A Review on the Use of Lumateperone in the Treatment of Schizophrenia

By

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A thesis submitted to the School of Pharmacy in partial fulfillment of the requirements for the degree of Bachelor of Pharmacy (Hons.)

School of Pharmacy
BRAC University
March, 2024

Declaration

It is hereby declared that

1. The thesis submitted is my own original work while completing a degree at BRAC University.
2. The thesis does not contain material previously published or written by a third party, except where this is appropriately cited through full and accurate referencing.
3. The thesis does not contain material which has been accepted, or submitted, for any other degree or diploma at a university or other institution.
4. I have acknowledged all main sources of help.

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Approval

The thesis/project titled "A Review on the Use of Lumateperone in the Treatment of Schizophrenia" submitted by Lamia Zabin Tisha (20146033) of Spring, 2020 has been accepted as satisfactory in partial fulfilment of the requirement for the degree of Bachelor of Pharmacy (Hons.) on March, 2024.

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Ethics Statement

This study does not involve any animal or human trial.

Abstract

Schizophrenia is a typical, possibly extreme psychotic problem found in patients around the world. It is an ongoing disease influencing roughly one percent of the general population. Consistently, approximately 1 out of 10,000 is determined to have this problem. While positive symptoms of schizophrenia, such as delusions and hallucinations, are frequently improved by modern antipsychotic therapy, their effectiveness in treating negative symptoms, cognitive symtoms and social functioning is limited. A new antipsychotic that has been approved by the Food and Drug Administration (FDA) which has been ensured to provide to adults suffering from schizophrenia. Diminishing both the positive and negative side effects of schizophrenia, it has become a promising treatment option. Compared to other treatments like risperidone, lumateperone has demonstrated effectiveness in reducing symptoms. Overall, lumateperone is a safe and well-tolerated treatment for a wide range of patients.

Keywords: schizophrenia; DSM-5 criteria; lumateperone; dopamine; glutamate; risperidone; nanosystem.

Dedication

Dedicated to those who have been suffering from schizophrenia.

Acknowledgement

First of all, I would like to give thanks and appreciation to Allah for granting me good health as well as the patience, dedication and knowledge that I needed to finish the thesis.

To my project supervisor, Namara Mariam Chowdhury, Program Coordinator and Senior Lecturer, School of Pharmacy, BRAC University, I would like to convey my profound gratitude for all of her help and support throughout my research. Working under her direction was a great honour and privilege.

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List of Acronyms

WHO	World Health Organisation
PANSS	Positive and Negative Syndrome Scale
GABA	Gamma-aminobutyric acid
CNS	Central Nervous System
NMDA	N-methyl-D-aspartate
5-HT	5-hydroxytryptamine
LAI	Long-Acting Injectable
FGA	First-Generation Antipsychotic
SGA	Second-Generation Antipsychotic
TGA	Third-Generation Antipsychotic
EPS	Extrapyramidal symptoms

Chapter 1: Introduction

1.1 Introduction to Schizophrenia

Schizophrenia is a typical, possibly extreme psychotic problem found in patients around the world. It is an ongoing disease influencing roughly one percent of the general population. Consistently, approximately 1 out of 10,000 is determined to have this problem. In various societies and nations, this amount stays constant through the times. The pervasiveness is approximately multiple times the yearly occurrence rate, demonstrating the ongoing idea of this problem. The World Health Organization mentions that schizophrenic patients are more likely to die early than the general population. This is frequently due to diseases that can be prevented, for example cardiovascular and metabolic disorders. It has been known to be the second-highest donor to the complete changes among the diseases. In spite of the fact that schizophrenia is viewed as a remediable problem, with the assistance of prescriptions and emotional support, there is zero real cure. Only a few of the patients meet the clinical and social betterment requirements for schizophrenia. It typically strikes teenagers between the ages of 20 and 35 (Amber et al., 2020).

