GENERAL PSYCHIATRY

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Lumateperone for the Treatment of Schizophrenia

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ABSTRACT ~ Introduction: *Schizophrenia is a severe psychotic disorder that is diagnosed by the presence of hallucinations or delusions along with disorganized speech, disorganized thought, or negative symptoms that are present for at least six months. Roughly 1 in 10,000 people a year are diagnosed with this psychiatric disorder. It is a chronic disorder requiring a lifetime of treatment of which antipsychotics have been the mainstay of this treatment. First-generation antipsychotics have dystonia, parkinsonism, and development of Tardive Dyskinesia as major side effects, and they are also nonspecific in terms of their actions. Second Generation antipsychotics target more specific dopamine and sometimes serotonin receptors with less dystonic side effects; however, there are additional concerns for the development of metabolic syndrome. This review aims to look at new medication on the market, lumateperone, for the treatment of Schizophrenia.* ***Recent studies:*** *In one four week study with 60mg and 120mg of Lumateperone compared, 4mg of Risperdal, and a placebo found that Lumateperone significantly decreased the total Positive and Negative Syndrome Scale (PANSS) from baseline. Safety analysis of this study also found that Lumateperone was not associated with EPS or significant weight gain. Another study found that 42mg of Lumateperone significantly decreased PANSS score over placebo and 28mg of Lumateperone with associated TEAEs of somnolence, sedation, fatigue, and constipation. In an open-label safety, patients were switched from their current antipsychotic to Lumateperone and then switched back to their previous treatment after six weeks.*

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PATIENTS were found to have statistically significant improvements in metabolic parameters, weight, and endocrine parameters, which were all lost when they were switched back to their previous treatment and their schizophrenic symptoms at pre-trial levels or improved them while on Lumateperone. In a continuation of the previous study over 12 months, 4 TEAEs occurred in 5% or more of the participants: diarrhea, dry mouth, weight decrease, and headache. Prolactin, metabolic labs, BMI, and weight all decreased as compared to the standard of care. Pooled studies revealed EPS related TEAEs were less frequent in patients receiving 42 mg lumateperone over Risperdal. Another pooled study looked at the safety profile; they found patients treated with lumateperone, two TEAEs occurred at twice the placebo rate and at a rate of 5% or more: dry mouth (5% vs. 2.2%) and sedation (24.1% vs. 10.0%) though TEAE discontinuation rates were lower than with Risperdal. ***Summary:*** *Taken together, data from these trials suggest that lumateperone can effectively treat positive symptoms, negative symptoms, and cognitive dysfunction in schizophrenia. Lumateperone entrance to the market introduces an innovative way to treat schizophrenia featuring both a novel mechanism of action and a markedly reduced side effect profile. Further research is needed to determine the efficacy of Lumateperone in treating bipolar disorder in addition to schizophrenia* Psychopharmacology Bulletin. *2020;50(4):32–59.*

Introduction

Schizophrenia is a common, potentially severe psychotic disorder seen in patients worldwide. Over the last century, there has been constant re-evaluation and progress made in both the diagnosis and treatment of schizophrenia. According to the most recent guidelines established by the DSM-5, schizophrenia can be diagnosed by "two (or more) of the following: 1. Delusions, 2. Hallucinations, 3. Disorganized speech, 4. Grossly disorganized or catatonic behavior, 5. Negative symptoms (i.e., diminished emotional expression or avolition);" one of these two symptoms should include 1–3.[1] The DSM-V also requires that there is significant social/occupational dysfunction and that symptoms must persist for at least six months prior to diagnosis. The symptoms must also not be attributed to the direct physiological effects of a substance or other medical conditions.

Schizophrenia is commonly misdiagnosed and confused with other similar psychotic and psychiatric disorders. Schizoaffective disorder shares symptoms of schizophrenia but also has concurrent major depressive or manic episodes.[1] Due to the high disease course variability, specifiers have been created to determine the phase of the disease that is currently present. Two broad categories of disease specifiers are cross-sectional and longitudinal. The cross-sectional point of view addresses the patient's symptoms at that moment in time and determines if the patient is in active-phase or remission, while a longitudinal specifier gives chronic information, categorizing it as episodic or continuous.[2]

Other psychotic disorders are different in terms of the time period. Brief psychotic disorder has symptoms that last less than one month, and a schizophreniform disorder has symptoms lasting 1–6 months. In addition to differentiation by timeframe, schizophrenia was also categorized into subtypes in prior DSM editions, but this naming system was omitted from the most recent criteria.[3]

Schizophrenia is one of the more common psychologic disorders. It has been estimated to have a prevalence of 4.6 out of every 1,000 people with a lifetime morbidity risk of 7.2 out of 1,000 persons.[4] Males have been shown to have a higher incidence of schizophrenia, with a diagnosed male-to-female ratio of 1.4.[5] Geographically, higher latitudes have demonstrated a higher prevalence estimate when compared to medium and low latitude bands.[4]

In terms of general health, the lifespan of a person diagnosed with schizophrenia has been shown to be 10–15 years shorter than that of someone in the general population.[6] First-generation antipsychotics that are commonly prescribed to patients with schizophrenia are also more likely to cause weight gain and metabolic syndrome, also resisting the improvement in health outcomes seen in the general population.[7] Additionally, one of the most concerning issues associated with schizophrenia is a higher rate of suicide than found in the general population.[8] It has been estimated that 10% of people diagnosed with schizophrenia will commit suicide and upwards of 2 to 5 times that amount will attempt at some point during their life[8,9] Sher and Kahn found that "having awareness of symptoms… or a negative feeling about, or nonadherence with, treatment are associated with greater suicide attempts".[9] Comprehensive treatment is the most protective and reliable factor to help in the prevention of suicide in schizophrenia patients.

