REVIEW ARTICLE

Comparative Study: Olanzapine and Lumateperone as Antipsychotic Drugs

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ABSTRACT
A new antipsychotic drug called Lumateperone has shown promise in the treatment of bipolar disorder and schizophrenia. It works by modulating dopaminergic, serotonergic, and glutamatergic neurotransmission. One characteristic that sets this dual-acting drug apart from other antipsychotics is its intermediate affinity for D 2 receptors and high affinity for 5 - HT2A receptors. According to clinical research, Lumateperone effectively reduces the symptoms of schizophrenia while having a relatively low risk of extrapyramidal symptoms and metabolic abnormalities. Notably, Lumateperone pharmacokinetic profile is characterized by extensive metabolism and low bioavailability, underscoring the significance of cautious dosage and possible medication interactions. Comparative research with the well-known antipsychotic Olanzapine has shown that Lumateperone is more tolerable and has a lower risk of weight gain and negative metabolic consequences. Clarifying Lumateperone effects on neurotransmitter systems and investigating for the clinical features of schizophrenia are two future research directions. The ultimate goal is precision medicine techniques that are adjusted to meet the needs of each patient. Lumateperone, with its distinct therapeutic profile and enhanced tolerability as antipsychotic drug.
Keywords: Lumateperone, Olanzapine, Comparative research, antipsychotic, pharmacokinetic profile
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INTRODUCTION

An estimated 1% of people worldwide suffer from schizophrenia, a chronic mental illness[1]. There are several neurotransmitter systems involved in this complicated disorder. It is a serious mental illness that impairs a person's behaviour, intellectual processes, emotional expression, and reality perception. This complicated illness, which includes a variety of positive, negative, and cognitive symptoms, usually manifests in adolescence or early adulthood. Hallucinations (including the senses of sight, hearing, taste, smell, or touch), delusions (such as feelings of grandeur or persecution), disordered speech and ideas, difficulty focusing, catatonic behaviour, and movement problems are examples of positive symptoms. Numerous genetic and environmental variables can contribute to the development of schizophrenia and can set the disorder off in susceptible people. For patients with life-limiting illnesses, palliative care is defined by the World Health Organization as concentrating on enhancing quality of life through symptom relief, spiritual support, and psychological care[2-5]. The article explains how Lumateperone lessens the likelihood or intensity of side effects brought on by Olanzapine. The United States Food and Drug Administration (US FDA) has approved two second-generation atypical antipsychotic medications for the treatment of schizophrenia: Olanzapine and Lumateperone. (Olanzapine, 1996; Lumateperone, 2019).

Lumateperone is categorized according to its extra mode of action. Additionally, they are used to treat resistant depression, agitation, and bipolar mania. The FDA broadened the use of Lumateperone in 2021 to cover depressive episodes linked to bipolar 1 or 2. The FDA broadened the use of Lumateperone in 2021 to include adult patients experiencing depressive episodes linked to bipolar 1 or 2 illness, either as a monotherapy or as an adjuvant treatment when lithium or valproate is being used concurrently. Despite being widely administered, Olanzapine's effectiveness profile leads numerous guidelines to suggest it as a second-line therapy choice. Olanzapine is useful in treating both positive and negative symptoms of schizophrenia, and its pharmacological characteristics are comparable to those of clozapine[6-9]. Lumateperone is more than just a "Me-too" because of its qualities. Schizophrenia is a serious mental illness that impairs a person's behaviour, intellectual processes, emotional expression, and reality perception. This complicated illness, which includes a variety of positive, negative, and cognitive symptoms, usually manifests in adolescence or early adulthood. Hallucinations (including the senses of sight, hearing, taste, smell, or touch), delusions (such as feelings of grandeur or persecution), disordered speech and ideas, difficulty focusing, catatonic behaviour, and movement problems are examples of positive symptoms. Numerous genetic and environmental

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variables can contribute to the development of schizophrenia and can set the disorder off in susceptible people[9-12].

Olanzapine, chemically known as 2-methyl-4-(4-methyl-1-piperazinyl)-10H-thieno (2,3-b[1,5] benzodiazepine), belongs to a unique class of medications called thienobenzodiazepines. This class of drugs was specifically designed to retain the beneficial effects of benzodiazepines while minimizing their muscle-relaxant properties. Lumateperone, also called ITI-007 or ITI-722 has a chemical identification number (CAS) of 313368-91-1.[16] And chemically known as (4 – (6bR, 10aS) -3-methyl -2,3,6b,9,10,10a – hexahydro -1H,7 H – Pyrido [3',4': 4,5] pyrrolyl [1,2,3 – de]- quinoxaline-8-yl] -1-(4-fluro-phenyl)-butan-1-one 4-methylbenzene-sulfonate)[14]. It is formulated as a tosylate salt, with a molecular formula of C24H28FN3O and a molecular weight of approximately 393.5 grams per mole[6,9].

