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Unlocking the potential of lumateperone and novel anti-psychotics for schizophrenia

S Rehan Ahmad[1*], Md Zeyaullah[2*], Abdullah M. AlShahrani[2], Mohammad Suhail Khan[3], Adam Dawria[3], Ali Mohieldin[3], Haroon Ali[3], Abdelrhman AG Altijani[3], Mohammad Shane Alam[4], Munzila Mehdi[5], Sabika Akram[5], Ejaz Rizvi Hussain[5], Mohammad Amjad Kamal[6,7,8]

[1]Hiralal Mazumdar Memorial College for Women, West Bengal State University, Kolkata , West Bengal , 700035, India
[2]Department of Basic Medical Science, College of Applied Medical Sciences, Khamis Mushayt Campus, King Khalid University, Abha 62561, Saudi Arabia
[3]Department of Public Health, College of Applied Medical Sciences, Khamis Mushait Campus, King Khalid University, Abha 62561, Saudi Arabia
[4]Department of Medical Laboratory Technology, College of Applied Medical Sciences, Jazan University, Kingdom of Saudi Arabia, Jizan 45142, Saudi Arabia
[5]Department of Botany, Aligarh Muslim University, Uttar Pradesh, Aligarh 202002, India
[6]Joint Laboratory of Artificial Intelligence in Healthcare, Institutes for Systems Genetics and West China School of Nursing, Frontiers Science Center for Disease-related Molecular Network, West China Hospital, Sichuan University, Chengdu 610000, Sichuan Province, China
[7]Department of Pharmacy, Faculty of Allied Health Sciences, Daffodil International University, Dhaka 1207, Bangladesh
[8]Enzymoics, 7 Peterlee place, Novel Global Community Educational Foundation, Hebersham, NSW 2770, Australia

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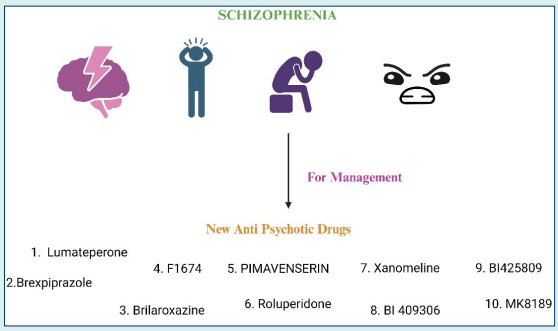
Abstract



Schizophrenia is a devastating chronic mental health illness which includes a complex set of symptoms like hallucination, illusion and delusion, and to manage, lifelong antipsychotic medications are needed. Schizophrenia affects 1% of the population worldwide, and to date, two different classes of antipsychotics, i.e., typical and atypical antipsychotics, are available in the market, and there is an urgent need for promising antipsychotic drugs. In this review, we focus on recently approved antipsychotics and then focus on different antipsychotic drugs under clinical trials. In this review, we first focus on lumateperone in detail, which was approved in December 2019 by the Food and Drug Administration (FDA) and simultaneously modulates serotonin, glutamate and dopamine neurotransmitters and is used at doses of 10.5-, 21- and 42 mg, which show mild adverse effects like constipation, sedation, somnolence and fatigue. This review also focuses on a few more emerging antipsychotics like brexpiprazole, brilaroxazine, roluperidone, F17464, pimavanserin (ACP-103), xanomeline, BI 409306, BI 425809 and MK-8189 which are under different phase of clinical trials and might get approved soon. Brexpiprazole and brilaroxazine act on dopamine receptors, whereas xanomeline, pimavanserin and roluperidone do not act on D2 receptors and manage the symptoms. All the antipsychotic drugs covered did not show any other severe adverse effects except gastrointestinal issues and cardiometabolic risk factors. However, still rigorous clinical trials and modifications are needed to manage adverse effects, and we can expect a few antipsychotics to be on the market soon.

Introduction

Schizophrenia is a complex mental illness coined in the early 1900s and means "to split the mind".[1] Schizophrenia affects around 1% of the world's population and is marked by hallucinations, delusions, and negative thoughts like alogia, apathy, avolition, anhedonia, asociality,

*Corresponding authors: S Rehan Ahmad, Email: professor.rehaan@gmail.com; Md Zeyaullah, Email: mdhafed@kku.edu.sa

and inattention.[2,3] Patients of schizophrenia have a reduced expectancy of 20 years compared to the general population.[4] For the management of schizophrenia, first-generation antipsychotics (FGAs) and second-generation antipsychotics (SGAs) are mainly used. First-generation psychotics are primarily used to treat largely positive symptoms, SGAs are used to treat primarily positive symptoms, and both generations of antipsychotics work on dopamine type 2 receptor antagonists, as well as atypical antipsychotics, also act to block serotonin receptors such as 5-HT2A.[5,6] Additionally, these antipsychotic drugs only partially alleviate negative feelings and cognitive impairment. Drugs that treat positive symptoms were created, which was a big step in the right direction for a patient's quality of life. However, it did not entirely resolve the issues that the patients had.[6,7]

As previously mentioned, negative and cognitive symptoms can seriously affect a patient's ability to go about their daily lives. Developing therapies that reduce symptoms may enhance a patient's day-to-day functionality and overall quality of life. Targeting 5-HT2A serotonin receptors and creating medications better tailored to 5-HT2A receptors may significantly help better manage the symptoms.[7-9] The dopamine hypothesis of schizophrenia states that dopaminergic neurotransmission disruption causes positive symptoms of schizophrenia.[1] Individuals with schizophrenia may have lower amounts of extracellular dopamine than normal individuals at rest.[10,11] In contrast, in the stimulated phasic state, they may have higher levels of intrasynaptic dopamine than normal individuals. Positive symptoms of schizophrenia may be linked to high intrasynaptic dopamine.[10,11] While first- and SGAs reduce some symptoms with metabolic and neurological side effects as well as the inability to control both positive and negative symptoms.[5,6] Due to the limitations and adverse effects of available antipsychotics, there is an urgent need for antipsychotics, so intense research and clinical trials are needed that can cure schizophrenia with minimal adverse effects. The prime focus of this article is understanding pharmacotherapy of *lumateperone tosylate* in detail and then focus on few emerging antipsychotic drugs like brexpiprazole, brilaroxazine, roluperidone, F17464, pimavanserin (ACP-103), xanomeline, BI 409306, BI 425809 and MK-8189 which are under different phase of clinical trials and their mechanism in depth. Antipsychotics discussed in this review can be approved soon and come into the market, which can help in the treatment and management of schizophrenia.

Established therapies – first and second-generation antipsychotic drugs

FGAs (*i.e.*, haloperidol, chlorpromazine) block D2 receptors to reduce the positive symptoms of schizophrenia.[12] FGAs act on multiple pathways such as mesolimbic, mesocortical, nigrostriatal, and tuberoinfundibular pathways and are metabolised by cytochrome P450 2D6 and P450 3A4 in the liver and excreted in urine and faeces. FGAs have reduced risk of replacement but show adverse effects like extrapyramidal syndrome (EPS) like dystonia, dyskinesia, and parkinsonism[13,14] FGAs are effective in positive symptoms of schizophrenia but not in negative symptoms of schizophrenia-like, like asociality, avolition, alogia, anhedonia, and blunted facial expression. SGAs or atypical antipsychotics (*i.e.*, aripiprazole, lurasidone, iloperidone, pimavanserin, and risperidone) are effective in both positive and negative symptoms of schizophrenia as these antipsychotics do not show EPS.[15-17] SGAs block the dopamine D2 receptor and act on serotonin receptors, *i.e.*, the 5-HT2A receptor and dopamine receptor.[18] Clozapine was the first SGA developed and used to manage schizophrenia.[19] Based on the similarity of the structure of clozapine, a few more drugs have been developed. SGAs can be further divided into groups based on binding affinity for D2 and 5-HT2A receptors. Olanzapine and clozapine are modest SGAs, whereas risperidone and lurasidone have high affinity. SGAs show multiple adverse effects like dyslipidemia, weight gain, sexual dysfunction, hypotension, and metabolic effects like elevated diabetes mellitus and lipids, and no significant evidence is present for EPS compared to FGAs.[19] Meltzer et al suggest that SGAs have a high chance of adverse effects if they have a higher 5-HT2A receptor relative to the D2 receptor.[20] This study supports the fact that SGA has reduced EPS compared to FGAs. FGAs and SGAs both show adverse effects, and there is an urgent need for a drug that can manage both the negative and positive effects of schizophrenia with minimum adverse effects.[21,22]

Overview of lumateperone

Lumateperone (CAPLYTA) is also known as ITI-007, exists as the tosylate salt got approved by Food and Drug Administration (FDA) in 2019 for treatment of schizophrenia and in 2021 for treatment of bipolar disorder I and II.[23,24] It is partially agonist at presynaptic D2 receptors and an antagonist at postsynaptic D2 receptors. It also shows promising responses towards dopaminergic, serotonergic, and glutamatergic neurotransmission for the relief of symptoms of schizophrenia as well as different neuropsychiatric disorders with minimal off-target receptor activity.[25,26] Lumateperone shows severe adverse effects like hyperglycemia, orthostatic hypotension, leukopenia, neutropenia, malignant syndrome, tardive dyskinesia, EPS, and dyslipidemia. In contrast, constipation, sedation, fatigue, and somnolence are the most common adverse effects of lumateperone. Lumateperone can react with alcohol and produce sedation, and it is advised to be used for treating patients with dementia psychosis. Lumateperone had got FDA

approval as an add-on antipsychotic with residual symptoms.[23-26] The 2D structure of lumateperone from PubChem is shown in Fig. S1 (Supplementary file 1).

Pharmacology

Lumateperone, a novel antipsychotic medication, possesses a diverse array of pharmacodynamic properties contributing to its action mechanism and potential therapeutic effects. Its unique profile encompasses interactions with neurotransmitter systems, including serotonin, dopamine, and glutamate. One of lumateperone's primary mechanisms involves its antagonism (Ki = 0.54 nM) of the serotonin 5-HT2A receptor.[27] By blocking the activity of this receptor, Lumateperone effectively modulates serotonergic signalling within the brain.[27,28] This modulation has implications for various aspects of neurotransmission and neural circuits involved in psychiatric disorders. In addition to its serotonergic effects, presynaptic dopamine D2 receptors are partially agonists by lumateperone. In contrast, postsynaptic D2 receptors are antagonised by it where it has an affinity (Ki = 32 nM), making it 60-fold less than serotonin 5-HT2A.[28] This unique combination of agonistic and antagonistic effects on dopamine receptors allows Lumateperone to regulate dopamine neurotransmission. By modulating dopamine release and receptor activity, Lumateperone helps restore the balance of dopaminergic signalling, which is disrupted in conditions such as schizophrenia.[29,30] Furthermore, glycogen synthase kinase 3 (GSK3) is reportedly more phosphorylated when lumateperone is present in neurons with the dopamine D2 (postsynaptic) receptor. GSK3 is involved in various intracellular signalling pathways related to neuronal function and plasticity. By influencing GSK3 phosphorylation, lumateperone affects cellular processes that contribute to overall neural functioning. Beyond its interactions with serotonin and dopamine systems, lumateperone affects glutamatergic neurotransmission.[31] It improves glutamate signalling in the prefrontal cortex *via* AMPA and NMDA channels. Depending on the dose, it also highly phosphorylates the GluN2B (NR2B), a subunit of the NMDA receptor, of dopamine D1 receptors (Ki = 52 nM).[8] This modulation of glutamate receptors suggests a potential role in improving cognitive function and synaptic activity, often impaired in psychiatric disorders. To offer an example from a study, lumateperone demonstrates selective inhibition of the 5-HT2A receptor at reduced dosages. In a research of 16 healthy men with a mean age of 30.7 years and an average basal metabolic index of 24.6 with a standard deviation of (3.0), 5-HT2A receptors were fully saturated (> 80%) by oral dosages of lumateperone as little as 10 mg. However, it exhibited only 33% occupancy on a dose of 40 mg.[32,33] This property has been observed to promote sleep and reduce hostility and aggression, providing additional therapeutic benefits beyond its antipsychotic effects. Importantly, Lumateperone displays a specific modulation of dopamine release in the medial prefrontal cortex while sparing the nigrostriatal pathways and motor system. This targeted modulation contributes to its efficacy as an antipsychotic while minimising the extrapyramidal side effects (EPSE) commonly associated with other antipsychotic medications. Furthermore, Lumateperone exhibits modest affinity for off-target receptors, ion channels, neurotransmitter transporters, and enzymes and demonstrates considerable occupancy of cortical serotonin 5-HT2A receptors and striatal serotonin transporter at various doses. When changing positions, these medications might cause adverse reactions such as gaining extra pounds, sleepiness, and low blood pressure. This shows a decreased affinity for binding (50% reduction at a concentration of 100 nM) against muscarinic and histamine receptor molecules.[5,27,28] It also has a modest binding strength for D4 receptors for dopamine and adrenergic receptors -1A and -1B (Ki guarded at 100 nM).[34] These interactions highlight lumateperone's engagement with the serotonergic system, which is implicated in mood regulation and other psychiatric symptoms. As research progresses, a deeper understanding of lumateperone's pharmacodynamics will provide valuable insights into the observed rates of side effects and therapeutic efficacy in clinical trials. The body's absorption of lumateperone, its distribution throughout the body, its conjugation with other substances in the liver, and its elimination from the body are the vital components of lumateperone's pharmacokinetics. Lumateperone, marketed as Caplyta by Intra-Cellular Therapies, is an innovative antipsychotic medication recently received approval due to its distinctive pharmacokinetic profile, differentiating it from other drugs. The FDA approved the medication in 2019 for managing schizophrenia.[35,36] In 2021, it has been further accepted to treat symptoms of depression connected to bipolar illness of type I or II.[37] This recognition underscores the potential of lumateperone as a valuable therapeutic option for individuals suffering from these psychiatric conditions. The pharmacokinetic properties of lumateperone provide valuable insights into its administration and metabolism.[35,36] The medication is available in different strengths, including 10.5 mg, 21 mg, and 42 mg, with the typical daily dose being 42 mg.[8,37] The uptake duration peaks between 3 and 4 hours after oral intake. After 8 hours of taking, it orally, levels of plasma of the substance Lumateperone and its metabolic compounds falling within the 0.2 to 100 ng/mL range were identified. Its duration of action is characterised by an extended half-life of 18 h, allowing for once-daily dosing. In around five days, steady-state concentrations are reached. Lumateperone's steady-state exposure rises approximately dose-proportionally with repeated doses between 21 and