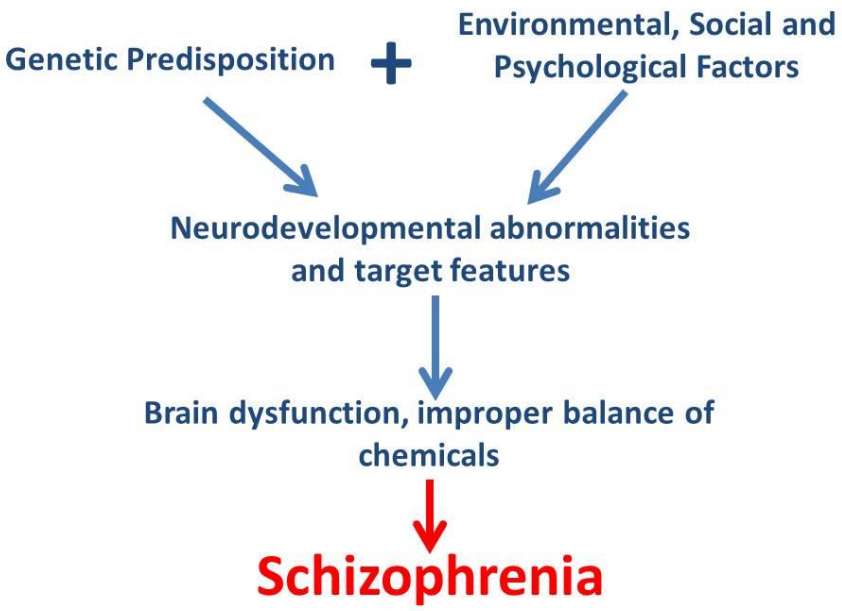

Figure 1 *Factors affecting the development of schizophrenia (Shawncho, 2012)*

1.2 Diagnostic Criteria of Schizophrenia

Schizophrenia takes place with a huge range of behavioural, psychological as well as cognitive symptoms. According to DSM-5 criteria-

- Schizophrenia can be analysed by at least two of these factors- hallucinations, delusions, speech disorder, complicated way of behaving and negative symptoms.
- Functioning level is very high.
- The symptoms are noticed constantly for six months.
- Chemical substances are not involved (Eskelinen, 2017).

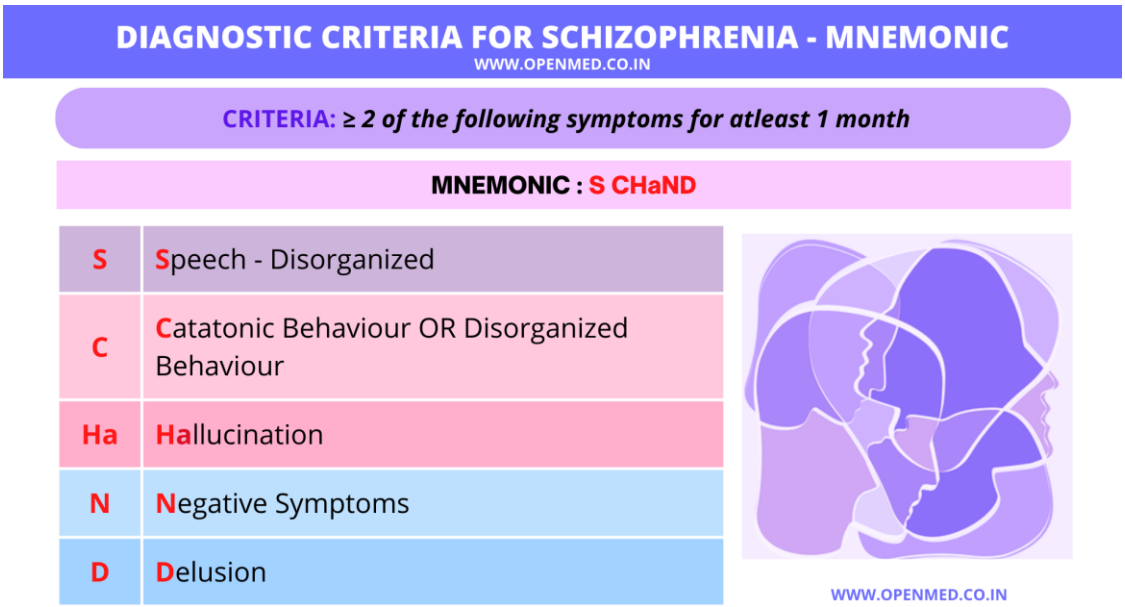

Figure 2 *Criterias of schizophrenia (DSM-5 Diagnostic Criteria for Schizophrenia - MNEMONIC, 2022)*

