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General

Lumateperone tosylate, A Selective and Concurrent Modulator of Serotonin, Dopamine, and Glutamate, in the Treatment of Schizophrenia

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Purpose of Review

This is a comprehensive review of the literature regarding the use of Lumateperone tosylate for schizophrenia. This review presents the background, evidence, and indications for the use of lumateperone tosylate in the treatment of schizophrenia.

Recent Findings

Schizophrenia is a chronic mental health disorder that affects approximately 3.3 million people in the United States. Its symptoms, which must be present more than six months, are comprised of disorganized behavior and speech, a diminished capacity to comprehend reality, hearing voices unheard by others, seeing things unseen by others, delusions, decreased social commitment, and decreased motivation. The majority of these symptoms can be managed with antipsychotic medication.
Lumateperone is a selective and concurrent modulator of serotonin, dopamine, and glutamate, which all mediate or modulate serious mental illness.

Summary

Schizophrenia is a complex, severe mental illness that affects how the brain processes information. There are many medications used to treat schizophrenia. One antipsychotic agent, lumateperone tosylate, is a newer agent that the FDA recently approved. The most common adverse effects are shown to be mild such as somnolence, constipation, sedation, and fatigue, with the 42 mg recommended dose. Lumateperone tosylate is an FDA-approved drug that can be given only at the 42mg dose once daily with no titration requirements.

INTRODUCTION

Schizophrenia is a complex, severe mental illness that affects how the brain processes information. The symptoms are broad but can be separated into three categories: positive, negative, or cognitive symptoms.[1] Positive symptoms are behaviors that are not present in a healthy individual. These can include hallucinations, delusions, confused thoughts, and unusual body movements.[2] Negative symptoms can be defined as the absence of certain behaviors, such as apathy, lack of emotion, or motivation and reduced facial expressions.[2] Lastly, cognitive symptoms can consist of memory impairment, attention problems, and learning difficulties.[3] Patients usually present with positive symp-

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toms to a clinician, but the negative and cognitive symptoms together can create a long-term burden on the patient.[4] The onset of cognitive and social impairments can be present from the time of early adolescence.[5] However, it frequently isn't until the onset of psychosis that patients are referred to a clinician. This onset usually occurs in early adulthood and differs between sexes. The onset of this disorder for males is typically in their early twenties, while the onset for females is slightly later in their early thirties.[6] Schizophrenia affects approximately 1% of the population worldwide.[7] Patients with this disorder typically have a life expectancy that is 20 years less than the general population.[8] These patients also face difficulties in multiple aspects of their everyday life, such as social and occupational impairments that can persist long-term. This can manifest as having trouble maintaining employment and relationships.[9] This may be due to the negative symptoms and cognitive deficits that patients are facing.[10] While there is an importance in treating positive symptoms, addressing negative and cognitive symptoms may help to improve these patients' quality of life.

Antipsychotics are the cornerstone of treatment for schizophrenia. There are two main classes of antipsychotics. First-generation antipsychotics, also known as conventional antipsychotics, were first used to treat schizophrenia. These medications treat largely positive symptoms of schizophrenia.[11] Second-generation antipsychotics, or atypical antipsychotics, also primarily treat positive symptoms. Both of these classes act as dopamine type 2 receptor (D_2R) antagonists.[12] However, atypical antipsychotics also act to block serotonin receptors such as 5-HT_{2A}.[11] There seems to be no significant difference in the efficacy of these two classes.[13] These antipsychotic medications also show limited efficacy for negative symptoms and cognitive deficits.[14] the development of drugs that treat positive symptoms was a significant step towards improving patients' quality of life. Still, it did not completely solve the problems that patients face.

As stated above, negative and cognitive symptoms can cause significant impairment to a patient's everyday life.[15] Creating treatments that target the alleviation of these symptoms may help to improve patients' daily functioning and overall quality of life. It is possible that targeting the 5-HT_{2A} serotonin receptors and developing drugs that are more specific to 5-HT_{2A} receptors can significantly affect these symptoms.[11] Lumateperone tosylate is a new second-generation antipsychotic indicated for treating schizophrenia that can potentially alleviate positive and negative symptoms.[16] This drug interacts with dopamine, serotonin, and glutamate, making it unique compared to other antipsychotics.[17] Its highly selective nature for D_2R receptors in specific brain regions decreases unfavorable adverse effects and makes it a safer drug.[16]