Pharmacology

Mechanism of Action

Dopamine and serotonergic receptors are the main targets of Olanzapine, an atypical second-generation antipsychotic. It blocks dopamine's action at post-synaptic receptors by acting as an antagonist at dopamine D 2 receptors in the mesolimbic pathway[13]. Lumateperone functions as a partial agonist and antagonist at presynaptic and postsynaptic dopamine D 2 receptors, thereby modulating the dopaminergic, serotonergic, and glutamatergic neurotransmitter systems. When compared to other antipsychotics like Olanzapine, Lumateperone's dual action on dopamine D 2 receptors is distinct; yet, Olanzapine's loose binding and easy dissociation from the receptor permit normal dopamine neurotransmitter function. Lumateperone, on the other hand, has a 60-fold higher binding affinity for the 5 HT2A receptor than it does for the D2 receptor, making it a very strong antagonist of the latter. Lumateperone is the first antipsychotic to demonstrate this mode of action due to its distinct pharmacological profile, which allows it to improve the function of NMDA(N-methyl-D-aspartate) and AMPA (α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid) receptors by modulating glutamatergic activity. To lessen the symptoms of schizophrenia, second-generation antipsychotics such as Olanzapine, which are partial agonists of the D2 receptor, need a high D2 receptor occupancy (60–80%), which raises the possibility of extrapyramidal side effects. Lumateperone, on the other hand, is effective at lower occupancy (40%) due to its dual-action mechanism, which combines pre-synaptic partial agonist and post-synaptic antagonist activity. This novel approach targets mesolimbic pathways, inhibits excessive dopamine release, and lowers the danger of extrapyramidal side effects, making it a potentially effective treatment for schizophrenia with fewer adverse effects[9-13]. According to research, schizophrenia may be influenced by NMDA receptors, a subtype of ionotropic glutamate receptors. Glutamate transmission dysregulation, especially in gamma-aminobutyric acid (GABA) interneurons, may be the cause of the cognitive deficits linked to the negative symptoms of schizophrenia. Interestingly, research shows that NMDA receptor expression is lower in people with schizophrenia.

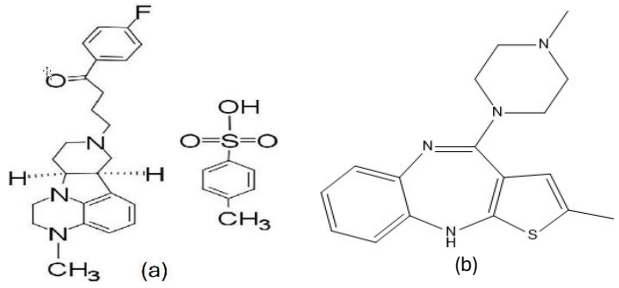

Figure 1: Chemical Structure of (a) Lumateperone; (b) Olanzapine

It has been demonstrated that the innovative therapeutic drug Lumateperone modifies NMDA receptor function compared to conventional antipsychotics, Olanzapine, a serotonin-dopamine receptor antagonist, successfully treats all types of symptoms of schizophrenia with fewer extrapyramidal symptoms and akathisia. It is a recommended treatment for schizophrenia and psychoses due to its better side-effect profile[13]. Olanzapine also functions as an antagonist at a number of receptors, such as muscarinic M1-5 receptors, alpha-one adrenoceptors, and histamine H1. Additionally, it binds weakly to beta-adrenoceptors, benzodiazepines, and GABA. Olanzapine works similarly to all other commercially available antipsychotics in that it blocks the D2 receptor[14-20].

Lumateperone's mechanism of action includes serotonergic modulatory activity in addition to its strong 5-HT2A receptor antagonistic effects. Notably, like selective serotonin reuptake inhibitor (SSRI) antidepressants, it inhibits the serotonin reuptake transporter, which may be part of the reason it has antidepressant effects and is effective in treating depression and other negative symptoms of schizophrenia. Lumateperone's effectiveness in treating schizophrenia and bipolar depression may be due to its special characteristics. Lumateperone, in contrast to other antipsychotics, acts on the brain's glutamatergic system, it has been linked to the pathophysiology of schizophrenia, namely the dysregulation of glutamate transmission[21-23].

Pharmacokinetics

Absorption and Bioavailability

Olanzapine used daily takes around a week to attain steady-state plasma concentrations. Oral formulations take six hours to reach peak concentration, while intramuscular (IM) formulations take fifteen to forty-five minutes. Olanzapine has a half-life of 30 hours on average, with a range of 21 to 54 hours. Olanzapine taken orally is nearly entirely absorbed, but because of first-pass metabolism, its total bioavailability is only about 60%[13-19].