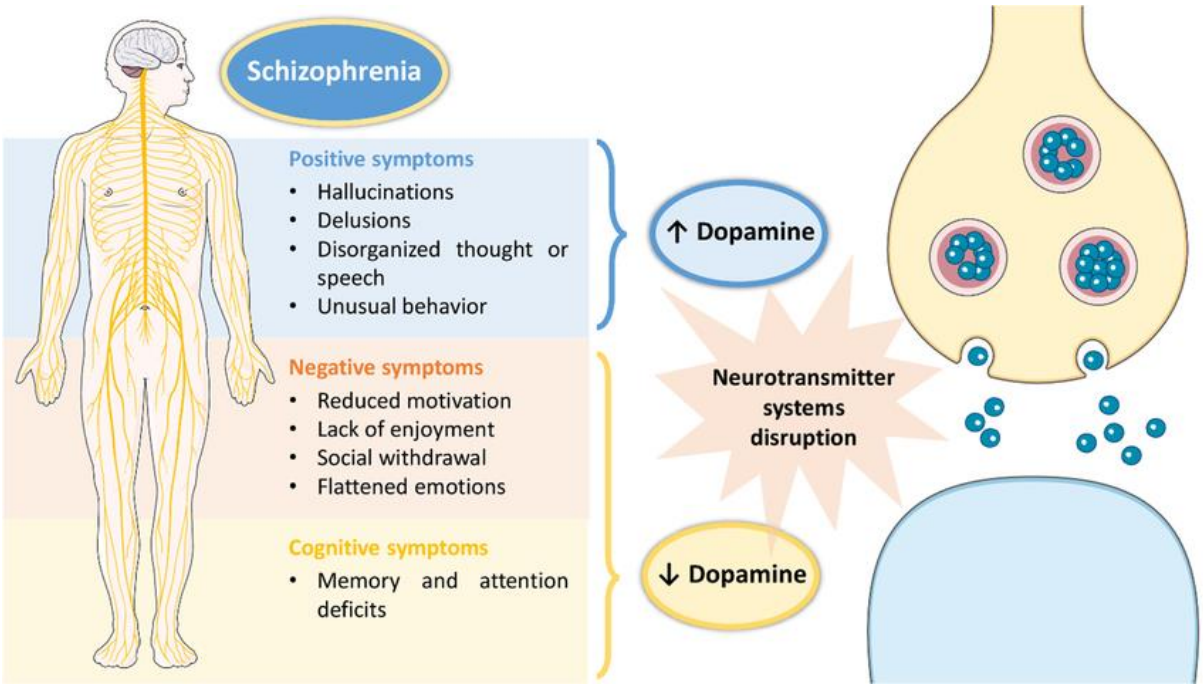

Figure 3 *Overall view of the symptoms of schizophrenia (Pires et al., 2022)*

1.3 Positive Symptoms of Schizophrenia

The positive symptoms related to this issue are delusions, hallucinations, uncommon manners of thinking, speech disability and peculiar way of behaving. Hallucinations are the impression of a tactile cycle without an outer source. They can be gustatory, olfactory, somatic, visual or auditory. The most common kind of hallucinations experienced by people with schizophrenia are auditory hallucinations, which can appear as music or other sounds as well as voices. Visual hallucinations include seeing items, individuals or lights that are not there. Patients with schizophrenia might have delusional clarification for their hallucinations because their perception of reality is impaired. Delusions are basically the beliefs that are not real, for instance accepting that somebody is infatuated with them in spite of no proof, with the belief that they have better capacities. Disorganisation is considered to be the central trait of schizophrenic patients. A patient's speech or behaviour may be disorganised, jumping from one subject to another or they may exhibit unpredictable agitation or childlike behaviour (Amber et al., 2020).

