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Lumateperone in the Treatment of Schizophrenia: A Review

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ABSTRACT

Schizophrenia is a devastating mental illness that afflicts about 1% of the world's population. This illness distorts a person's perception of reality and consists of positive symptoms such as hallucinations and delusions, negative symptoms such as inattention and withdrawal, and cognitive deficits. Antipsychotic drugs are primarily used for the pharmacotherapy of schizophrenia. In this article, we provide a succinct review of a recently approved novel antipsychotic, lumateperone. We present an overview and history of schizophrenia, its symptoms, epidemiology, etiology, and pathophysiology. The classification of antipsychotic agents as first and second-generation based on their receptor affinity is discussed. The review focuses on describing the background, development, receptor pharmacology, mechanism of action, pharmacokinetics, clinical trials, adverse effects, therapeutic uses, and future prospects of lumateperone.

Keywords: antipsychotic, atypical, lumateperone, schizophrenia, 5-HT2A serotonin receptor

INTRODUCTION

Schizophrenia

Schizophrenia, a severe mental disorder of unknown etiology, afflicts about 1% of the global population.[1] In 2019, the World Health Organization reported over 20 million cases of schizophrenia globally.[2] The Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) currently defines schizophrenia as the presence of two or more of the following symptoms: delusions, hallucinations, disorganized speech, grossly disorganized or catatonic behavior, and diminished emotional expression with the symptoms being present for a significant portion of time during a 1-month period. At least one of these symptoms must be delusions, hallucinations, or disorganized speech.[3] Schizophrenia has a history, stemming back as early as the 19th century when the French psychiatrist, Bénédict Augustin Morel, first coined the term 'démence précoce'. This term would later evolve into the term 'dementia precox' by the renowned German psychiatrist Emil Kraepelin. It was in 1908 that the Swiss psychiatrist, Eugen Bleuler, created the term 'schizophrenia' to replace the term 'dementia precox'.[4,5]

Schizophrenia symptoms are primarily classified as positive and negative in nature. Positive symptoms, primarily experienced during a psychotic episode, include delusions, hallucinations, and disorganized thoughts, speech, and behavior. Negative symptoms, which are deficits in normal emotional response, are anhedonia (inability to experience pleasure), alogia (poverty of speech or thought), avolition (inability to initiate and persist in goal directed activities), apathy (lack of interest, enthusiasm, or concern), blunted affect, and social withdrawal. Patients with schizophrenia also show cognitive deficits such as impaired working memory, decreased verbal fluency, and decreased abilities in reasoning and problem solving.[3,6]

Although the etiology of schizophrenia is unclear, several risk factors have been implicated in the pathogenesis of this chronic debilitating mental illness. Schizophrenia is classified as a neurodevelopmental disorder with no known precise cause. Schizophrenia is thought to develop from complex gene-environment interactions. Environmental risk factors such as

childhood trauma, stress, pregnancy complications, nutritional deficiencies; genetic and hereditary factors and family history; as well as structural abnormalities such as hypofrontality (decreased blood flow in the prefrontal cortex) have all been implicated in the development of schizophrenia.[7,8]

The pathophysiology of schizophrenia is extremely complex, and there is no single theory that can explain the pathogenesis of this mental illness.[9]

Role of neurotransmitters in schizophrenia

The dopamine dysregulation hypothesis has been fundamental in the development of antipsychotic medications. The hypothesis states that excessive dopaminergic activity in the mesolimbic pathway contributes to positive symptoms such as hallucinations and delusions. Hypodopaminergic activity in the mesocortical pathway may contribute to negative symptoms such as apathy and anhedonia. Besides dopamine, dysfunction in other neurotransmitter systems such as glutamatergic, serotonergic, cholinergic, and GABA-ergic systems have also been implicated in the pathogenesis of schizophrenia.[10,11]

Neurodevelopmental model of schizophrenia

The neurodevelopmental aspects in the pathophysiology of schizophrenia have been extensively studied using techniques such as imaging and using biomarkers. Risk factors include prenatal infection, inflammation, malnutrition, and stress. Studies have found significant anatomical alternations in several brain structures of high-risk youth. It is hypothesized that abnormal neuronal pruning of neurons, altered communication, and decreased neuronal connectivity, contribute to the development of schizophrenia.[12,13]