Lumateperone takes three to four hours to reach its maximum concentration (Tmax) after oral ingestion. By eight hours, Lumateperone's plasma levels fall between 0.05 and 50 ng/ml, while its metabolites accumulate to values between 0.2 and 100 ng/ml. Within one to two hours of ingestion, Lumateperone's plasma concentration reaches its peak. Exposure increases dose proportionately for dosages between 21 and 56 mg, reaching steady-state concentrations in around 5 days. However, with a coefficient of variation ranging from 68 to 97%, individual

pharmacokinetics can differ greatly. The absolute bioavailability of Lumateperone is about 4.4%. Its pharmacokinetics can be impacted by food consumption, especially high-fat meals, which can increase exposure and peak concentration by 33% and 9%, respectively, and delay peak concentration by roughly an hour[24-28].

Distribution

Olanzapine is extensively disseminated throughout the body and has a large volume of distribution (about 1000 Liters). 93% of it is attached to plasma proteins, namely albumin and alpha-1 acid glycoprotein[13]. Lumateperone has a volume of distribution of roughly 4.1 L/kg after intravenous injection. Furthermore, at concentrations around 70 times greater than therapeutic levels, 97.4% of it is bound to plasma proteins, demonstrating its strong affinity for binding plasma proteins[29].

Metabolism

Olanzapine undergoes extensive metabolism in the liver via glucuronidation and the cytochrome P450 system, primarily by CYP1A2 and to a lesser extent by CYP2D6[5]. Lumateperone undergoes extensive metabolism, resulting in over 20 metabolites. This process involves multiple enzymes, including uridine diphosphate glycosyltransferases (UGTs), aldo-keto reductases (AKRs), and cytochrome P450 enzymes (CYP3A4, CYP2C8, and CYP1A2), highlighting the complexity of its metabolic pathway[29].

Excretion

The renal pathway and faeces are the main ways that Olanzapine is eliminated. It is expected that less than 10% of the medication is eliminated by the kidneys unmetabolized[8]. The original chemical and its glucuronidated metabolites make up roughly 2.8% and 51% of total plasma radioactivity after a single dosage of radiolabelled Lumateperone, respectively. Less than 1% of the unaltered medication is expelled in the urine, while the majority of the radioactivity is removed through the faeces (29%), and urine (58%). Lumateperone's pharmacokinetic profile is defined by a 17.9 L/h clearance rate after intravenous administration and a terminal half-life of roughly 18 hours[29].

Pharmacodynamics

Dopamine, serotonin, histamine, and muscarinic receptors are among the neurotransmitter receptors for which Olanzapine, a thienobenzodiazepine derivative, has a wide affinity profile. It has a greater affinity for serotonin 5-HT2 receptors than dopamine D2 receptors, and its receptor binding activity is comparable to that of clozapine. According to electrophysiological research, Olanzapine may be less likely to cause extrapyramidal symptoms (EPS) because of its distinct effects on the mesolimbic and nigrostriatal systems. Olanzapine has shown antipsychotic effects in numerous animal models and has been proven to suppress dopamine and serotonin agonist-induced behaviours. Furthermore, Olanzapine has been shown to have a reduced tendency to induce EPS than traditional antipsychotics, and it has little influence on prolactin levels in schizophrenia patients. A second-generation antipsychotic called Lumateperone affects serotonin, dopamine, and glutamate—all of which are linked to serious mental diseases. It acts as an antagonist at 5-HT2A and D2 receptors, with high affinity for 5-HT2A and moderate affinity for D2. Lumateperone reduces dopaminergic transmission through a novel mechanism that combines postsynaptic antagonism and presynaptic partial agonism at D2 receptors. Aripiprazole and its derivatives use a similar strategy. Lumateperone's regional specificity for mesolimbic and mesocortical D2 receptors adds to its antipsychotic efficacy without extrapyramidal side effects. Furthermore, Lumateperone inhibits kinase activity and causes GSK-3 to become phosphorylated, which may be therapeutically beneficial for bipolar disorder and schizophrenia. Additionally, it increases glutamatergic neurotransmission through partial agonism on D1 receptors, which may help with negative symptoms and cognitive impairments. Furthermore, Lumateperone's high antagonism at 5-HT2A receptors and inhibition of serotonin reuptake transporters may contribute to its comparatively low risk of extrapyramidal symptoms and antidepressant effects[21-28].