Schizophrenia- Background

Epidemiology

Schizophrenia is a chronic illness affecting approximately one percent of the general population.[10] Every year roughly 1 in 10,000 is diagnosed with this disorder. In different cultures and countries, this rate remains stable over time.[11] The prevalence is roughly ten times the annual incidence rate, indicating the chronic nature of this disorder. Although this is a disorder with a low prevalence, the burden of disease is substantial. It was ranked as the second-highest contributor to the overall burden of diseases, behind cardiovascular disease.[12] According to the World Health Organization, patients with schizophrenia are two to three times more likely to die early compared to the general population.[13] This is

often due to preventable diseases, such as cardiovascular and metabolic diseases. Although schizophrenia is considered a treatable disorder, with the help of medications and psychosocial support, there is no actual cure. Very few people recover with only 13.5% of patients meeting the clinical and social recovery criteria.[14] Schizophrenia typically presents in young adults between 20–35 years of age. Women, on average, have slightly later ages of onset by three to four years.[11]

Schizophrenia presents with a wide variety of behavioral, emotional, and cognitive symptoms. The positive symptoms associated with this disorder are hallucinations, delusions, unusual thought processes, disorganized speech, and bizarre behavior. Hallucinations are the perception of a sensory process in the absence of an external source. They can be auditory, visual, somatic, olfactory, or gustatory. Auditory hallucinations are the most common type of hallucinations seen in schizophrenia patients.[15] Although they are typically heard as voices, they can also take the form of music or other sounds. Visual hallucinations involve seeing objects, people, or lights that are not there. Because the perception of reality is impaired in this disorder, schizophrenic patients may have delusional explanations for their hallucinations. Delusions can be defined as a belief or impression that is maintained despite being contradicted by what is accepted as reality. They range from erotomaniac, believing that someone is in love with them despite no evidence, to grandiose delusions, believing that they have superior abilities. Disorganization is a principal characteristic of schizophrenia. A patient may show disorganization in their speech, jumping from one topic to another, or in their behavior, behaving in a child-like manner or unpredictable agitation.

According to the Positive and Negative Syndrome Scale (PANSS), negative symptoms are deficits of emotional responses or other thought processes.[16] These include diminished emotional expression and avolition and typically present five years prior to positive symptoms.[11] The flat affect seen with schizophrenia is characterized by facial unresponsiveness and reduced body language. Avolition is characterized by the inability to initiate or continue in goal-oriented activities. This could display as a lack of interest in activities or social interaction.

The cognitive impairments in schizophrenia range from being mild-to-moderate, and have no common pattern in patients. At least 60%–80% of patients with schizophrenia have some mild cognitive impairment.[17] Some of the most commonly impaired functions include attention, visual and verbal learning, working memory, psychomotor speed, and executive function.[18] Among these, verbal learning/memory and executive function tend to be more severe than the other cognitive dysfunctions.[19] A patient's memory is most impaired encoding relationships between items and retrieving this relational information.

They may remember the individual items but are unable to recall the relationship.[20] Executive functions consist of a wide range of processes that ultimately prevail in purposeful, goal-oriented behavior. Patients with schizophrenia have difficulty with planning, problem-solving, and adapting to changes that require a behavioral response.[21] This intransigent thinking correlates with difficulties in occupational and interpersonal relationships, which leads to the inability to build stable relationships.[19] It has been shown that the level of cognitive impairment is a stronger predictor of a patient's ability to function independently than the severity of psychopathology.[22] A study done on the relationship between executive functioning and schizophrenia showed that there was no correlation between age, length of illness, and defects in executive function.[21] This shows that impairments in cognitive function are usually present at, if not before, the first episode prevails. The severity of the behavioral, emotional, and cognitive symptoms in schizophrenia are what make this such a debilitating disorder. These attributes leave patients unable to live independently and are the reason patients suffering with schizophrenia are more likely to be unemployed, homeless, and living in poverty.[23]

Risk Factors

The pathogenesis of schizophrenia is influenced by many risk factors, both environmental and genetic. Environmental factors include pregnancy and birth complications, advanced paternal age, childhood trauma, migration, social isolation, urbanicity, and substance abuse.[24] Three types of obstetric complications have been significantly linked to schizophrenia, including complications with pregnancy, abnormal fetal growth and development, and complications during delivery.[25] Complications in pregnancy and delivery associated with increased susceptibility involve preeclampsia, bleeding during pregnancy, asphyxia, and emergency Cesarean section. Studies have shown that certain effects on the fetus lead to an increased risk of developing schizophrenia, which are maternal infections, medications, nutritional deficiency, maternal stress, and rhesus incompatibility.[26] A strong link has been found between childhood trauma and schizophrenia symptoms, especially positive symptoms. Children with seven or more adverse childhood events had a five-fold increase in the risk of reporting hallucinations, compared to people without these adverse events.[27]

Although there are many external factors that can contribute to schizophrenia, genetics plays a significant role in developing this disorder. The overall heritability of schizophrenia is between 70% and 80%.[28] The risk of developing schizophrenia increases, as the genetic

relationship to a schizophrenic family member draws closer. If one parent suffers from the condition, the probability that it will be passed down to the offspring is 13%. If it is present in both parents, the risk is more than 20%.[10]

There is likely no single mutation to account for the totality of symptoms in schizophrenia. Schizophrenia is a collection of traits, and genomic studies provide strong evidence that this is a polygenic disorder. The largest Genome-Wide Association Study of Schizophrenia concluded that there are 108 independent loci and 352 candidate genes that are associated with Schizophrenia. Several categories of genes were identified: calcium signaling (e.g., calcium channel genes), synaptic transmission (e.g., syntaxin and K+ channels), and NMDA receptor (e.g., GRIN2A and GRM3). It provided evidence for genes with known association to schizophrenia, involving glutamatergic neurotransmission, synaptic plasticity, and dopamine receptor D_2.[29] Although we do not know the exact genes responsible for schizophrenia, the wide variety of phenotypes stem from a multitude of factors, including genetic and environmental influences.

Pathophysiology

Schizophrenia stimulates from the altered activity of dopaminergic, glutamate, serotonin, GABA, and acetylcholine neurons. The abnormal levels of dopamine are a persistent topic in schizophrenia and the target of most antipsychotic drugs. Studies have shown that patients with schizophrenia have altered presynaptic dopaminergic function causing increased presynaptic dopamine synthesis and release.[30] This increase in dopamine causes an increase in D_2 receptor activation and is thought to be due to a disturbance in the mesolimbic pathway through the nucleus accumbens.[31,32] Positron emission tomography (PET) imagining studies show increased levels of dopamine are associated with the activation of positive symptoms, including delusions and hallucinations.[33] Studies on drug effects also support this conclusion: dopamine agonists provoke psychotic symptoms in normal subjects and those with schizophrenia. The mesocortical pathway projects from the ventral tegmental area to the prefrontal cortex.[12] Decreased activation of the D_1 receptor in the prefrontal cortex is thought to be a contributing factor to the negative symptoms of schizophrenia.[32,34] Although dopamine dysfunction is one of the contributing factors of schizophrenia, it does not explain all of the symptoms, especially cognitive impairment.