Genetic factors in schizophrenia

The role of genetic contribution and heritability in the development of schizophrenia has been widely studied. First-degree relatives of patients with schizophrenia have a 10% risk of developing the disease. This risk increases to 40% when both parents have schizophrenia. About 40% identical twins of patients with schizophrenia are affected. There is no particular "schizophrenia gene" that has been identified, and research continues in the area. A genetic burden may combine with environmental and social factors to trigger symptoms.[14]

Antipsychotics

Antipsychotic medications are classified as typical and atypical agents. Typical antipsychotics, which were introduced earlier, are also known as first generation antipsychotics (FGAs), and atypical agents, introduced later, are known as second generation antipsychotics (SGAs). Both classes of antipsychotics significantly differ in mechanism of action, adverse effect profile, and receptor pharmacology.[15,16] (Table 1)

FGAs, such as chlorpromazine, thioridazine,

Antipsychotics	Adverse effect	Mechanism of action
Typical Antipsychotics (FGAs)		
Chlorpromazine	Akathisia Dystonia Tardive dyskinesia Drug-induced Parkinsonism	Antagonism of dopamine D_2 receptors
Thioridazine		
Fluphenazine		
Trifluoperazine		
Haloperidol		
Atypical Antipsychotics (SGAs)		
Clozapine	Agranulocytosis, weight gain, diabetes, lipid abnormalities	Antagonism of dopamine D_2 and serotonin 5-HT_{2A} receptors
Olanzapine	Weight gain, diabetes, lipid abnormalities	
Quetiapine	Sedation	
Risperidone	Movement disorders	
Ziprasidone	Cardiac arrhythmias	

Table 1. Mechanism of action and adverse effects of antipsychotics

and haloperidol, are primarily dopamine D2 receptor antagonists. FGAs block the dopaminergic mesolimbic pathway and are effective in the management of positive symptoms. FGAs produce movement disorders known as extrapyramidal symptoms (EPS), pseudoparkinsonism, or drug-induced Parkinsonism by blocking the dopaminergic nigrostriatal pathway. FGAs produce EPS such as akathisia (motor restlessness), dystonia (abnormal repetitive twisting muscle movements), and tardive dyskinesia (involuntary abnormal facial movements).[17] FGAs also elevate prolactin levels due to inhibition of the dopaminergic tuberoinfundibular pathway which regulates prolactin secretion. Typical antipsychotic-induced hyper-prolactinemia is associated with amenorrhea, osteoporosis, and increased risk for developing breast cancer.[18]

Clozapine was the first SGA that was developed followed by other SGAs, such as olanzapine and risperidone. The atypicality of SGAs arises from their antagonist properties at the D2 receptor, which improves positive symptoms, as well as the antagonism of serotonin 5-HT2A receptor. Blockade of the 5-HT2A receptors in the dopaminergic mesocortical pathways enhances dopamine levels and improves negative symptoms. Thus, SGAs are effective in improving both positive and negative symptoms of schizophrenia. Besides the D2 and 5-HT2A receptors, SGAs also display antagonism at a multitude of other dopaminergic, serotonergic, muscarinic, and histaminergic receptors. SGAs produce several serious adverse effects such as diabetes, obesity, and cardiac disturbances.[19,20]

In this review, we describe the background, development, receptor pharmacology, mechanism of action, pharmacokinetics, clinical trials, adverse effects, therapeutic uses, and future prospects of lumateperone.

LUMATEPERONE

Lumateperone was developed by Intra-Cellular Therapies, New York, NY, primarily for the treatment of schizophrenia with potential use in other neuropsychiatric disorders such as major depressive disorders and bipolar disorder. Lumateperone was called ITI-007 during its development phase, both pre-clinical studies, and clinical trials. Based on the clinical data, the FDA approved lumateperone for the treatment of schizophrenia in adults in December 2019. Lumateperone, branded as Caplyta®, was available in February 2020 and is administered in capsule form at a daily dose of 42 mg.[21,22,23,24]