56 mg.[32,37] Individual differences exist in the pharmacokinetics of lumateperone, with a range of 68% to 97% for the area under the curve (AUC) and Cmax at steady state. The overall bioavailability of this treatment equals 4.4%.[32] If lumateperone is given alongside a high-fat meal, Cmax increases by a third, and AUC rises by 9%. The average time for Cmax is postponed by approximately one hour, shifting from 1 h while fasting to 2 h with food around. The liver plays a crucial role in metabolising lumateperone, necessitating dose adjustments for individuals with liver impairment to ensure optimal therapeutic outcomes. Lumateperone has a unique binding profile; it demonstrates a higher affinity for serotonin 5-HT2A receptors than D2 receptors, classifying it as a 5-HT2A antagonist. Additionally, lumateperone potentially affects the glutamatergic system, contributing to its pharmacological diversity. This distinct binding profile leads to lower dopamine receptor occupancy than other antipsychotics, possibly explaining its effectiveness in treating psychosis despite its lower D2 receptor occupancy (D2RO). Medical research has shown proof of the effectiveness of the medication in managing schizophrenia and psychiatric disorders.[38,39] Scientific experiments have consistently indicated that lumateperone is better than placebo in alleviating symptoms related to these conditions. Nevertheless, more investigation should be undertaken to comprehensively grasp the long-lasting consequences it entails. People's elevated plasma protein binding level (97.4%) suggests the potential that the particular substance stays in the human body for a prolonged period. Importantly, lumateperone demonstrates similar effectiveness with risperidone, a different frequently prescribed antipsychotic, for addressing acute psychotic conditions for patients who have previously reacted to the application of the antipsychotic intervention. Moreover, the medication has demonstrated the potential to decrease adverse symptoms in individuals with schizophrenia, like avoiding social contact and decreasing the display of emotions.[39] Within the domain of manic depression, ITI-007 has broadened the narrow range of pharmaceuticals sanctioned for the care of episodes of depression in manic depression I and II.[40] Medical studies have revealed notable decreases in Montgomery-Åsberg Depression Rating Scale ratings among individuals taking lumateperone, pointing to its possibility as a viable therapy choice for those suffering from bipolar depression. After receiving a solitary dosage with radioactively labelled lumateperone, metabolites conjugated with glucuronic acid and combined with lumateperone comprise 2.8% and 51% of the plasma's total radioactivity independently. Around 58% of the radioactive substances are removed *via* the urine. One per cent of the drug is excreted in its original state in the urinary system, and a considerable amount is removed in bowel movements. The final duration of activity after intravenous delivery is 18 hours. The space is measured as 17.9 L every hour.[32] Regarding its safety and tolerability profile, the side effects of lumateperone are still under investigation. However, preliminary data suggest a favourable tolerability profile with low rates of metabolic and extrapyramidal symptoms, such as weight gain and movement disorders. Nonetheless, long-term data and comprehensive head-to-head comparisons with other antipsychotics are necessary to fully evaluate and understand the safety and efficacy profile of lumateperone. In summary, lumateperone's unique pharmacodynamic profile, characterised by its distinctive pharmacokinetics and binding properties, presents a promising addition to the treatment armamentarium for schizophrenia and bipolar disorder.[41,42] Clinical studies have demonstrated its efficacy in reducing symptoms and improving patients' well-being. However, ongoing research and further investigation are essential to better comprehend its long-term safety, tolerability, and comparative efficacy against other antipsychotic medications.

Pre-clinical efficacy of lumateperone

The preclinical research focused on investigating the neurobiology of lumateperone, specifically its neuropharmacology and toxicological profile.[16,27] Lumateperone is a potent antagonist of the serotonin 2A receptor in both in vivo and in vitro studies. It acts as a partial agonist on presynaptic receptors and an antagonist on postsynaptic dopamine receptor 2 (D2). Additionally, it modulates glutamatergic transmission through the dopaminergic D1 receptor and inhibits the reuptake of serotonin.[27] Similar to other unconventional antipsychotic drugs, lumateperone demonstrates a strong attraction (at doses measured in nanomoles) to human serotonin 5HT2A and dopamine D2 receptors.[16] Lumateperone has a higher affinity for binding to the 5HT2A receptor (with a Ki value ranging from 0.52 to 10 nM) than the dopamine D2 receptor (with a Ki value ranging from 19.2 to 32 nM). However, there were variances in different dosage regimens. Furthermore, it shows a moderate to high attraction to dopamine D1 receptors (20 to 78 nM), D4 receptors (39.7 to 104 nM), and α 1b adrenergic receptors (36.9 nM), all of which play a role in the efficacy of specific antipsychotic medications.[16] In addition, lumateperone has a strong binding affinity to the serotonin transporter (SERT), with a Ki value ranging from 16 to 33 nM.[16] The greater affinity for 5HT2A receptors compared to D1 and D2 receptors enables the full saturation of cortical 5HT2A receptors. This leads to the effectiveness of antipsychotic treatment at doses that do not cause motor side effects due to the full occupancy of striatal D2 receptors.[27] Lumateperone is subject to significant metabolism, leading to the formation of many metabolites that have pharmacological activity. This applies to both humans and non-human species.[16] The presence of these metabolites in the bloodstream

can be identified at levels comparable to or greater than lumateperone, presumably playing a role in its overall pharmacological effects. The desmethyl-metabolite IC20161 and the reduced carbonyl-metabolite IC200131 have binding characteristics similar to lumateperone.[27] Lumateperone and its metabolites lack significant binding affinity to D3, 5-HT1A, and 5-HT7 receptors, which are targets that contribute to the effectiveness of other atypical antipsychotic medications.[27] Studies were undertaken in mice, rats, and dogs to assess the toxicological effects of lumateperone. Lumateperone was administered orally for durations of 3, 6, and 9 months. Furthermore, studies were conducted to assess its potential to cause cancer by administering it orally to rats and mice for a duration of up to 21 months. Lumateperone, when given orally, caused the accumulation of coloured material within the cells of dogs, rats, and mice throughout their bodies. The distribution and amount of this pigment deposition seemed to rise with greater doses and longer treatment durations.[27] Especially noteworthy is the buildup of coloured substances in tissues that cannot regenerate. Pigment deposition was seen in the brain and spinal cord of all three species and in the cardiomyocytes and retina of rats. Nevertheless, the evaluation of healing occurred within a relatively short timeframe of 1 to 2 months. During necropsy, pigmented material aggregated in rats, primarily in parenchymal cells, macrophages, and other mononuclear inflammatory cells in various organs. Over time, this material accumulates in extracellular spaces, such as fibrous connective tissue, displacing myocardiocytes in the heart and accumulating in the pulmonary interstitium. The accumulation of pigmented material was linked to negative consequences in various parts of the body, including the central nervous system (such as inflammation in the brain and degeneration of nerve fibres in the spinal cord), peripheral nervous system (such as degeneration of nerve fibres in peripheral nerves), eye (retinal degeneration), and heart (cardiomyopathy).[28] The exact composition of the intracellular coloured material seen in toxicological research has not been thoroughly described. However, it does not seem like a typical naturally occurring pigment found within the cytoplasm, such as lipofuscin or hemosiderin.[27,28] According to laboratory tests, the coloured substance inside cells is most likely composed of polymers and protein clusters of aniline metabolites of lumateperone, IC201337, and IC201338.[27] The physiological and clinical significance of the preservation of coloured materials remains uncertain. However, if these materials are derived from aniline metabolites, they likely contribute to lysosomal dysfunction.[29,30] The aniline metabolites are cationic amphiphilic amines (CADs).[31] At a typical pH for the body, CADs are not in an ionised state and can readily pass through lipid bilayers. When cationic amphiphilic drugs (CADs) are introduced into a cellular organelle with an acidic pH, such as lysosomes, they become ionised. This leads to the buildup of CADs inside the lysosomes, which in turn causes cellular dysfunction[31]. It is crucial to emphasise that the aniline metabolites of lumateperone, namely IC201337 and IC201338, which appear to be accountable for the accumulation of pigmented substances, were not found in people at quantifiable concentrations. Nevertheless, it cannot be ruled out that lumateperone or other metabolites may concentrate in lysosomes and contribute to the observed toxicities in vivo and in vitro.[27] The toxicological capacity of these accumulations is comparable to that of other antipsychotic drugs that are known to accumulate in lysosomes, such as cariprazine and aripiprazole.[32,33] The NOAEL (No Observed Adverse Effect Level) for general toxicity in rats was 2.4 times the maximum recommended human daily dose (MRHD) of 42 mg when adjusted for body surface area (mg/m^2). In dogs, the MRHD was two times the 42 mg when adjusted for body surface area (mg/m^2). It was approximately 2.4 times the MRHD of 42 mg lumateperone in mice when adjusted for body surface area (mg/m^2). The LD50 was not established.[27]

Clinical efficacy of lumateperone

Lumateperone, an investigational drug currently being studied for the treatment of schizophrenia, has undergone a series of comprehensive clinical trials to evaluate its safety and effectiveness. These trials have provided valuable insights into the drug's potential as a therapeutic option for individuals with schizophrenia.[42,43] The initial phase of clinical trials, phase I, focused on assessing the safety profile of lumateperone.[44,45] During this phase, a single dose of lumateperone was administered to healthy male volunteers. The study revealed no serious adverse events, indicating that lumateperone was well-tolerated at the tested dosage level. Additionally, no noticeable alterations were detected in laboratory or cardiovascular system parameters. This also confirms the medication's good safety reputation. Expanding on the favourable outcomes in Phase I, phase II studies were carried out to explore both the protection and performance of the medication.[8,32] The experiments included the application of various doses of the medication to cured participants and individuals with stable conditions with psychological illness.[29,43] The findings demonstrated encouraging impacts for alleviating symptoms and improving the quality of life. The results demonstrated promising outcomes in terms of both safety and effectiveness. One of the phase II clinical trials registered as NCT01499563 (ITI-007-005) specifically targeted critical psychotic schizophrenia patients.[27] Around 335 patients in total were randomly assigned to acquire lumateperone (60 mg or 120 mg), risperidone (4 mg) as an active control, or a placebo for four weeks.[28] The trial showed that the 60 mg dosage of lumateperone exhibited a significant improvement in symptoms of schizophrenia in contrast to the placebo,

as estimated by the Positive and Negative Syndrome Scale (PANSS). Additionally, the lumateperone group demonstrated a diminution in PANSS scores, distinctly in the realm of positive symptom scores. Subgroup analysis indicated potential benefits for negative symptoms and comorbid symptoms of depression, further highlighting the drug's potential as a comprehensive treatment option. Another phase II trial, NCT02288845, focused on investigating the D2RO in stable schizophrenic patients who received a daily dose of 60 mg lumateperone for two weeks.[8,32] D2RO was assessed using positron emission tomography with 11C-raclopride as the radiotracer. The results of this trial revealed that lumateperone exhibited a peak D2RO of 39% at the 60 mg dosage level.[8] These dopamine D2RO measurements are low, usually seen with alternative atypical antipsychotics when administered at their effective dosages. The decreased D2RO displayed by this medication might contribute to its positive safety and tolerability profile. It was associated with no important modifications in body functions, heart, and metabolic assessments, and a diminished likelihood for motor dysfunctions and excess prolactin levels. Considering the positive results in the phase II studies, the phase III studies were carried out to investigate the effectiveness and safety of the drug among a larger patient cohort.[28,32] A significant study, listed as NCT02282761 (ITI-007-301), encompassed 450 individuals who were chosen randomly to receive lumateperone (60 mg or 40 mg) or a placebo for four weeks.[27,40] The main focus of this study was the alteration in PANSS assessments from the reference point to the conclusion of medical care. The results demonstrated that the 60 mg dosage of lumateperone exhibited significantly greater antipsychotic efficacy than the placebo, as indicated by the PANSS scores. However, the 40 mg dosage of lumateperone on placebo possesses little to no significant improvement.[32] Nevertheless, the 60 mg and 40 mg dosages of lumateperone demonstrated improvements in the clinical global impression (CGI) scale for severity of illness, PANSS positive subscale scores, and PANSS prosocial symptoms. One more phase III trial, registered as NCT02600131 (ITI-007-302), involved 515 patients who were randomly assigned to receive lumateperone (60 mg or 20 mg), risperidone (4 mg), or a placebo for six weeks.[8,32] The primary endpoint of this trial was the change in PANSS total score from baseline to the end of treatment.[42] The results revealed a statistically significant improvement in PANSS scores for the 60 mg dosage of lumateperone compared to the placebo. Furthermore, the risperidone group showed the greatest overall improvement, suggesting its comparative efficacy as an active control. Additionally to the effectiveness and safety evaluations, a safety switching trial without a label was performed to explore the impacts of transitioning stable schizophrenia patients from their existing drug to lumateperone.[36] The study aimed to examine the safety and ability to tolerate lumateperone in this group of patients. The trial showed improvements in cardiovascular, motor impairments, endocrine parameters, weight, and cardiometabolic parameters while patients were on lumateperone.[34,35] Notably, these improvements were switched back when previous medications were again administered, suggesting specific benefits associated with lumateperone. Ongoing trials are currently being conducted to estimate the prolonged exposure and safety of lumateperone in patients with schizophrenia. Preliminary findings indicate sustained efficacy, as assessed by PANSS scores, along with a decrease in weight gain, cholesterol levels, prolactin levels, and comorbid symptoms of depression.[35] In conclusion, the clinical trials conducted thus far have demonstrated the potential of lumateperone as an ultimate treatment for schizophrenia.[35] Several other clinical trials were conducted on schizophrenic patients who were given lumateperone to evaluate the efficacy and safety of the drug. In a phase II positron emission tomography (PET) study (NCT02288845), with 14 stable schizophrenic patients evaluating lumateperone dose, plasma levels, and brain receptor occupancy showed that the patients have a good tolerance for lumateperone and a favourable safety profile.[42] Phase III (NCT02282761) trials were also conducted where lumateperone was evaluated for the brief treatment of schizophrenia in patients with acute exacerbation of psychosis.[32] Lumateperone 42 mg once daily showed remarkable improvements compared to the placebo based on the PANSS total score, indicating its efficacy in treating schizophrenic symptoms. Another phase III study (NCT02469155) evaluated the antipsychotic efficacy of lumateperone in patients with a sudden worsening of psychological disturbances.[27] When lumateperone and risperidone were compared to placebo with no significant difference among doses, lumateperone demonstrated a favourable safety profile and efficacy for improving schizophrenic symptoms. Pooled analyses of phase II and phase III trials validated the effectiveness of lumateperone in lowering the PANSS scores [Least Square (LS) mean difference *vs* placebo -4.76; $P<0.001$] and establishing proportional efficacy to risperidone (LS mean difference *vs* placebo -4.97; $P=0.014$).[32] The phase II and III trials have provided substantial evidence of its efficacy in mitigating schizophrenic symptoms, as indicated by enhancement in PANSS scores. The unique pharmacological profile of lumateperone, characterised by lower D2RO, may contribute to its favourable safety and tolerability profile. Further research is ongoing to confirm the long-term efficacy and assess the full therapeutic potential of lumateperone in individuals with schizophrenia.[32,42]