SCHIZOPHRENIA EPIDEMIOLOGY/ PATHOPHYSIOLOGY/RISK FACTORS/ PRESENTATION

Schizophrenia is a severe mental disorder that can cause severe impairment to cognition and perception. The term was coined in the early 1900s and means "to split the mind." Schizophrenia affects approximately 1% of the world's population but can vary geographically.[18] The disorder can manifest differently in individual patients, with some patients having only a few acute episodes to others having recurrent episodes with symptoms that worsen over time.[19] Additionally, patients have a 4.9% higher risk of committing suicide than the general population.[20] Schizophrenia is more prevalent in lower socio-economic groups.[19] Although the disorder generally manifests during early adulthood, there is evidence that the development of schizophrenia can begin during neurodevelopment.[21] Cognitive impairment can present in individuals before they are diagnosed in early adulthood.[22] Children can present with neurologic development impairment, such as attention deficits and motor function problems.[23] Overall, there are several risk factors, both environmental and genetic, that can contribute to the development of schizophrenia.

Environmental risk factors that have been linked to the development of schizophrenia can be tied to incidences during the prenatal period, childhood, adolescence, and early adulthood.[24] Experiencing complications during pregnancy or birth can cause an increased risk for an individual to develop schizophrenia.[25] Some complications include diabetes, pre-eclampsia, abnormal fetal development, and complications during delivery such as asphyxia.[26] Additionally, a disproportionate number of patients with schizophrenia were born in the winter and late spring.[27] There is about a 10% increase in the incidence of individuals with schizophrenia born in the winter versus the summer.[28] This may be due to an increase in respiratory tract infections and influenza during the winter months. Mothers who contract the influenza virus during their second trimester of pregnancy are at an increased risk of having a child with schizophrenia.[29] Other risk factors include a vitamin D deficiency from insufficient sunlight or a folic acid deficiency from an inadequate diet.[5] Another environmental risk factor is paternal age, as older fathers are at a higher risk of having a child with schizophrenia.[30] The group at the highest risk are those with the paternal age of 55 years or older.[31] However, further studies have shown that older paternal age is only relevant in individuals with a family history of schizophrenia, meaning there could be potential additional biologic factors.[32] Trauma, death of a parent, and infection during childhood can also lead to an increased risk of developing schizophrenia.[33] Children who experienced significant stress and hardships are also at a higher risk.[34] There is some debate whether the use of cannabis during adolescence is associated with a higher risk of developing the disorder. Some studies have shown that individuals who have used cannabis are 2 to 25 times more likely to develop schizophrenia.[35] However, other studies have shown that the use of this drug only affects individuals who are already vulnerable to the disorder.[36] Other illicit drugs, such as amphetamines and cocaine, can produce psychotic episodes similar to schizophrenia.[37] Individuals who are raised in an urban environment are also at a higher risk of developing schizophrenia.[1]

There is also a genetic component to the development of schizophrenia, as having an affected family member dramatically increases the risk of developing the disorder. Mul-

tiple twin studies have been done to show the genetic aspect of schizophrenia. Dizygotic twins, who share 50% of their DNA, have a lower risk of both twins developing schizophrenia than monozygotic twins, who share 100% of their DNA.[38] Heritability of the disorder is estimated to be about 80%.[39] If one parent has schizophrenia, the probability that they will pass it down to their child is 13%, and if both parents are affected, the probability is more than 20%.[19] It is hard to tell if an abnormality in specific genes can cause the development of schizophrenia. However, there are structural abnormalities of particular chromosomes that have been tied to an increased risk of developing schizophrenia.[40] Some abnormalities that have been recorded are a deletion of several megabases of chromosome 22q11.2 and the balanced reciprocal translocation of chromosomes 1q42/11q14.[41] The deletion on chromosome 22q11.2 has been linked to a 30% to 40% increased risk of developing schizophrenia.[42] Linkage analysis has also been done to find the relationship between specific genes located close to each other on a chromosome.[43] These genes are sometimes inherited together during meiosis. Using this data, "candidate genes" that may have a role in the pathogenesis of schizophrenia have been identified.[43] Some include DISC1, DNTNBP1, NRG1, and COMT.[43] However, there is still conflicting evidence, and the topic remains widely debated.