Structure

Lumateperone, similar to haloperidol, is derived from a butyrophenone core (Figure 1A, 1B, 1C). The IUPAC name for lumateperone is 1-(4-fluorophenyl)-4-(4-methyl-1,4,12-triazatetracyclo [7.6.1.05,16.010,15]hexadeca-5,7,9(16)-trien-12-yl) butan-1-one, and it has a molecular formula of C24H28FN3O and a molecular weight of 393.5. Lumateperone is formulated as a tosylate salt to provide stability to the medication. Lumateperone tosylate has an IUPAC name 1-(4-fluorophenyl)-4-[(10R,15S)-4-methyl-1,4,12-triazatetracyclo[7.6.1.05,16.010,15] hexadeca-5,7,9(16)-trien-12-yl]butan-1-one;4-methylbenzenesulfonic acid; its molecular formula is C31H36FN3O4S and a molecular weight of 565.7.[24,25,26]

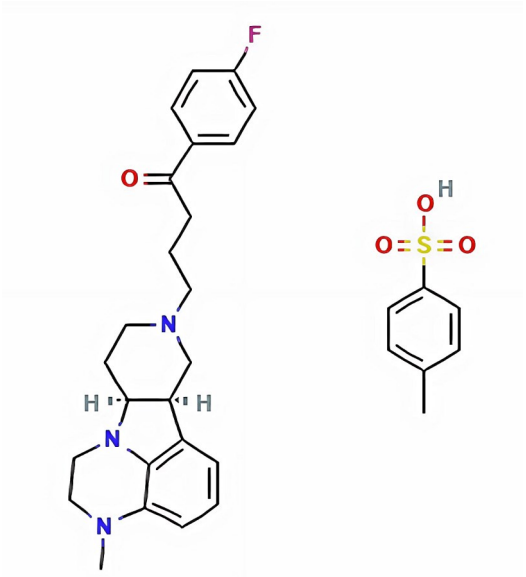

Figure 1A. Structure of lumateperone tosylate[43]

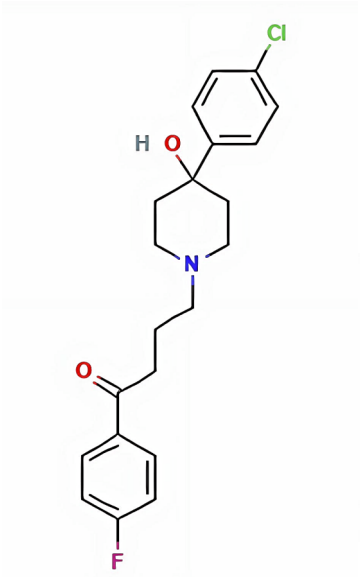

Figure 1B. Structure of haloperidol[44]

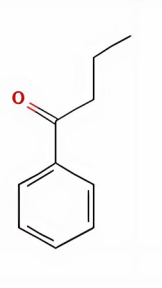

Figure 1C. Structure of butyrophenone[45]

Figure 1. Comparison of the structures of lumateperone and haloperidol with their butyrophenone core

Pharmacology

Lumateperone is an atypical antipsychotic, and similar to other SGAs, has antagonist properties at both the D2 and 5-HT2A receptors. Lumateperone has high binding affinity for the 5-HT2A receptors and displays moderate binding affinity for the D1 and D2 receptors. It has low binding affinity for adrenergic α1 and histaminergic H1 receptors.[27,28,29] Lumateperone has a 60-fold higher affinity for the 5-HT2A receptor compared to the D2 receptor.[28,29,30,31] The high 5-HT2A / D2 binding ratio, a characteristic of SGAs, contributes to improvement of negative symptoms.[32] It acts as a presynaptic partial agonist and a postsynaptic antagonist at the D2 receptor. This pharmacological effect of decreased presynaptic release of dopamine and postsynaptic D2 receptor blockade significantly dampens dopaminergic signaling and thus improves positive symptoms.[28] Lack of binding to muscarinic and histaminergic receptors results in fewer adverse effects associated with muscarinic and histaminergic antagonism in several other antipsychotics.[27] Lumateperone causes increased phosphorylation of the N-methyl-D-aspartate (NMDA) receptor GluN2B subunit which results in indirect glutamatergic activation.[27] Lumateperone inhibits the serotonin reuptake transporter (SERT) which may produce antidepressant effects and also contribute to improvement of negative symptoms.[25]

Comparison of receptor binding affinity of lumateperone with other antipsychotics