Pregnancy and lumateperone

Untreated schizophrenia increases the possibility of relapse, hospitalisation, poor perinatal outcomes, and suicide in pregnant women; nevertheless, lumateperone

exposure in the third trimester may cause EPS and withdrawal symptoms in infants. In pregnant rats and rabbits, lumateperone administration during organogenesis did not cause abnormalities at dosages up to 2.4 and 9.7 times, respectively, the highest amount permitted for humans. However, there was a rise in cleft palate and abnormalities in the skeleton of pregnant rats and rabbits given human metabolite of lumateperone. The uncertainty lies in whether the lumateperone-exposed neonates will demonstrate pharmacokinetics similar to grown-ups since there is currently no information concerning the occurrence of the drug or its compounds in both animal and human milk. Thus, breastfeeding is not advised while receiving therapy with lumateperone. Use in this specific population should be kept to a minimum until additional clinical trials are acquired and experiments involving lumateperone among pregnant females are carried out.[46]

Geriatric and lumateperone

Due to an elevated mortality risk, lumateperone and other antipsychotic medications are not licensed for the ministration and therapy of psychosis associated with dementia. The clinical studies evaluating lumateperone did not involve persons over 65.[24]

Safety concerns related to lumateperone

Lumateperone is deemed a safe and well-tolerated antipsychotic based on the safety characteristics assessed in multiple clinical trials.[11,17,39] The most common side effects observed at the FDA-approved dosage of 60 mg/d include drowsiness, sleepiness, tiredness, and constipation.[5] Lumateperone exhibits a reduced metabolic risk and induces modest weight gain when compared to frequently employed second-generation antipsychotics.[1,5,43] There were no notable changes in metabolic indices, ECG abnormalities (such as QTc prolongation), and prolactin levels following lumateperone treatment.[16,44] Furthermore, there is a reduced frequency of extrapyramidal symptoms (EPS).[17] Lumateperone has been found to have a minor effect on serum aminotransferase levels for the entire course of treatment. However, there have been no reported cases of acute liver impairment associated with its usage that have been clinically observed.[44] In phase II/III placebo-controlled trials (ITI-007-005; ITI-007-301; ITI-007-302), the most common side effects observed with lumateperone 60 mg (LUM) were nausea (9% LUM vs 5% placebo (PBO)), somnolence/sedation (24% LUM vs 10% PBO), dizziness (5% LUM vs 3% PBO), increased liver enzymes (2% LUM vs 1% PBO), dry mouth (6% LUM vs. 2% PBO), fatigue (3% LUM vs 1% PBO), increased creatine phosphokinase (4% LUM vs. 1% PBO), and vomiting (3% LUM vs 2% PBO).[40] Lumateperone showed no significant propensity to induce EPS compared to the placebo. In the 6-week research ITI-007-302, only two patients who received lumateperone 60 mg experienced tardive dyskinesia.[17] Tardive dyskinesia is an extrapyramidal condition that occurs after prolonged therapy with antipsychotic medication—the number 27. The probability of a new antipsychotic causing tardive dyskinesia within the initial 6 weeks of medication is quite improbable.[27] It is more plausible that the observed instances of tardive dyskinesia were indications of withdrawal dyskinesia. Withdrawal dyskinesia may resemble tardive dyskinesia when assessed and can happen in persons who change antipsychotic drugs or stop long-term antipsychotic treatment.[31] Lumateperone demonstrated negligible metabolic, extrapyramidal, and cardiovascular safety issues compared to the current standard of care antipsychotic medication in an open-label study (ITI-007-303). Only one patient (0.2%) who received lumateperone 42 mg developed tardive dyskinesia as a result of the medication.[39] The primary reason for cessation of drug administration in this trial was the worsening of symptoms associated with schizophrenia, which resulted in significant adverse events. Nevertheless, it is not uncommon for persons with schizophrenia to experience periods of worsening symptoms within one year. It is possible that a considerable number of these patients may not have adequately followed the recommended study medication.[39] Recently, age, sex, or race have not been found to significantly affect the pharmacokinetics of lumateperone in clinical studies, which makes it safe for universal consumption. However, caution is advised when administering lumateperone alongside moderate or potent inhibitors of the enzymes CYP3A4 and UGT.[32] CYP3A4 is responsible for metabolising many drugs, while UGT is involved in metabolising various substances.[27] Co-administering lumateperone with these inhibitors can increase the risk of toxicity. The reason for this caution is that inhibitors of these enzymes can slow down the breakdown of lumateperone, leading to higher drug concentrations in the body and a potential increase in adverse effects. In contrast, compounds that induce or inhibit the CYP3A4 enzyme can affect the concentration of lumateperone in the body.[8,32] The provided information states that co-administration of lumateperone with such compounds is contraindicated. Inducers of CYP3A4 can speed up the metabolism of lumateperone, potentially reducing its effectiveness. On the other hand, inhibitors of CYP3A4 can slow down the drug's metabolism, leading to higher concentrations and a higher risk of side effects.[8,32,41]

Overview of brexpiprazole

Pharmacology

Demyttenaere et al reported that brexpiprazole belongs to the same class as aripiprazole and cariprazine, functioning as a dopamine partial agonist. In a comparative assay, brexpiprazole displayed 43% intrinsic agonist activity at D2 receptors, while aripiprazole exhibited 61% activity in a study directly comparing the two antipsychotics.[47,48] As a result, despite having a greater receptivity for D2

receptors, brexpiprazole exhibits lower intrinsic activity as an agonist at this dose than aripiprazole. Peak plasma concentrations of brexpiprazole are reached four hours after a single dosage, and steady-state levels are reached over 10-12 days of recurrent treatment.[49] Brexpiprazole, like cariprazine, is broken down by CYP3A4 and CYP2D6 enzymes, although its primary metabolite, DM-3411, has no contribution to pharmacological effect. Brexpiprazole has a three to four-day removal half-life.[49] The 2D structure of Brexpiprazole from PubChem is shown in Fig. S1.

Pre-clinical efficacy

Brexpiprazole, also known as OPC-34712, is a new medicine being studied for the treatment of psychiatric diseases. It can bind strongly to serotonin, dopamine, and noradrenaline receptors. Specifically, it exhibited a strong binding affinity (Ki < 1 nM) to human serotonin 1A (h5-HT1A), h5-HT2A, long isoform of human D2 (hD2L), ha1B, and ha2C adrenergic receptors. The compound exhibited modest agonistic activity at h5-HT1A and hD2 receptors in cloned receptor systems while demonstrating strong antagonistic effects on h5-HT2A receptors and ha1B/2C-adrenoceptors. Brexpiprazole had a strong binding affinity (Ki = 5 nM) for hD3-, h5-HT2B-, h5-HT7-, ha1A-, and ha1D-adrenergic receptors. It also showed a moderate affinity for hH1 receptors (Ki = 19 nM) and a low affinity for hM1 receptors (Ki > 1000 nM). Brexpiprazole exhibited strong affinity for rat 5-HT2A and D2 receptors in live animals, and further binding experiments outside of the body verified its powerful binding to 5-HT1A receptors. Brexpiprazole suppressed the occurrence of head twitches generated by DOI (2,5-dimethoxy-4-iodoamphetamine) in rats, indicating an antagonistic effect on the 5-HT2A receptor. Moreover, the in vivo D2 partial agonist action of brexpiprazole was verified through its ability to reduce reserpine-induced DOPA buildup in rats. In rat microdialysis studies, aripiprazole had a minor effect on reducing extracellular dopamine levels in the nucleus accumbens but no effect on the prefrontal cortex. However, there were moderate increases in the levels of dopamine metabolites, homovanillic acid and DOPAC in these areas, which indicated that aripiprazole might have partial agonist activity on the D2 receptors in vivo. Specifically, due to its lower inherent activity at D2 receptors and stronger ability to bind to 5-HT1A/2A receptors compared to aripiprazole, brexpiprazole possesses a promising potential as an antipsychotic without the undesirable side effects associated with D2 receptor agonists and antagonists. Ultimately, brexpiprazole is a substance that modulates serotonin and dopamine activity in the brain, with a distinct pharmacological profile. This characteristic makes it a promising candidate for treating various illnesses affecting the central nervous system.[50]

Clinical efficacy

Brexpiprazole was studied in five temporary randomised placebo-controlled studies that included 2683 people. During a six-week treatment period, these trials looked at the efficacy of brexpiprazole in individuals having a rapid relapse of schizophrenia. The increase or decrease in PANSS score from the start was chosen as the primary outcome measure. Brexpiprazole 2-4 mg demonstrated a statistically significant improvement in PANSS score over placebo when combined with data from multiple investigations.[51] Post-hoc analyses revealed that the brexpiprazole group, especially those with more severe symptoms, showed a more considerable mean reduction in PANSS scores.[52]

Safety concern

In a network meta-analysis, brexpiprazole ranked low among oral antipsychotics for total symptom improvement but performed relatively better for social behaviour.[53] Brexpiprazole drastically delayed the recurrence time compared to placebo in the 'Equator' maintenance study.[54] Brexpiprazole 14 mg exhibited average PANSS score reductions of 12.2 and 6.8 in label extension trials[55,56] Five ongoing trials are looking into the use of brexpiprazole in specific patient demographics, such as teenagers and concurrent drug users, in addition to the occurrence of adverse events. In Forbes et al[55] 52-week open-label research, the most prevalent side effects associated with treatment were sleeplessness (8.6%), increased body weight (7.8%), hypertension (6.4%), and anxiety (5.4%). Similar frequencies were observed in a smaller open-label study by Hakala et al.[56] In comparison with placebo, brexpiprazole had a significantly lower risk of akathisia (5.5%) than aripiprazole (10.0%) and did not affect glucose, lipids, Low-Density Lipoprotein Cholesterol, triglycerides, or QTc interval.[53,57] Brexpiprazole was not related to long-term hyperprolactinemia.[58]

Overview of brilaroxazine

Pharmacology

Brilaroxazine (RP5063), which has a similar chemical structure to aripiprazole, is a high-affinity partial agonist on serotonin 5-HT1A and 5-HT2A receptors, and it also acts on D2, D3, and D4 receptors, with Ki values of 0.37 nM, 3.7 nM, and 6.0 nM, respectively.[59] Brilaroxazine also has a Ki value of 107 nM for the serotonin transporter and works as an inhibiting agent on the serotonin 5-HT2B, 5-HT2C, 5-HT6, and 5-HT7 receptors, with Ki values of 0.19 nM, 39 nM, 51 nM, and 2.7 nM, respectively.[59] Brilaroxazine has a half-life of more than 40 h, which allows for a once-daily dosage, and it achieves a steady state of action around 8 days of treatment.[59] The 2D structure of brilaroxazine from PubChem is shown in Fig. S1.