Glutamate neurotransmission, mediated through NMDA-type receptors, is deficient in schizophrenic patients and is thought to play a contributing role in cognitive impairments and negative symptoms.[35,36]

Glutamate is the major excitatory neurotransmitter in the CNS, while the NMDA receptor plays key roles in attention, perception, and cognition. As stated earlier, there are genes identified that correlate the risk of schizophrenia and the interaction of the NMDA receptor.

Serotonin (5-hydroxytryptamine) is another main target for some antipsychotics, especially the 5-HT_2 receptors. The 5-HT_{2A} receptors are involved in the regulation of many functions, especially mood and impulse control.[37] Any alteration in this receptor's expression or function can result in the destabilization of one's mood. The activation of 5-HT_{2A} receptors facilitates the release of dopamine in the mesolimbic system. The 5-HT_{2C} receptor can modulate both mesolimbic and nigrostriatal dopamine activity. In the mesolimbic pathway, the activation of the 5-HT_{2C} receptor inhibits dopamine neurotransmission. PET imagining study showed that selective inhibition of the 5-HT_{2C} receptor resulted in increased dopamine release in the nucleus accumbens, caudate nucleus, and putamen.[38] Any alteration in the receptor's expression or function will indirectly result in an alteration of dopamine release. This makes serotonin another key factor in contributing to the symptoms of schizophrenia.

Current Treatment of Schizophrenia

Symptomatic management of schizophrenia through pharmacotherapy is the mainstay of treatment, primarily through antipsychotic drugs. As a class, the antipsychotics predominantly modulate dopamine receptors, but they can also have effects at histaminergic, adrenergic, and muscarinic receptors.[39,40] Most are available in oral form, and many are available in a long-acting injectable form (LAI), which has proved equally effective.[41–43] The LAI form offers advantages of reduced hospitalization risk, improved patient satisfaction, and improved quality of life over traditional oral formulations.[43–45] Because of the chronicity of the disease, the treatment of schizophrenic patients should be continued with an antipsychotic agent indefinitely.[46] These drugs are potent, particularly for treating positive symptoms, but they also cause significant side effect burdens, which vary on the agent being used. These side effects, coupled with different mechanisms of action, divide the antipsychotics into first, second, and third generations.

First-Generation Antipsychotics

The first agents developed to treat schizophrenia are aptly named First-Generation Antipsychotics (FGAs). FGAs are subdivided into two subclasses, low potency agents (e.g., chlorpromazine, thioridazine)

and high potency agents (e.g., haloperidol, pimozide, fluphenazine). Their primary mechanism of action is through nonselective D2 receptor antagonism in the brain.[39,47] FGAs are effective for treating psychotic symptoms, but they are not as effective in treating negative symptoms or cognitive dysfunction as other classes of antipsychotics.[48,49] Because of their aforementioned non-selectivity, FGAs can cause myriad side effects, most prominently prolactinemia and extrapyramidal side effects, such as akathisia, parkinsonism, tardive dyskinesia.[50–52] Of all the FGAs, haloperidol has the highest risk of EPS.[53,54] In a systematic review by Gao et al., haloperidol was demonstrated to have a significantly higher risk of akathisia than placebo.[55] Multiple studies have found that haloperidol and other FGAs are far more likely to cause tardive dyskinesia than second-generation antipsychotics.[54,56,57] The EPS risk in FGA use is not limited only to haloperidol—a metanalysis by Leucht et al. revealed that chlorpromazine, zotepine, and haloperidol induced more EPS than other antipsychotics.[58]

Second Generation Antipsychotics

The second-generation antipsychotics (SGA) are more varied than FGAs in their mechanism of action, side effect profiles, and efficacy. The SGA class includes quetiapine, risperidone, paliperidone, ziprasidone, olanzapine, and clozapine, among others. Though they act on D2 receptors like FGAs, SGAs also work on multiple other receptors, depending on the agent, including D1, D3, D4, D5, M1–4, adrenergic receptors, 5-HT1A, 5-HT2A, and 5-HT2C receptors.[39,59] SGA have multiple benefits, including improved cognition. The EUFEST clinical trial revealed SGAs improved cognition more effectively when compared with FGAs.[49] A metanalysis by Keefe et al. revealed olanzapine, quetiapine, and risperidone produced improvements in neurocognition,[60] and a randomized control trial (RCT) by Harvey et al. revealed risperidone and olanzapine to improve cognition over an eight week period.[61] In addition to improving cognition, SGAs are also less likely to cause EPS than FGAs. A metanalysis by Leucht et al. revealed clozapine, sertinadole, olanzapine, quetiapine, and aripiprazole did not produce a significant difference in EPS when compared to placebo.[58] Though the SGAs confer many benefits, one SGA is more notable than the rest—clozapine. Clozapine is the drug of choice for treating the 20% of patients who have refractory schizophrenia.[58,62] It even has the benefit of reducing suicidality.[63] Its use is limited, however, by its serious side effects, including agranulocytosis and cardiomyopathy.[64] The other SGAs notably cause metabolic side effects.[58] Olanzapine is associated with the development of diabetes, and olanzapine and quetiapine

are associated with BMI increases.[65,66] In addition, prolactinemia can occur with multiple SGAs, particularly amisulpride, risperidone, and paliperidone.[67–69]

Third Generation Antipsychotics

The third-generation antipsychotics (TGA) are the most recently discovered class of the antipsychotic medications. They include aripiprazole, brexpiprazole, and cariprazine. Whereas other classes of antipsychotics work as D2 antagonists, TGAs work as functionally selective, partial D2 agonists to stabilize dopamine levels.[70] TGAs also are active at other dopaminergic and serotonergic receptors.[59] The unique mechanism of TGAs confers tangible benefits. RCTs for aripiprazole, brexpiprazole, and cariprazine demonstrated significant reductions in both positive and negative symptoms of schizophrenia.[71–75] Another randomized controlled trial evaluating cariprazine revealed greater improvement in negative symptoms when compared with risperidone.[76] Concerning side effects, the TGAs can induce EPS and metabolic changes; however, they are less intense than FGA and SGA side effects.[71,74,77,78]

