥ 10% body weight gain with combination treatment versus olanzapine monotherapy, with results extending to early phase patients [73, 75, 76]. In addition, in patients free of metabolic syndrome or hypertension, compared with olanzapine, the olanzapine–samidorphan combination minimized the incidence of metabolic syndrome and hypertension by approximately 50% [77]. These results, together with data from augmentation studies with metformin and the glucagon-like peptide-1 receptor agonist liraglutide, [25, 78–82] illustrate that treatment with available and effective antipsychotics combined with medications that may mitigate the metabolic adverse effects of these drugs may be one strategy by which to reduce the inherent risks associated with dopamine receptor-blocking medications. However, to further obviate the concerns about potential adverse consequences of D_2 receptor blockade, non-postsynaptic dopamine receptor–modulating treatments that target alternative receptor systems implicated in the pathophysiology of schizophrenia have also been heavily studied.

3.1 Glutamate

The excitatory–inhibitory imbalance in cortical/hippocampal glutamatergic and hippocampal parvalbumin GABAergic interneuron neurotransmission were obvious targets for treatments to potentially address positive, negative, and cognitive symptoms of schizophrenia (Fig. 2) [83]. The NMDA receptor has co-agonist binding sites for glutamate and glycine, and the glycinergic site is also stimulated by D-serine. On the basis of the NMDA-hypofunction hypothesis of schizophrenia discussed above, facilitating NMDA receptor activity via adjunctive glycine or D-serine was studied, and initial clinical trials demonstrated improvements in both positive and negative symptoms; however, these findings could not be replicated in larger studies [41, 84–86]. Agonists of the glycine-modulatory site can either interact directly or indirectly with the glutamatergic system. D-cycloserine is an antibiotic metabolite that interacts directly with the NMDA glycine site as a partial agonist. In preclinical studies, administration of D-cycloserine has resulted in improved cognition, facilitated conditioned fear extinction, and improved memory consolidation and visual recognition memory [87]. Clinical studies with D-cycloserine have, however, been inconsistent, with some showing therapeutic efficacy for negative symptoms and cognition and others showing no effect. Explanations for the inconsistent results include insufficient central blood levels, drug–drug effects, a small therapeutic window for D-cycloserine, and possible neurotoxic effects.

Indirect effects at the glycine-modulatory site involve enhancement of synaptic glycine/D-serine through blocking astrocytic glycine transporters [87]. Studies with glycine transporter type 1 inhibitors have been investigated, but the most extensively studied, bitopertin, failed in phase 2 and phase 3 trials [88, 89]. Conversely, slowing D-serine metabolism using a D-amino acid oxidase inhibitor (DAAO) has shown early promise in patients with chronic schizophrenia, although recent trials for negative symptoms have not been positive [90, 91] (press release). Unfortunately, some inhibitors of D-serine metabolism show both poor bioavailability and inability to effectively cross the blood–brain barrier [92]. Nevertheless, luvadaxistat, a DAAO inhibitor, is currently being studied for cognitive impairment in schizophrenia [93, 94]. Furthermore, iclepertin, a glycine transporter-1 inhibitor

separated from placebo in a phase 2 trial for cognition versus placebo (not statistically significant for functional improvement) [95], and is being tested in phase 3 trials for cognitive impairment in schizophrenia [94]. Table 1 outlines study designs, safety, and available metabolic results for all of the discussed emerging treatments.

3.2 Nicotinic and Muscarinic Receptor Agonists

As mentioned, cholinergic targets have been of interest, with preclinical and early proof-of-concept studies indicating that α7 nicotinic acetylcholine receptor (α7-nAChR) and muscarinic acetylcholine receptor (mAChR) activation results in antipsychotic/pro-cognitive effects in animal models, as well as improvements in positive and cognitive symptoms in patients with schizophrenia [96]. α7-nAChR agonists have been shown to reverse the hyperdopaminergic state in the methylazoxymethanol acetate development disruption rodent model of schizophrenia, likely through ventral hippocampal modulation of dopamine neuron population activity, and have been shown to contribute to the release of dopamine in the nucleus accumbens [97]. Postmortem immunohistochemical/binding studies show reduced levels of α7-nAChR in brain regions thought to be affected in schizophrenia (e.g., hippocampus, thalamus, cingulate cortex) [96]. Genetic studies also link dysfunction in the α7-nAChR to increased risk for schizophrenia, and nicotinic agonists can normalize many sensory processing deficits that occur in schizophrenia [98]. From these insights, nicotinic α7 receptor agonists were studied for many years for the treatment of positive and cognitive symptoms of schizophrenia, but with mixed results. Issues with dosing and subtype selectivity of α7-nAChR agonists may have been confounding factors in understanding the role of activation of this receptor in schizophrenia, and new ligands with more specificity were developed [i.e., full agonists, partial agonists, and positive allosteric modulators (PAMs)]. Results with these α7-nAChR agonists, however, have been inconclusive. In a meta-analysis of eight double-blind, placebo-controlled studies examining efficacy and safety of various α7-nAChR agonists in treating the negative and cognitive symptoms of schizophrenia, no significant effects of the agonists on cognitive function or negative symptoms were found over placebo [99]. DMXB-A is a partial α7-nACh agonist that showed improvements in attention and working memory as well as reductions in hippocampal neuronal hyperactivity in phase 2 clinical studies; however, no significant benefits were observed with a slow-release version of the drug [98]. Encenicline, another α7 partial agonist, had statistically significant benefits over placebo on multiple cognitive measures when administered as adjunctive treatment in patients with schizophrenia [100]. In phase 3 studies, however, encenicline had significant adverse effects and showed no treatment benefits for schizophrenia [98]. Similar inconsistent results have been observed following adjunctive treatment with α7-nAChR full agonists, and although positive allosteric modulators showed promise in preclinical studies, none have shown significant benefits in cognition or negative symptoms in phase 3 trials [41]. Further, a recent meta-analysis of 13 randomized controlled trials of adjunctive α7-nAChR agonists in schizophrenia found that no significant effects were observed in speed of processing, attention/vigilance, working memory, verbal learning, visual learning, social cognition, or problem solving versus placebo [101]. Thus, the role of α7-nAChR modulation in schizophrenia remains unclear, and additional well-controlled clinical trials will be necessary to provide a clearer picture of how this receptor can function in the treatment of the disorder.

While nicotinic strategies have been disappointing to date, muscarinic agonism has now moved to the forefront of viable non-postsynaptic antidopaminergic antipsychotic mechanisms with positive data in clinical trials. There are five known G protein-coupled human muscarinic receptor subtypes (M_1–M_5) that are widely distributed in the central nervous system [102, 103]. These receptor subtypes are subdivided into two classes based on their coupling to G protein-dependent signal transduction pathways. M_1, M_3, and M_5 are located mostly postsynaptically and are stimulatory, coupling primarily through $G_{q/11}$ to stimulate phospholipase C, which releases inositol 1,4,5-trisphosphate (IP_3) [104, 105]. IP_3 release increases intracellular calcium, resulting in greater excitatory postsynaptic currents. M_2 and M_4, which make up the second class of mAChRs, are located mostly presynaptically and are inhibitory, coupling with $G_{i/o}$, which inhibits adenylate cyclase and leads to a decrease in cyclic adenosine monophosphate (cAMP), resulting in suppression of neuronal excitation [104, 105]. Elucidating and isolating the individual mechanisms of action of these receptors in schizophrenia is a challenge in part because the orthosteric binding site is highly conserved across all five receptor subtypes, making synthesis of selective ligands difficult [104, 105].