Pre-clinical efficacy

Preclinical investigations have confirmed the efficacy, pharmacokinetics, and safety of brilaroxazine in animals, although these findings have not been published. Studies

using rodent models have shown that brilaroxazine effectively reduces both psychosis and cognitive symptoms associated with schizophrenia.[60]

Clinical efficacy

The brilaroxazine 15 mg and 50 mg groups revealed a significantly more significant decrease in PANSS overall scores than in the placebo group in a phase II randomised controlled trial (RCT) for the rapid recurrence of schizophrenia.[59] Compared to placebo, brilaroxazine exhibited more significant improvements in PANSS negative and prosocial symptoms than positive symptoms.[59] Although the authors of the reported phase II research state their intention to begin two further phases III trials, no new clinical trials for brilaroxazine are registered on clinicaltrials.gov.[61]

Safety concern

EPS symptoms, akathisia, and increased liver enzymes were among the most commonly reported treatment-emergent adverse events in the NCT0149008 study. It is worth noting, however, that more than 95% of these adverse effects were low to moderate in intensity and occurred in just 2% of people in either brilaroxazine group, with no reports in the placebo group.[59] Four substantial treatment-emergent side effects linked to elevated liver enzyme levels were found in people using brilaroxazine.

Overview Of F17464

Pharmacology

F17464 is a partial agonist of 5-HT1A receptors while acting as a D3 antagonist. Its affinity for 5-HT1A and D3 receptors, akin to cariprazine, is notably high, with a Ki value of 0.17 nM.[60] Furthermore, F17464 indicates a significant resemblance for D2 receptors, with a Ki value of 9.3 nM, albeit functioning as a weak partial agonist. PET scans in healthy volunteers suggest that F17464 exhibits over 80% occupancy of D3 receptors and only 20% occupancy of D2 receptors at doses between fifteen and thirty mg, respectively.[62] The D3 receptor's presence primarily within specific brain regions raises the possibility of influencing glutamatergic pathways involved in limbic brain functions.[63] F17464's D3 antagonism is believed to enhance cognition by addressing dopamine tone in the prefrontal cortex, while its partial 5-HT1A agonism may also offer cognitive benefits.[60] F17464 exhibits peak plasma concentration between 0.5 and 4 h post-oral administration.[61] After 15 d of use, steady-state conditions are achieved.[63] According to a PET study, F17464 possesses a mean plasma half-life of 1.32 h, remaining detectable at D3 receptors for up to 22 h post-treatment, supporting its suitability for twice-daily dosing.[64] The 2D structure of F17464 from PubChem is shown in Fig. S1.

Pre-clinical efficacy

F17464 is a compound with the chemical formula N-(3-{4-[4-(8-Oxo-8H-[1,3]The compound is called dioxolo-[4,5-g].(-chromen-7-yl)The compound is called butyl. The compound is piperazine-1-yl. The compound is referred to as "-phenyl". The compound is methanesulfonamide hydrochloride. It is a novel antipsychotic with a distinct profile. The molecule demonstrates a strong attraction to the human dopamine receptor subtype 3 (hD3) with a binding constant (Ki) of 0.17 nM, as well as to the serotonin receptor subtype 1a (5-HT1a) with a Ki of 0.16 nM. However, its affinity for the human dopamine receptor subtype two short and long-form (hD2s/l) is more than 50 times lower, with Ki values of 8.9 nM and 12.1 nM, respectively. The text "[14C]" remains unchanged. The dynamic tests reveal that F17464 has a longer dissociation rate from the hD3 receptor (t1/2 = 110 min) than the hD2s receptor (t1/2 = 1.4 min). Furthermore, functional studies showed that F17464 acts as an antagonist for the D3 receptor and a partial agonist for the 5-HT1a receptor. F17464 inhibits the morphological changes generated by ketamine in human dopaminergic neurons, and the D3 receptor mediates this effect. The displacement tests conducted in the mouse brain reveal the target engagement of both D2 and 5-HT1a receptors by F17464 in vivo. F17464 enhances dopamine release in rats' prefrontal cortex and mice's lateral forebrain-dorsal striatum. Additionally, it mitigates the impact of MK801 on the percentage of medium-expressing neurons containing c-fos mRNA in both cortical and subcortical areas. F17464 also mitigates the harmful effects of valproate-induced dysfunction in a rat model of autism that measures social interaction. The neurochemistry and behavioural impact of F17464 can be demonstrated within the dose range of 0.32–2.5 mg/kg i.p. in both rats and mice. The pharmacological characteristics of F17464 in preclinical models, support its potential therapeutic application in treating schizophrenia as well as autism.[65]

Clinical efficacy

A single phase II RCT was conducted to evaluate the efficacy of F17464. The trial employed a double-blinded design and yielded results indicating a statistically significant enhancement in PANSS score among participants receiving a dosage of 20 mg BD of F17464 compared to those administered a placebo. In addition, secondary efficacy studies revealed a statistically significant impact of the F17464 on the PANSS positive score. In contrast, no significant differences were observed in the PANSS negative score or Marder harmful component. However, due to the limited research population consisting of individuals experiencing an acute relapse of schizophrenia, as well as the short duration of the investigation, it is doubtful that the trial sufficiently examined the possible impact on negative symptoms.[63-65] The present study employed post-hoc analysis to examine the impact of F17464 on cognitive ability, utilising the Wallwork components of the PANSS items. The findings did indicate a positive effect of F17464 on cognitive ability. It is worth mentioning that the authors indicated

that ten patients who were part of the randomised study were excluded from the article. This exclusion resulted from a breach of Good Clinical practice guidelines by one of the study centres. Additionally, there were significant protocol deviations seen in 19 additional patients. The complete analysis set included These subjects' data but not the per-protocol set.[66]

Safety concern

The treatment-emergent adverse effects seen in the clinical trial NCT02151656, with a higher prevalence in the F17464 group compared to the placebo group, including sleeplessness (10.4%), agitation (7.5%), hyperlipidemia (7.5%), and akathisia (4.5%). All significant adverse events within this context. The study revealed a notable absence of side events associated with efficacy, with a prevalence of 14.9% in the F17464 group and 22.4% in the placebo group. 13 patients (19.4%) in the F17464 arm of the study terminated treatment.[65] The reasons for discontinuation included treatment inefficacy in 11 patients, elevated liver enzymes in 1 patient, and suicidal ideation in 1No EPS symptoms were symptoms recorded among the patients who were administered F17464. Furthermore, the administration of F17464 did not result in any significant alterations in the electrocardiogram (ECG) parameters that would have had clinical implications. The study revealed a correlation between F17464 and elevated levels of prolactin. Furthermore, hyperprolactinemia was shown to be more prevalent and pronounced in female subjects.[65,66]

Overview of pimavanserin (ACP-103)

Pharmacology

In the United States, pimavanserin (ACP-103) is approved for treating psychosis in Parkinson's disease (PD) and is currently in trials for schizophrenia. Pimavanserin has a lower affinity for dopamine receptors than the innovative therapies mentioned (Ki > 1000 nM). It is believed to act as an inverse agonist at the 5HT2A receptor with high affinity (Ki = 0.087 nM) (ACADIA Pharmaceuticals Inc., 2016).[67,68] Additionally, pimavanserin exhibits high affinity for 5HT2C receptors (Ki = 0.44 nM), moderate affinity for sigma-1 receptors (Ki = 120 nM), and negligible affinity (Ki > 1000 nM) at 5-HT1A, 5-HT2B, histamine, muscarinic, and alpha receptors. Pimavanserin has a half-life of 57 h with a peak concentration of 6 h; its primary metabolite has a half-life of around 200 h.[66,67] In healthy volunteers, 10 mg of pimavanserin effectively occupied over 90% of the brain's 5HT2A receptors, as observed in a positron emission tomography study.[68] Plasma levels of pimavanserin decrease when used with inducers like rifampicin and increase when used with inhibitors of the CYP 450 system, according to a study by Kitten et al[68] in 2018. The 2D structure of pimavanserin from PubChem is shown in Fig. S1.

Pre-clinical efficacy

The behavioural characteristics of Pimavanserin in rodents[69] align with those of other 5-HT2A antagonists, such as AC-90179 and MDL-100,907. Therefore, it inhibits DOI-induced head twitch and MK-801-induced hyperactivity. In addition, it inhibits disturbances in prepulse inhibition produced by DOI and MK-801. These behavioural effects are observed in atypical antipsychotic drugs (APDs) such as risperidone, clozapine, and quetiapine. These drugs have significant antagonist activity at 5-HT2A receptors. However, in contrast to the APDs, Pimavanserin does not possess DA D2 antagonist action, resulting in the absence of consistent and dose-dependent inhibition of amphetamine-induced activity. Therefore, Pimavanserin exhibits some, but not all, of the preclinical behavioural traits identified in APDs. To evaluate the potential efficacy of Pimavanserin in treating PDP, a rodent model of PD was utilised, in which rats were subjected to bilateral lesions of the substantia nigra (SN). Through this method, there was a swift decline (within 24 hours) of tyrosine hydroxylase, which serves as an indicator of robust dopaminergic neurons in the SN. The loss persisted until it reached a maximum of around 75% about two weeks after the injury. Significantly, after sustaining an SN lesion, the animals experienced challenges in both starting and sustaining motor activities, which were effectively reversed with the administration of L-DOPA. Furthermore, these rats exhibited a psychosis-like pattern of behavioural alterations, namely changes in behaviours commonly employed to evaluate the effectiveness of antipsychotic medicines. These effects consisted of a higher occurrence of spontaneous head twitches, intensified amphetamine-induced hyperactivity, and impaired prepulse inhibition. Pimavanserin effectively reversed psychosis-like behaviours without exacerbating motor difficulties or interfering with the motor-enhancing effects of L-DOPA.[69] The presence of modified 5-HT2A-dependent behaviours in rats with lesions is in line with evidence indicating that the destruction of dopaminergic neurons in animals results in changes in serotonergic signalling. These changes include elevated levels of extracellular 5-HT, increased serotonin transporters, growth of serotonergic connections to the striatum, and increased 5-HT2A mRNA expression in the striatum.[69]

Clinical efficacy

When tested in schizophrenia, pimavanserin proved to be better tolerated than a placebo when added to the standard course of care.[70] While pimavanserin add-on treatment did not significantly affect the overall PANSS score or CGI, as stated in a second-phase clinical trial press release, it notably enhanced unfavourable symptoms evaluations compared to the placebo group.[71] However, it is worth noting that this assertion gave an uncorrected p-value of 0.047, which may not resist numerous statistical test corrections. There was no noticeable improvement in total PANSS scores or CGI in a phase-III trial of pimavanserin in addition to standard antipsychotic

medication, according to a press statement from ACADIA Pharmaceuticals Inc.[72] However, add-on pimavanserin significantly improved the PANSS Marder negative factor score and the PANSS negative symptoms subscale, with unadjusted *P* values of 0.047 and 0.034, respectively. Whether these results hold up after correction for multiple comparisons is still being determined. Detailed results can be accessed *via* the National Library of Medicine Clinical Trials Database, and information on safety and adherence has been published in abstracts.[72] However, neither trial has yet undergone full peer-reviewed reporting. Three additional ongoing schizophrenia investigations explore the effect of supplementary pimavanserin on negative symptoms, with one actively recruiting participants (NCT04531982). Two open-label studies are in progress, one lasting a year to assess tolerability (NCT03121586) and the other comparing the effectiveness of pimavanserin monotherapy with measurements of 5HT2A occupancy obtained by positron emission tomography.[73]

Safety concern

In the realm of undesirable effects, pimavanserin, comparable to brexpiprazole and lumateperone, demonstrates an insignificant tendency to induce EPS in schizophrenia.[74] Furthermore, it does not worsen neurological symptoms in PD[75] Notably, according to Abbas and Roth in 2008, pimavanserin does not cause an increase in blood prolactin levels. However, like several other recent antipsychotic cautions, there is a black box warning about an increased risk of death when used in the elderly.[76] In a study involving Parkinson's patients over 40, pimavanserin was found to lengthen QT intervals by an average of 7.2 ms. The manufacturer advises caution when prescribing pimavanserin alongside other medications that can potentially prolong QT intervals and recommends avoiding its use in individuals with established QT prolongation.[76] During PD trials, there was an increased incidence (between 1% and 7%) of nausea, peripheral edema, confusion, hallucinations, constipation, and gait disturbance in the pimavanserin group compared to the placebo group.[77,78]

Overview of roluperidone (MIN-101)

Pharmacology

Roluperidone (MIN-101) illustrates significant affinity as a 5-HT2A inhibitor (Ki = 8.19 nM) and a sigma two receptor antagonist (Ki = 7.53 nM). It also has some activity as an alpha1-adrenergic antagonist, according to a patent application and a critical report of a current phase-II trial.[79,80] However, detailed techniques for these results have yet to be recorded,[78] including if these binding tests were performed on human brain tissue. Nonetheless, roluperidone has been shown to have relatively little affinity for muscarinic, cholinergic, and histaminergic receptors.[79] The molecule's half-life is approximately six hours.[79] Phase I and II studies have shown that a daily dose of 32 or 64 mg is sufficient to achieve plasma concentrations comparable to those required to induce an antipsychotic-like effect in rats.[78] Rats reached a steady state after 7 day at a dose of 1 mg/kg.[78] The 2D structure of roluperidone from PubChem is shown in Fig. S1.