Dosage and Administration

Dosage and Administration In order to achieve 10 mg/day in a few days, the initial recommended dosage of Olanzapine is 5–10 mg once daily, with or without food. Dosage adjustments can be made in increments of 5 mg, but only after a minimum of one week has elapsed. Higher doses (≥15 mg/day) should only be used after careful evaluation. Certain patients may require a lower initial dose of 5mg/day, including those who are debilitated, prone to hypotension, or may metabolize Olanzapine more slowly (such as elderly women who are nonsmokers). Maintenance treatment should utilize the lowest effective dose[21].

Warnings and Precautions

Olanzapine should be used with caution in patients with certain medical conditions, including cardiovascular, cerebrovascular, or liver disease, as well as those at risk of seizures. Patients should also be aware that Olanzapine can cause drowsiness, which may impair their ability to operate machinery or drive safely[29]. Lumateperone is taken orally, specifically in capsule form, with a recommended dose of 42 mg, preferably at bedtime. Clinical trials have shown that higher doses, such as 120 mg/day, do not provide significant improvements in efficacy[20,30].

Clinical Trials

Lumateperone

In clinical study Syed & Brašić[31]. First trial: In the first phase, Lumateperone showed considerable improvements in symptoms of schizophrenia, including positive symptoms, negative symptoms, and overall psychopathology. Patients with concomitant depression and significant negative symptoms showed larger improvements. Second trial:602 schizophrenia affected individuals were moved to Lumateperone 42 mg once daily for a maximum of one year in the second phase of the study. The findings indicated that person affected with severe depression experienced the biggest progress in both depression and schizophrenia symptoms. Third trial: According to a comprehensive review of 520 research, Lumateperone 42 mg once daily was just as effective as risperidone at reducing symptoms of schizophrenia.

Additionally, reaction rates and both positive and negative symptoms significantly improved with Lumateperone.

Olanzapine

Olanzapine, a highly effective second-generation antipsychotic (SGA) used to treat schizophrenia, bipolar disorder, major depressive disorder (MDD) as an adjuvant treatment, and agitation associated with schizophrenia or bipolar disorder, has regained attention since the FDA approved new formulations and other formulations that are presently undergoing clinical trials. Clinical trials indicate an ideal daily dose of 10 mg to 20 mg for schizophrenia, with higher doses demonstrating effectiveness in treatment-resistant cases. Olanzapine has been consistently ranked among the most effective antipsychotic medications for bipolar disorder and schizophrenia by meta-analyses, efficacy trials, and comparison trials. Olanzapine should be tapered gradually to reduce the risk of psychiatric decompensation and cholinergic rebound, which can occur when the medication is stopped abruptly. Haloperidol, risperidone, and quetiapine all pass through the placenta similarly to olanzapine. On the other hand, low birth weight and more neonatal critical care unit admissions have been associated with olanzapine treatment during pregnancy.

In comparison to newborns who were not exposed to antipsychotics during pregnancy, olanzapine was linked to a nearly fourfold greater risk of musculoskeletal abnormalities and a doubled chance of severe congenital deformities, according to a population-based study. Therefore, it's crucial to discuss Olanzapine with pregnant women and thoroughly consider the benefits and drawbacks of doing so. It is preferred to use antipsychotic medications that have minimum negative effects on breastfed infants and low excretion into breast milk. Because olanzapine is present in trace amounts in breast milk and is usually undetectable in the serum of breastfed neonates, it is preferred while nursing. A study of SGAs found that olanzapine is safe to use while nursing, which makes it a good therapeutic choice for nursing mothers with psychotic illness[21].

Contraindication

Lumateperone is broken down in the body by the CYP3A4 enzyme, which can lead to interactions with medications that affect this enzyme, such as inhibitors or inducers. To minimize potential interactions, it's recommended to avoid using Lumateperone with strong CYP3A4 inducers and moderate to potent CYP3A4 inhibitors. Furthermore, Lumateperone can interact with other substances that cause sedation, including alcohol and other sedatives, particularly at lower doses where sedative effects are more pronounced[31-34].

Olanzapine is not recommended for persons with a history of hypersensitivity to any of its components or those with narrow-angle glaucoma. Caution is suggested when providing Olanzapine to individuals with cardiovascular or cerebrovascular disorders, or other conditions that may raise the risk of hypotension. People who have liver or kidney problems or are prone to seizures should also use it with caution. Patients who have paralytic ileus or prostatic hypertrophy should also be cautious because of possible anticholinergic effects[35].