The various subtypes of muscarinic AChRs seem to play a unique role in the pathophysiology of schizophrenia and in modulation of striatal dopamine release. The distribution of muscarinic AChRs is not uniform throughout the brain, with the M_1 and M_4 receptors being predominantly expressed in the striatum [104]. Striatal cholinergic interneurons (SCIs) tonically inhibit striatal dopamine release, primarily through the M_4 receptor [106, 107]. These neurons play a crucial role in regulating the activity of other striatal neurons, particularly the medium spiny neurons (MSNs), which are the main striatal output neurons [108]. Studies have implicated dysfunction in SCIs (e.g., alterations in density, morphology, and gene expression) in patients with schizophrenia, which could result in abnormal cholinergic signaling in the

Table 1. Study design, safety, and metabolic results for clinical trials of discussed emerging treatments [73, 75, 76, 88, 89, 95, 100, 103, 128, 130, 140, 152]

Drug	Daily doses	Study type	Sample size	Treatment length	Patient population	Overall safety				Metabolic data[a]				
						Deaths	AEs, *n* (%)	SAEs, *n* (%)	AE-related discontinuations, *n* (%)	Weight	Glucose (mg/dL)	Insulin (μIU/mL)	HbA1C (%)[b]	LDL/HDL (mg/dL)
Olanzipine/Samidorphan	OLZ/SMDP 5 mg/5 mg 10 mg/10 mg 20 mg/20 mg or OLZ/PBO	Randomized, PBO-controlled, ph 2, multicenter, safety, dose-ranging, open-label OLZ, double-blind SMD	*N* = 347	12 weeks	18–50 years of age, clinically stable schizophrenia, BMI 17–30 kg/m^2	0	OLZ + SMDP: 127 (54.3) OLZ + PBO: 41 (54.7)	OLZ + SMDP: 11 (4.7) OLZ + PBO: 2 (2.7)	OLZ + SMDP: 21 (9.0) OLZ + PBO: 3 (4.0)	− 37% versus OLZ monotherapy	OLZ + SMDP: 5.4 OLZ + PBO: 4.1	OLZ + SMDP: 5.0 OLZ + PBO: 10.8	NA	OLZ + SMDP: 7.4/− 2.1 OLZ + PBO: − 11.5/− 3.2
	OLZ/SMDP 10 mg/10 mg 20 mg/10 mg or OLZ 10 or 20 mg	Randomized, ph 3, multicenter, double-blind (ENLIGHTEN-2)	*N* = 550	24 weeks	18–55 years of age, clinically stable schizophrenia, BMI 18–30 kg/m^2	0	OLZ + SMDP: 203 (74.1) OLZ: 227 (82.2)	OLZ+SMDP: 10 (3.6) OLZ: 7 (2.5)	OLZ + SMDP: 33 (12.0) OLZ: 27 (9.8)	OLZ/SMDP: 4.21% OLZ: 6.59% (LS mean diff − 2.38%)	OLZ+SMDP: 4.5 OLZ: 2.3	OLZ + SMDP: 3.22 OLZ: 3.40	OLZ + SMDP: 0.06 OLZ: 0.07	OLZ + SMDP: 0.6/− 5.1 OLZ: 0.9/− 4.5
	OLZ/SMDP 10 mg/10 mg 15 mg/10 mg 20 mg/10 mg	Open-label, ph 3, multicenter, extension (ENLIGHTEN-2-EXT)	*N* = 265	52 weeks	Completers of ENLIGHTEN-2, 18–55 years of age, clinically stable schizophrenia, BMI 18–30 kg/m^2	0	161 (60.8)	5 (1.9%)	15 (5.7)	Mean (SD), kg − 0.03 (6.22)	1.3	2.5	0.03	− 1.5/− 1.3
Iclepertin	Iclepertin 2, 5, 10, 25 mg PBO	Randomized, ph 2, double-blind, parallel-group, multicenter, PBO-controlled	*N* = 509	12 weeks	18–50 years of age, clinically stable schizophrenia ≥ 3 months before randomization, on stable treatment	0	Iclepertin 2 mg: 50 (59) Iclepertin 5 mg: 44 (52) Iclepertin 10 mg: 35 (41) Iclepertin 25 mg: 36 (42) PBO: 74 (44)	Iclepertin 2 mg: 2 (2) Iclepertin 5 mg: 4 (5) Iclepertin 10 mg: 2 (2) Iclepertin 25 mg: 4 (5) PBO: 4 (2)	Iclepertin 2 mg: 5 (6) Iclepertin 5 mg: 4 (5) Iclepertin 10 mg: 0 (0) Iclepertin 25 mg: 2 (2) PBO: 4 (2)	NA	NA	NA	NA	NA
Xanomeline	Xanomeline 225 mg PBO	Randomized, pilot study, double-blind, PBO-controlled	*N* = 20	4 weeks	18–60 years of age, diagnosis of schizophrenia or schizoaffective disorder, acute exacerbation of schizophrenia	NA	NA	NA	NA	NA	NA	NA	NA	NA

Table 1. (continued)

Drug	Daily doses	Study type	Sample size	Treatment length	Patient population	Overall safety				Metabolic data[a]				
						Deaths	AEs, *n* (%)	SAEs, *n* (%)	AE-related discontinuations, *n* (%)	Weight	Glucose (mg/dL)	Insulin (μIU/mL)	HbA1C (%)[b]	LDL/HDL (mg/dL)
Xanomeline-Trospium	Xanomeline 125 mg + Trospium 30 mg bid PBO	Randomized, ph 2, double-blind, multicenter, PBO-controlled	*N* = 182	5 weeks	18–60 years of age, primary diagnosis of schizophrenia, PANSS total score ≥ 80 (≥ 5 on one positive symptom or ≥ 4 on 2 positive symptoms)	0	Xanomeline + trospium: 48 (54) PBO: 39 (43)	Xanomeline + trospium: 1 (1) PBO: 0 (0)	Xanomeline + trospium: 2 (2) PBO: 2 (2)	Mean, kg Xanomeline + trospium: 1.5 ± 2.8 PBO: 1.1 ± 3.5	NA	NA	NA	NA
Emraclidine	Emraclidine 5–40 mg PBO	Part A: Sequential assignment, randomized, ph 1b, multiple ascending-dose	*N* = 49	NA	18–50 years of age, primary diagnosis of schizophrenia, PANSS total score ≤ 80	0	Emraclidine: 16 (41) PBO: NA	NA	NA	NA	NA	NA	NA	NA
	Emraclidine 30 mg qd Emraclidine 20 mg bid PBO	Part B: Randomized, ph 1b, PBO-controlled	*N* = 49	6 weeks	18–55 years of age, primary diagnosis of schizophrenia, PANSS total score ≥ 80, CGI-S score ≥ 4, PANSS positive subscale score ≥ 4 for at least 2 positive subscale items	0	Emraclidine 30 mg qd: 14 (52) Emraclidine 20 mg bid: 15 (56) PBO: 14 (52)	Emraclidine 30 mg qd: 2 (7.0) Emraclidine 20 mg bid: 1 (4.0) PBO: 0 (0)	Emraclidine 30 mg qd: 2 (7.0) Emraclidine 20 mg bid: 1 (4.0) PBO: 0 (0)	Mean (SD), kg Emraclidine 30 mg qd: 1.4 (4.3) Emraclidine 20 mg bid: 1.7 (3.1) PBO: 1.6 (4.0)	NA	NA	NA	NA

Table 1. (continued)

Drug	Daily doses	Study type	Sample size	Treatment length	Patient population	Overall safety				Metabolic data[a]				
						Deaths	AEs, *n* (%)	SAEs, *n* (%)	AE-related discontinuations, *n* (%)	Weight	Glucose (mg/dL)	Insulin (μIU/mL)	HbA1C (%)[b]	LDL/HDL (mg/dL)
Ulotaront	Ulotaront 50 mg Ulotaront 75 mg PBO	Randomized, ph 2, double-blind, multicenter	*N* = 245	4 weeks	18–40 years of age, diagnosis of schizophrenia ≥ 6 months, acute exacerbation of psychotic symptoms for ≤ 2 months, PANSS total score ≥ 80 and CGI-S score ≥ 4	1	Ulotaront 50 or 75 mg: 55 (45.8) PBO: 63 (50.4)	Ulotaront 50 or 75 mg: 2 (1.6) PBO: 4 (3.2)	Ulotaront 50 or 75 mg: 10 (38.5) PBO: 8 (30.8)	Mean, kg Ulotaront 50 or 75 mg: 0.3 ± 1.9 PBO: − 0.1 ± 2.3	Median change from baseline, mmol/L Ulotaront 50 or 75 mg: 0.0 PBO: 0.1	NA	NA	LDL, mmol/L Ulotaront 50 or 75 mg: − 0.1 PBO: 0
	Ulotaront 25 mg Ulotaront 50 mg Ulotaront 75 mg	Open-label safety extension study	*N* = 157	26 weeks	18–40 years of age, diagnosis of schizophrenia ≥ 6 months, acute exacerbation of psychotic symptoms for ≤ 2 months, PANSS total score ≥ 80 and CGI-S score ≥ 4, completion of 4 week lead in study	0	Ulotaront 25, 50, or 75 mg: 88 (56.4)	Ulotaront 25, 50, or 75 mg: 15	Ulotaront 25, 50, or 75 mg: 18 (11.5)	Mean (SD), kg Ulotaront 25, 50, or 75 mg: − 0.3 (3.7)	Median Ulotaront 25, 50, or 75 mg: 2.0	NA	Median Ulotaront 25, 50, or 75 mg: 0.0	Ulotaront 25, 50, or 75 mg: − 9.0/0.0

AE adverse event, *bid* twice daily, *BMI* body mass index, *CGI-S* Clinical Global Impressions Scale, *HbA1c* hemoglobin A1c, *HDL* high-density lipoprotein, *LDL* low-density lipoprotein, *LS* least squares, *NA* not available, *OLZ* olanzapine, *PANSS* Positive and Negative Syndrome Scale, *PBO* placebo, *ph* phase, *qd* once daily, *SAE* serious adverse event, *SD* standard deviation, *SMDP* samidorphan

[a]Change from baseline to study end. [b]Nonfasting.

striatum [109]. Numerous consequences of this imbalance in signaling are possible. For example, increased cholinergic activity in the striatum due to dysfunction of SCIs could lead to excessive inhibition of MSNs [104]. This increased inhibition could disrupt the normal balance between the direct and indirect dopaminergic pathways of the basal ganglia circuitry that are involved in numerous processes including motor control and cognition, as well as positive and negative symptoms observed in schizophrenia [110]. Modulation of dopamine release in the striatum through cholinergic signaling may, thus, result in an imbalance between dopamine and acetylcholine, which may have significant impact in the pathophysiology of schizophrenia.