So far, the pathogenesis of schizophrenia can be thought of as being due to a combination of environmental and genetic risk factors. These factors disrupt brain development and can lead to some of the symptoms of schizophrenia.[22] Postmortem studies have shown that patients with schizophrenia have "lower levels of synaptic proteins, dendritic spines and gamma-aminobutyric acid (GABA)."[44] Abnormal GABAergic function has been primarily associated with patients who have schizophrenia.[45] Reduced GABA activity can be due to the downregulation of a gene that encodes the enzyme for GABA synthesis, glutamate decarboxylase I (GAD1).[46] Abnormal dopamine receptor activity has also been recorded in individuals with schizophrenia. There is some evidence that these patients have an increased expression of dopamine receptors in the striatum region of their brain.[47] Current antipsychotic drugs are dopaminolytic, while dopamine agonists can cause psychosis.[1] Negative and cognitive symptoms may present well before the onset of the first psychotic episode.[48] As stated, schizophrenia generally develops in individuals during early adulthood, and it is positive symptoms that usually cause an individual to seek clinical assistance. However, cognitive and negative symptoms may manifest during childhood as apathy or attention and memory deficits. The creation of synaptic connections during childhood and subsequent synaptic pruning during adolescence usually are developmental events that happen in an individual's lifetime.[49] These processes are known to be disrupted in patients with schizophrenia, leading to abnormal neural communication and loss of grey matter.[50,51] Synchronized neural oscillations are associated with cognitive processes and are tied to functional networks in healthy individuals.[52] In patients with schizophrenia, these oscillations are disrupted and can lead to the cognitive and negative symptoms experienced by these individuals.[53] The disrupted balance of excitatory and inhibitory neurons can also lead to these symptoms, caused in part by the decrease in dendritic spines mentioned previously.[54] Additionally, abnormal serotonin levels can lead to an increased risk of developing schizophrenia.[55] Serotonin affects multiple other neurotransmitters such as glutamate, GABA, and acetylcholine, altering their activity.[56] One serotonin receptor, serotonin 2A receptor (HTR2A), has been linked to the pathophysiology of schizophrenia.[57] Studies have shown that the expression of this receptor can change over time in patients with schizophrenia.[58] The development of drugs that target this receptor may eventually provide the path to the treatment of schizophrenia.

CURRENT TREATMENT OF SCHIZOPHRENIA

FIRST-GENERATION ANTIPSYCHOTICS

First-generation antipsychotics (FGA) drugs act by blocking dopamine D_2 receptors in the central nervous system to reduce the positive symptoms of schizophrenia and reduce the risk of relapse. FGAs do not express selective binding for dopamine receptors in the CNS, and this lack of specificity causes a range of side effects, most notably extrapyramidal symptoms (EPS).[59] The binding affinity of these drugs for D_2 receptors is strongly associated with their therapeutic doses.[60] *In vitro* studies show that high potency FGAs, like haloperidol, bind stronger to D_2 receptors and dissociate more slowly than low potency FGAs.[61] Moreover, studies have shown that antipsychotic effects are achieved with 65–70% D_2 receptor occupancy, but a D_2 occupancy greater than 80% markedly increases the risk of EPS.[62,63] Also, studies have shown that approximately 30% of patients with acute symptoms have little or no response to FGAs, and up to 50% of patients only show a weak or partial response.[64] Furthermore, FGAs offer little benefit for the negative symptoms or cognitive impairment seen in schizophrenia patients; high doses of FGAs may exacerbate negative symptoms and worsen cognitive impairment by blocking dopamine receptors in the mesocortical pathway.[59,65] Due to the risk of severe EPS, FGAs are preferred for patients that have a history of a positive response and tolerable side effects to the drugs.

SECOND-GENERATION ANTIPSYCHOTICS

Second-generation antipsychotics (SGA) are currently the preferred treatment for schizophrenia. SGAs were revolutionary as they can markedly decrease the positive and negative symptoms seen in schizophrenia patients while not producing the EPS seen in patients taking FGAs.[59,66] In comparison to the typical antipsychotics that selectively block dopamine D_2 receptors, SGAs act on dopamine receptors and act on serotonin receptors, mainly 5-HT_{2A} receptors.[59,67] Clozapine was the first SGA developed and used in clinical practice, and many newer SGAs have been developed based on the structure of clozapine.[66] All of the SGAs have unique pharmacologic properties, but they all principally have antagonistic activity on dopaminergic D_2 and serotoninergic 5-HT_{2A} receptors. SGAs can be divided into groups based on binding affinity for D_2 and 5-HT_{2A} receptors, SGAs with modest binding affinity, such as clozapine and olanzapine, and SGAs with high affinity, such as

risperidone and lurasidone.[68] There is significant evidence that antagonistic effects on 5-HT_{2A} receptors seen in SGAs contribute to the decreased risk of producing EPS compared to FGAs. Meltzer et al. suggest that an SGA will show increased atypical antipsychotic effects if it has a higher affinity for 5-HT_{2A} receptors relative to D_2 receptors.[69] Furthermore, this principle can explain the enhanced efficacy and reduced EPS of SGAs compared to FGAs.[70]