Safety and Tolerability

In clinical trials, sleepiness was the most common side effect of Olanzapine (12–39% of participants) when compared to a placebo. About 6 to 15% of people suffer from constipation. Weight gain in 0–12% of patients compared to haloperidol, and Olanzapine showed fewer tremors, anxiety, salivation, and mobility issues. Weight gain, dry mouth, and increased appetite Low-Risk Extrapyramidal Symptoms (EPS). There is little chance that Olanzapine can cause EPS, such as parkinsonism, akathisia, or dystonia. In reality, haloperidol had far higher ratings than Olanzapine, which either had no effect or only marginally improved scores[29].

Other Safety Findings

Compared to haloperidol, Olanzapine was less likely to cause treatment-emergent dyskinetic symptoms. Olanzapine may occasionally raise liver enzyme levels, although no signs of liver damage have been discovered, and these increases seem to be transient. Even in patients who have previously experienced blood problems while on clozapine, Olanzapine has not been demonstrated to significantly affect blood cell counts[29].

Adverse Effects of Lumateperone

Lumateperone often has several side effects: Somnolence (drowsiness) bowel irregularity, exhaustion, and sedation 64.7% of 148 participants in a clinical trial reported adverse effects, with drowsiness accounting for 17.6%, sedation for 12.7%, and exhaustion for 5.3%. Minimal Chance of Metabolic Alterations and Extrapyramidal Symptoms Less than 5% of participants experience extrapyramidal symptoms, indicating that Lumateperone has a low risk of causing them. Furthermore, Lumateperone had no discernible effects on blood glucose, prolactin levels, lipids, or weight.

Comparing Conventional Antipsychotics

Lumateperone was contrasted with a common antipsychotic drug in a different clinical study. Triglycerides, prolactin, and LDL cholesterol were significantly improved in patients who went to Lumateperone. Decreased chance of adverse reactions. All things considered; the evidence points to Lumateperone having a lower chance of side effects than other second-generation antipsychotics. Long-term research is still being done, nevertheless, to verify Lumateperone effectiveness and safety[20].

Metabolic Side Effects

When administered orally, 42 mg of Lumateperone was typically well tolerated by schizophrenic patients. The most frequent adverse effects in 6- to 8-week clinical studies were dizziness, dry mouth, nausea, and drowsiness/sedation. These adverse effects were comparable to those of participants receiving a placebo and were minor. The safety and tolerability of Lumateperone and another antipsychotic drug, risperidone, were compared in a pooled analysis of three clinical trials. According to the findings, Lumateperone was less likely than risperidone to cause weight gain. Compared to risperidone, which caused average weight change of +2.6 kg, Lumateperone caused a mean weight change of +1.6 kg. Furthermore, Lumateperone was less likely than risperidone to cause akathisia or restlessness. Lumateperone was shown to be

safe and well-tolerated overall. Its side effect profile was similar to that of risperidone, although it was less likely to cause akathisia and weight gain. Long-Term Monitoring
For 12 months, individuals in a longer-term study were given 42 mg of Lumateperone every day. The most frequent side effects of Lumateperone, which affected at least 5% of patients, were diarrhoea, headaches, dry mouth, and weight loss. These incidents were generally mild to moderate in intensity. Additionally, studies have demonstrated that Lumateperone has no effect on the QTc interval or other cardiac functions[36,37].
Lumateperone showed an acceptable safety profile in bipolar affective disorder patients. Adverse events associated with treatment were comparable to those in the placebo group, according to a multinational trial that included 377 patients. However, the group treated with Lumateperone experienced nausea and somnolence more frequently. No fatalities happened throughout the trial, although the Lumateperone group did experience one major adverse event, mania. Additionally, compared to 10.1% of patients receiving a placebo, 5.3% of individuals receiving Lumateperone reported having suicidal thoughts, according to the study. During the trial, no reports of suicide attempts were made. Additionally, Lumateperone did not result in appreciable weight increases or modifications to metabolic markers such as insulin, cholesterol, or fasting glucose levels. In contrast to the placebo group, prolactin levels in Lumateperone-using patients stayed constant. Growing worries about Olanzapine's metabolic adverse effects, especially weight gain, led to a drop in its use in the mid-2000s.
Around this time, other second-generation antipsychotics were licensed, providing more "metabolically friendly" alternatives[36,37].