The receptor binding of lumateperone is compared with two other SGAs, risperidone[33] and olanzapine[34], and a FGA, haloperidol,[35] in Table 2. For drug-receptor binding, the smaller the inhibitory constant (Ki), the greater the binding affinity and the smaller amount of medication needed in order to inhibit the activity of that receptor. Lumateperone has robust binding to the 5-HT2A receptor, which is comparable to both the SGAs listed in Table 2. Lumateperone shows moderate binding at the D2 receptor similar to olanzapine. This accounts for decreased EPS in lumateperone and olanzapine therapy. Risperidone can cause significant EPS due to strong binding at the D2 receptor comparable to haloperidol. Lumateperone's antidepressant potential is due to its binding at SERT, which is not present in the other antipsychotic agents. In summary, Lumateperone's therapeutic efficacy and safety are due to its robust binding at the 5-HT2A receptor, moderate binding at the D2 receptor, inhibition of SERT, and lack of muscarinic and histaminergic binding. Lumateperone does not cause movement disorders observed with FGAs. Lumateperone does not produce serious adverse effects produced by SGAs such as agranulocytosis, weight gain, diabetes, lipid abnormalities, and cardiac arrythmias. Lumateperone also is effective in management of both positive and negative symptoms and also improves cognition.[36,37]

Safety

Lumateperone displays a favorable safety profile due to its receptor binding profile.[36] In clinical trials, it was well tolerated and did not display the adverse motor effects nor the metabolic, endocrine, and cardiovascular effects typically associated with other FGAs and SGAs.[38,39] Some common adverse effects of lumateperone are headache, dizziness, sedation, fatigue, nausea, constipation, and vomiting. Lumateperone was not clinically studied in patients older than 65 years old and is not recommended for the treatment of dementia-related psychosis.[25,26,38,39]

Pharmacokinetics

Lumateperone is rapidly absorbed after oral absorption, and displays high lipophilicity, which increases its passage through the blood brain barrier. Peak plasma concentration is achieved in 1-2 hours and steady state concentration is achieved in about 5 days. Lumateperone has a bioavailability of about 4% and is 97.4% protein bound. About 58% of lumateperone is excreted in urine as water soluble glucuronide metabolites. Less than 1% of unmetabolized drug is

Drug	**Receptors**						
	D_1	**D_2**	**$5HT_{2A}$**	**SERT**	**α_1**	**α_2**	**H_1**
Lumateperone	41 nM	32nM	0.54 nM	62 nM	<100 nM	N/A	>1000 nM
Risperidone	N/A	3.13 nM	0.16 nM	>1000 nM	0.8 nM	7.54 nM	2.23 nM
Olanzapine	11 nM	31 nM	4 nM	>1000 nM	19 nM	N/A	7.0 nM
Haloperidol	83 nM	nM	N/A	N/A	N/A	3 nM	N/A

N/A- no significant binding / binding data not available

Table 2. Comparison of inhibitory constant (Ki) of lumateperone with other antipsychotics

excreted in the urine and 29% is excreted in the feces.[38,39]

Lumateperone is a substrate for the enzymes Cytochrome P450 3A4 (CYP3A4) and Uridine 5'-diphospho-glucuronosyltransferase (UGT), and thus there is potential for drug-drug, drug-food, and drug-herb interactions. Lumateperone should not be taken with CYP3A4 inducers such as the anticonvulsant, carbamazepine, and the herbal supplement, St. John's wort, as they would reduce the plasma concentrations of the drug. Lumateperone is also contraindicated with CYP3A4 inhibitors, such as the antidepressant, fluvoxamine, and grapefruit juice, as they would lead to an increase in plasma levels of the drug and increase the chances for toxicity. Drugs known to be UGT inhibitors such as the anticonvulsant, valproic acid, should not be used with lumateperone.[38,39]

Clinical Trials

Lumateperone was clinical evaluated to study its therapeutic effectiveness and potential adverse effects. Two clinical trials were conducted to determine the efficacy and safety of lumateperone are discussed in this section.