Lumateperone

Lumateperone is a new, Food and Drug Administration (FDA)-approved antipsychotic that can be given to treat adult patients with schizophrenia. Intra-Cellular Therapies released Caplyta (lumateperone) to the public in March 2020. Caplyta is also known as ITI-007 in studies, operating as an antipsychotic that binds at serotonin ($5\text{-}HT_{2A}$) receptors and dopamine (D_2) receptors. Lumateperone also binds at α-1 and histaminergic receptors but with a lower affinity. It also serves as a partial dopamine agonist, serotonin reuptake inhibitor, and indirect modulator of glutamatergic systems.[79]

According to the FDA label, lumateperone should be administered as a 42 mg oral dosage that is to be taken once daily with food. Visually, the capsule is opaque white imprinted with "ITI-007 42 mg" with a blue cap. There is no current need for dose titration or renal adjustment based on previous studies' reports. It has a clearance of approximately 27.9 L/hour, and the terminal half-life is reported as 18 hours after IV administration.

At this time, lumateperone is only indicated for adults aged 18 and older to treat schizophrenia.[79] It should not be used for the treatment of dementia-related psychosis. Thus far, there have not been any clinical studies observing the safety and effectiveness in pediatric (younger than 18 years old) or geriatric (older than 65 years old) populations,

thus making it limited to a population of 18–65-year-olds. Within this population, there have been no observed differences in effect based on age, sex, or race.

When prescribing lumateperone, there are several precautions and warnings on the label of which to be aware. Patients with moderate to severe hepatic impairment based on the Child-Pugh classifications should not be prescribed lumateperone. Patients should also be aware of the possible side effects of lumateperone which are neuroleptic malignant syndrome, tardive dyskinesia, metabolic changes, leukopenia, orthostatic hypotension, falls, and seizures. The vast majority of the side effects are seen in various other second-generation antipsychotics and are not individual to just lumateperone.

Mechanism of Action

Lumateperone is a second-generation antipsychotic drug used to treat schizophrenia through modulation of multiple different neurotransmitter receptors. Generally speaking, 2nd-generation antipsychotics tend to have lower dopamine (D_2) receptor affinities and higher serotonin (5-HT_{2A}) affinities when compared with their first-generation counterparts, increasing the safety of extrapyramidal symptoms (EPS) side effects at the cost of weight gain and possible metabolic issues. While the exact mechanism of action of lumateperone is not completely clear, it has been proven that it increases binding at the 5-HT_{2A} receptor without excess binding at the D_2 receptor.[80] More traditionally used 2nd-generation drugs, such as risperidone and olanzapine, demonstrate a ratio of 12:1 when comparing the affinity of binding of D_2 and 5-HT_{2A} receptors. In lumateperone, this affinity ratio separates to 60:1.[81] This larger separation allows for increased binding at the 5-HT_{2A} receptor, possibly decreasing the extrapyramidal side effects of binding at D_2 receptors.

Lumateperone also serves as a presynaptic D_2 partial agonist and postsynaptic D_2 antagonist. This allows for a highly efficient reduction of dopaminergic signaling, both through decreasing presynaptic release and preventing postsynaptic binding.[80,82] The only previous drugs that utilized this "dual-method" of D_2 presynaptic-agonism and postsynaptic-antagonism are aripiprazole and its derivatives. All other second-generation antipsychotics function as antagonists to both pre- and postsynaptic receptors.[80]

Lumateperone has also proven to have a slightly different therapeutic level than previous antipsychotics. A study done by Vanover et al. evaluated the degree of dopamine D_2 receptor occupancy (D_2RO) necessary for therapeutic effect.[82] For antipsychotics to be efficacious, they must have D_2RO binding.[83] Different drugs bind to various D_2RO threshold

levels in order to establish therapeutic effects. Drugs that bind with higher D_2RO levels (80%–95%) to achieve treatment of antipsychotic symptoms typically have issues with extrapyramidal side effects such as akathisia and hyperprolactinemia.[82] At its therapeutic level established in clinical trials, lumateperone has been shown to achieve antipsychotic efficacy at 39% D_2RO, a much lower level than previously used drugs on the market, contributing to its beneficial safety and tolerability profile.

Lastly, lumateperone also acts on two other additional receptors: dopamine 1 (D_1) receptors and serotonin transporters (SERT).[81] Acting as an agonist, lumateperone acts on D_1 receptors causing increased activation of N-methyl-D-aspartate (NMDA) receptor phosphorylation.[84] In patients that have schizophrenia, it has been shown that NMDA-mediated glutamate signaling can be impaired. lumateperone combats this through increasing phosphorylation, thus increasing glutamate signaling. lumateperone also acts to inhibit SERT, increasing serotonin in the synaptic cleft.[82]

Pharmacokinetics/Pharmacodynamics

Lumateperone simultaneously modulates serotonergic, dopaminergic, and glutamatergic neurotransmission, all of which are implicated in schizophrenia. The compound has a high binding affinity for serotonin 5-$HT2_A$ receptors (K_i = 0.54 nM), a moderate binding affinity for serotonin transporters (K_i = 33 nM) and dopamine D_2 and D_1 receptors (K_i = 32 nM and K_i = 52nM).[85] Thus, lumateperone has approximately a 60-fold higher affinity for 5-$HT2_A$ receptors than for D_2 receptors. This allows for lumateperone to be used in different doses for specific receptors.[84] At low doses, it can selectively target 5-$HT2_A$ receptors, promoting sleep, and reduced hostility and aggression. While at higher doses, it can also act upon dopamine D_2 receptors and serotonin transporters, showing a reduction in depressive and psychotic symptoms.[86] Lumateperone showed negligible binding to the receptors associated with the cognitive and metabolic side effects of other antipsychotic drugs, including H_1 Histaminergic, 5-$HT2_C$, and muscarinic.[81,84] Its effects on the dopamine D_2 receptor occur more efficient reduction of dopaminergic signaling than most antipsychotic drugs.[36] This creates the antipsychotic efficacy without extrapyramidal side effects or hyperprolactinemia.[87] Lumateperone's partial agonism of dopamine D_1 receptor results in increased phosphorylation of glutamatergic *N*-methyl-d-aspartate (NMDA) GluN2B receptors in the mesolimbic brain region. Therefore, it increases the glutamatergic neurotransmission in the AMPA and NMDA channels. This assists in the deficiency of glutamate through NMDA-type receptors that is thought

to play a contributing role in cognitive impairments and negative symptoms of schizophrenic patients.[35,36]