In terms of dopaminergic input to the striatum, M_5 AChRs on the cell bodies of dopaminergic neurons in the VTA receive cholinergic input from the laterodorsal tegmental (LDT) and the pedunculopontine (PPT) nuclei (Fig. 3A) [105]. Stimulation of the LDT triggers a long-term increase in dopamine release from the VTA to the nucleus accumbens in the ventral striatum, another area implicated as having dysfunctional dopamine neurotransmission in schizophrenia [111, 112]. This sustained increase in dopamine release is not observed in M_5 knockout mice, likely due to a lack of excitatory M_5 receptors located on the dopaminergic VTA neurons in these mice [111, 112]. While M_5 AChRs serve to increase dopaminergic release from the VTA, activation of upstream midbrain M_4 autoreceptors may decrease dopaminergic output through attenuation of acetylcholine release from LDT and PPT inputs (Fig. 3A) [105, 107]. In the nucleus accumbens, M_4 autoreceptors on cholinergic interneurons regulate acetylcholine release, which indirectly modulates the release of dopamine through nicotinic autoreceptors on the dopaminergic neurons (Fig. 3B) [108]. This modulation of release is complex, resulting in an interneuronal fine tuning of dopamine that depends on the amount of dopamine release. During low-frequency dopamine firing, activation of these nAChRs may result in excitatory stimulation and increased dopamine release. However, during

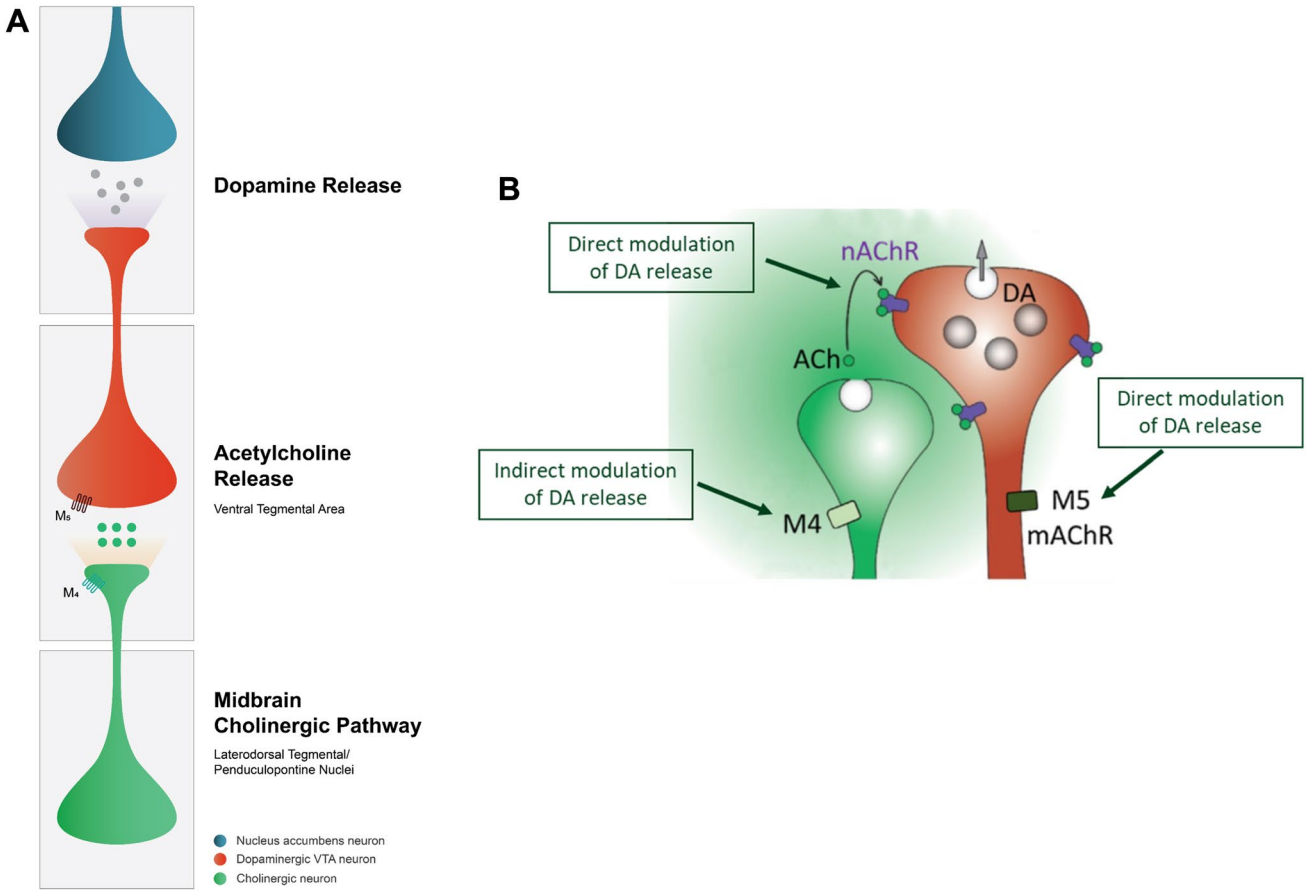


Fig. 3 **A** Midbrain muscarinic input increases dopamine release through activation of M_4 and M_5 receptors in areas related to psychosis [105]. **B** Modulation of dopamine release by acetylcholine via subtypes of nicotinic and muscarinic cholinergic receptors in the nucleus accumbens Sulzer, Cragg, Rice [108]. Reprinted from *Basal Ganglia*, Sulzer and Cragg [108], Copyright 2016, with permission from Springer Publishing Company. *ACh* acetylcholine, *DA* dopamine, *M_5 or M_4 mAChR* M5 or M4 subtype of muscarinic acetycholine receptor, *nAChR* nicotinic acetycholine receptor, *VTA* ventral tegmental area

high-frequency dopamine firing, activation of these nACh autoreceptors suppresses dopamine release in the nucleus accumbens. At the same time, M_5 AChRs located on the dopaminergic neuron can also directly decrease the release of dopamine in the nucleus accumbens (Fig. 3B). Localization of these AChRs in the VTA, nucleus accumbens, and ventral striatum, along with evidence of their various effects, indicates that AChRs have the propensity to regulate dopaminergic transmission in numerous subtle ways that could have sizeable implications for patients with schizophrenia.

Preclinical studies in muscarinic knockout mice have demonstrated the importance of muscarinic receptors in the pathophysiology of schizophrenia, especially of the M_1 and M_4 subtypes [106, 113]. Multiple studies of postmortem brains from patients with schizophrenia and healthy controls have shown that patients with schizophrenia had significantly lower expression of M_1/M_4 receptors in various areas of the hippocampus and PFC than brains of those who had no history of psychiatric illness; across these studies, ~ 25% of patients expressed ~ 75% lower levels of the M_1 receptor compared with control individuals [114–116]. M_1 receptor-mediated modulation of psychosis may be due to regulation of top-down cortical circuits, modulation of the excitability of striatal neurons, and/or enhanced collateralization between basal ganglia pathways [117]. More specifically, disinhibition of excitatory output from the frontal cortex may lead to hyperstimulation of mesocorticolimbic neurons, including in the associative striatum, resulting in positive symptoms of schizophrenia. The M_1 receptor is expressed on cortical GABAergic neurons that connect to the primary output neurons of the frontal cortex, such that when M_1 receptors are activated they increase GABA release onto cortical pyramidal neurons leading to decreased glutamatergic input to the midbrain dopamine neurons [117]. Functionally, M_1 activation in the hippocampus/forebrain potentiates NMDA receptor currents, which play a considerable role in the regulation of cognitive functions and neural circuitry that is disrupted in schizophrenia, suggesting that modulation of M_1 AChRs may have effects on cognitive and psychotic deficits present in schizophrenia [96]. M_4 receptors are also highly expressed in the central nervous system (CNS) as pre- or postsynaptic autoreceptors in the hippocampus, cortex, limbic system, and basal ganglia, and have been implicated in regulating dopaminergic neurons involved in movement and cognition [104, 107].