Pre-clinical efficacy of roluperidone

Roluperidone has been demonstrated to enhance the release and transcription of brain-derived neurotrophic factors in cultured brain hippocampus neurons and astrocytes, indicating a potential involvement in neuroplasticity and neuroprotection. Therefore, it is plausible that roluperidone functions by enhancing neuroplasticity and mitigating the abnormal functioning of dopaminergic and glutamatergic circuits that are associated with schizophrenia. Still, limited in vitro and in vivo studies has been performed so, in depth investigation of roluperidone is needed and it might show positive result in different psychiatric disorders too.[81]

Clinical efficacy of roluperidone

In the initial phase II study,[82] roluperidone did not exhibit a discernible advantage over placebo regarding total PANSS scores. However, in a second phase II trial,[78,79] 32 mg and 64 mg of roluperidone significantly improved the primary outcome of change in PANSS negative symptom factor and total PANSS score at 12 weeks compared to placebo. According to one researcher,[82] patients in the high-dose group also demonstrated a statistically significant improvement at 12 weeks compared to placebo in a composite cognition score obtained from the Brief Assessment of Cognition in Schizophrenia. According to a recent presentation, both high and low doses were substantially more beneficial than placebo regarding the PANSS negative symptoms component at four weeks. However, this advantage was significant for the high dose at 8 weeks, while there was no significant distinction between the two doses at the primary endpoint of 12 weeks.[83] The phase III trial exhibited more of a placebo effect than the second phase of the trial. When bare subscale evaluations for negative symptoms were selected as the endpoint, the significant advantages of high-dose treatment continued to be evident at 12 weeks, according to the presentation.[83]

Safety concern

Davidson et al[79] found that the people receiving the treatment group had a greater rate of headache (7.5% *vs* 3.6%), asthenia (5.6% *vs* 2.4%), and somnolence (3.7% *vs* 0%) than the placebo group. Insomnia was more uncommon in those receiving treatment than in the placebo groups, most likely due to higher rates of somnolence. Unfortunately, no data on adverse effects from the more significant phase III trial was available.[83] While no cases of severe QTc prolongation at therapeutic levels have been recorded in clinical studies, there is a stated possible risk of QTc prolongation with plasma concentrations surpassing 80 ng/mL, as mentioned in

the patent application.[84] Aside from the recurrence of schizophrenia symptoms, two patients in the phase II study suffered significant adverse events: One complained of vomiting and abdominal pain, and the other reported syncope and bradycardia.[85] Compared to contemporary antipsychotics, roluperidone does not influence prolactin levels or cause EPSE.[85]

Overview of xanomeline

Pharmacology

According to Shekhar et al[86] and Watson et al,[87] xanomeline is a muscarinic activator primarily affecting M1 and M4 receptor subtypes. Among the recently evaluated antipsychotics, it has an extremely high affinity for muscarinic receptors. Notably, other long-established antipsychotics, such as chlorpromazine, olanzapine, and clozapine, have a comparable affinity for muscarinic receptors, but not uniformly. It is worth noting that many of these antipsychotics work as muscarinic receptor antagonists. There is strong evidence that the muscarinic cholinergic system is involved in schizophrenia, with decreased muscarinic receptors shown in patients with the disorder in both postmortem and *in vivo* imaging investigations.[88] Despite its low selectivity for receptors that respond to dopamine, xanomeline exhibits functional dopamine antagonism in mouse models. Rodent cell recordings have also demonstrated its capacity to block dopamine cell activity in the limbic front tegmental region.[88] The 2D structure of xanomeline from PubChem is shown in Fig. S1.

Pre-clinical efficacy

Xanomeline, an M1R/M4R agonist, enhances cognitive performance and exhibits antipsychotic effects in individuals diagnosed with Alzheimer's disease (AD) and schizophrenia. Nevertheless, the clinical advancement of the drug was halted due to its cholinomimetic adverse effects. A study assessed the pharmacological characteristics of a new M1R-selective positive allosteric modulator called TAK-071 with Xanomeline in rodents. Xanomeline had inhibitory effects on both methamphetamine- and MK-801-induced hyperlocomotion in mice, while TAK-071 only showed suppression of MK-801-induced hyperlocomotion. These findings suggest that Xanomeline holds promise as a treatment for schizophrenia.[89]

Clinical efficacy

In a randomised placebo-controlled trial of twenty people with schizophrenia or schizoaffective disorder, xanomeline outperformed the control group on specific cognitive screening tests (though cognition statistical tests were not adjusted for multiple testing), the overall PANSS score, and the entire Brief Psychiatric Rating Scale score. It is worth noting that all participants were given a placebo during the first week, which might jeopardise the treatment arm's blinding when switching to xanomeline in the second week. In a more recent, well-designed RCT, 182 people with an immediate relapse of schizophrenia were given a 5-week therapy of xanomeline with trospium. As stated by Rovner, trospium, a peripherally active muscarinic receptor antagonist that does not penetrate the barrier between the brain and the bloodstream, was also delivered.[86] This combination was expected to provide therapeutic effectiveness while avoiding adverse peripheral cholinergic effects.[87] The xanomeline-trospium group saw substantially higher decreases in PANSS overall scores, PANSS positive subscale scores, and PANSS negative subscale scores compared to the placebo group. The only available studies on xanomeline's tolerability in schizophrenia patients are the aforementioned clinical trials.

Safety concern

Due to its muscarinic receptor influence, xanomeline can lead to various peripheral adverse effects. Despite the small sample size of 20, the Shekhar et al[86] research found that the xanomeline group experienced more nauseated (70%), puking (60%), pain in the gastrointestinal tract (70%), salivation (20%), diarrhoea (20%), and constipated (20%) than the placebo group. Similarly, with the xanomeline-trospium combination, prevalent adverse side effects included constipation, nausea, dry mouth, and vomiting, suggesting that trospium mitigates gastrointestinal effects but does not eliminate them. Notably, individuals receiving xanomeline-trospium in the Brannan et al[87] study did not significantly gain more weight than the placebo group. Despite a peak mean spike in heart rate of 6.9 beats per minute on day 8 in the treatment group, there were no statistically significant between-group differences in blood pressure or corrected QT intervals. EPSE and akathisia were similar in the treatment and placebo groups. Additionally, the researchers found no notable variations in drowsiness or restlessness when xanomeline-trospium was used instead of a placebo. The xanomeline-trospium group experienced one critical and one extreme adverse event. In comparison, the therapy group experienced one severe adverse event, but the nature of these events was not further described.[87]

Overview of BI 409306

Pharmacology

BI 409306 is a PDE9A inhibitory agent that was designed to treat cognitive dysfunction in psychosis and AD.[88,89] PDE9A hydrolyses and controls the intracellular content of cyclic guanosine monophosphate (cGMP) in glutamatergic neurons. PDE9A inhibition may boost intracellular cGMP availability and NMDA receptor signalling, improving synaptic plasticity and memory function. BI 409306 is swiftly ingested and removed. The highest possible plasma concentration is attained 30 minutes and 45 minutes post oral treatment, with a half-life for elimination of 1.10-1.85 h.[88,89] The 2D structure of BI 409306 from PubChem is shown in Fig. S1.

Pre-clinical efficacy

BI 409306 is a new inhibitor of PDE9A, a protein involved in synaptic plasticity. Its effects on synaptic plasticity were assessed using long-term potentiation (LTP) in hippocampal slices taken from living organisms. Additionally, its impact on cognitive performance was studied in rodents. BI 409306 has been shown in in vitro studies to be a very effective and specific inhibitor of human and rat PDE9A. The mean concentrations required for half-maximal inhibition (IC50) are 65 nM and 168 nM, respectively. BI 409306 elevated cGMP levels in rats' prefrontal cortex and cerebrospinal fluid and mitigated the decrease in cGMP in the striatum of mice caused by the NMDA-receptor antagonist MK-801. BI 409306 increased LTP in rat brain slices ex vivo, following both weak and vigorous tetanic stimulation. Administration of BI 409306 to mice effectively restored the working memory impairments caused by MK-801 in a T-maze spontaneous-alternation challenge. Additionally, it enhanced long-term memory in an object recognition task. These results indicate that BI 409306 is a potent and specific inhibitor of PDE9A. BI 409306 demonstrates target engagement by elevating cGMP levels in the brain, promoting synaptic plasticity through enhanced hippocampus LTP, and enhancing episodic and working memory function in animals. These data indicate that BI 409306 has the potential to treat schizophrenia and other neurological illnesses.[88-90]

Clinical efficacy

The primary outcome measure of change in MATRICS Consensus Cognitive Battery (MCCB) (measurement and treatment research to improve cognition in schizophrenia consensus cognitive battery) score over placebo was not significantly impacted by adjunctive BI 409306 in one phase II study.[90] For the subsequent goals of the Schizophrenia Cognition Rating Scale score or CGIs-Severity scale score, there was no statistically significant variance comparing the treatment and placebo arms.[90] Due to the coronavirus disease 2019 pandemic, two more ongoing research investigations of BI 409306 (NCT03351244 and NCT03230097) were stopped.

Safety concern

According to Dhingra et al,[91] PDE9A is found in the retina's inner layer, where cGMP governs signalling in retinal cells. Visual symptoms have been noted in safety investigations with BI 409306 in healthy volunteers.[92,93] Eye abnormalities (blurred vision, photophobia, visual brightness, flashes, and colour disruption) were observed in 11.1% of the individuals taking BI 409306 in the second phase trial in schizophrenia patients, exhibiting a dose-dependent relationship in frequency.[90] Nasopharyngitis (3.2%), nausea (2.6%), and dizziness (2.6%) also occurred more frequently in the therapy group, with a prevalence of 2%.[90]

Overview of BI 425809

Pharmacology

It is similar to BI 425809 in that it is designed to focus on cognition and memory in disorders such as schizophrenia and AD. It achieves this by preventing glycine transporter 1 (GlyT1), enhancing synaptic glycine levels, and improving glutamate's effect on NMDA receptors.[94] When taken orally, BI 425809 reaches peak plasma concentrations in 3 to 4.5 h and reaches a stable state in 6 to 10 days, with a half-life of more than 30 hour.[95] The 2D structure of BI 425809 from PubChem is shown in Fig. S1.

Pre-clinical efficacy

Glycine transporter-1 inhibitors have the potential to improve cognitive impairments in individuals with Schizophrenia. BI 425809 was shown to induce CYP3A4 and inhibit P-gp in a concentration-dependent manner, as demonstrated by in vitro experiments. Out of the 13 patients in the clinical investigation, 12 completed both sessions. When BI 425809 was supplied along with midazolam, the area under the plasma concentration curve from administration to the final measurement (AUC0–tz) and the maximum plasma concentration (Cmax) of midazolam was reduced compared to when midazolam was administered alone. The adjusted geometric mean ratios (with a 90% confidence interval) were 70.6% (ranging from 63.9% to 78.1%) for AUC0–tz and 77.6% (ranging from 67.3% to 89.4%) for Cmax. The area under the curve (AUC0–tz) and maximum concentration (Cmax) of warfarin and digoxin were comparable, regardless of the presence or absence of BI 425809. BI 425809 had a minor effect on reducing the AUC0–tz of omeprazole but did not affect the Cmax when compared to omeprazole alone. No more indications of safety concerns were detected. The results suggest that administering once-daily BI 425809 25 mg leads to the activation of CYP3A4. These data indicate that BI 425809 has potential as a therapeutic option for both schizophrenia and neurodegenerative illnesses.[96]

Clinical efficacy

The NCT02832037 trial's BI 425809 10 mg and 25 mg groups showed statistically improved composite T-scores on the MCCB; however, the clinical significance remains unknown due to small to moderate effect sizes (0.34 and 0.30 for 10 mg and 25 mg, respectively).[97,98] Secondary assessments of social and daily functioning revealed no significant differences. Ongoing trials will give more information on behavioural symptom effects throughout 26 weeks, including a phase II trial (NCT03859973) and three phase III clinical studies (NCT04846868, NCT04846881, and NCT04860830).

Safety concern

In NCT02832037, when the treatment group is compared to placebo groups, BI 425809 treatment groups had higher incidences of headaches (8%-12%), drowsiness (2%-6%), and problems with the digestive tract (2%-

11%).[98] Haemoglobin levels decreased dose-dependently, with 1%-5% of treatment groups experiencing anaemia.[99] Other indices, including vision and ECG, were intact, and no EPSE were seen. Suicidality and disease progression did not worsen in the therapeutic groups, although 3.5% of those receiving BI 425809 had serious side events, compared to 2% in the placebo group.[98-100] No fatalities occurred during the study, though the nature of major adverse events was not detailed.

Overview of MK-8189

Pharmacology

A phosphodiesterase 10A inhibitor modifies the dopamine D1-direct and D2-indirect striatal pathways and controls striatal glutamate receptor phosphorylation.[101,102] This method addresses the dopaminergic and glutamatergic system abnormalities associated with schizophrenia. Peak plasma concentration occurs 12 to 24 h after oral administration, with an elimination half-life of 7.6 to 10.9 h based on data from NCT 03565068, available at clinicaltrials.gov but has not been officially published.[103-106] The 2D structure of MK-8189 from PubChem is shown in Fig. S1.