SYSTEMATIC REVIEWS

In 2016, a randomized, double-blind, placebo-controlled, and active-controlled trial-tested lumateperone against risperidone and a placebo in 335 acutely psychotic adults with schizophrenia.[71] Risperidone, the active control, as compared to two doses of lumateperone and a placebo group.[71] After the 28-day study, lumateperone showed a statistically and clinically significant reduction in symptoms, measured by PANSS total score, at a dose of 60 mg but showed no distinction from the placebo group at 120 mg.[11] In a randomized, double-blind, placebo-controlled, phase 3 clinical trial of 450 patients with acute exacerbation of schizophrenia, lumateperone demonstrated an ability to reduce symptoms without producing clinically significant adverse effects.[72] A 42 mg dose of lumateperone has shown statistically significant differences in reducing symptoms of schizophrenia without producing clinically significant motor, cardiometabolic, or endocrine adverse effects compared with the placebo.[72]

LUMATEPERONE TOSYLATE DRUG INFORMATION

Lumateperone (CAPLYTA) is a newly FDA-approved, first-in-class drug used for the treatment of schizophrenia. It is available in 42 mg capsules for a once-daily recommended dose. In November 2017, the U.S. Food and Drug Administration (FDA) granted fast-track designation for lumateperone to treat schizophrenia. Lumateperone received approval in the USA to treat schizophrenia in adults in December 2019.[73] The most common adverse effects are mild, such as somnolence, constipation, sedation, and fatigue with the 42 mg recommended dose.[72] Serious adverse events include orthostatic hypotension, hyperglycemia, dyslipidemia, leukopenia, neutropenia, extrapyramidal disease, neuroleptic malignant syndrome, and tardive dyskinesia.[74] The drug has a black-box warning for elderly patients with dementia-related psychosis who are at an increased risk for a serious cerebrovascular accident when taking the medication; lumateperone is not approved to treat patients with dementia-related psychosis.[73] It is contraindicated in patients with known hypersensitivity reactions to lumateperone (Caplyta FDA Label). Also, patients taking CYP3A4 inducers or moderate to potent CYP3A4 inhibitors are advised to avoid lumateperone.[72] Lumateperone may react with alcohol and other sedatives to produce sedation. Lumateperone does not have FDA approval as an “add-on” treatment for patients prescribed another antipsychotic with residual symptoms.

MECHANISM OF ACTION

Lumateperone is a selective and concurrent modulator of serotonin, dopamine, and glutamate, which are all involved with serious mental illness. Lumateperone is selective for D_2 receptors and acts as a dopamine receptor phosphoprotein modulator (DPPM).[75] It acts as a presynaptic partial agonist and postsynaptic antagonist at D_2 receptors.[75] This novel action causes reduced presynaptic release of dopamine and blockade of postsynaptic dopamine activity, allowing for marked reduction of dopaminergic signaling.[75] Lumateperone shows selectivity for the mesocortical and mesolimbic pathways receptors and has a decreased affinity for the receptors of nigrostriatal pathways.[16,76] Lumateperone also acts as an antagonist of serotonin 5-HT_{2A} receptors and has a 60-fold higher affinity for 5-HT_{2A} receptors than D2 receptors.[71,77] Moreover, it acts as an inhibitor of the serotonin reuptake transporter (SERT), potentially causing antidepressant effects while reducing some of the negative symptoms of schizophrenia, such as depression.[16,78] Lumateperone modulates glutaminergic activity by increasing the phosphorylation of mesolimbic GluN2B subunits of NMDA receptors, enhancing glutamatergic NMDA function.[78] This augmentation of NMDA receptors may contribute to the drug’s effects as an antipsychotic and antidepressant as NMDA receptor activity is insufficient in schizophrenic patients.[78] Lumateperone has shown fewer adverse effects than other antipsychotics, as it does not interact with the muscarinic and histaminergic receptors that contribute to common adverse effects that occur with other antipsychotic drugs.[78] The pharmacological actions of the drug mainly cause sedation and reduction of agitation and aggression at lower doses while showing antipsychotic and antidepressant effects at higher doses.[77] The effects of lumateperone seen at low dosages may result from its lack of D_2 receptor binding and favored 5-HT_{2A} receptor antagonism at low dosages. Increasing the dose allows for D_2 receptor binding in addition to 5-HT_{2A} receptor binding, resulting in antipsychotic effects.[16]