NCT01499563

This clinical trial was a phase II multicenter study that compared placebo and risperidone (4 mg), as positive control, with two doses of ITI-007 (lumateperone tosylate) (60 mg and 120 mg) which are equivalent to 42 mg and 84 mg of lumateperone being used to determine effects of ITI-007 on psychosis. The study was conducted from December 2011 to November 2013. The study was conducted in a randomized double-blind manner in a 1:1:1:1 fashion. A total of 355 acutely psychotic patients were enrolled into the study.

Inclusion Criteria:

- "Patient's age is 18-55
- Patient has current diagnosis of schizophrenia and is experiencing an acute exacerbation of psychosis
- Patient has a history of at least three months exposure to one or more antipsychotic therapy(ies) and a prior response to antipsychotic therapy within the previous five years"[40]

Exclusion Criteria:

- "Any female patient who is pregnant or breast-feeding
- Any patient presenting with concurrent dementia, delirium, mental retardation, epilepsy, drug-induced psychosis, or history of significant brain trauma
- Any patient presenting with schizoaffective disorder, bipolar disorder, acute mania, or major depression with psychotic features
- Any patient considered to be an imminent danger to themselves or others
- Any patient with hematological, renal, hepatic, endocrinological, neurological, or cardiovascular disease or substance abuse as defined by protocol
- Any patient judged by the investigator to be inappropriate for the study"[40]

The medication and placebo were administered once daily for 28 days. The primary end point was the Positive and Negative Syndrome Scale (PANSS). There was a significant difference between placebo and ITI-007 (60 mg). Risperidone also showed a significant difference compared to placebo. ITI-007 (120 mg) did not show any statistically significant difference compared to placebo. A subgroup of patients with symptoms of depression were evaluated with the Calgary Depression Scale for Schizophrenia (CDSS). Only ITI-007 (60 mg) showed a significant difference compared with placebo for the depression symptoms.[40]

NCT02282761

This phase III clinical trial compared placebo with two doses of ITI-007 (lumateperone tosylate), 40 and 60 mg, which are equivalent to 28 and 48 mg of lumateperone base. This clinical study was conducted from November 2014 to September 2015. 450 patients with schizophrenia were enrolled in this study in a randomized, double-blind, 1:1:1 fashion.

Inclusion Criteria:

- "Patient's age is 18-60
- Patient has a clinical diagnosis of schizophrenia
- Patient is male or female of any race
- Patient is experiencing an acute exacerbation of psychosis"[41]

Exclusion Criteria:

- "Any female patient who is pregnant or breast-feeding
- Any patient unable to provide informed consent
- Any patient judged by the Investigator to be inappropriate for the study."[41]

The patients were administered medication or placebo once daily for a period of 28 days. The primary end point was the PANSS. ITI-007 (60 mg) showed a significant difference compared to placebo for PANSS while the lower dose of 40 mg did not. Both doses of ITI-007 showed significant difference compared to placebo for secondary end points, Clinical Global Impression-Severity of Illness (CGI-S) scores, and the general psychopathology subscale scores.[41]

Overall, lumateperone showed efficacy in improving symptoms of schizophrenia as well as depression symptoms and also demonstrated a superior safety profile in both aforementioned clinical trials.

CONCLUSION

Schizophrenia is an extremely complex and debilitating mental illness with poorly elucidated pathophysiology. The pharmacotherapy of schizophrenia is beset with serious and life-threatening adverse effects such as movement disorders, agranulocytosis, weight gain, diabetes, and cardiac arrythmias. Thus, there exists a critical need for the development of newer antipsychotic agents with an improved therapeutic and safety profile. The receptor pharmacology of antipsychotic agents is well characterized and is linked to their therapeutic and adverse effects. This knowledge is advantageous in the development of newer antipsychotics

Lumateperone is one of the newly developed atypical antipsychotics in recent years. It has significantly higher binding affinity to the 5-HT2A receptor and moderate binding at the D2 receptor. It has a good safety profile and has been shown to be devoid of any significant motor, metabolic, endocrine, and cardiovascular adverse effects. It has been shown to be effective in the management of schizophrenia symptoms. Lumateperone's ability to inhibit SERT contributes to it's ability to manage negative and depression symptoms. Lumateperone was approved by the FDA for the treatment of bipolar depression in December 2021.[42] Since the drug has been on the market for less than three years, there are no studies evaluating any possible long-term effects of lumateperone.

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CONFLICTS OF INTEREST

All authors declare no conflicts of interest.

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