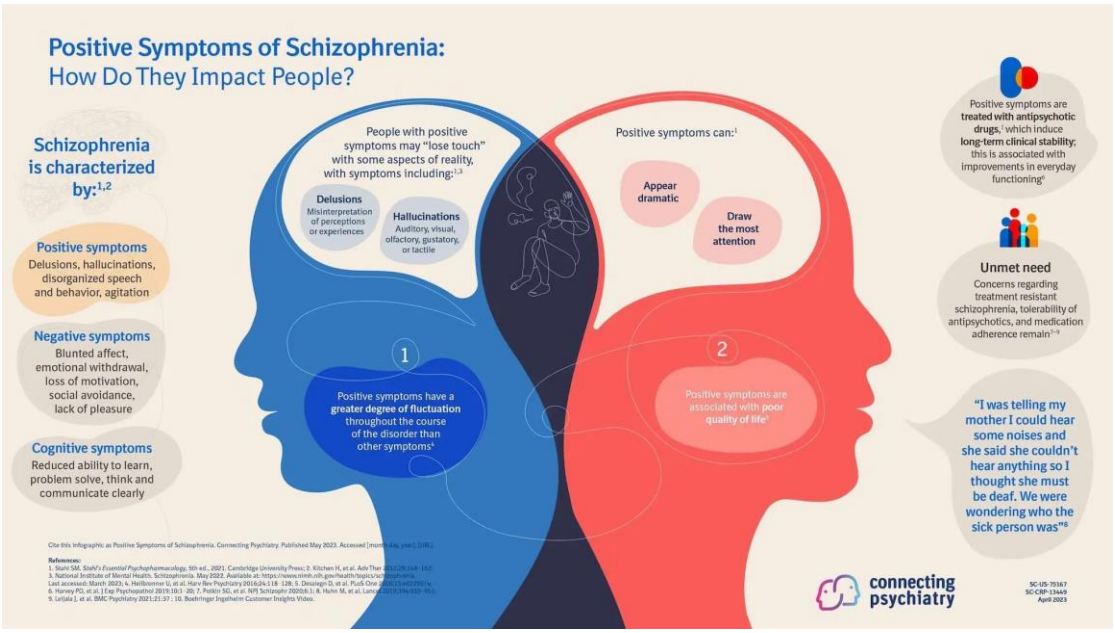

Figure 4 *Summary of positive symptoms of schizophrenia (Schizophrenia Primer 1 of 3: Positive Symptoms of Schizophrenia, n.d.)*

1.4 Negative Symptoms of Schizophrenia

As indicated by the Positive and Negative Syndrome Scale (PANSS), negative symptoms are shortfalls of emotions or other idea processes. These incorporate lessened emotional appearance and avolition and normally present five years before certain symptoms. The level of influence seen with schizophrenia is described by facial lethargy and diminished non-verbal communication. Avolition is described by the disability to start or go on in objective situated activities. This could show an indifference toward social collaboration (Amber et al., 2020).

Figure 5 *Negative symptoms of schizophrenia (Correll, 2019)*

1.5 Cognitive Symptoms of Schizophrenia

The cognitive symptoms in schizophrenic patients varry from being gentle to direct and do not normal example. No less than patients ranging from 60%-80% with schizophrenia have some gentle mental disablement. Probably the most generally disabled capabilities incorporate visual, attention and verbal learning, psychomotor speed, working memory and self-regulation. Among these, verbal learning and focusing ability will more often than not be more serious than the other mental dysfunctions. Executive functions are a vast array of processes that ultimately result in behaviour that is focused on achieving a goal. Patients with schizophrenia experience issues with arranging, critical thinking and adjusting to variations that ask a conduct response. This reasoning connects with troubles in word related and relational connections, which prompts the failure to fabricate fixed connections. It has been shown that the degree of cognitive symptoms is a more grounded indicator of a patient's capacity to work freely than the seriousness of psychopathology.