Pharmacokinetics

Absorption and Distribution

Following the oral administration of lumateperone while fasting, it is rapidly absorbed with a mean time of maximum concentration (Tmax) at three to four hours. The compound reaches a steady-state approximately five days after a once-daily consumption. Following a high-fat meal, the maximum concentration (Cmax) of lumateperone is lowered by 33% while increasing the area under the concentration-time curve (AUC) by 9%. The mean Tmax was delayed by 1 hour following the consumption of food compared at a fasted state. lumateperone exhibits a human plasma protein binding percentage of 97.4% and a volume of distribution of about 4.1 L/kg following intravenous administration.[84]

This compound is highly permeable (apical-to-basal permeability of 15.8 × 10–6 cm-s) and demonstrates a bidirectional permeability through multidrug resistance protein 1 (MDR1), while also being very lipophilic at a pH of 7.4.[88] These characteristics allow the drug to cross both the small intestine as well as the blood-brain barrier.

Metabolism

Lumateperone is extensively metabolized, with over twenty metabolites. Multiple enzymes are involved in the metabolism of lumateperone, including uridine 5'- diphospho-glucuronosyltransferases (UDP-glucuronosyltransferase, UGT), aldoketoreductase, and cytochrome P450. The side-chain carbonyl is reduced to an alcohol via ketone reductases forming the primary metabolite (ICI00131). The cytochrome P450 system, primarily the CYP3A4 isoezyme, dealkylates lumateperone to either an N-desmethylated carbonyl or alcohol metabolite (1C200161 or IC200565).[89] These metabolites have very similar mechanisms to lumateperone, both prolonging and extending the activity of the compound.

Excretion

The half-life of lumateperone is 13 hours, with half-lives of the metabolites approximately 20 hours for IC200161 and 21 hours for IC200131.[89] According to radioactivity data, 51% of lumateperone metabolites are glucoronidated. Glucuronidation is the major pathway in phase II metabolism rendering substances more water-soluble.

This allows for subsequent elimination of the compound from the body through urine or feces.[85]

Clinical Studies

Study 005

Study ITI-007–005 was a four week-long, double-blinded, multicentered randomized controlled trial (RCT) that inquired into the safety and efficacy of 60 mg and 120 mg of lumateperone as compared to 4 mg risperidone and placebo in patients with schizophrenia. The primary outcome of the study was the efficacy of lumateperone vs. risperidone or placebo. This outcome was measured through a reduction in patient Positive and Negative Syndrome Scale (PANSS) total score, a standard measuring system used to quantify schizophrenia symptoms,[90] from baseline to 28 days postintervention. Lumateperone significantly decreased total PANNS from baseline when compared to placebo [Least squares mean change (LSMC) −13.2 points vs. −7.4 points; $p = 0.017$].[91]

Using the PANNS subscale, posthoc analyses were done to examine patient subgroups experiencing depression at baseline, patients experiencing pronounced negative symptoms at baseline, and changes in social function. The Calgary Depression Scale for Schizophrenia (CDSS) was also employed for measuring changes in depressive symptoms. In patients with depression at baseline, 60 mg lumateperone was shown to significantly reduce both the PANSS sub-score, with a greater Effect Size (E.S.) (E.S. = 1.13) than risperidone (E.S. = 0.6) when compared to baseline. This result was recapitulated in the CDSS score when compared to baseline (Lumateperone EF = .99; Risperidone E.F. = −0.46). In patients with pronounced negative symptoms, 60 mg lumateperone was more efficacious at reducing the PANNS negative subscale (E.F. = .34) than risperidone (E.F. = 0). Notably, 60 mg lumateperone also significantly reduced PANSS prosocial factor (E.F. = 0.6), indicating improved social behavior, whereas risperidone had a lower E.F. (E.F. = 0.4).[91]

Study 005 also reported safety data for lumateperone. Patients in the 60 and 120 mg lumateperone arms did not experience any serious treatment-emergent adverse events (TEAE). Lumateperone was not associated with EPS or significant weight gain. In addition, when compared with risperidone, lumateperone had significantly lower total cholesterol (60 mg lumateperone, $p = 0.012$; 120 mg lumateperone, $p = 0.004$), triglycerides (120 mg lumateperone, $p = 0.002$), prolactin levels (60 and 120 mg lumateperone, $p < 0.01$), and fasting glucose (60 mg lumateperone, $p = 0.007$; 120 mg lumateperone, $p = 0.023$).[92]

Study 301

Like study 005, study ITI-007–301was conducted as a 4 week long, double-blinded, multicentered RCT that investigated the safety and efficacy of lumateperone in patients with schizophrenia. However, the lumateperone dosages tested were 28 and 42 mg, and lumateperone was compared only to placebo. The primary outcome was PANSS total score mean change from baseline to 28 days postintervention as compared to placebo. 42 mg lumateperone was shown to significantly reduce PANSS total score vs. placebo (LSMC −4.2 points, multiplicity-adjusted p = 0.04). 28 mg lumateperone, on the other hand, did not significantly reduce PANSS total score vs. placebo (LSMC −2.6, multiplicity-adjusted p = .18).[93]

Secondary endpoints were investigated as well, such as illness severity [measured by the Clinical Global Impression-Severity of Illness (CGI-S) score] and CDSS. Researchers also recorded patient PANSS negative, positive, personal, and social performance (PSP), and prosocial factor subscales. CGI-S scores were found to be significantly reduced in 42 mg lumateperone vs. placebo (LSMC −0.3, multiplicity-adjusted p = 0.003). Also, both 28 mg (LSMC -1.2, nominal p = 0.04) and 42 mg (LMSC −0.12, nominal p = 0.006) lumateperone dosages improved PANSS positive subscale significantly as compared to placebo. Significant improvements in both measures of social function were also noted for 42 mg lumateperone. CDSS scores, however, were not significantly different between lumateperone and placebo, nor were PANSS negative subscale scores.