Pre-clinical efficacy

MK-8189 is a potent and particular inhibitor of PDE10A, which is currently being studied as a new treatment for schizophrenia. MK-8189 demonstrates favourable in vitro safety and off-target profile. MK-8189 demonstrates a strong affinity for ion channels, specifically Iks, Cav1.2, and Nav1.5 at concentrations over 30 μM. Additionally, it exhibits a functional hERG Ikr IC50 of 33 μM. Transporter tests demonstrate that MK-8189 is likely to cross the blood-brain barrier and enter the central nervous system. MK-8189 has a significant level of passive permeability, ranging from 35.4 to 42.6×10−6 cm/s. Furthermore, it does not serve as a human and monkey P-gp substrate, as indicated by a B-A/A-B ratio of less than 2. Although MK-8189 has a low affinity for rat P-gp (with a B-A/A-B ratio of approximately 2.6), it could fully occupy the enzyme in the rat striatum. In a study conducted on live rats, the administration of MK-8189 orally resulted in the displacement of [3H]MK-8193 in a manner that depended on the quantity of the substance in the plasma. The PDE10A inhibitor exhibits a high affinity for binding sites mostly found in rat brains' caudate-putamen and accumbens nuclei. Male Wistar-Hannover rats were given MK-8189I orally at a dosage range of 0.1 to 10 mg/kg one hour before receiving an intravenous injection of [3H] MK-8193 at a dose of 20 mCi. MK-8189 demonstrated the anticipated pharmacological effects in rodent models of psychosis and cognitive function. MK-8189 showed complete effectiveness in the MK-801-induced psychomotor activity test. MK-8189 was given orally at doses of 0.25-0.75 mg/kg, 1 hour before treatment with MK-801, a non-competitive antagonist of the N-methyl-D-aspartate receptor. Locomotor activity was observed for 90 minutes. Following oral administration, MK-8189 effectively reduced the hyperactivity elicited by psychostimulants in rats in a manner that was dependent on the dose and concentration. The trial concluded with plasma concentrations ranging from 17 nM in the group receiving a dose of 0.25 mg/kg to 50 nM in the group receiving a dose of 0.75 mg/kg. In general, MK-8189 exhibits exceptional efficacy in inhibiting PDE10A, exhibits selectivity towards PDE, possesses favourable pharmacological characteristics, a favourable ancillary profile, and promising oral pharmacokinetics in pre-clinical species. Studies conducted on live rodents show that PDE10A effectively targets and improves symptoms of psychosis and cognition when administered orally.[107]

Clinical efficacy

Additionally, no more than one study looked at the clinical efficacy of 12-milligram MK-8189 in schizophrenia. Patients experiencing an acute recurrence were enrolled in this four-week examination.[108] Whereas the active regulation, risperidone, distinguished itself from placebo in this brief research, MK-8189 12 mg showed no significant difference in mean PANSS total score change compared to placebo.[109] A more extensive phase II trial is being conducted to evaluate MK-8189 at 16 and 24 mg dosages.

Safety concern

The final findings of testing NCT03565068 on MK-8189's effectiveness and efficacy have yet to be released.[108] In Table 1, an overview of drugs, focusing on their unique characteristics, dosage forms, and other relevant factors, is provided. Drugs in various phases of clinical trials, excluding those in the recruitment phase, are shown in Table 1. The 2D structures of all drugs, retrieved from PubChem, are presented in Supplementary file 1 (Fig. S1).

Future challenges and Conclusion

Schizophrenia is a complex mental disorder in which a patient needs to take antipsychotic medicine their entire life. To date, two classes of antipsychotics are available, i.e., typical and atypical antipsychotics. Recently, in 2019, the FDA approved lumateperone for schizophrenia. Lumateperone has a distinct pharmacological, pharmacokinetic, and early safety profile, suggesting it is a potential medication for schizophrenia treatment. Lumateperone has shown notable efficacy against both positive and negative parameters of schizophrenia.[41] It is a medication with quick absorbance that crosses the blood-brain barrier, is well-digested and removed by the body, and has a short half-life. Serotonin 5-HT2A receptors, saturated at decreased dosages, are highly affine for it. It can be used in various neuropsychiatric and neurodegenerative illnesses at varying levels, improving effectiveness and minimising adverse effects by recruiting alternative receptors, including SERT, D2,

Table 1. Different antipsychotic drugs under different phases of trials except recruiting

Drug name	Clinical trials ID	Start date	Study completion date (estimated)	Phase	Reference
Lumateperone	NCT05890768	2023-05-11	2026-06	Phase 4	110
Lumateperone	NCT04959032	2021-07-08	2023-12	Phase 3	111
Lumateperone	NCT05850689	2023-05	2025-10	Phase 3	112
Lumateperone	NCT05061706	2021-09-30	2023-10	Phase 3	113
Lumateperone	NCT04985942	2021-07-30	2023-08	Phase 3	114
Brexpiprazole	NCT03526354	2018-03-19	2025-03-19	Phase 4	115
MK-8189	NCT05893862	2023-06-26	2024-01-24	Phase 1	116

D1/GluN2B (glutamate) at increased doses. Additionally, lumateperone is regioselective for dopamine D2RO at mesolimbic and mesocortical regions and has minimal to no affinity for off-target receptors, minimising adverse effects on the heart, metabolism, and movement that are present in currently available antipsychotic drugs. Lumateperone's potential could be developed further to meet the demand for a secure and more potent antipsychotic medication. While lumateperone shows promise for treating the symptoms of schizophrenia with fewer side effects, a thorough assessment of its effectiveness in extended human research will be necessary to establish it as a superior treatment option to the antipsychotics that are now the gold standard of therapy. An antipsychotic with a potentially unique mode of action, lumateperone, is simple to give. Data to date show that it has little adverse effects on EPS and is safe for metabolism. There is conflicting but encouraging evidence in favour of its usage in schizophrenia. Moreover, lumateperone offers a different treatment option for bipolar depression, a significant unmet medical need. However, there are still patients receiving lumateperone, with few long-term data. Additional research will demonstrate how effectively this medicine compares to others. Other antipsychotic drugs like brexpiprazole, brilaroxazine, roluperidone, F17464, pimavanserin (ACP-103), xanomeline, BI 409306, BI 425809, and MK-8189 are under clinical trials. Brexpiprazole, Brilaroxazine, F17464, and lumateperone act directly on dopamine receptors, while Xanomeline, Pimavanserin, and Roluperidone do not act on D2 and reduce symptoms. These drugs will open a new door for drug development, which will be based on a non-D2 blocking approach and help us understand the pathophysiology of psychosis. We can hope all the antipsychotics will be on the market shortly after the successful completion of trials, but MK8189 is on the stage of termination due to severe adverse effects, and we might expect a few more terminations due to adverse events of these drugs. We can expect researchers to come up with novel drugs that can reduce the adverse effects of drugs as these drugs are hoped for Schizophrenia patients.

Research Highlights

What is the current knowledge?

- Currently, two class of antipsychotic drugs i.e; typical and atypical drugs like olanzapine, quetiapine, etc show adverse effects like weight gain, EPS,etc.

What is new here?

- This review discuss about different anti-psychotic drugs which are under different phase of clinical trials.
- This review is unique which include in depth information like pre clinical studies, comprehensive table for all the drugs.

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Authors' Contribution

Conceptualization: S Rehan Ahmad, Md Zeyaullah.
Funding acquisition: Md Zeyaullah.
Investigation: S Rehan Ahmad, Md Zeyaullah, Abdullah M. AlShahrani, Mohammad Suhail Khan, Adam Dawria, Ali Mohieldin, Haroon Ali, Abdelrhman AG Altijani, Mohammad Shane Alam.
Supervision: S Rehan Ahmad, Md Zeyaullah, Mohammad Amjad Kamal.
Writing–original draft: S Rehan Ahmad, Md Zeyaullah, Munzila Mehdi, Sabika Akram, Ejaz Rizvi Hussain.
Writing–review editing: Munzila Mehdi, Sabika Akram, Ejaz Rizvi Hussain.

Competing Interest

There is no conflict of interest associated with any of the senior author or other coauthors contributed their efforts in this manuscript.

Ethical Statement

No need of ethical Committee approval needed.

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Supplementary files

Supplementary files 1 contains Table S1 and Fig. S1.

References

1. McGrath J, Saha S, Chant D, Welham J. Schizophrenia: a concise overview of incidence, prevalence, and mortality. *Epidemiol Rev* **2008**; 30: 67-76. doi: 10.1093/epirev/mxn001.
2. Brašić JR, Kim J. The nicotine hypothesis. In: Madras B, Kuhar M, eds. *The Effects of Drug Abuse on the Human Nervous System*. Boston: Academic Press; **2014**. p. 313-32. doi: 10.1016/b978-0-12-418679-8.00010-1.
3. Battle DE. Diagnostic and statistical manual of mental disorders (DSM). *Codas* **2013**; 25: 191-2. doi: 10.1590/s2317-17822013000200017.
4. Laursen TM, Nordentoft M, Mortensen PB. Excess early mortality in schizophrenia. *Annu Rev Clin Psychol* **2014**; 10: 425-48. doi: 10.1146/annurev-clinpsy-032813-153657.
5. Jones MT, Strassnig MT, Harvey PD. Emerging 5-HT receptor antagonists for the treatment of Schizophrenia. *Expert Opin Emerg Drugs* **2020**; 25: 189-200. doi: 10.1080/14728214.2020.1773792.
6. Kapur S, Remington G. Dopamine D2 receptors and their role in atypical antipsychotic action: still necessary and may even be sufficient. *Biol Psychiatry* **2001**; 50: 873-83. doi: 10.1016/s0006-3223(01)01251-3.
7. Sinha JK, Sachdeva P, Ahmad F, Sarkar J, Izhar R, Rahman A, et al. Pharmacotherapy and emerging treatment strategies for schizophrenia. In: Chatterjee I, ed. *Cognizance of Schizophrenia: A Profound Insight into the Psyche*. Singapore: Springer; **2023**. p. 149-79. doi: 10.1007/978-981-19-7022-1_10.
8. Vyas P, Hwang BJ, Brašić JR. An evaluation of lumateperone tosylate for the treatment of schizophrenia. *Expert Opin Pharmacother* **2020**; 21: 139-45. doi: 10.1080/14656566.2019.1695778.
9. Ceskova E, Silhan P. Novel treatment options in depression and psychosis. *Neuropsychiatr Dis Treat* **2018**; 14: 741-7. doi: 10.2147/ndt.s157475.
10. Ahmad F, Virmani A, Irfan M, Rankawat S, Pathak U. Critical appraisals on depression and psychotic symptoms. *J Neuro Behav Sci* **2021**; 8: 81-8. doi: 10.4103/jnbs.jnbs_17_21.
11. Grace AA. Dysregulation of the dopamine system in the pathophysiology of schizophrenia and depression. *Nat Rev Neurosci* **2016**; 17: 524-32. doi: 10.1038/nrn.2016.57.
12. Davis RE, Vanover KE, Zhou Y, Brašić JR, Guevara M, Bisuna B, et al. ITI-007 demonstrates brain occupancy at serotonin 5-HT_2A and dopamine D_2 receptors and serotonin transporters using positron emission tomography in healthy volunteers. *Psychopharmacology (Berl)* **2015**; 232: 2863-72. doi: 10.1007/s00213-015-3922-1.
13. Davis RE, Correll CU. ITI-007 in the treatment of schizophrenia: from novel pharmacology to clinical outcomes. *Expert Rev Neurother* **2016**; 16: 601-14. doi: 10.1080/14737175.2016.1174577.
14. Campbell M, Young PI, Bateman DN, Smith JM, Thomas SH. The use of atypical antipsychotics in the management of schizophrenia. *Br J Clin Pharmacol* **1999**; 47: 13-22. doi: 10.1046/j.1365-2125.1999.00849.x.
15. Miyamoto S, Duncan GE, Mailman RB, Lieberman JA. Developing novel antipsychotic drugs: strategies and goals. *Curr Opin Cent Peripher Nerv Syst Invest Drugs* **2000**; 2: 25-39.
16. Stępnicki P, Kondej M, Kaczor AA. Current concepts and treatments of schizophrenia. *Molecules* **2018**; 23: 2087. doi: 10.3390/molecules23082087.
17. Creese I, Burt DR, Snyder SH. Dopamine receptor binding predicts clinical and pharmacological potencies of antischizophrenic drugs. *J Neuropsychiatry Clin Neurosci* **1996**; 8: 223-6. doi: 10.1176/jnp.8.2.223.
18. Farde L, Nordström AL, Wiesel FA, Pauli S, Halldin C, Sedvall G. Positron emission tomographic analysis of central D1 and D2 dopamine receptor occupancy in patients treated with classical neuroleptics and clozapine. Relation to extrapyramidal side effects. *Arch Gen Psychiatry* **1992**; 49: 538-44. doi: 10.1001/archpsyc.1992.01820070032005.
19. Nordström AL, Farde L, Wiesel FA, Forslund K, Pauli S, Halldin C, et al. Central D2-dopamine receptor occupancy in relation to antipsychotic drug effects: a double-blind PET study of schizophrenic patients. *Biol Psychiatry* **1993**; 33: 227-35. doi: 10.1016/0006-3223(93)90288-o.
20. Meltzer HY, Matsubara S, Lee JC. Classification of typical and atypical antipsychotic drugs on the basis of dopamine D-1, D-2 and serotonin2 pKi values. *J Pharmacol Exp Ther* **1989**; 251: 238-46.
21. Miyamoto S, Duncan GE, Marx CE, Lieberman JA. Treatments for schizophrenia: a critical review of pharmacology and mechanisms of action of antipsychotic drugs. *Mol Psychiatry* **2005**; 10: 79-104. doi: 10.1038/sj.mp.4001556.
22. Dimitrelis K, Shankar R. Pharmacological treatment of schizophrenia–a review of progress. *Prog Neurol Psychiatry* **2016**; 20: 28-35. doi: 10.1002/pnp.430.
23. National Center for Biotechnology Information. PubChem Database. Lumateperone CID = 21302490. Available from: https://pubchem.ncbi.nlm.nih.gov/compound/Lumateperone. Accessed November 25, **2019**.
24. Caplyta [package insert]. New York: Intra-Cellular Therapies Inc; **2021**. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/209500s005s006lbl.pdf.
25. Cooper D, Gupta V. Lumateperone. In: *StatPearls*. Treasure Island, FL: StatPearls Publishing; **2022**. Available from: https://www.ncbi.nlm.nih.gov/books/NBK560844/.
26. Vanover KE, Davis RE, Zhou Y, Ye W, Brašić JR, Gapasin L, et al. Dopamine D2 receptor occupancy of lumateperone (ITI-007): a Positron Emission Tomography Study in patients with schizophrenia. *Neuropsychopharmacology* **2019**; 44: 598-605. doi: 10.1038/s41386-018-0251-1.
27. Syed AB, Brašić JR. The role of lumateperone in the treatment of schizophrenia. *Ther Adv Psychopharmacol* **2021**; 11: 20451253211034019. doi: 10.1177/20451253211034019.
28. Davis RE, Correll CU. ITI-007 in the treatment of schizophrenia: from novel pharmacology to clinical outcomes. *Expert Rev Neurother* **2016**; 16: 601-14. doi: 10.1080/14737175.2016.1174577.
29. Yildiz M, Incedere A, Buğrahan Gürcan M, Osman E. Brief Clinical Assessment Scale for Schizophrenia (BCASS): development, validity, and reliability study. *Noro Psikiyatr Ars* **2022**; 59: 14-20. doi: 10.29399/npa.27592.
30. Greenwood J, Acharya RB, Marcellus V, Rey JA. Lumateperone: a novel antipsychotic for schizophrenia. *Ann Pharmacother* **2021**; 55: 98-104. doi: 10.1177/1060028020936597.
31. Pahwa M, Sleem A, Elsayed OH, Good ME, El-Mallakh RS. New antipsychotic medications in the last decade. *Curr Psychiatry Rep* **2021**; 23: 87. doi: 10.1007/s11920-021-01298-w.
32. Maini K, Hollier JW, Gould H, Bollich V, John LaForge J, Cornett EM, et al. Lumateperone tosylate, a selective and concurrent modulator of serotonin, dopamine, and glutamate, in the treatment of schizophrenia. *Health Psychol Res* **2021**; 9: 24932. doi: 10.52965/001c.24932.
33. Kaczmarek A, Szymajda W, Dettlaff K. Lumateperone in the treatment of psychiatric disorders–a review of the literature. *Farmakoter Psychiatr Neurol* **2023**; 39: 39-52. doi: 10.5114/fpn.2023.127423.
34. Lobo MC, Whitehurst TS, Kaar SJ, Howes OD. New and emerging treatments for schizophrenia: a narrative review of their pharmacology, efficacy and side effect profile relative to established antipsychotics. *Neurosci Biobehav Rev* **2022**; 132: 324-61. doi: 10.1016/j.neubiorev.2021.11.032.
35. Suzuki T, Uchida H, Sakurai H, Ishizuki T, Tsunoda K, Takeuchi H, et al. Relationships between global assessment of functioning and other rating scales in clinical trials for schizophrenia. *Psychiatry Res* **2015**; 227: 265-9. doi: 10.1016/j.psychres.2015.02.024.
36. Edinoff A, Wu N, deBoisblanc C, Feltner CO, Norder M, Tzoneva V, et al. Lumateperone for the treatment of schizophrenia. *Psychopharmacol Bull* **2020**; 50: 32-59.
37. Snyder GL, Vanover KE, Davis RE, Li P, Fienberg A, Mates S. A review of the pharmacology and clinical profile of lumateperone for the treatment of schizophrenia. *Adv Pharmacol* **2021**; 90: 253-76. doi: 10.1016/bs.apha.2020.09.001.