Studies in rodent models confirmed the antipsychotic activity of xanomeline, an orthosteric M_1/M_4 agonist. Results showed reduced dopamine firing in the VTA, reversal of dopamine agonist-induced disruptions, and low likelihood of inducing catalepsy with xanomeline [118–120]. In addition, radioligand binding studies have shown that xanomeline is a 5-HT_{1A} and 5-HT_{1b} agonist, which may allow for benefits in cognition; however, these results have not been fully confirmed [121, 122]. The preclinical profile of xanomeline indicates that binding is nonselective, while the functional effects are much more selective [118, 120, 123–126]. In early clinical trials, xanomeline was shown to significantly improve cognitive function and psychotic behaviors in patients with Alzheimer's disease (N = 343); however, gastrointestinal adverse events (AEs) suggested tolerability issues with treatment [124, 127]. These results have been similar to those seen in patients with schizophrenia.

An exploratory 4 week, double-blind, placebo-controlled study was conducted to assess the efficacy of xanomeline on various clinical outcomes in patients with schizophrenia (N = 20) [103]. Results showed statistically significant improvements with xanomeline versus placebo in Positive and Negative Syndrome Scale (PANSS) total score, positive and negative symptom subscale scores, and Clinical Global Impression (CGI) scores. No significant extrapyramidal symptoms were detected. Unfortunately, similar to the study of xanomeline in Alzheimer's disease, gastrointestinal AEs were reported more frequently in the xanomeline groups versus those on placebo, although most were mild or moderate with none leading to discontinuation of treatment. No significant metabolic or weight changes were reported with xanomeline treatment compared with placebo. Although this was a small pilot study, these data indicated that xanomeline should be further investigated as a potential new treatment for schizophrenia that may not induce the metabolic and extrapyramidal AEs observed with current antidopaminergic antipsychotics. Nevertheless, the risk of syncope, nausea, and vomiting, among other peripheral procholinergic AEs, stalled the further development of xanomeline.

More recently, however, the efficacy and safety of xanomeline combined with the non-centrally active anticholinergic trospium, added to neutralize the peripheral pro-cholinergic AEs, was assessed in a 5 week phase 2 trial in adults with acute exacerbations of schizophrenia [128]. Treatment with xanomeline–trospium resulted in greater improvements in PANSS positive and negative symptom subscores, categorical CGI severity (CGI-S) scores, and PANSS Marder negative symptom subscore at week 5 compared with placebo (Fig. 4A–E). The effect size for reduction in total PANSS score was in the high–medium range, 0.75, hypothesized to possibly be related to a very low placebo response (Fig. 4F). The incidence of cholinergic/anticholinergic AEs was higher in the

active treatment group versus placebo, including gastrointestinal AEs; however, the percentage of patients who discontinued treatment were similar across both groups, and no discontinuations in the xanomeline–trospium group occurred due to gastrointestinal AEs (Table 2). Additionally, no differences in weight gain, somnolence, restlessness, or extrapyramidal symptoms were observed across the two groups. These study results provide positive evidence for the use of xanomeline–trospium as an alternative treatment for schizophrenia that does not appear to induce the metabolic or extrapyramidal AEs seen with many of the dopaminergic antipsychotics. Lastly, topline results of the phase 3 trial in adults with an acute exacerbation of schizophrenia were announced in a press release on 8 August 2022 [129]. Like the phase 2b study, this was a 5 week, fixed titration, double-blind, placebo-controlled inpatient trial, but in this study, 252 adults were randomized in a 1:1 manner to xanomeline-trospium or placebo. The results confirmed the findings of the phase 2b trial, with an effect size for reduction in total PANSS score in the medium range (Cohen's $d = 0.61$), and a similar efficacy and tolerability profile as reported for the 2b trial. Overall discontinuation rates were similar between treatment and placebo groups (25% versus 21%), and discontinuation rates related to adverse effects were also similar between the two groups (xanomeline–trospium 7% versus placebo 6%).

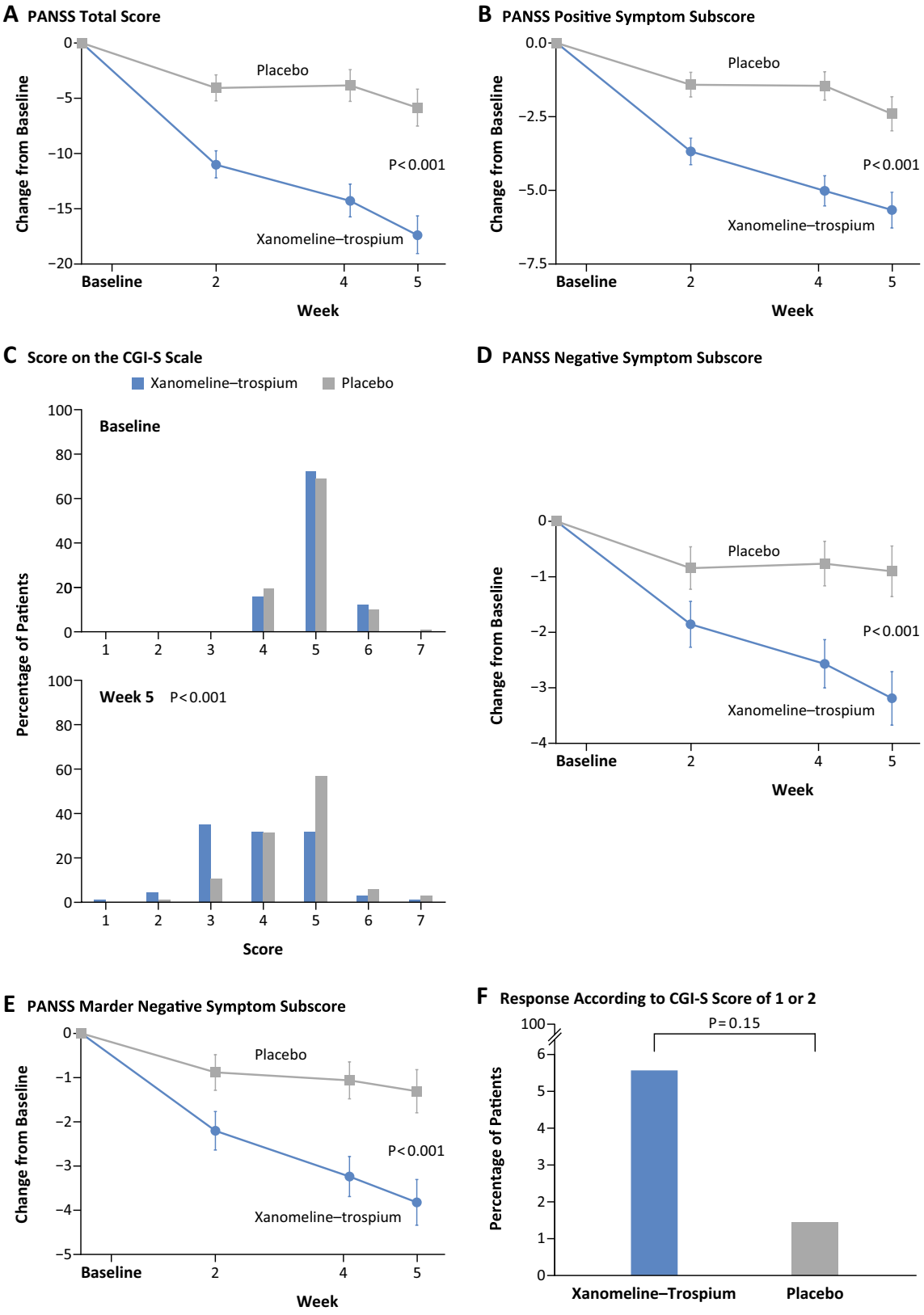
Emraclidine (CVL-231) is a muscarinic M_4-selective PAM in development for schizophrenia [130]. While the orthosteric site is highly conserved across all five muscarinic receptor subtypes, the allosteric sites vary considerably, thereby allowing a targeted approach to modulating M_4 activity through the use of allosteric binding sites. A small phase 1b study in 81 adults with acutely exacerbated schizophrenia demonstrated statistically significant and clinically meaningful antipsychotic effects, both with the 30 mg once daily and 20 mg twice daily doses, in PANSS total, positive, and negative scores. Emraclidine was generally well tolerated, with a similar incidence of treatment-emergent AEs (TEAEs) to placebo, including only few peripheral procholinergic AEs and no weight gain or extrapyramidal symptoms.