PHARMACOKINETICS/PHARMACODYNAMICS

ABSORPTION AND DISTRIBUTION

Lumateperone is absorbed rapidly in the G.I. tract with peak concentration (C_{max}) occurring at approximately 1 hour (T_{max}), after the once-daily oral administration of 42 mg capsule, in the fasted state.[72,74] Ingestion of a high-fat meal leads to an approximate decrease in C_{max} of 33%, and T_{max} is extended to approximately 2 hours.[73,79] Dosages at 120 mg/day have not been shown to produce any statistically significant improvement in efficacy. When taken with a high-fat meal, the area under the plasma-concentration-time curve (AUC) increases by 9%.[73] Steady-state is achieved in about five days, and the half-life of the drug is 13 to 21 hours. The volume of distribution of lumateperone is approximately 4.1 L/ kg following intravenous administration.[72] The drug is 97.4% bound to plasma proteins with a bioavailability of 4.4% when taken orally.[74]

METABOLISM

Lumateperone is extensively metabolized in the liver through multiple enzyme systems yielding over 20 metabolites. However, lumateperone is predominantly metabolized via ketone reductases, the CYP3A system, and UGT enzymes.[16,71,73] Following a single oral dose of radiolabeled lumateperone, lumateperone, and its glucuronidated metabolites represent approximately 2.8 and 51% of the total plasma radioactivity.[73] Because of this metabolic profile, various drug interactions are observed. Patients taking CYP3A4 inducers should avoid the use of lumateperone, as coadministration will decrease the exposure of lumateperone.[71] Concomitant administration of lumateperone with moderate or potent CYP3A4 inhibitors should be avoided as increased lumateperone exposure may increase the risk of toxicity.[72] Also, the use of lumateperone with UGT inhibitors should be avoided as coadministration can lead to increased exposure of lumateperone and its metabolites.[79]

ELIMINATION

When taken orally, 58% radiolabeled lumateperone is excreted in the urine, and 29% is excreted in the feces.[79] Less than 1% of the dose is excreted in the urine unchanged.[73,79] The metabolites of lumateperone are water-soluble. Thus they are entirely excreted in the urine.[16] Lumateperone has a total body clearance of 27.9 L/h with IV administration.[74]

SAFETY AND EFFICACY

PHASE I CLINICAL TRIALS

Single doses of lumateperone (ITI-007) were given to healthy male volunteers and were safe and well-tolerated with no serious adverse effects (A.E.s). No clinically significant time or dose-related variations were seen in laboratory or cardiovascular parameters.

In another phase I clinical trial, healthy volunteers were given once-daily oral doses of ITI-007 for five days and determined to be safe and well-tolerated. In part 2 of the study, patients with schizophrenia were given once-daily oral doses of ITI-007 for five days. The drug was safe and well-tolerated in this patient population as well.

In both trials, there were no clinically relevant changes noted in vital signs, ECG, laboratory tests, or physical exams. No dose-limiting side effects observed.[71]

PHASE II CLINICAL TRIALS

FDA approval was given for lumateperone for the treatment of schizophrenia based on two randomized, double-blind, placebo-controlled trials: a phase II trial (ITI-007-500; NCT01499563) and a phase III trial (ITI-007-301; NCT00282761).[79] In ITI-007-500; NCT01499563, patients ranging in age from 18-55 years with acute exacerbation of psychosis were given 60 mg ITI-007, 120 mg ITI-007, risperidone 4 mg, or placebo once daily for four weeks. The primary endpoint was the measurement of the PNSS total score with secondary analyses performed on symptom subscales. There was a significant difference between 60 mg ITI-007 and placebo in PANSS total score (LSMD -13.2 vs. -7.4 for placebo; p=0.017). 4 mg risperidone also showed a significant change when compared to placebo (LSMD -13.4 vs. -7.4 for placebo; p=0.013). 120 mg ITI-007 did improve positive symptoms and general psychopathology; however, the differences were not significant when compared to placebo.[80] Both 60 mg of ITI-007 and 4 mg risperidone significantly improved PANSS positive symptoms and PANSS general psychopathology compared to placebo.[73] Negative symptoms only improved with 60 mg ITI-007; however, this improvement was not significant. Neither 4 mg risperidone or 120 mg ITI-007 showed improvement in negative symptoms. The lack of improvement seen in negative symptoms maybe be due to low negative symptomology at baseline. Of those with prominent negative symptoms at baseline, 60 mg ITI-007 reduced the severity of negative symptoms as measured by the PANSS negative symptom scale (ES 0.34). In the risperidone group, the improvement in negative symptoms was less than in the placebo group. In patients that met the criteria of comorbid symptoms of depression, 60 mg ITI-007 significantly reduced the total PANSS score and CDSS score with an E.S. of ~1 on both measures. 60 mg ITI-007 significantly improved prosocial behavior measured by the PANSS prosocial factor (ES 0.6).[80] 120 mg ITI-007 did not change substantially PANSS scores when compared to placebo. It is unknown why the 120 mg dose showed a lack of efficacy, although it may be attributed to differences in population, measurement errors, or the possibility that the combined effect presynaptic dopamine D_2 agonism and postsynaptic D_2 antagonism could make the higher dose less effective.[71]