38. Kaczmarek A, Szymajda W, Dettlaff K. Lumateperone in the treatment of psychiatric disorders–a review of the literature. *Farmakoter Psychiatr Neurol* **2023**; 39: 39-52. doi: 10.5114/fpn.2023.127423.
39. Correll CU, Davis RE, Weingart M, Saillard J, O'Gorman C, Kane JM, et al. Efficacy and safety of lumateperone for treatment of schizophrenia: a randomized clinical trial. *JAMA Psychiatry* **2020**; 77: 349-58. doi: 10.1001/jamapsychiatry.2019.4379.
40. Mazza M, Marano G, Traversi G, Sani G, Janiri L. Evidence on the new drug lumateperone (ITI-007) for psychiatric and neurological disorders. *CNS Neurol Disord Drug Targets* **2020**; 19: 243-7. doi: 10.2174/1871527319666200601145653.
41. Blair HA. Lumateperone: first approval. *Drugs* **2020**; 80: 417-23. doi: 10.1007/s40265-020-01271-6.
42. Jawad MY, Alnefeesi Y, Ceban F, Lui LM, Jaberi S, Di Vincenzo JD, et al. Lumateperone for the treatment of adults with schizophrenia: a systematic review. *Curr Psychiatry Rep* **2022**; 24: 359-68. doi: 10.1007/s11920-022-01344-1.
43. Bell MD, Lysaker PH, Beam-Goulet JL, Milstein RM, Lindenmayer JP. Five-component model of schizophrenia: assessing the factorial invariance of the positive and negative syndrome scale. *Psychiatry Res* **1994**; 52: 295-303. doi: 10.1016/0165-1781(94)90075-2.
44. Suppes T, Durgam S, Kozauer SG, Chen R, Lakkis HD, Davis RE, et al. Adjunctive lumateperone (ITI-007) in the treatment of bipolar depression: results from a randomized placebo-controlled clinical trial. *Bipolar Disord* **2023**; 25: 478-88. doi: 10.1111/bdi.13310.
45. Barman R, Majumder P, Doifode T, Kablinger A. Newer antipsychotics: brexpiprazole, cariprazine, and lumateperone: a pledge or another unkept promise? *World J Psychiatry* **2021**; 11: 1228-38. doi: 10.5498/wjp.v11.i12.1228.
46. Lieberman JA, Davis RE, Correll CU, Goff DC, Kane JM, Tamminga CA, et al. ITI-007 for the treatment of schizophrenia: a 4-week randomized, double-blind, controlled trial. *Biol Psychiatry* **2016**; 79: 952-61. doi: 10.1016/j.biopsych.2015.08.026.
47. Demyttenaere K, Detraux J, Racagni G, Vansteelandt K. Medication-induced akathisia with newly approved antipsychotics in patients with a severe mental illness: a systematic review and meta-analysis. *CNS Drugs* **2019**; 33: 549-66. doi: 10.1007/s40263-019-00625-3.
48. Maeda K, Sugino H, Akazawa H, Amada N, Shimada J, Futamura T, et al. Brexpiprazole I: in vitro and in vivo characterization of a novel serotonin-dopamine activity modulator. *J Pharmacol Exp Ther* **2014**; 350: 589-604. doi: 10.1124/jpet.114.213793.
49. Mauri MC, Paletta S, Di Pace C, Reggiori A, Cirnigliaro G, Valli I, et al. Clinical pharmacokinetics of atypical antipsychotics: an update. *Clin Pharmacokinet* **2018**; 57: 1493-528. doi: 10.1007/s40262-018-0664-3.
50. Maeda K, Akazawa H, Sugino H, Stensbøl TB, Kikuchi T. Brexpiprazole, a novel serotonin-dopamine activity modulator: in vivo evaluation of its antipsychotic-like profile. 69th Annual Meeting of the Society of Biological Psychiatry; **2014** May 8–10; New York, NY.
51. Marder SR, Hakala MJ, Josiassen MK, Zhang P, Ouyang J, Weiller E, et al. Brexpiprazole in patients with schizophrenia: overview of short- and long-term phase 3 controlled studies. *Acta Neuropsychiatr* **2017**; 29: 278-90. doi: 10.1017/neu.2016.57.
52. Meade N, Shi L, Meehan SR, Weiss C, Ismail Z. Efficacy and safety of brexpiprazole in patients with schizophrenia presenting with severe symptoms: post-hoc analysis of short- and long-term studies. *J Psychopharmacol* **2020**; 34: 829-38. doi: 10.1177/0269881120936485.
53. Huhn M, Nikolakopoulou A, Schneider-Thoma J, Krause M, Samara M, Peter N, et al. Comparative efficacy and tolerability of 32 oral antipsychotics for the acute treatment of adults with multi-episode schizophrenia: a systematic review and network meta-analysis. *Lancet* **2019**; 394: 939-51. doi: 10.1016/s0140-6736(19)31135-3.
54. Fleischhacker WW, Hobart M, Ouyang J, Forbes A, Pfister S, McQuade RD, et al. Efficacy and safety of brexpiprazole (OPC-34712) as maintenance treatment in adults with schizophrenia: a randomized, double-blind, placebo-controlled study. *Int J Neuropsychopharmacol* **2017**; 20: 11-21. doi: 10.1093/ijnp/pyw076.
55. Forbes A, Hobart M, Ouyang J, Shi L, Pfister S, Hakala M. A long-term, open-label study to evaluate the safety and tolerability of brexpiprazole as maintenance treatment in adults with schizophrenia. *Int J Neuropsychopharmacol* **2018**; 21: 433-41. doi: 10.1093/ijnp/pyy002.
56. Hakala M, Gislum M, Skuban A, Meehan S. Long-term safety and tolerability of brexpiprazole in patients with schizophrenia. *Schizophr Bull* **2018**; 44(Suppl 1): S94-5. doi: 10.1093/schbul/sby015.234.
57. Pillinger T, McCutcheon RA, Vano L, Mizuno Y, Arumuham A, Hindley G, et al. Comparative effects of 18 antipsychotics on metabolic function in patients with schizophrenia, predictors of metabolic dysregulation, and association with psychopathology: a systematic review and network meta-analysis. *Lancet Psychiatry* **2020**; 7: 64-77. doi: 10.1016/s2215-0366(19)30416-x.
58. Ivkovic J, Lindsten A, George V, Eriksson H, Hobart M. Effect of brexpiprazole on prolactin: an analysis of short- and long-term studies in schizophrenia. *J Clin Psychopharmacol* **2019**; 39: 13-9. doi: 10.1097/jcp.0000000000000979.
59. Cantillon M, Prakash A, Alexander A, Ings R, Sweitzer D, Bhat L. Dopamine serotonin stabilizer RP5063: a randomized, double-blind, placebo-controlled multicenter trial of safety and efficacy in exacerbation of schizophrenia or schizoaffective disorder. *Schizophr Res* **2017**; 189: 126-33. doi: 10.1016/j.schres.2017.01.043.
60. Bhat L, Adiey K, Bhat SR, Mohapatra P. Brilaroxazine (RP5063), a novel serotonin-dopamine stabilizer, displays antipsychotic efficacy in rodents. *Med Res Arch* **2023**; 11: 1-13. doi: 10.18103/mra.v11i4.3834.
61. Cantillon M, Bhat L. Response to concerns over Cantillon et al. dopamine serotonin stabilizer RP5063 clinical trial's design, analyses and findings (SCHRES-D-17-00455) by Ahmed S Aboraya, MD, DrPh. *Schizophr Res* **2018**; 195: 581-2. doi: 10.1016/j.schres.2017.09.010.
62. Bitter I, Groc M, Delsol C, Fabre C, Fagard M, Barthe L, et al. Efficacy of F17464, a new preferential D3 antagonist in a placebo-controlled phase 2 study of patients with an acute exacerbation of schizophrenia. *Eur Psychiatry* **2017**; 41: S387. doi: 10.1016/j.eurpsy.2017.02.428.
63. Slifstein M, Abi-Dargham A, Girgis RR, Suckow RF, Cooper TB, Divgi CR, et al. Binding of the D3-preferring antipsychotic candidate F17464 to dopamine D3 and D2 receptors: a PET study in healthy subjects with [(11C)]-(+)-PHNO. *Psychopharmacology (Berl)* **2020**; 237: 519-27. doi: 10.1007/s00213-019-05387-w.
64. Sokoloff P, Le Foll B. The dopamine D3 receptor, a quarter century later. *Eur J Neurosci* **2017**; 45: 2-19. doi: 10.1111/ejn.13390.
65. Cosi C, Martel JC, Auclair AL, Collo G, Cavalleri L, Heusler P, et al. Pharmacology profile of F17464, a dopamine D3 receptor preferential antagonist. *Eur J Pharmacol* **2021**; 890: 173635. doi: 10.1016/j.ejphar.2020.173635.
66. Bitter I, Lieberman JA, Gaudoux F, Sokoloff P, Groc M, Chavda R, et al. Randomized, double-blind, placebo-controlled study of F17464, a preferential D3 antagonist, in the treatment of acute exacerbation of schizophrenia. *Neuropsychopharmacology* **2019**; 44: 1917-24. doi: 10.1038/s41386-019-0355-2.
67. Acadia Pharmaceuticals Inc. Nuplazid (pimavanserin) [package insert]. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/207318lbl.pdf. Accessed January 2, **2021**.
68. Kitten AK, Hallowell SA, Saklad SR, Evoy KE. Pimavanserin: a novel drug approved to treat Parkinson's disease psychosis. *Innov Clin Neurosci* **2018**; 15: 16-22.
69. Hacksell U, Burstein ES, McFarland K, Mills RG, Williams H. On the discovery and development of pimavanserin: a novel drug candidate for Parkinson's psychosis. *Neurochem Res* **2014**; 39: 2008-17. doi: 10.1007/s11064-014-1293-3.
70. Baltzersen OB, Meltzer HY, Frokjaer VG, Raghava JM, Baandrup