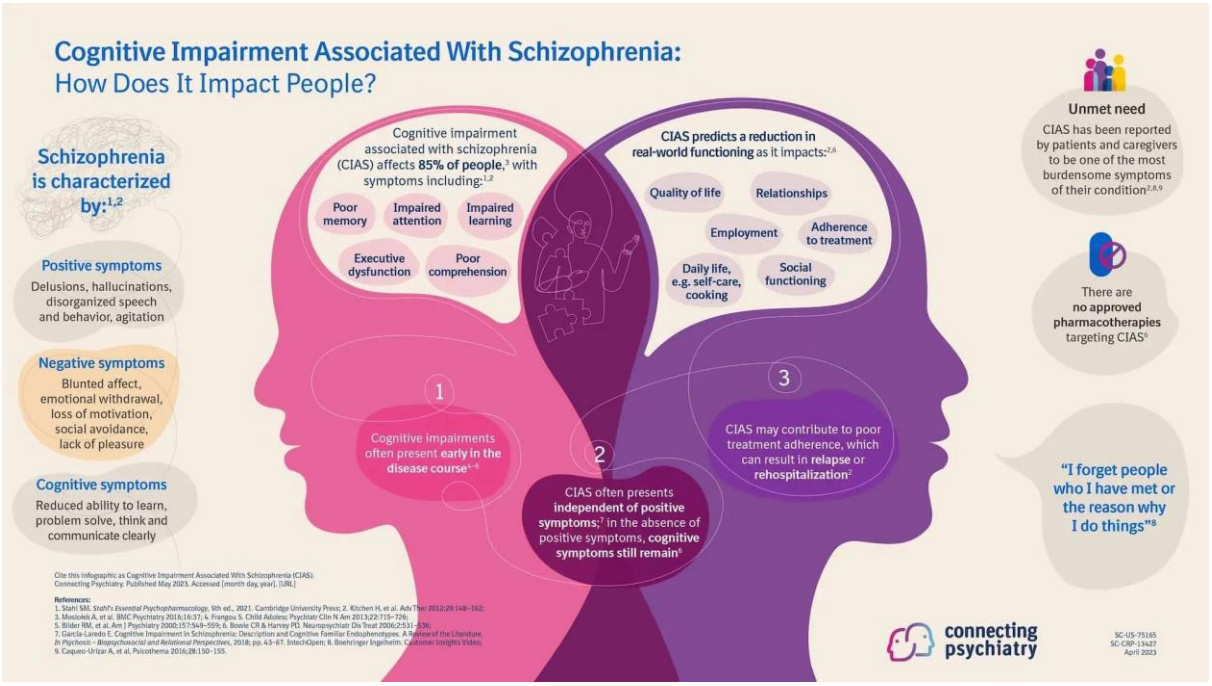

Figure 6 *Cognitive symptoms of schizophrenia (Schizophrenia Primer 3 of 3: Cognitive Impairment Associated With Schizophrenia (CIAS), n.d.)*

The earnestness of the social, profound and mental side effects in schizophrenia makes this such a debilitating issue. These properties leave patients ill-suited to dwell independently and are the clarification why patients with schizophrenia will undoubtedly be jobless, destitute and living in neediness (Amber et al., 2020).

1.6 Pathology

Schizophrenia energises from the changed development of dopaminergic, glutamate, serotonin, GABA and acetylcholine neurons. Most antipsychotic drugs focus on the strange degrees of dopamine which are a tireless element of schizophrenia. Schizophrenic patients have adjusted presynaptic dopaminergic ability causing extended presynaptic dopamine association and delivery. This dopamine extension is responsible for a development in D2 receptor establishment and is accepted to be a result of a disturbance in the mesolimbic pathway through the centre accumbens. The dopamine extended levels are connected with the incitation of positive aftereffects, counting hallucinations as well as delusions. Dopamine agonists actuate deranged secondary effects in regular subjects and those with schizophrenia. Dopamine trouble is one of the supplying variables of schizophrenia yet it does not make sense of the side effects as a whole, particularly mental disability. The mesocortical pathway interfaces the ventral tegmental region to the prefrontal cortex. Diminished enactment of the D1 receptor in the prefrontal cortex is believed to be an element of the negative side effects of schizophrenia.