Regarding safety of the drug, lumateperone was found to have a favorable side effect profile. The notable TEAEs occurring more than 2x placebo and in 5% or more patients include somnolence, sedation, fatigue, and constipation. Two serious TEAEs were also recorded: one case of convulsions in the 28 mg lumateperone arm, and one case of orthostatic hypotension in the 42 mg lumateperone arm. EPS, weight changes, ECG changes, and metabolic changes were not found to be significant in either lumateperone dose when compared with placebo.[93]

Study 302

This six-week-long RCT compared 20 mg and 60 mg doses of lumateperone with risperidone or placebo in patients with schizophrenia. Like the preceding trials, the primary endpoint was a reduction in PANSS total score from baseline when compared to placebo. Neither the 20 mg nor 60 mg dose of lumateperone was significantly different than placebo in reducing PANSS total score, differentiating the results

from the prior two trials. The investigators postulate that the high placebo response seen was responsible for the results.[94]

Study 303a

Study 303 was an open-label safety trial in which patients with stable schizophrenia were switched from their maintenance antipsychotic to lumateperone. After six weeks of lumateperone therapy, patients were switched back to their prior antipsychotic agent and followed for two weeks. Patients were found to statistically significant improvements in metabolic parameters, weight, and endocrine parameters. These improvements were lost when patients were switched back to their prior maintenance antipsychotic. Although drug safety was the primary endpoint for this study, researchers also collected data on drug efficacy. Switching to lumateperone from maintenance antipsychotics kept patient schizophrenic symptoms at pre-trial levels or improved them. Improvements were more likely to be seen in patients with predominantly negative symptoms and in patients with comorbid depression.[95]

Study 303b

This continuation of study 303, conducted predominantly to evaluate for potential side effects of lumateperone, followed patients for as long as a year. Patients with stable schizophrenia were given 42 mg lumateperone and monitored for TEAEs, EPS, weight changes, and lab values. During this study period, 4 TEAEs occurred in 5% or more of the participants: diarrhea, dry mouth, weight decrease, and headache. Most of the TEAEs were mild to moderate intensity. Prolactin, metabolic labs, BMI, and weight all decreased as compared to the standard of care.[96]

The trial also examined the efficacy of lumateperone as well. As in prior studies, patients were monitored for changes in the PANSS total score and CDSS. In terms of secondary measures, lumateperone reduced the symptoms of schizophrenia. This is demonstrated by a significant decrease in PANSS total score as compared to baseline. PANSS scores continued to improve with study progression. In addition, patients with moderate-to-severe depression, lumateperone decreased mean CDSS from a baseline of 7.4 to 3.1 when measured at day 300.[96]

Pooled Studies

A pooled study conducted by Durgam et al. evaluated three short-term RCTs (Studies 005, 301, and 302) to evaluate for motor symptoms and EPS in patients with schizophrenia. The year-long open-label

study 303 was also analyzed for evaluating the risk of EPS development in long-term treatment. The pooled short-term data revealed EPS related TEAEs were less frequent in patients receiving 42 mg lumateperone (3.0%) or placebo (3.2%) than patients receiving risperidone (4.9%). Of the EPS-related TEAEs, akathisia was the most prevalent to occur with lumateperone use (2.0%). However, the rates of akathisia in patients receiving placebo (2.9%) or risperidone (6.3%) were higher. Regarding the time to onset of EPS in the short-term RCTs, side effects manifested earlier in risperidone (9 days) than either placebo (14 days) or lumateperone. In patients on long-term symptom management with lumateperone, there was a low rate of EPS-related TEAEs (0.8%). Time to EPS symptom onset in patients treated long-term with lumateperone was 38 days.[97]

A pooled study conducted by Kane et al. examined the same three short-term clinical trials to collectively evaluate the safety profile of lumateperone in patients with schizophrenia. In patients treated with lumateperone, two TEAEs occurred at twice the placebo rate and at a rate of 5% or more: dry mouth (5% vs. 2.2%) and sedation (24.1% vs. 10.0%). TEAE-induced discontinuation rates with lumateperone (0.5%) and placebo (0.5%) were lower than risperidone (4.7%). Metabolic and endocrine changes were lower in both placebo and 42 mg lumateperone when compared to risperidone.[98]

Summary of Lumateperone Safety and Efficacy for Treating Schizophrenia

Taken together, data from these trials suggest that lumateperone can effectively treat positive symptoms, negative symptoms, and cognitive dysfunction in schizophrenia. All of this is accomplished with a mild side effect profile, potentially due to the drug's unique mechanism of action, via D2 "stabilization".[59] Vanover et al. recently conducted an open-label clinical trial to further elucidate D2 occupancy by lumateperone. Patients with a history of schizophrenia underwent a drug-free, inpatient, two-week washout period before having a baseline PET scan performed. Patients were then admitted for inpatient management and received 42 mg lumateperone by mouth each morning for two weeks. At twelve to fifteen days of treatment, patients then underwent up to 3 PET scans to measure D2 receptor occupancy (D2RO) by lumateperone. This was accomplished through measuring non-displaceable binding potential (NDBP) for D2RO and [^{11}C]-RAC, a radiotracer used for PET scans. Peak dorsal striatal D2RO was 39% 1 hour following lumateperone administration, with D2RO reductions following thereafter. Similar to dorsal striatal D2RO, ventral

striatal D2RO mean D2RO was 40.9% in patients with normal baseline NDBP.[82]

At roughly 40% D2RO, lumateperone was clinically effective, reducing PANSS scores. It is very unusual for an antipsychotic to be effective at such low D2RO. Most antipsychotic agents have D2RO of 65%–80%, with higher occupancy linked to side effect severity.[99–101] The effectiveness of lumateperone at lower D2RO, therefore, may be responsible for the drug's favorable side effect profile.