Taken together, these data indicate that modulation of mAChRs should be further explored as a mechanism for the treatment of schizophrenia, as it could lead to benefits in various symptoms without causing many of the AEs seen with currently available antipsychotics. However, further studies are necessary to better understand the true potential for this mechanism of treatment across different symptom domains and patient subgroups with schizophrenia.

3.3 Trace Amine-Associated Receptor 1 Agonists

Another target that may lead to promising treatments for schizophrenia is agonism of trace amine-associated receptor 1 (TAAR1). TAAR1 is a G protein-coupled receptor discovered in 2001 that is activated by endogenous trace amines and interacts functionally with dopamine and serotonin receptors [41, 131–133]. Endogenous levels of trace amines in the CNS are very low (several hundred-fold lower than monoamine neurotransmitters) [134]. The regional expression of mammalian TAAR1 receptors shows their presence in the PFC, striatum, amygdala, nucleus accumbens, VTA, and dorsal raphe, all of which are implicated in the pathophysiology of schizophrenia [131, 134, 135]. Genetically, the TAAR family of receptors have been localized to human chromosome 6q23.2, a putative susceptibility locus for schizophrenia; moreover, several rare variants in TAAR1 have been observed in both patients with psychiatric and metabolic disorders [134–136]. TAAR1 may also be activated by monoamine neurotransmitters, such as dopamine, serotonin, norepinephrine, and some of their metabolites [134, 135, 137]. Activation of TAAR1 may modulate presynaptic dopamine synthesis, producing antipsychotic effects, and may also induce changes in D_2 receptor-mediated signaling through the formation of heterodimers that are internalized from the cell surface to inside the cell [137–139].

Results from TAAR1-knockout mice studies and trials showing that selective TAAR1 agonism inhibits both dopaminergic and serotonergic neuronal activity led to further studies characterizing the role of TAAR1 in the modulation of monoaminergic circuits (Fig. 5) [139–142]. TAAR1 is an intracellular $G\alpha_s$-coupled receptor that stimulates adenylyl cyclase and increases production of cAMP, which can lead to protein kinase A and protein kinase C phosphorylation; these kinases regulate many cognitive processes that are disrupted in schizophrenia (e.g., attention, decision-making) [132, 133, 143, 144]. Although TAAR1 receptors are bound to intracellular ligands, a recent in vitro study with the TAAR1 agonist SEP-363856 (ulotaront) indicates that agonists can activate the TAAR1–D_2 receptor complex at the cell surface plasma membrane [137]. This surface activation results in recruitment of the G-protein $G\alpha_s$ and stimulation of G-protein-coupled inwardly rectifying potassium channels, which is one putative mechanism by which TAAR1 agonism may reduce dopaminergic activity in the VTA [134, 137]. A G-protein-independent, β-arrestin2-mediated pathway may be affected once TAAR1 and D_2 receptors form heterodimers. Formation of these heterodimers causes a shift


A PANSS Total Score
Change from Baseline
0
−5
−10
−15
−20
Placebo
P<0.001
Xanomeline–trospium
Baseline
2
4
5
Week
B PANSS Positive Symptom Subscore
Change from Baseline
0.0
−2.5
−5.0
−7.5
Placebo
P<0.001
Xanomeline–trospium
Baseline
2
4
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Week
C Score on the CGI-S Scale
Xanomeline–trospium
Placebo
Percentage of Patients
Baseline
Week 5 P<0.001
100
80
60
40
20
0
1
2
3
4
5
6
7
Score
D PANSS Negative Symptom Subscore
Change from Baseline
0
−1
−2
−3
−4
Placebo
P<0.001
Xanomeline–trospium
Baseline
2
4
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Week
E PANSS Marder Negative Symptom Subscore
Change from Baseline
0
−1
−2
−3
−4
−5
Placebo
P<0.001
Xanomeline–trospium
Baseline
2
4
5
Week
F Response According to CGI-S Score of 1 or 2
Percentage of Patients
100
6
5
4
3
2
1
0
P=0.15
Xanomeline–Trospium
Placebo

◂**Fig. 4** Efficacy of twice-daily xanomeline-trospium versus placebo in patients with acute schizophrenia exacerbation as measured by **A** PANSS total score, **B** PANSS Positive Symptom Subscore, **C** CGI-S scale, **D** PANSS Negative Symptom Subscore, **E** PANSS Marder Negative Symptom Subscore, and **F** response by CGI-S score [128]. From *New England Journal of Medicine*, Brannan et al. [128]. Copyright © 2021 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society. *CGI-S* Clinical Global Impressions Severity, *PANSS* Positive and Negative Syndrome Scale

from cAMP accumulation with TAAR1 alone to β-arrestin2 recruitment with the D_2 heterodimers. This process could have important implications, given the increasing recognition of the role played by non-G-protein-coupled pathways in the pathophysiology of schizophrenia [135, 145].

Other proposed active heterodimerizations between TAAR1 and G-protein-coupled receptors include 5-HT_{1B}, 5-HT_{2A}, and 5-HT_{1A}; however, the specific effects of these receptors in schizophrenia are not yet fully understood [134]. Behavioral deficits induced by NMDA receptor antagonists PCP, L-687, 414, and ketamine can be attenuated by TAAR1 agonists [134, 146]. Thus far, TAAR1 agonists have shown no direct affinity for NMDA receptors or any monoamine receptor beyond those discussed. Although TAAR1 seems to modulate a number of neurotransmitter systems indirectly [147], there is no evidence of direct binding to these receptors. There is preclinical evidence that TAAR1 may modulate inflammatory cytokine production, is expressed in human macrophages, and is involved in immunomodulation [148, 149]. However, the manner in which this activity may affect metabolic dysfunction and symptoms of schizophrenia is not yet clear and requires further elucidation. The underlying mechanisms behind this effect require further elucidation but may either involve modulation of glutamate-mediated transmission directly or effects on dopaminergic circuits, which lie downstream of cortical/hippocampal inputs. As stated earlier, cortical glutamatergic neurotransmission partly underlies the pathophysiology of schizophrenia, and the effects of TAAR1 on this circuitry has the propensity to reduce cognitive impairment through modulation of excitatory/inhibitory imbalances mediated by glutamate dysfunction in the cortex.

Of note, TAAR1 is also expressed in the β-cells of the pancreas, the stomach, and the small intestine [143, 150]. TAAR1 activation has been shown to reduce food intake, control glucose, delay gastric emptying, and, likely due to its colocalization with GLP-1 in the duodenum, may regulate hormone secretion that modulates gastric function and nutrient absorption (Fig. 6) [143]. TAAR1 also has the propensity to reduce metabolic dysfunction, in that TAAR1 agonism promotes antidiabetic signaling via a $G\alpha_s$-mediated pathway [150]. This pathway results in increased insulin secretion, improved β-cell function, and β-cell proliferation. In addition, TAAR1 agonists do not induce weight gain and can protect against olanzapine-induced weight gain [131]. Reduction in brain monoaminergic signaling via TAAR1 agonism also leads to reduced binge eating and impulsive behavior, which can both contribute to mitigating obesity and metabolic disease [150]. This effect is thought to occur via TAAR1-mediated downregulation of dopamine reward circuits. These findings further highlight the therapeutic potential of TAAR1. The combined effects of TAAR1-mediated reductions in binge eating, beneficial TAAR1 effects on pancreatic β-cells, insulin, gastric emptying, glucose control, and the many mechanisms by which TAAR1 can attenuate the symptoms of schizophrenia make it an exciting possible new target for treatment.

Following the identification of various preclinical pharmacological characteristics, two TAAR1 agonists are in development for the treatment of schizophrenia, with one already showing therapeutic potential in patients with schizophrenia. Ralmitaront (RO6889450) is a TAAR1 partial agonist, with more antagonism than agonist activity, that was in phase 2 development (NCT03669640). Two double-blind, placebo-controlled, randomized trials were underway to examine the preliminary efficacy and safety of ralmitaront in patients with schizophrenia (NCT03669640 and NCT04512066). However, a recent press release indicated that in both trials, ralmitaront missed its primary endpoint versus placebo, the reduction in total PANSS scores, and is no longer being studied [151].