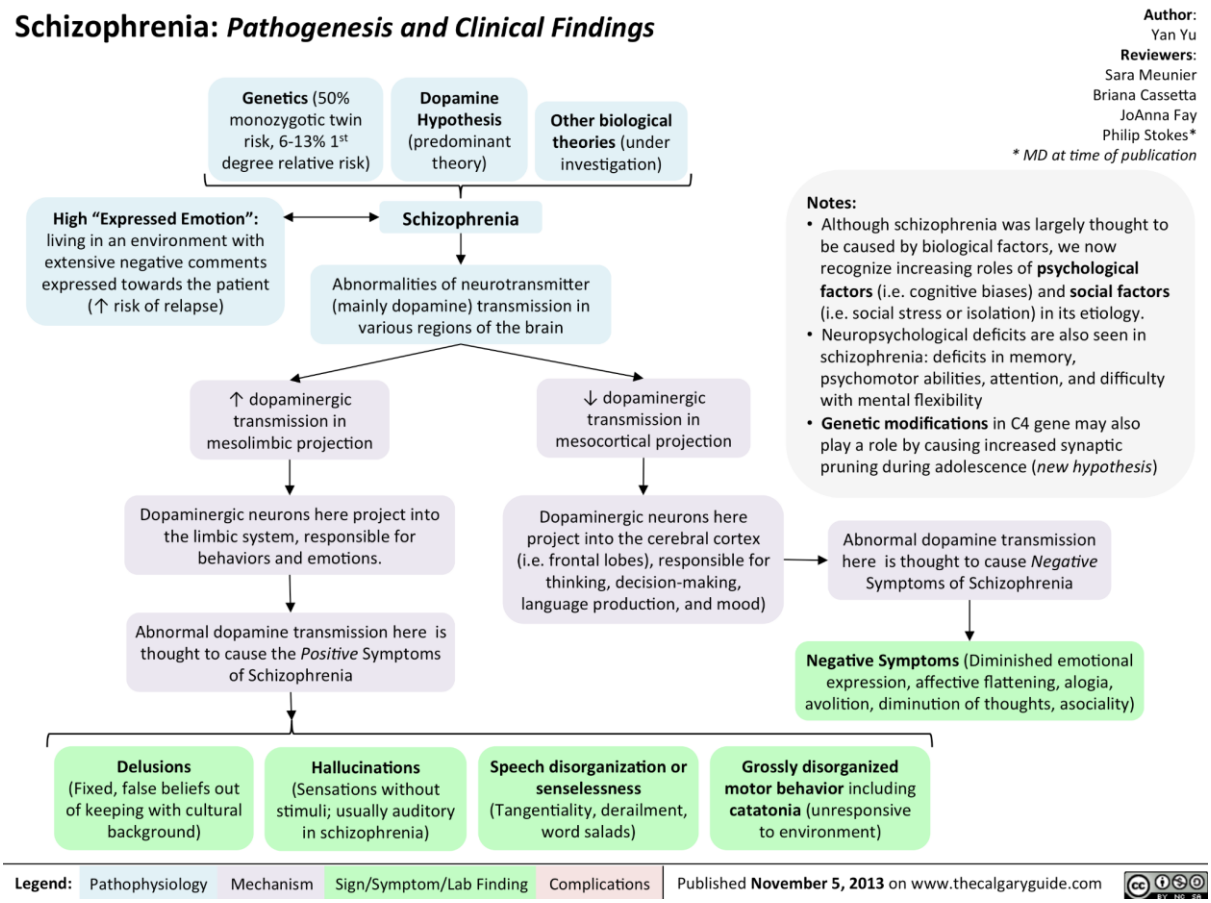

Figure 7 *Pathogenesis of schizophrenia and how it takes place (Yu, 2013)*

Glutamate is the most important excitatory neurotransmitter in the central nervous system (CNS) and the NMDA receptor is essential for attention, perception and cognition. This deficiency in glutamate neurotransmission, which is mediated by receptors like NMDA, is believed to be a donating component in mental disabilities and negative side effects in patients with schizophrenia. There are genes that recognize the factors which associate the danger of schizophrenia and the joint effort of the NMDA receptor.

Serotonin (5-hydroxytryptamine) is another major target for specific antipsychotics, especially the 5-HT2 receptors. The 5-HT2A receptors are locked in with the rule of numerous capacities, especially attitude and drive control. Any adjustment of this receptor's appearance or ability can

achieve the destabilisation of a patient's personality. The authorization of 5-HT2A receptors works with the appearance of dopamine in the mesolimbic pathway. The 5-HT2C receptor can change both mesolimbic and nigrostriatal dopamine development. Dopamine neurotransmission is repressed when the 5-HT2C receptor is actuated in the mesolimbic pathway. Specific restraint of the 5-HT2C receptor brought about expanded dopamine discharge. Any adjustment in the expression or function of the receptor will indirectly modify the discharge of dopamine. This turns the serotonin to be another vital component in adding to the symptoms of schizophrenia (Amber et al., 2020).