In another phase II study, ten patients ranging in age from 18-60 years old with stable schizophrenia were given 60 mg ITI-007 once daily for two weeks, and D_2 receptor occupancy was measured using positron emission tomography. The D_2 receptor occupancy for 60 mg ITI-007 was found to be 39% which is lower than the effective doses of second-generation antipsychotics. This finding may contribute to the favorable safety and tolerability of ITI-007.[16]

PHASE III CLINICAL TRIALS

In a randomized, double-blind phase III trial (ITI-007-301; NCT00282761), 450 patients ranging in age from 18-60 were randomly assigned to receive one of three treatments: 60 mg (42 mg active moiety) ITI-007, 40 mg (28 mg active moiety) ITI-007, or a placebo once daily for four weeks. The primary endpoint was a change in PANSS score from baseline to the end of treatment on day 28 compared to placebo.[73] The secondary endpoints were the CGI-S score and other secondary efficacy measures, including positive, negative, and psychopathological PANSS subscales, Personal and Social Performance Scale (PSP), PANSS derived prosocial factor, and Calgary Depression Scale for Schizophrenia.[72] In the intention-to-treat analysis, the least-squares mean change from baseline in the PANSS score upon completion of treatment was -14.5 in the patients who received 42 mg ITI-007 vs. -10.3 in the placebo group.[73] Statistically significant differences from placebo in the PANSS total score were seen by day 8 of the trial and continued until completion on day 28 in the 42 mg ITI-007 group. Consistent treatment effects were seen amongst subgroups of race, ethnic-

ity, age, and sex to compare 42 mg ITI-007 and placebo. Those in the 42 mg ITI-007 group also saw a statistically significant change in CGI-S score from baseline compared to placebo (LSMD from placebo -0.3; unadjusted *P*=0.003). The effects of the 28 mg ITI-007 group were not significant regarding the primary endpoint; however, a significant difference was seen in the CGI-S score compared to placebo (LSMD from placebo -0.2; nominal *P*=0.02). Both treatment groups showed significant improvements in the PANSS positive symptom from baseline to day 28 compared to placebo (42 mg LSMD -1.7; nominal P=0.006 and 28 mg: LSMD -1.2; nominal P=0.04). Changes in PANSS negative sub score did not change significantly between baseline and day 28 in either group compared to placebo. When compared to placebo, the 42 mg group showed significant improvements in the general psychopathology subscale score and the psychosocial function as measured by the PANSS derived prosocial factor and PSP scale (general psychopathology subscale: LSMD -2.4; nominal *P*=0.01; PANSS derived prosocial factor: LSMD -1.1; nominal *P*=0.04; PSP scale: LSMD 3.3; nominal *P*=0.05. Change in Calgary Depression Scale for Schizophrenia from baseline throughout treatment changed significantly in neither the 42 mg ITI-007 nor the 28 mg ITI-007 group when compared to placebo.[72]

In another phase III trial, ITI-302 (NCT02469155), 696 patients with acute schizophrenia were given either 42 mg ITI-007, 14 mg ITI-007, risperidone 4 mg, or placebo once daily for a total of 6 weeks. Neither dosage of ITI-007 showed significant changes in PANSS total score when compared to placebo.[73]

POOLED ANALYSES

A pooled study was conducted by combining ITI-007-301 (NCT00282761), ITI-302 (NCT02469155), and ITI-500 (NCT01499563).[73] The efficacy data were pooled from the two positive studies (ITI-007-005 and ITI-007-301), and safety data was pooled from all three studies. In the efficacy analyses, which included 520 patients, ITI-007 42 mg significantly reduced PANSS total score (L.S. mean difference -4.76; *P*<0.001). 42 mg ITI-007 showed similar efficacy when compared to 4 mg risperidone (LSMD -4.97; *P*=0.014). ITI-007 42 mg also showed significant improvement in CGI-S score (LSMD -0.29; *P*<0.001).[81]