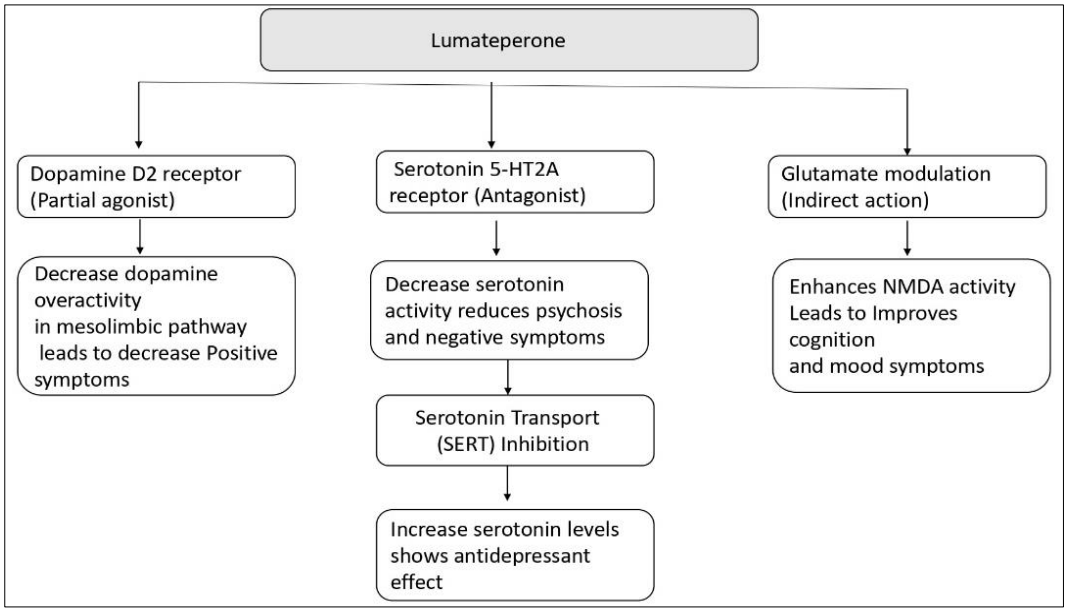

Figure 2: Mechanism of action of Lumateperone[9-11]

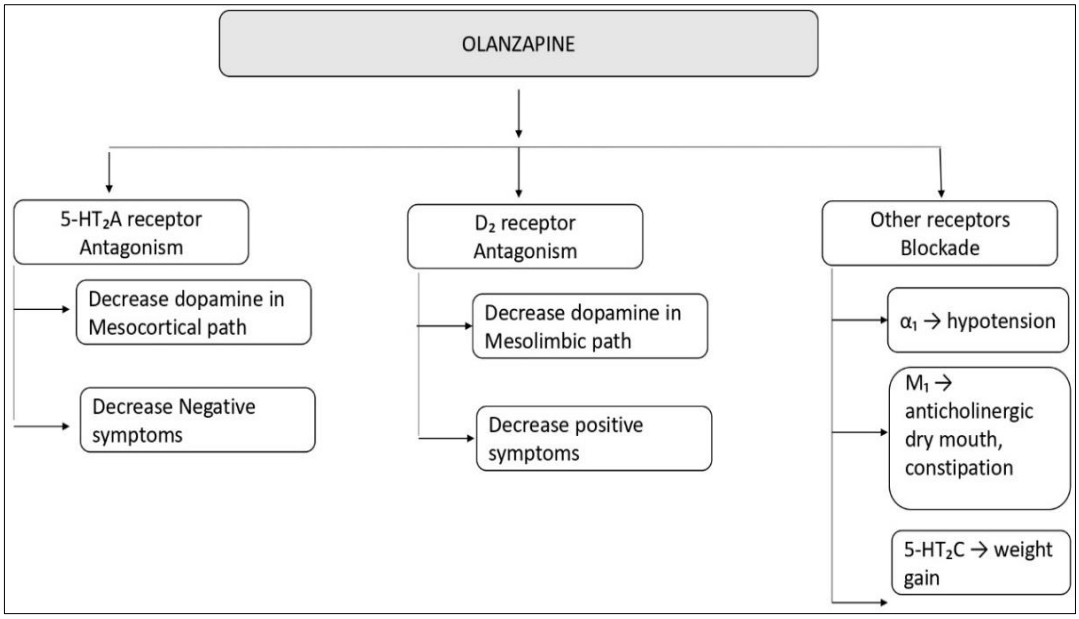

Figure 3: Mechanism of action of Olanzapine[2-7]

It has been repeatedly demonstrated that Olanzapine causes noticeable weight gain. Olanzapine, zotepine, and sertindole caused noticeably higher weight gain than the majority of other medications, according to a recent meta-analysis evaluating the short-term tolerability of 32 antipsychotic medications. Over the course of six weeks, patients gained 2.78 kg on average. Additionally, patients who took Olanzapine were most likely to gain at least 7% of their body weight.