Ulotaront (SEP-363856) is a TAAR1 agonist with functional 5-HT_{1A} agonist activity that was discovered based in part on a mechanism-independent approach using the in vivo phenotypic SmartCube® platform (PsychoGenics, Paramus, NJ, USA) and artificial intelligence (AI) algorithms [140, 152]. This approach involves training the AI system on the signature of known psychotropics (e.g., antipsychotics, antidepressants, anxiolytic) using over 2000 behavioral outcomes (e.g., activity, grooming). Importantly, this discovery process specifically eliminated molecules with D_2 or 5-HT_{2A} antagonism (antitargets) prior to animal behavioral screening. Ulotaront has been shown to inhibit dorsal raphe serotonergic neuronal firing and attenuate phencyclidine-induced hyperactivity in rodent models [140, 153]. In terms of cardiometabolic issues, preclinical data have shown that rats switched from olanzapine to ulotaront showed rapid reversal of olanzapine-induced weight gain and food intake compared with placebo (Fig. 7), supporting previous studies showing that TAAR1 agonism can reverse cardiometabolic dysfunction [131].

Table 2 Adverse events and safety during 5 weeks of treatment with xanomeline–trospium demonstrate that incidence of cholinergic/anticholinergic adverse events was higher with active treatment versus placebo, but the percentage of patients who discontinued treatment were similar across both groups (safety population) [128]

Variable	Xanomeline–trospium ($N = 89$)	Placebo ($N = 90$)
Any AE	48 (54)	39 (43)
SAE[a]	1 (1)	0 (0)
Severe AE[b]	1 (1)	1 (1)
AE leading to discontinuation	2 (2)	2 (2)
AE occurring in ≥ 2% of patients in xanomeline–trospium group		
Constipation	15 (17)	3 (3)
Nausea	15 (17)	4 (4)
Dry mouth	8 (9)	1 (1)
Dyspepsia	8 (9)	4 (4)
Vomiting	8 (9)	4 (4)
Headache	6 (7)	5 (6)
Somnolence	5 (6)	4 (4)
Akathisia	3 (3)	0 (0)
Dizziness	3 (3)	3 (3)
Increased weight	3 (3)	4 (4)
Tachycardia	3 (3)	2 (2)
Sedation	2 (2)	2 (2)
Diarrhea	2 (2)	4 (4)
Increased γ-glutamyltransferase level	2 (2)	0 (0)
Agitation	2 (2)	1 (1)
Insomnia	2 (2)	2 (2)
Decreased appetite	2 (2)	0 (0)
Hyperhidrosis	2 (2)	1 (1)
Mean change from baseline to week 5 in body weight, kg	1.5 ± 2.8	1.1 ± 3.5
Mean change from baseline to week 5 in score Simpson–Angus Scale[c]	− 0.1 ± 0.7	− 0.1 ± 0.8
Mean change from baseline to week 5 in Barnes Akathisia Rating Scale[d]	− 0.1 ± 1.0	0.0 ± 0.7

Data are given as *n* (%) or mean ± SD. The safety population included all the patients who had undergone randomization and had received at least one dose of xanomeline–trospium or placebo. Adverse events that occurred during the treatment period were defined as those that started or worsened from the time of the first dose of xanomeline–trospium or placebo (visit 1 at day 2) to the time of discharge (visit 9 at day 35). From *New England Journal of Medicine*, Brannan et al. [128]. Copyright © 2021 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.

AE adverse event, *SAE* serious adverse event

[a]A serious adverse event was defined as any adverse event that resulted in death, was immediately life threatening, led to inpatient hospitalization or prolongation of hospitalization, or caused persistent or clinically significant disability or incapacity

[b]A severe adverse event was defined as any event that was incapacitating or caused an inability to perform normal activities of daily living

[c]Scores on the Simpson–Angus Scale range from 0 to 40; higher scores indicate greater severity of drug-induced parkinsonian symptoms

[d]Scores on the Barnes Akathisia Rating Scale range from 0 to 14; higher scores indicate greater symptoms of akathisia

In 2020, data were published from a phase 2, randomized, flexible-dose, placebo-controlled, 4 week inpatient study of ulotaront in 245 acutely psychotic adult patients with schizophrenia [140]. Results for the primary endpoint showed a mean change from baseline in PANSS total score at week 4 that was significantly greater than placebo, with a least squares (LS) mean difference of − 7.5 between ulotaront and placebo (Fig. 8). Of note, statistically significant separation from placebo did not occur until week 3 for total symptoms and week 4 for CGI-S score, an interesting finding that requires further exploration once phase 3 results are available.

AEs with ulotaront were similar to those with placebo, including with respect to extrapyramidal symptoms (3.3

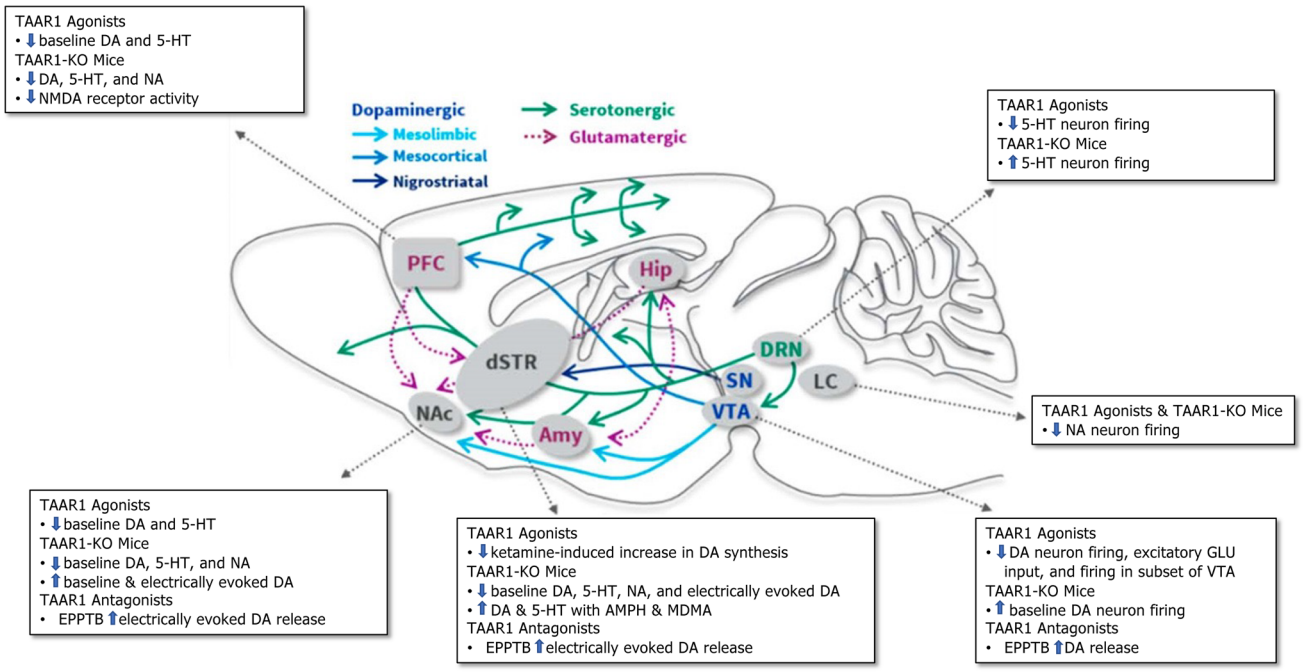

Fig. 5 TAAR1-mediated modulation of monoaminergic and glutamatergic circuits [134]. Simplified schematic of key serotonergic, dopaminergic, and glutamatergic pathways in the rodent brain including evidence from studies with synthetic ligands and TAAR1-KO mice. Reused from Dedic et al., *International Journal of Molecular Sciences* (under Creative Commons license CC BY). ↑ increase, ↓ decrease, − no change, *5-HT* serotonin, *AMPH* amphetamine, *Amy* amygdala, *dSTR* dorsal striatum/caudoputamen, *DA* dopamine, *DRN* dorsal raphe nucleus, *EPPTB* *N*-(3-ethoxyphenyl)-4-(1-pyrrolidinyl)-3-(trifluoromethyl)benzamide TAAR1 antagonist, *GLU* glutamate, *Hip* hippocampus, *KO* knockout, *LC* locus ceruleus, *MDMA* 3,4-methyl enedioxy methamphetamine, *NA* noradrenalin, *NAc* nucleus accumbens, *NMDA* *N*-methyl-D-aspartate, *PFC* prefrontal cortex, *SN* substantia nigra, *TAAR1* trace amine-associated receptor 1, *VTA* ventral tegmental area