Safety and Efficacy of Lumateperone for Other Conditions

Because of its mild side effect profile, lumateperone has potential use beyond schizophrenia in treating bipolar disorder. 2 clinical trials have recently been conducted to test the efficacy of lumateperone for bipolar disorder (BPD) I and II. The first of the two trials are being conducted in two parts: part A is a double-blinded RCT, and part B is an open-label extension of part A for patients who completed the first component. Participants must have BPD I or II, be currently experiencing a depressive exacerbation, be medically appropriate for the trial, and may not be pregnant or breastfeeding. Patients are assigned to receive 28 mg lumateperone, 40 mg lumateperone, or placebo for six weeks. The primary outcome of the study is a reduction of depression, as measured by the Montgomery-Åsberg Depression Rating Scale (MADRS).[102]

The second study examining the efficacy of lumateperone for managing BPD I and II is a multicentered, double-blinded RTC comparing 40 mg lumateperone to placebo over a period of 6 weeks in patients with BPD I or II experiencing a depression exacerbation. Patient inclusion/exclusion criteria are analogous to the other BPD lumateperone trial. The primary outcome is the reduction of depression, measured by MADRS. The secondary outcomes being examined in this trial include patient quality of life, quantified through the Quality of Life Enjoyment and Satisfaction Questionnaire – Short Form, and reduction of bipolar symptoms, quantified through the Clinical Global Impression Scale, Bipolar Version (CGI-BP-S).[103] The primary endpoint was met, with MADRS total score improving from baseline as compared to placebo ($p < 0.0001$, E.S. = 0.56). When further parsed, the data also indicate MADRS total score improvements in both BPD I ($p < 0.0001$, ES 0.49) and BPD II ($p < 0.001$, ES 0.81) were significant as compared to placebo. One of the secondary endpoints, improvement as determined by the GGI-BP-S, was also met when lumateperone was compared to placebo ($p < 0.001$, E.S. = 0.50), with statistically significant improvement at week 1. The safety profile data in this study was analogous to previously determined safety data.[104]

TABLE 1

Clinical Efficacy and Safety

AUTHOR (YEAR)	GROUP STUDIES AND INTERVENTION	RESULTS AND FINDINGS	CONCLUSIONS
Lieberman et al. (2016)[42]	Phase II double blind, placebo controlled, multicenter RCT on managing schizophrenia with lumateperone. 3 study arms: 60 mg lumateperone, 120 mg lumateperone, 4 mg risperidone, and placebo. Primary endpoint was efficacy of lumateperone in managing schizophrenia. Seconday endpoints included evaluation of lumateperone's ability to treat positive symptoms, negative symptoms, depressive symptoms, and social dysfunction.	60 mg lumateperone was as effective as 4 mg risperidone in managing combined positive and negative symptoms (lumateperone LSMC −13.2, $p = 0.017$; risperidone LSMC −13.2, $p = 0.013$), whereas 120 mg lumateperone did not reach significance (LSMC 28.3, $p < .708$). 60 mg lumateperone more effectively managed negative symptoms (EF = 1.13) than 4 mg risperidone (EF = 0.6), and it more effectively managed social dysfunction (EF = 0.34) than 4 mg risperidone (EF = 0).	60 mg lumateperone is equally as effective as 4 mg risperidone in managing positive symptoms of schizophrenia and is superior to risperidone in managing both negative symptoms and social dysfunction in schizophrenic patients.
Correll et al. (2020)[43]	Phase III double blind, placebo controlled, multicenter RCT conducted to investigate the efficacy and safety of lumateperone to treat schizophrenia. Patients received 28 mg lumateperone, 42 mg lumateperone, or placebo.	Though 28 mg lumateperone singificantly improved positive symptoms in schizophrenic patients (LSMC −1.2, nominal $p = 0.04$), it did not singificantly improve total positive and negative symptoms metrics (LSMC −0.2, multiplicity adjusted $p = .16$), depressive symptoms (LSMD 0.2, nominal $p = .57$), or social function as measured by PANSS prosocial factor subscore (LSMC −1, $p = 0.09$) or the PSP scale (LSMC 2.9, $p = 0.09$).	28 mg lumateperone is only superior to placebo in treating the positive symptoms of schizoprenia when compared to placebo. 42 mg lumateperone is superior to placebo in treating positive symptoms, negative symptoms, and social dysfunction in patients with schizophrenia.

(*Continued*)

TABLE 1 (*Continued*)

Clinical Efficacy and Safety

AUTHOR (YEAR)	GROUP STUDIES AND INTERVENTION	RESULTS AND FINDINGS	CONCLUSIONS
	The primary endpoint was mean change from baseline to 28 days in positive and negative symptoms. Secondary outcomes investigated include improvement of illness severity and improvement of depressive symptoms.	Coversely, 42 mg lumateperone was found to reduce total positive and negative symptoms (LSMC −4.2, multiplicity-adjusted p = 0.04), positive symptoms (LSMC −1.7, p = 0.006), and both metrics of prosocial function , the PSP (EF = 0.26, 0.05) and PANSS prosocial factor (−0.24, 0.04).	
Vanover et al. (2017)[44]	Phase II double blind, placebo-controlled RCT comparing 20 mg and 60 mg doses of lumateperone to risperidone and placebo for the treatment of schizophrenia. Primary endpoints for the trial were a reduction in total positive and negative symptoms of schizophrenia.	Neither 20 mg nor 60 mg lumateperone doses were significantly different than placebo in treating schizophrenia, whereas risperidone did reach significance.	Lumateperone dosed at either 20 mg or 60 mg was not effective in treating schizophrenia.
Vanover et al. (2019)[45]	Phase III open-label safety switching study with the goal of examining the safety profile of lumateperone over the course of 6 weeks. Secondary endpoint was evaluation of drug efficacy in managing schizophrenia as compared to patient's original maintenance antipsychotic.	Compared to the standard of care antipsychotic, lumateperone caused statistically significant improvements in endocrine, metabolic, and weight parameters. These improvements were lost when patients were switched back to their original maintenance medication.	Lumateperone has a favorable side effect profile in terms of weight, endocrine, and metabolic parameters as compared to standard of care antipsychotic agents.