Significant weight gain has also been linked to long-term Olanzapine treatment, second only to clozapine among second-generation antipsychotics. Olanzapine-induced weight gain may be dose-related, according to research. Furthermore, weight gain brought on by antipsychotics is typically greatest early in the course of treatment. According to a recent study, early weight gain—more precisely, a weight rise of 1.0 kg or more after two weeks of treatment—could predict weight gain at six weeks of Olanzapine treatment. Growing worries about Olanzapine's metabolic adverse effects, especially weight gain, led to a drop in its use in the mid-2000s. Around this time, other second-generation antipsychotics were licensed, providing more "metabolically friendly" alternatives.

Olanzapine's long-acting injectable form has been linked to a higher rate of sedation, with 8.2% of patients experiencing it as opposed to 2.0% in the placebo group. Furthermore, 0.07% of patients have been found to experience post-injection delirium, underscoring the importance of post-injection monitoring.

When Olanzapine was originally made available in the United States in 1996, it was believed that a daily dose of approximately 10 mg was useful in treating schizophrenia, with a maximum approved dose of 20 mg. Research indicates that some people with severe and ongoing symptoms would need greater dosages, even if the majority of patients might not benefit from doses above 20 mg per day.

When combined with fluoxetine, Olanzapine has been shown to be useful in treating a number of illnesses, including depression that are resistant to treatment. Additionally, it has been used to treat anorexia nervosa, agitation, and nausea and vomiting brought on by chemotherapy. However, because patients with concurrent drug use disorders are frequently excluded from clinical studies, its usage in these patients is limited[1].

Olanzapine has been thoroughly investigated in clinical trials for schizophrenia, and according to a recent meta-analysis, it is the sixth most effective antipsychotic for symptom reduction. Olanzapine has also been found to be useful in treating clinically high-risk patients, children with schizophrenia, and first-episode schizophrenia. The efficacy of low dosages of Olanzapine, such as 10 mg daily or a daily combination of 5 mg Olanzapine and 5 mg trifluoperazine, has been investigated.

Antipsychotic drugs, especially first- and second-generation versions, can affect lipid levels in addition to causing weight gain. Olanzapine, clozapine, and risperidone all raised the risk of dyslipidemia, according to a recent meta-analysis, with Olanzapine and clozapine carrying the biggest risks.

Table 1. Basic pharmacological properties, clinical efficiency, side effects and dosing and administration of the olanzapine and Lumateperone[5,6,9,10,15,16]

Property	Olanzapine	Lumateperone
Pharmacological properties		
Drug Class	Atypical Antipsychotic	Atypical Antipsychotic
Mechanism of Action	D2, 5-HT2A antagonist, etc	D2, 5-HT2A, serotonin transporter modulator, etc
Half-life	~30 hours	~18–20 hours
Metabolism	CYP1A2, CYP2D6	CYP3A4
FDA Approval Year	1996	2019
Clinical efficiency		
Target	Schizophrenia, Bipolar	Schizophrenia, Bipolar
Side effect		
Weight Gain	High	Low
Sedation	Common	Mild
Extrapyramidal symptoms	Moderate	Low
Metabolic Effects	↑glucose	Minimal
Dosing and administration		
Dose Range	5–20 mg/day	42 mg/day
Frequency	Once daily	Once daily
Route	Oral / IM	Oral

Antipsychotics, such as Olanzapine, are one risk factor for schizophrenia, which is linked to an elevated risk of diabetes. Olanzapine may raise the risk of diabetes, according to research, which shows increases in triglycerides, fasting glucose, weight, BMI, and waist circumference and decreases in insulin sensitivity. According to a meta-analysis evaluating 12 antipsychotic drugs, Olanzapine considerably raised blood glucose levels when compared to a placebo. Additionally, compared to ziprasidone, lurasidone, or risperidone, Olanzapine was linked to larger changes in glucose levels. The safety profile of Olanzapine's long-acting injectable (LAI) version is comparable to that of its oral form, with the exception of the possibility of delirium and post-injection drowsiness[1].

Accessibility and Cost

To examine the efficacy of various schizophrenia treatment methods, a simulation model was employed. Olanzapine, either in the form of an oral disintegrating tablet (ODT) or an ODT with standard oral tablet (SOT), was found to be the most effective therapy choice. This was predicated on the greater percentage of patients who stayed stable (79%) and the lowest number of inpatient relapses (11%). By contrast, aripiprazole and risperidone had lower stability rates and higher relapse rates. Olanzapine therapy has been shown to be both cost-efficient and effective. Olanzapine ODT plus SOT was found to be more cost-effective than risperidone and aripiprazole ODT plus SOT, according to the incremental cost-effectiveness ratio (ICER)[38].

A 30-day supply of Lumateperone costs $1584, with an average wholesale price of $52.80 per 42-mg capsule when it was first released on the market in March 2020[22-26].