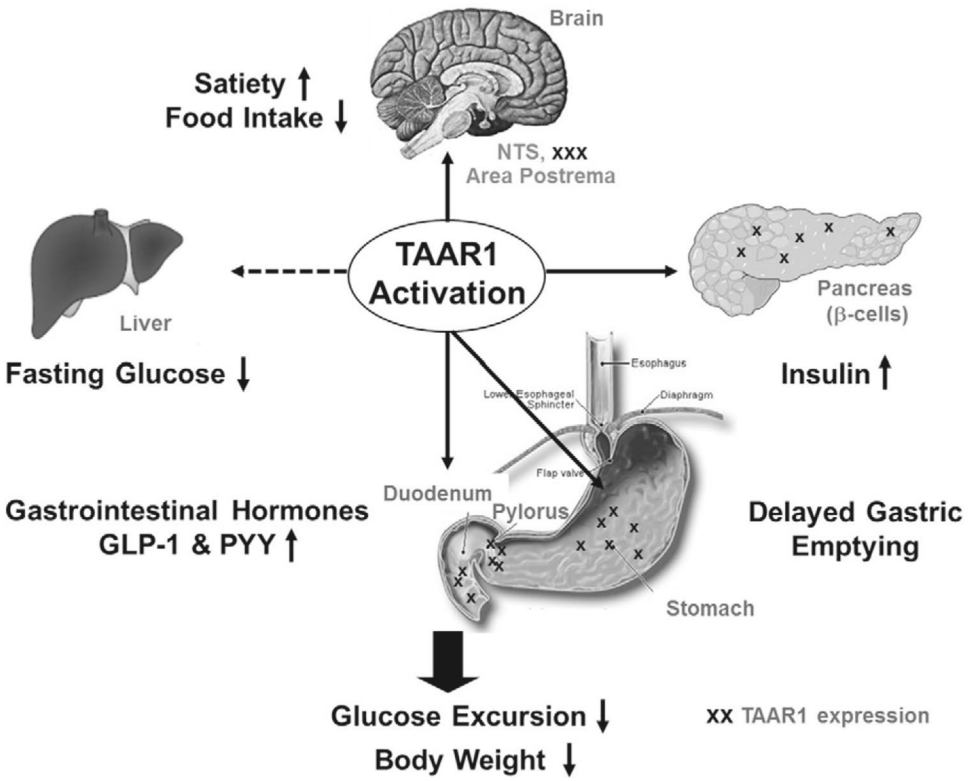

Fig. 6 TAAR1 effects on the gastrointestinal system [143, 150]. TAAR1 activation decreases food intake, reduces plasma glucose concentrations, and lowers body weight in part through insulin secretion and incretin-like effects in the gastrointestinal tract. TAAR1 expression in the periphery is denoted by "X." Reprinted from *Pharmacology and Therapeutics*, Berry et al. [143]. Copyright 2017, with permission from Elsevier. *GLP-1* glucagon-like peptide-1, *NTS* nucleus of the tractus solitarius, *PYY* peptide YY, *TAAR1* trace amine-associated receptor type 1

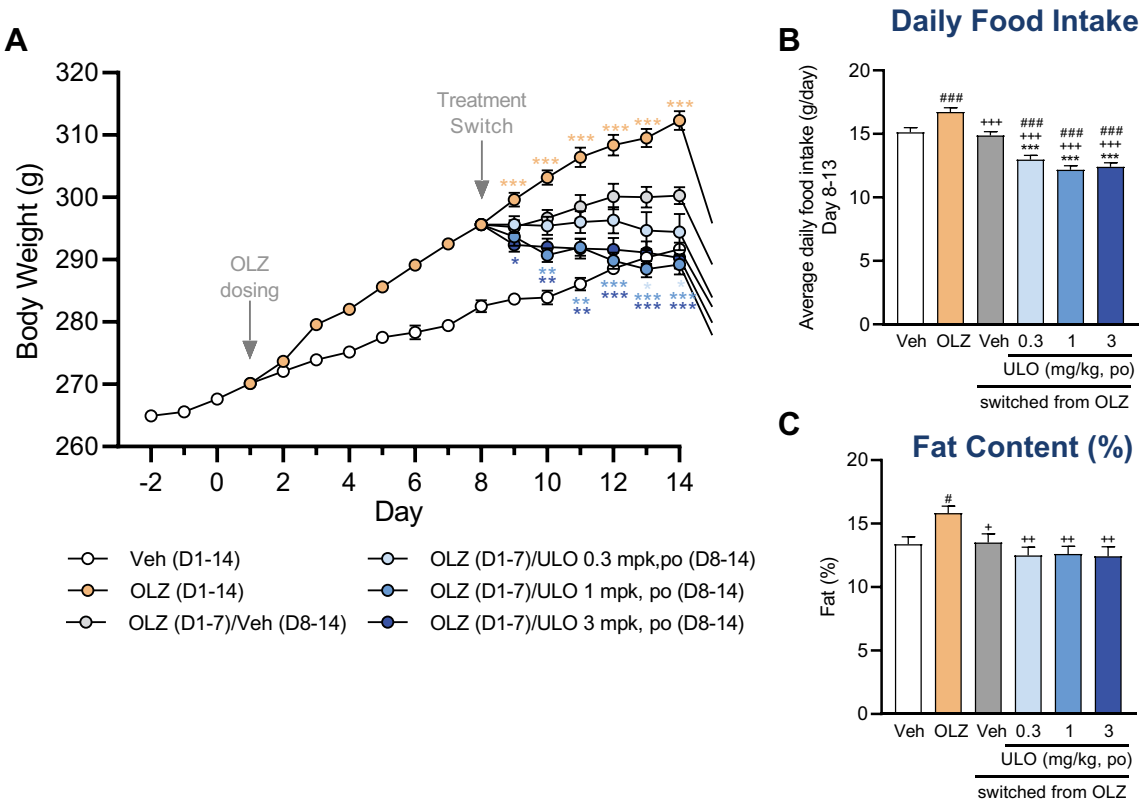

Fig. 7 Switch to ulotaront produced a more rapid reversal of olanzapine-induced weight gain and food intake compared with vehicle alone [154]. **A** Rats were dosed once daily (po) with vehicle or olanzapine (3 mg/kg, po) from day 1. From day 8 onwards, rats continued to receive olanzapine or were switched to vehicle or ulotaront (0.3, 1 or 3 mg/kg, po). **B** Average daily food intake (days 8–13). Water intake was not significantly altered. **C** Percent body fat content on day 15. Results are adjusted means and SEM; $^{*}p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.001$ versus OLZ/Veh; $^{\#}p < 0.05$, $^{\#\#\#}p < 0.001$ versus Veh/Veh; $^{+}p < 0.05$, $^{++}p < 0.01$ $^{+++}p < 0.001$ versus OLZ.; *N*= 12/group (D8–14). Reused with permission from Dedic et al. *D* day, *mpk* milligrams per kilogram, *OLZ* olanzapine, *po* oral administration, *SEM* standard error of the mean, *ULO* ulotaront, *Veh* vehicle

versus 3.2%, respectively), the percentage of patients who had to use medication to treat extrapyramidal symptoms, and results on movement disorder scales [140]. Changes in body weight, lipid levels, glucose, and prolactin were similar across treatment groups, and no other changes in metabolic laboratory or electrocardiogram results were observed. These safety data are consistent with expected results in the absence of D_2-binding with ulotaront. However, although no adverse metabolic changes were observed, longer and larger studies are necessary to further investigate the effects of ulotaront on cardiometabolic parameters. This study had one interesting limitation, namely, that patients over 40 years of age and those with greater illness chronicity (≥ 2 previous hospitalizations for schizophrenia exacerbations) were not included [140]. However, in the phase 3 trial program of ulotaront, the age range was extended to 60 years of age.