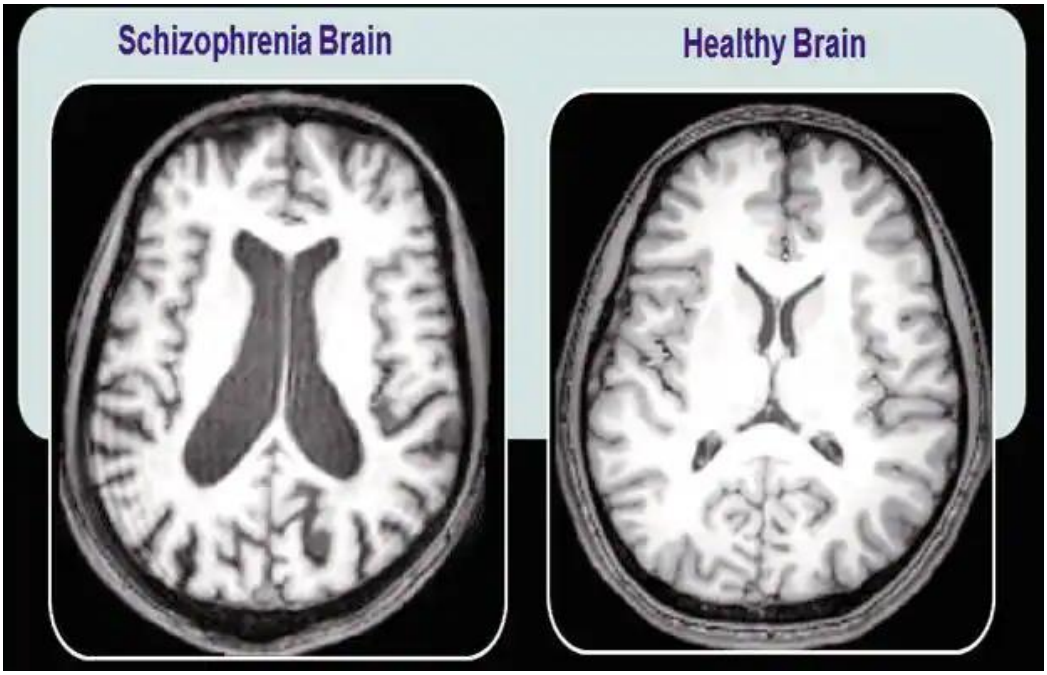

Figure 8 *The portrayal of schizophrenic brain in contrast to healthy brain (Mehta, 2014)*

1.7 Existing Treatments

Suggestive handling of schizophrenia by pharmacotherapy is the foundation of treatment, on a very basic level through drugs with antipsychotic efficacy. The antipsychotic drugs dominatingly regulate the receptors of dopamine but they can in like manner have influences at histaminergic,

adrenergic and muscarinic receptors. Most of the drugs are open in the form of oral design and numerous are available in a long-acting injectable structure (LAI), which is shown to be comparatively powerful. The LAI structure provides advantages of diminished hospitalisation chance and individual fulfilment over oral details. Because of the chronicity level of the ailment, the treatment of patients with schizophrenia should be ongoing with the help of an antipsychotic expert endlessly. The meds are strong, particularly for the treatment of positive aftereffects, yet these moreover bring out immense coincidental impact inconveniences that change depending on the drug being used. These aftereffects, combined with various components of activity, partition the antipsychotics into first, second, and third generations (Amber et al., 2020).

1.8 First-Generation Antipsychotics

The principal specialists made to treat schizophrenia are suitably named first-generation antipsychotics (FGAs). FGAs are partitioned among two parts, drugs with less potency (chlorpromazine, thioridazine) and drugs with peak potency (haloperidol, pimozide, fluphenazine). Their fundamental part of action is done by nonselective D2 receptor hostility in the cerebrum. FGAs are strong for the treatment of maniacal aftereffects but these are not as reasonable in regarding negative side effects as various classes of antipsychotics. Because of their non-selectivity, FGAs can cause prolactinemia and extrapyramidal incidental effects, for example akathisia, parkinsonism and tardive dyskinesia (Amber et al., 2020).

1.9 Second-Generation Antipsychotics

The process of activity, incidental effect profiles and adequacy of the second-generation antipsychotics (SGAs) differ from the FGAs. Quetiapine, risperidone, paliperidone, ziprasidone, olanzapine and clozapine are individuals from the SGA class. Anyway, they circle back to D2 receptors like FGAs and furthermore, have impact on various receptors, including D1, D3, D4, D5,

M1-4, adrenergic receptors, 5-HT1A, 5-HT2A and 5-HT2C receptors. SGAs have various advantages with further developed insight and cognition. Olanzapine, quetiapine, and risperidone made improvements in neurocognition. These are similarly less mindful to cause EPS in contrast to FGAs. One of the SGAs is more noticeable in comparison to others and that is clozapine. The others prominently cause metabolic aftereffects. Olanzapine is related with the advancement of diabetes and olanzapine as well as quetiapine are related with BMI rise. Additionally, prolactinemia can happen with different SGAs, especially amisulpride, risperidone and paliperidone (Amber et al., 2020).