Patient Perspective

70% of patients completed the study, which was a rather high completion rate. Approximately half of the 139 patients who finished the research (49.6%) and their physicians (41.7%) gave explanations for why they were continuing to take Olanzapine. Regarding baseline characteristics, the patients did not significantly differ from one another. who gave reasons for continuing Olanzapine and those who did not. On average, physicians gave 7.3 reasons for continuing Olanzapine, compared to 8.5 for patients. According to the patient, benefits for good symptoms (13.3%), improvements in functioning (25%), and the patient's views of progress (23.3%) were the main justifications for continuing Olanzapine. However, the main reasons given by clinicians were benefits for pleasant symptoms (24.5%), benefits for functioning (20.8%), and benefits for patients' perceptions of progress (22.6%). Patients' views of improvement (29% and 25.9%, respectively), benefits for positive symptoms (24.6% and 24.1%, respectively), and benefits for functioning (24.6% and 24.1%, respectively) were the main reasons given by both patients and physicians for continuing Olanzapine[39-42]. When prescribing Lumateperone, there are a number of restrictions to take into account. The management of patients with liver failure or those who are already stabilized on Lumateperone and are started on a medicine that interacts with it, for example, is not well-defined. Notwithstanding these drawbacks, Lumateperone can be a good choice for patients who are experiencing extrapyramidal symptoms (EPS) or metabolic side effects that make them intolerant to their current antipsychotic medication[23,26,43].

The role of Lumateperone in treating bipolar depression will be ascertained through ongoing clinical trials. Because of its high monthly cost, several healthcare systems with limited funding may think about postponing the incorporation of Lumateperone as a first-line treatment in their formularies. Lumateperone, on the other hand, might be a good course of treatment for individuals who have not responded to prior antipsychotics or who have encountered unbearable side effects[22,44].

Future Directions

The effects of Lumateperone on neurotransmitter systems and other possible pathways will be determined with the aid of multimodal studies. Additionally, thorough research projects conducted by global expert teams will make it easier to find biomarkers for schizophrenia's clinical characteristics. In the end, this will give medical professionals the resources they need to use precision medicine on patients with schizophrenia, adjusting treatment regimens to meet each patient's specific requirements[31,45,46].

DISCUSSION

This article shows how Lumateperone overcomes the side effects of Olanzapine. This is a new drug. The negative effects of Olanzapine, a common antipsychotic, have been shown to be mitigated by the new antipsychotic drug Lumateperone. Patients with schizophrenia and bipolar disorders can benefit from Lumateperone safer and more efficient treatment by reducing the side effects of Olanzapine, which include weight gain, metabolic problems, and extrapyramidal symptoms. of note, Lumateperone stands out from other antipsychotics since it is the only medication with a dual mechanism of action. With a more favourable side effect profile than Olanzapine, Lumateperone is an emerging medication that has demonstrated potential in treating a variety of illnesses, including bipolar disorders and schizophrenia.

Second-generation antipsychotic drugs, such as Olanzapine and Lumateperone, are used to treat bipolar disorder and schizophrenia. They function by going for serotonin and dopamine receptors in the brain. Nevertheless, Lumateperone is different from other antipsychotics like Olanzapine because of its special dual action on dopamine D2 receptors. Lumateperone works at lower D2 receptor occupancy levels than Olanzapine, which needs high occupancy to lessen schizophrenia symptoms. This lessens the possibility of extrapyramidal adverse effects like stiffness in the muscles and tremors. Conversely, Olanzapine needs greater occupancy to work because it is a partial agonist of the D2 receptors. According to pharmacokinetics, Olanzapine and Lumateperone are widely dispersed throughout tissues, have a high binding affinity for plasma proteins, and are well absorbed when taken orally. Urine and faces are the products of their liver metabolism. Lumateperone has an FDA-approved dosage of 42 mg, whereas Olanzapine works best at levels of 20–40 ng/ml. A number of adverse effects, such as weight gain, dyslipidaemia, diabetes mellitus, and hyperglycemia, have been linked to Olanzapine. Lumateperone's distinct method of action, on the other hand, reduces these adverse metabolic consequences. The receptor binding characteristics of the two drugs also vary. Dopamine, adrenergic, histamine, muscarinic, and serotonergic receptors are all highly receptive to Olanzapine. Lumateperone, on the other hand, has less affinity for histaminergic, muscarinic, alpha 1 adrenergic, and dopamine D2 receptors. On the other hand, it exhibits a high affinity for the serotonin 5HT2A receptor and a moderate affinity for the serotonin transporter (SERT). Overall, Olanzapine and Lumateperone are both powerful antipsychotic drugs; however, their receptor binding patterns and modes of action differ. Lumateperone's distinct dual action on dopamine D2 receptors decreased risk of metabolic adverse effects.

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