SAFETY

In a phase II trial (ITI-500; NCT01499563), ITI-007 was safe and well-tolerated in individuals with schizophrenia. There were no serious adverse events in individuals treated with ITI-007. During the trial, five patients discontinued treatment due to an adverse event: one patient who received ITI-007 experienced dry mouth, and one patient who received ITI-007 experienced worsening of schizophrenia. The relative risk of treatment-emergent adverse event (TEAEs) for 60 mg ITI-006 is 1.14, which does not vary significantly from placebo (*p*=0.346). The relative risk for 120 mg ITI-007 was 1.3 (*p*=0.024). The most frequent adverse event was somnolence and sedation. Neither 60 mg ITI-007 nor 120 mg ITI-007 was associated with extrapyramidal symptoms (EPS). Risperidone caused akathisia in 7% of subjects. Median weight from day -7 to day 28 was approximately 1 kg for patients who received placebo, 60 mg ITI-007, and 120 mg ITI-007. Weight gain from day -7 to day 28 was 2.5 kg for the risperidone group. Placebo adjusted mean weight gain by site indicated a weight gain of 0.3 to 0.4 for both 60 mg ITI-007 and 120 mg ITI-007 and a weight gain of 2.3 kg for risperidone. Both doses of ITI-007 showed less weight gain when compared to placebo. Both doses of ITI-007 showed significantly lower levels of prolactin, fasting glucose, total cholesterol, and triglycerides. Levels of insulin, glucose, triglycerides, and prolactin remained low through the course of treatment with ITI-007 but increased when switched to the standard of care after the trial period.[80]

In the phase III trial (ITI-007-301; NCT00282761), patients were randomized to receive either 42 mg ITI-007, 28 mg ITI-007, or a placebo once daily for four weeks. TEAEs occurred in 64.7% of patients in the 42 mg lumateperone group, 56.7% of the 28 mg ITI-007 group, and 50.3 % of the placebo group. TEAEs occurring in either ITI-007 group in greater than 5% of patients and twice the rate in placebo were somnolence, sedation, fatigue, and constipation. Two patients experienced severe TEAEs and discontinued treatment: one experienced orthostatic hypotension, and one experienced convulsion. No severe or adverse drug effects were reported throughout the study. Neither treatment option of ITI-007 was associated with increased EPS. The median change in weight from baseline to day 28 was 0.9 kg for 42 mg ITI-007, 0.6 mg for 28 mg, and 0.7 kg for placebo. No significant changes were seen in metabolic parameters, physical exam results, vital signs, or ECG findings.[72]

Lumateperone comes with a black box warning because elderly patients with dementia-related psychosis treated with antipsychotics are at an increased risk of death. As a result, lumateperone is not approved to treat patients with dementia-related psychosis. The only contraindication for the use of lumateperone is a hypersensitivity to the drug. Monitoring is recommended for orthostatic hypotension, metabolic and endocrine abnormalities such as hyperglycemia, dyslipidemia, weight gain, and body temperature dysregulation. Patients on lumateperone are at an increased risk for falls due to somnolence, postural hypotension, and motor and sensory instability; thus, monitoring is recommended. Esophageal dysmotility and aspiration may occur in patients on antipsychotics. Hematologic abnormalities such as leukopenia and neutropenia may occur in patients with pre-existing low WBC or neutrophil counts or a history of drug-induced leukopenia or neutropenia. Therefore, CBC during the first few months of treatment is recommended. Fetal risk in pregnant mothers and infant risk in breastfeeding cannot be ruled out. A toxic dose has not been established, nor has overdose been reported with the use of lumateperone. It is recommended that adults take an oral 42 mg dose once daily with food, with no requirement for dose titration. Safety and efficacy in patients has not been established in pediatric patients.[74]

Nonadherence to medication in the treatment of schizophrenia is primarily due to adverse effects. Since the 2000s, the second-generation antipsychotics that have been introduced have lower rates of sedation, metabolic, and endocrine adverse effects; however, they are not without com-

Table 1. Safety and Efficacy

Author (Year)	Groups Studied and Intervention	Results and Findings	Conclusions
Study 1: Davis and Correll[71]	In a phase I trial, single oral doses ranging from 2.5-30 mg of ITI-007 were given to 30 healthy male volunteers.	Oral doses were safe and tolerated with no serious adverse effects or clinically significant time or dose-related changes in laboratory or cardiovascular parameters.	ITI-007 has a favorable safety and tolerability profile in healthy patients
Study 2: Davis and Correll[71]	In a phase I trial, 18 healthy volunteers were given once-daily oral doses of ITI-007 ranging from 5-20 mg for 5 days. In another group, 34 patients with stable schizophrenia were given once-daily oral doses of ITI-007 ranging from 30-140 mg for 5 days.	Doses were safe and well-tolerated in both trial groups with no clinically relevant dose-related changes in lab tests, vitals, or cardiovascular parameters.	ITI-007 has a favorable safety and tolerability profile in healthy patients and patients with schizophrenia
Study 3: Lieberman et al.[80]	In phase II randomized, double-blind, placebo-controlled trial, 335 acutely psychotic adults with schizophrenia were randomized to receive 60 mg ITI-007, 120 mg ITI-007, 4 mg risperidone, or placebo once daily for 28 days	60 mg ITI-007 and 4 mg risperidone demonstrated efficacy over placebo as shown in improved PANSS total score. 60 mg ITI-007 also showed improvements in negative and depressive symptoms. 120 mg ITI-007 did not show any significant changes when compared to placebo. Both doses of ITI-007 were well tolerated	60 mg ITI-007 was effective for treatment of schizophrenia and showed no differences from placebo on safety measures.
Study 4: Correll et al.[72]	In phase II randomized, double-blind, placebo-controlled trial, acutely psychotic patients with schizophrenia were given either 60 (42 mg active moiety) mg ITI-007, 40 mg (28 mg active moiety) ITI-007, or placebo once daily for 4 weeks	60 mg significantly improved PANSS total score from baseline to day 28 when compared to placebo. Both doses of ITI-007 were safe and well-tolerated	60 mg ITI-007 showed efficacy in treating the symptoms of schizophrenia. Both doses of ITI-007 had a favorable safety profile