A 26 week open-label extension (OLE) was performed to provide more data on efficacy and safety (e.g., long-term metabolic changes) [152]. Over 26 weeks, ulotaront treatment resulted in mean (95% CI) change from baseline in PANSS total score of − 22.6 (− 25.6 to − 19.6; effect size, 1.46); however, this should be interpreted with caution due to the open-label nature of OLEs and the lack of a control. Nevertheless, even following 6 months of treatment with ulotaront, only slight changes from baseline in body weight [mean (SD), − 0.3 (3.7) kg], cholesterol (median, − 2.0 mg/dL), triglycerides (median, − 5.0 mg/dL), and prolactin (female median, − 3.4 ng/mL; male median, − 2.7 ng/mL) were observed. On the basis of available clinical data and its unique mechanism of action, ulotaront is a promising new agent that is in phase 3 development for the treatment of schizophrenia. Taken together, the TAAR1 agonists represent a novel pharmacologic class that may be effective in the treatment of schizophrenia without both cardiometabolic adverse effects and the typical side effects stemming from blockade of D_2 signaling.

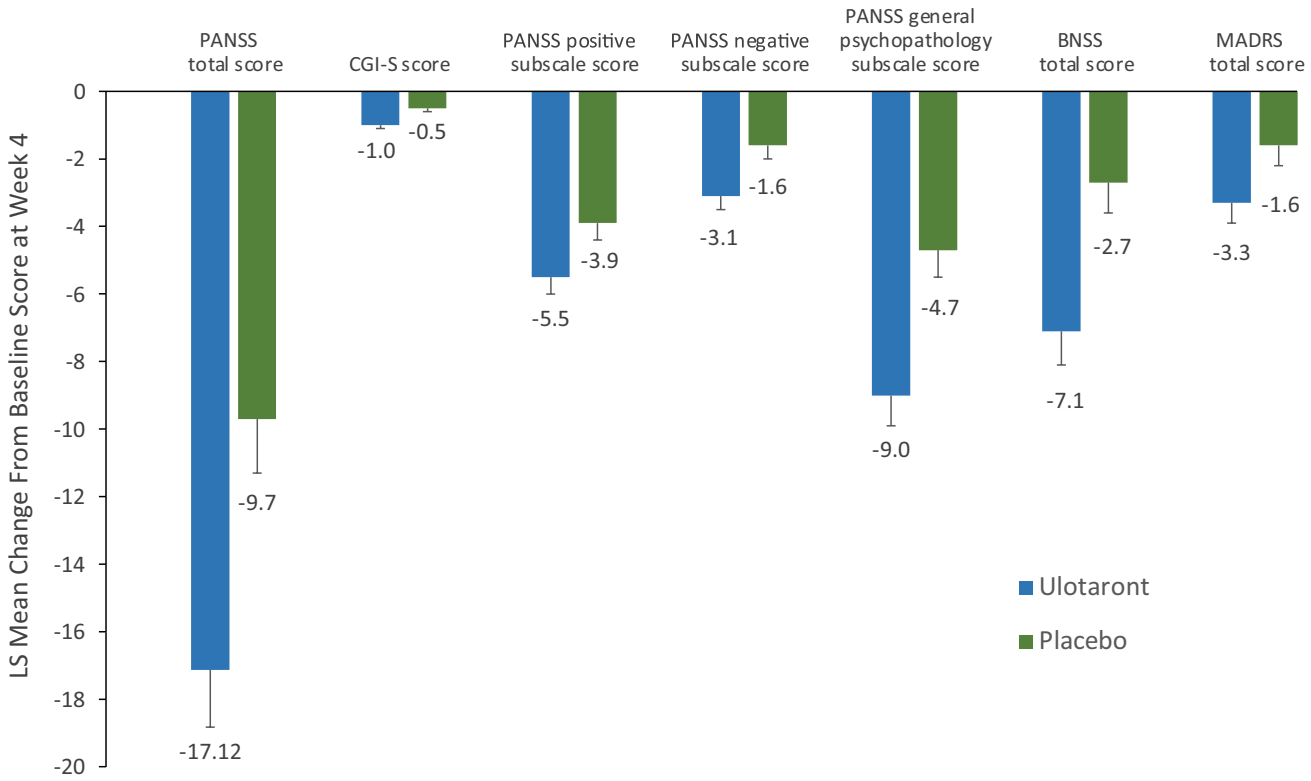

Fig. 8 Changes from baseline in efficacy measures at week 4 [140]. Values are mean ± SE. Changes in efficacy measures were evaluated with the use of a mixed model for repeated measures. The model included trial group, visit [day 4 and weeks 1, 2, 3, and 4 (categorical variables)], clinical site (pooled by country), and trial-group-by-visit interaction as factors and included the baseline PANSS total score as a covariate. At baseline, the PANSS total score and positive, negative, and general psychopathology subscale scores, the CGI-S score, and the MADRS total score were evaluated in 120 patients in the ulotaront group and in 125 patients in the placebo group, and at week 4, these scores were evaluated in 96 and 100 patients, respectively. At baseline, the BNSS total score was evaluated in 113 patients in the ulotaront group and in 119 patients in the placebo group, and at week 4, the BNSS score was evaluated in 89 and 96 patients, respectively. The estimated effect size was for PANSS total score was 0.45 (p = 0.001). Effect size was calculated as the absolute value of the difference between the ulotaront group and the placebo group in the change in score from baseline at week 4, divided by the pooled standard deviation of the between-group difference in the change in score. For all secondary endpoints, no inferences can be made from the results for the secondary end points because there was no plan for adjustment for multiple comparisons. *BNSS* Brief Negative Symptom Scale; *CGI-S* Clinical Global Impression–Severity scale, *LS* least squares, *MADRS* Montgomery-Åsberg depression rating scale, *PANSS* Positive and Negative Syndrome Scale

4 Conclusions

It is important to again note that medications are but one input into the overall metabolic burden associated with schizophrenia. As stated, there are also direct underlying biological components of the illness itself (e.g., inflammatory/neuroendocrine factors, genetics) as well as lifestyle elements, often driven by economic necessity, which make a significant contribution to the metabolic dysfunction observed in these patients. Because patients with schizophrenia have this increased risk for cardiometabolic abnormalities, despite antipsychotic exposure, the effects of novel medications on cardiometabolic status beyond neutrality (i.e., improvement in patients' existing comorbidities) are of great importance. Thus far, for the newer compounds discussed above, appropriate long-term results for cardiometabolic effects have not yet been released, with the exception of continued cardiometabolic neutrality in a 6 month open-label extension study with ulotaront [152]. Although short-term clinical and preclinical data regarding effects such as weight gain, glucose control, and lipid levels may be an indication of how these drugs may perform in patients with schizophrenia, long-term clinical results will be of great interest.

Future investigations should include examination of the effects of novel medications on cardiometabolic comorbidities, negative and cognitive symptoms, functionality, quality of life, and relapse prevention in patients with schizophrenia. Medications that also provide improvements in treatment-resistant patients and those with multiple diagnoses (e.g., substance use, depression) would be advantageous. The potential for genotyping/subtyping patients with

schizophrenia is also an area of interest for future research, as a fuller understanding of the heterogeneity within the disease is a critical aspect in attaining success in individualized treatment.

Replication of acute efficacy and safety findings for all of the novel treatments currently under investigation in further phase 3 trials will be of interest. The effects of illness duration and prior antidopaminergic treatments on the effects of any newly introduced drugs will also be beneficial in learning how best to utilize these therapies. The efficacy and safety of muscarinic agonists/positive allosteric modulators and TAAR1 agonists, when coadministered with postsynaptic D_2 blockers, would be of interest since it is possible that concomitant treatment of these novel agents with postsynaptic dopamine antagonists/partial agonists could ameliorate residual positive and/or negative symptoms. The possibility of TAAR1 agonist add-on therapy benefiting patients with insufficient response to currently available dopamine receptor blocking agents is quite intriguing based on preclinical data. Although the initial focus of the development program has been on patients with acute psychotic exacerbation, a TAAR1 adjunctive study of patients with residual psychotic symptoms despite ongoing dopamine receptor blocking treatment would be of great interest. Combination treatment may also allow for reduced dosing of current dopamine-blocking antipsychotics, thereby mitigating D_2 antagonism-related adverse effects, and possibly leading to a decrease in antipsychotic-induced cardiometabolic abnormalities, insofar as they are dose dependent [22].

With a newly emerging understanding of the complex mechanisms underlying schizophrenia and metabolic dysfunction, future studies of medications with novel mechanisms of action and their effects on psychosis and cardiometabolic dysfunction may lead to considerable advancements in the treatment of schizophrenia.

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Author contributions All authors participated equally in the conceptualization and data curation for the article; writing, reviewing, and editing of the draft; the authors have provided approval of the final submitted manuscript and agree to be accountable for the work.

Declarations

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Availability of data and materials Not applicable.

Code availability Not applicable.

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