		Switching from patient's maintenance antipsychotic to lumateperone either kept patient symptoms at basal level or improved them further than the maintenance antipsychotic did, with improvements more likely to be seen in patients with comorbid depression or predominant negative symptoms	Lumateperone is as effective as the standard of care antipsychotic in managing symptoms, with potential benefits in schizophrenic patients with predominant negative symptoms or depressive symptoms.
Correll et al. (2020)[46]	Continuation of the phase III open-label safety trial with the goal of examining the safety profile of 42 mg lumateperone for up to a year. Secondary endpoint was comparison of lumateperone efficacy to patient's standard of care antipsychotic. Lumateperone efficacy was also investigated and compared to the patient's maintenance antipsychotic.	42 lumateperone was found to have 4 TEAEs occurring in 5% or less of patients - headache, diarrhea, dry mouth, and weight loss. Prolactin, metabolic parameters, weight, and BMI all singificantly decreased from the standard of care baseline. Lumateperone did not significantly cause EPS. Regarding drug efficacy, 42 mg lumateperone significantly reduced the total positive and negative symptoms of schizophrenia, with particular improvement of depressive symptoms.	42 mg lumateperone side effect profile is mild and most frequently causes headache, dry mouth, weight loss, and diarrhea. It does not EPS, increased weight, elevations in metabolic parameters, or prolactinemia. 42 mg lumateperone is effective in managing the positive and negative symptoms of schizophrenia, particularly depressive symptoms.

(*Continued*)

TABLE 1 (*Continued*)

Clinical Efficacy and Safety

AUTHOR (YEAR)	GROUP STUDIES AND INTERVENTION	RESULTS AND FINDINGS	CONCLUSIONS
Durgam et al. (2020)[47]	Pooled study evaluating 3 short-term RCTs and one long-term RCT conducted to evaluate for motor symptoms and EPS in schizophrenic patients treated with lumateperone.	Short-term RCT data revealed EPS-related TEAEs were less frequent in patients receiving 42 mg lumateperone (3.0%) or placebo (3.2%) when compared to patients receiving risperidone (4.9%). Though short term RCT data revealed a 2% incidence of akathesia in patients receiving lumateperone, akathesia was more frequently seen in placebo (2.9%) and risperidone (6.3%). In addition, these data showed earlier symptom on set in patients taking risperidone than those taking placebo or lumateperone. Long-term RCT data showed a low rate of EPS-related TEAEs (0.8%), with those experiencing these TEAEs at an average of 38 days after treatment initiation.	42 mg lumateperone is less likely than risperidone to cause EPS in both short-term and long-term use. Of all the manifestations of EPS, lumateperone is most likely to induce akathesia.
Kane et al. (2020)[48]	Pooled study evaluating 3 short-term RCTs to evaluate the overall safety profile of lumateperone.	When compared to patients treated with placebo, patients treated with lumateperone were most likely to experience two TEAEs: dry mouth (5% vs 2.2%) and sedation (24.1% vs 10%). TEAE-related discontinuation rates in patients taking lumateperone (0.5%) or placebo (0.5%) were lower than those of patients taking risperidone (4.7%). lumateperone induced lower rates of endocrine and metabolic changes than risperidone.	If it were to cause a TEAE, lumateperone is most likely to cause dry mouth or sedation. Lumateperone is less likely to induce metabolic changes or endocrine changes than risperidone.

Intra-Cellular Therapies (2020)[53]	RCT conducted to investigate the efficacy of lumateperone in treating BPD I and II. It is broken into a part A and a part B. Part A is a 6 week long, double-blind RCT, and part B is an open-label continuation of part A for patients wishing to continue being treated with lumateperone. The arms of the trial include 28 mg lumateperone, 40 mg lumateperone, and placebo. Primary outcome is a reduction of depression in patients with BPD I or II.	Ongoing investigation.	Ongoing investigation.
Intra-Cellular Therapies (2020)[55,56]	Multicentered, 6 week long, double blind RCT comparing 40 mg lumateperone to placebo in managing BPD I and II. Patients were assigned to receive either 40 mg lumateperone or placebo. The primary outcome was amelioration of depression. Secondary outcomes investigated include patient quality of life and reduction of bipolar symptoms.	40 mg lumateperone was shown to significantly reduce depressive symptoms in patients with either BPD I and II when compared to placebo ($p<0.0001$, E.S. = 0.56). Further analysis revealed this to be true for both BPD I ($p < 0.0001$, ES 0.49) and BPD II ($p < 0.001$, ES 0.81). Improvement in bipolar symptoms in patients receiving lumateperone was also noted ($p < 0.001$, E.S. = 0.50), but the quality of life changes were not reported.	40 mg lumateperone is efficacious in treating depressive symptoms in patients with BPD I and BPD II. It is also useful in managing bipolar symptoms in these patients.

Conclusion

The standard of care when treating schizophrenia is pharmacologic in nature. Historically, drugs used to treat schizophrenia have had a wide range of unwanted corollaries, particularly akathisia and various other extrapyramidal side effects as well as metabolic issues. Lumateperone's entrance to the market introduces an innovative way to treat schizophrenia featuring both a novel mechanism of action and a markedly reduced side effect profile.

While previous antipsychotic medications function as an antagonist to pre- and postsynaptic dopamine (D_2) receptors, lumateperone acts as a partial agonist at the presynaptic receptor but as an antagonist at the postsynaptic receptor to effectively reduce dopaminergic signaling. Lumateperone also has shown to bind at the serotonin 5-HT_{2A} receptor with a higher affinity, reducing the extrapyramidal side effects in comparison to other pharmacologic treatments.

Lumateperone has been shown to effectively reduce both the positive and negative symptoms of schizophrenia when compared with placebo. In several studies, lumateperone has also been shown to decrease both subsets of symptoms when compared with other treatments on the market, including risperidone. As a whole, lumateperone has been shown to be safe for a broad audience and very few serious treatment-emergent adverse events (TEAEs). Studies have shown that the most common TEAEs observed when prescribed lumateperone are bowel changes (diarrhea and constipation), dry mouth, and weight loss. Additionally, there is reduced weight gain, hyperglycemia, decreased occurrences of EPSs, hyperprolactinemia, and dyslipidemia compared to other antipsychotics on the market currently utilized as the standard of care. There are also fewer TEAEs when treated with lumateperone when compared to standard of care treatment, such as risperidone.

Given this information, lumateperone offers great promise to serve as a pharmacologic treatment used to treat schizophrenia, specifically in patients that are intolerant to extrapyramidal side effects or metabolic dysfunction. Further research is needed to determine the efficacy of lumateperone in treating bipolar disorder in addition to schizophrenia. ✤

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