plications. Asenapine causes weight gain and sedation, but still relatively less than other antipsychotics such as olanzapine or quetiapine. Partial agonists such as aripiprazole, brexpiprazole, and cariprazine cause akathisia. Lurasidone is known to cause dose-dependent EPS and akathisia, and iloperidone is known to cause orthostasis. In a meta-analysis of oral antipsychotics, the differences in efficacy between medications are small; however, the side effects vary greatly. Novel medications like lumateperone have so far shown a favorable tolerability profile with minimal risk for adverse events and no need for titration.[82] Table 1 summarizes the studies discussed in this section.

CONCLUSION

Schizophrenia is a mental disorder that disrupts the way an individual thinks, feels, and perceives reality. Symptoms can be classified as positive, negative, or cognitive Positive symptoms are abnormal behaviors such as hallucinations, confused thoughts, and delusions. Negative symptoms are the absence of certain behaviors, such as isolating oneself or lack of emotion. Cognitive symptoms are cognition impairments such as reduced memory capacity or learning disabilities. The onset of schizophrenia occurs later in females than in males, affecting around 1% of the population. Schizophrenia is thought to be caused by a mixture of environmental and genetic factors. Environmental factors include complications during pregnancy and birth, vitamin D deficiency, parental age, childhood stress, and drug use. Genetic factors include having a relative that has schizophrenia and chromosomal mutations.

Antipsychotics are the drug of choice for the treatment of schizophrenia. First-generation antipsychotics (FGA) drugs block dopamine D_2 receptors non-selectively. The non-selective nature of these drugs can cause a range of side effects in the patient. FGAs have low efficacy and may exacerbate negative and cognitive symptoms of schizophrenia. Second-generation antipsychotics (SGA) drugs selectively block dopamine D_2 receptors and serotonin 5-HT_{2A} receptors and are the preferred treatment for schizophrenia. SGAs have an increased efficacy compared to FGAs and decrease positive and negative symptoms in patients. Examples SGAs include clozapine, olanzapine, risperidone, and lurasidone.

Lumateperone is a newly approved drug in the treatment of schizophrenia. In a 2016 clinical trial, Lumateperone markedly decreased symptoms of schizophrenia when com-

pared to risperidone. In 2019, the FDA approved a 42 mg dose to be taken once daily. Lumateperone is contraindicated in patients with hypersensitivity to the drug, elders with dementia-related psychosis, and patients who take CYP3A4 inhibitors. Lumateperone is selective for dopamine D_2 receptors and inhibits serotonin 5-HT_{2A} receptors as well as serotonin reuptake transporter. This drug can cause antidepressant effects as well as cause a decrease in negative symptoms.

During phase I of the clinical trial, Lumateperone was given to both healthy and individuals with schizophrenia for five days. No serious adverse effects occurred. In phase II, patients with acute exacerbation of psychosis were given either 60 mg Lumateperone, 120 mg Lumateperone, risperidone 4 mg, or a placebo once daily for four weeks. The 60 mg dose reduced negative symptoms and improved prosocial behavior as measured by the PANSS score. There was no significant change in the PANSS score with the 120 mg dose. In phase III, patients were given either 42 mg Lumateperone, 28 mg Lumateperone, or a placebo daily for four weeks. Both doses showed an improvement in positive symptoms using the PANSS scale, but only the 42 mg dose showed a significant improvement in negative symptoms. No serious or adverse effects were reported in phases II or III of the clinical trial. Overall, Lumateperone has so far shown to cause fewer negative side effects than other antipsychotics that are currently in use.

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