L, Fagerlund B, et al. Identification of a serotonin 2A receptor subtype of schizophrenia spectrum disorders with pimavanserin: the Sub-Sero Proof-of-Concept Trial Protocol. *Front Pharmacol* **2020**; 11: 591. doi: 10.3389/fphar.2020.00591.
71. Nordstrom AL, Mansson M, Jovanovic H, Karlsson P, Halldin C, Farde L, et al. PET analysis of the 5-HT2A receptor inverse agonist ACP-103 in human brain. *Int J Neuropsychopharmacol* **2008**; 11: 163-71. doi: 10.1017/s1461145707007869.
72. Abbs B, Bugarski-Kirola D, Liu IY, Darwish M, Stankovic S. T42. High adherence to current antipsychotic and adjunctive pimavanserin in the ENHANCE study, a phase 3 trial to evaluate the treatment of schizophrenia in patients with an inadequate response to antipsychotic treatment. *Schizophr Bull* **2020**; 46: S247-8. doi: 10.1093/schbul/sbaa029.602.
73. Acadia Pharmaceuticals Inc. ACADIA Pharmaceuticals Announces Positive Top-line Results from ADVANCE Trial of Pimavanserin as Treatment for Negative Symptoms of Schizophrenia. Acadia Pharmaceuticals Inc; **2019**.
74. Acadia Pharmaceuticals Inc. ACADIA Pharmaceuticals Announces Top-line Results from Phase 3 ENHANCE Trial of Pimavanserin as Adjunctive Treatment for Patients with Schizophrenia. Acadia Pharmaceuticals Inc; **2019**.
75. Bugarski-Kirola D, Nunez R, Odetalla R, Bari MA, Bitter I, Feldman PD, et al. T41. Safety profile of adjunctive pimavanserin in the enhance study, a phase 3 trial for the potential treatment of schizophrenia in patients with an inadequate response to antipsychotic treatment. *Schizophr Bull* **2020**; 46(Suppl 1): S247. doi: 10.1093/schbul/sbaa029.601.
76. Meltzer HY, Mills R, Revell S, Williams H, Johnson A, Bahr D, et al. Pimavanserin, a serotonin(2A) receptor inverse agonist, for the treatment of Parkinson's disease psychosis. *Neuropsychopharmacology* **2010**; 35: 881-92. doi: 10.1038/npp.2009.176.
77. Markham A. Pimavanserin: first global approval. *Drugs* **2016**; 76: 1053-7. doi: 10.1007/s40265-016-0597-9.
78. Cummings J, Isaacson S, Mills R, Williams H, Chi-Burris K, Corbett A, et al. Pimavanserin for patients with Parkinson's disease psychosis: a randomised, placebo-controlled phase 3 trial. *Lancet* **2014**; 383: 533-40. doi: 10.1016/s0140-6736(13)62106-6.
79. Bailey JM, Shively JE. Carboxy-terminal sequencing: formation and hydrolysis of C-terminal peptidylthiohydantoins. *Biochemistry* **1990**; 29: 3145-56. doi: 10.1021/bi00464a035.
80. Davidson M, Saoud J, Staner C, Noel N, Luthringer E, Werner S, et al. Efficacy and safety of MIN-101: a 12-week randomized, double-blind, placebo-controlled trial of a new drug in development for the treatment of negative symptoms in schizophrenia. *Am J Psychiatry* **2017**; 174: 1195-202. doi: 10.1176/appi.ajp.2017.17010122.
81. Luthringer R. Efficacy and safety of MIN-101: a new drug for the treatment of negative symptoms in schizophrenia a 12-week randomized, double blind, placebo-controlled trial. *Eur Psychiatry* **2017**; 41 Suppl 1: S191. doi: 10.1016/j.eurpsy.2017.01.2120.
82. Miller ML, Harvey PD. Treatment of schizophrenia: focus on roluperidone. *Drugs Future* **2020**; 45(12): 893-902. doi: 10.1358/dof.2020.45.12.3168474.
83. Ebdrup BH, Rasmussen H, Arnt J, Glenthøj B. Serotonin 2A receptor antagonists for treatment of schizophrenia. *Expert Opin Investig Drugs* **2011**; 20: 1211-23. doi: 10.1517/13543784.2011.601738.
84. Marder SR, Davis JM, Chouinard G. The effects of risperidone on the five dimensions of schizophrenia derived by factor analysis: combined results of the North American trials. *J Clin Psychiatry* **1997**; 58: 538-46. doi: 10.4088/jcp.v58n1205.
85. Keefe RS, Harvey PD, Khan A, Saoud JB, Staner C, Davidson M, et al. Cognitive effects of MIN-101 in patients with schizophrenia and negative symptoms: results from a randomized controlled trial. *J Clin Psychiatry* **2018**; 79: 17m11753. doi: 10.4088/JCP.17m11753.
86. Minerva Neurosciences Inc. Roluperidone: Topline Results from the Phase 3 Trial: A Multicenter, Randomized, Double-blind, Parallel Group, Placebo-Controlled, Monotherapy, 12-Week Study to Evaluate the Efficacy and Safety of 2 Fixed Doses of MIN-101 in Adult Patients with Negative Symptoms of Schizophrenia, Followed by 40-Week Open-Label Extension. Minerva Neurosciences Inc; **2020**.
87. Shekhar A, Potter WZ, Lightfoot J, Lienemann J, Dubé S, Mallinckrodt C, et al. Selective muscarinic receptor agonist xanomeline as a novel treatment approach for schizophrenia. *Am J Psychiatry* **2008**; 165: 1033-9. doi: 10.1176/appi.ajp.2008.06091591.
88. Watson J, Brough S, Coldwell MC, Gager T, Ho M, Hunter AJ, et al. Functional effects of the muscarinic receptor agonist, xanomeline, at 5-HT1 and 5-HT2 receptors. *Br J Pharmacol* **1998**; 125: 1413-20. doi: 10.1038/sj.bjp.0702201.
89. McKinzie DL, Bymaster FP. Muscarinic mechanisms in psychotic disorders. *Handb Exp Pharmacol* **2012**; 233-65. doi: 10.1007/978-3-642-25758-2_9.
90. Mandai T, Kasahara M, Kurimoto E, Tanaka M, Suzuki M, Nakatani A, et al. In vivo pharmacological comparison of TAK-071, a positive allosteric modulator of muscarinic M1 receptor, and xanomeline, an agonist of muscarinic M1/M4 receptor, in rodents. *Neuroscience* **2019**; 414: 60-76. doi: 10.1016/j.neuroscience.2019.07.003.
91. Bymaster FP, Shannon HE, Rasmussen K, Delapp NW, Mitch CH, Ward JS, et al. Unexpected antipsychotic-like activity with the muscarinic receptor ligand (5R,6R)6-(3-propylthio-1,2,5-thiadiazol-4-yl)-1-azabicyclo[3.2.1]octane. *Eur J Pharmacol* **1998**; 356: 109-19. doi: 10.1016/s0014-2999(98)00487-7.
92. Rovner ES. Trospium chloride in the management of overactive bladder. *Drugs* **2004**; 64: 2433-46. doi: 10.2165/00003495-200464210-00005.
93. Brannan SK, Sawchak S, Miller AC, Lieberman JA, Paul SM, Breier A. Muscarinic cholinergic receptor agonist and peripheral antagonist for schizophrenia. *N Engl J Med* **2021**; 384: 717-26. doi: 10.1056/NEJMoa2017015.
94. Brown D, Daniels K, Pichereau S, Sand M. A phase IC study evaluating the safety, tolerability, pharmacokinetics, and cognitive outcomes of BI 409306 in patients with mild-to-moderate schizophrenia. *Neurol Ther* **2018**; 7: 129-39. doi: 10.1007/s40120-017-0085-5.
95. Dorner-Ciossek C, Kroker KS, Rosenbrock H. Role of PDE9 in cognition. *Adv Neurobiol* **2017**; 17: 231-54. doi: 10.1007/978-3-319-58811-7_9.
96. Desch M, Schlecker C, Hohl K, Liesenfeld KH, Chan T, Müller F, et al. Pharmacokinetic-interactions of BI 425809, a novel glycine transporter 1 inhibitor, with cytochrome P450 and P-glycoprotein substrates: findings from in vitro analyses and an open-label, single-sequence phase I study. *J Clin Psychopharmacol* **2023**; 43: 113-21. doi: 10.1097/jcp.0000000000001656.
97. Brown D, Nakagome K, Cordes J, Brenner R, Gründer G, Keefe RSE, et al. Evaluation of the efficacy, safety, and tolerability of BI 409306, a novel phosphodiesterase 9 inhibitor, in cognitive impairment in schizophrenia: a randomized, double-blind, placebo-controlled, phase II trial. *Schizophr Bull* **2019**; 45: 350-9. doi: 10.1093/schbul/sby049.
98. Dhingra A, Tummala SR, Lyubarsky A, Vardi N. PDE9A is expressed in the inner retina and contributes to the normal shape of the photopic ERG waveform. *Front Mol Neurosci* **2014**; 7: 60. doi: 10.3389/fnmol.2014.00060.
99. Moschetti V, Schlecker C, Wind S, Goetz S, Schmitt H, Schultz A, et al. Multiple rising doses of oral BI 425809, a GlyT1 inhibitor, in young and elderly healthy volunteers: a randomised, double-blind, phase I study investigating safety and pharmacokinetics. *Clin Drug Investig* **2018**; 38: 737-50. doi: 10.1007/s40261-018-0660-2.
100. Fleischhacker WW, Podhorna J, Gröschl M, Hake S, Zhao Y, Huang S, 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. doi: 10.1016/s2215-0366(20)30513-7.
101. Krogmann A, Peters L, von Hardenberg L, Bödeker K, Nöhles VB, Correll CU. Keeping up with the therapeutic

advances in schizophrenia: a review of novel and emerging pharmacological entities. *CNS Spectr* **2019**; 24: 38-69. doi: 10.1017/s109285291900124x.

102. Grauer SM, Pulito VL, Navarra RL, Kelly MP, Kelley C, Graf R, et al. Phosphodiesterase 10A inhibitor activity in preclinical models of the positive, cognitive, and negative symptoms of schizophrenia. *J Pharmacol Exp Ther* **2009**; 331: 574-90. doi: 10.1124/jpet.109.155994.
103. NIH US National Library of Medicine. A Safety, Tolerability, and Pharmacokinetics Study of MK-8189 in Participants with Schizophrenia and in Healthy Participants. ClinicalTrials.gov Identifier: NCT03565068. Available from: https://clinicaltrials.gov/ct2/show/NCT03565068.
104. NIH US National Library of Medicine. A Randomized, Double-Blind, Placebo-Controlled, Two-Period, Cross-over Proof of Activity Study to Evaluate the Effects of TAK-041 on Motivational Anhedonia as Add-on to Antipsychotics in Participants with Stable Schizophrenia. ClinicalTrials.gov Identifier: NCT03319953. Available from: https://clinicaltrials.gov/ct2/show/NCT03319953.
105. NIH US National Library of Medicine. A Study to Assess the Effects of RO6889450 (Ralmitaront) in Participants with Schizophrenia or Schizoaffective Disorder and Negative Symptoms. ClinicalTrials.gov Identifier: NCT03669640. Available from: https://clinicaltrials.gov/ct2/show/NCT03669640.
106. NIH US National Library of Medicine. NCT03745820: A Study to Evaluate the Safety and Efficacy of BIIB104 in Participants with Cognitive Impairment Associated with Schizophrenia (CIAS) (TALLY). ClinicalTrials.gov Identifier: NCT03745820. Available from: https://clinicaltrials.gov/ct2/show/NCT03745820.
107. Layton ME, Kern JC, Hartingh TJ, Shipe WD, Raheem I, Kandebo M, et al. Discovery of MK-8189, a highly potent and selective PDE10A inhibitor for the treatment of schizophrenia. *J Med Chem* **2023**; 66: 1157-71. doi: 10.1021/acs.jmedchem.2c01521.
108. NIH US National Library of Medicine. A Trial of the Efficacy and the Safety of RO6889450 (Ralmitaront) vs Placebo in Patients with an Acute Exacerbation of Schizophrenia or Schizoaffective Disorder. ClinicalTrials.gov Identifier: NCT04512066. Available from: https://clinicaltrials.gov/ct2/show/NCT04512066.
109. US National Library of Medicine. An Active Controlled Early Phase Study of MK-8189 in Adults with Schizophrenia. ClinicalTrials.gov Identifier: NCT03055338. Available from: https://clinicaltrials.gov/ct2/show/NCT03055338.
110. NIH US National Library of Medicine. Relationship Between Efficacy of Lumateperone and Brain Glutamate and Dopamine (Lumafep). ClinicalTrials.gov Identifier: NCT05890768. Available from: https://clinicaltrials.gov/study/NCT05890768.
111. NIH US National Library of Medicine. Lumateperone for the Prevention of Relapse in Patients with Schizophrenia. ClinicalTrials.gov Identifier: NCT04959032. Available from: https://clinicaltrials.gov/study/NCT04959032.
112. NIH US National Library of Medicine. Study of Lumateperone as Adjunctive Therapy in the Treatment of Patients with Major Depressive Disorder. ClinicalTrials.gov Identifier: NCT05850689. Available from: https://clinicaltrials.gov/study/NCT05850689.
113. NIH US National Library of Medicine. Multicenter Study of Lumateperone as Adjunctive Therapy in the Treatment of Patients with Major Depressive Disorder. ClinicalTrials.gov Identifier: NCT05061706. Available from: https://clinicaltrials.gov/study/NCT05061706.
114. NIH US National Library of Medicine. Clinical Trial of Lumateperone as Adjunctive Therapy in the Treatment of Patients with Major Depressive Disorder. ClinicalTrials.gov Identifier: NCT04985942. Available from: https://clinicaltrials.gov/study/NCT04985942.
115. NIH US National Library of Medicine. Brexpiprazole Study. ClinicalTrials.gov Identifier: NCT03526354. Available from: https://clinicaltrials.gov/study/NCT03526354.
116. NIH US National Library of Medicine. A Study to Evaluate the Effect of a Supratherapeutic Dose of MK-8189 on the QTc Interval in Participants with Schizophrenia (MK-8189-019) (TQT). ClinicalTrials.gov Identifier: NCT05893862. Available from: https://clinicaltrials.gov/study/NCT05893862.