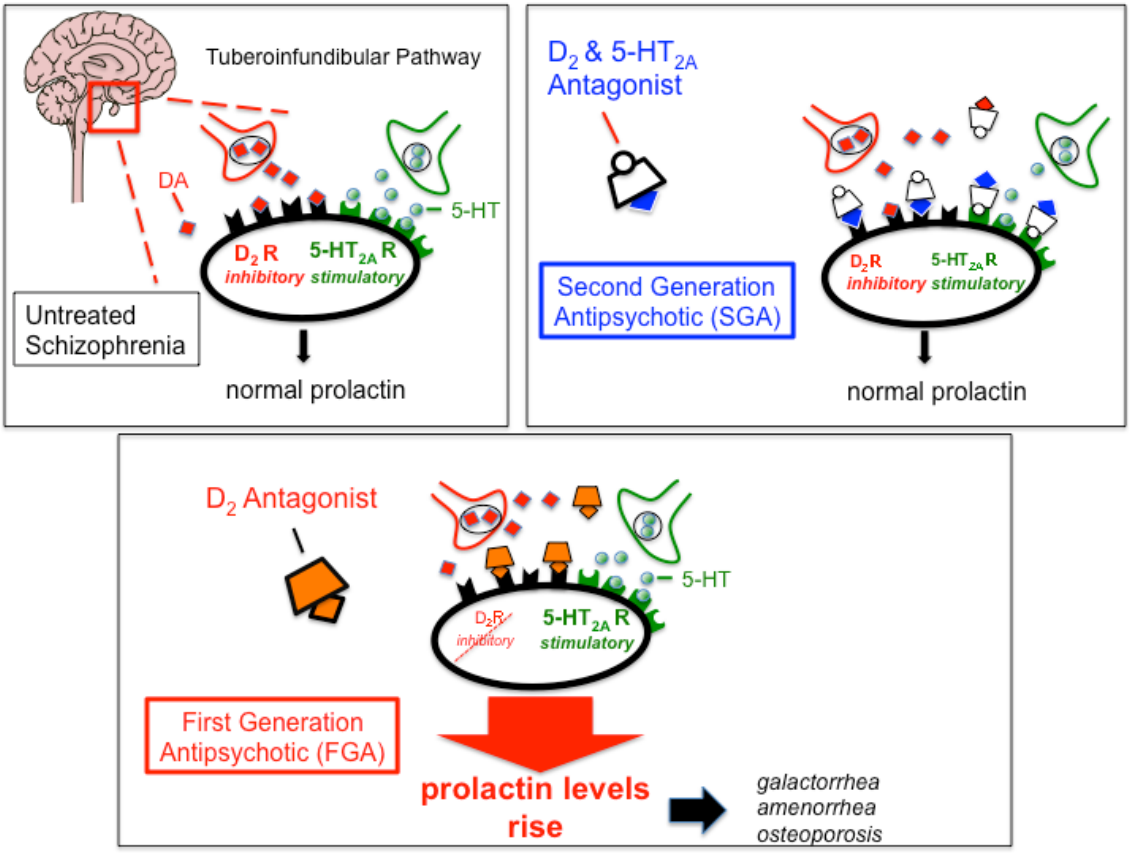

Figure 9 *Mechanism of action of FGAs and SGAs (Treatment of Schizophrenia, 2022)*

1.10 Third-Generation Antipsychotics

The class of antipsychotics that has only recently been discovered is known as the third-generation antipsychotics (TGA). They incorporate aripiprazole, brexpiprazole and cariprazine. TGAs function as practically specific, fractional D2 agonists to settle levels of dopamine and additionally are dynamic at various receptors of dopamine and serotonin. The extraordinary component of TGAs presents substantial advantages. Aripiprazole, brexpiprazole and cariprazine exhibited critical decreases in two of the positive as well as negative side effects of patients with schizophrenia. TGAs can prompt EPS and metabolic changes but these are not as severe as the aftereffects of FGAs and SGAs (Amber et al., 2020).

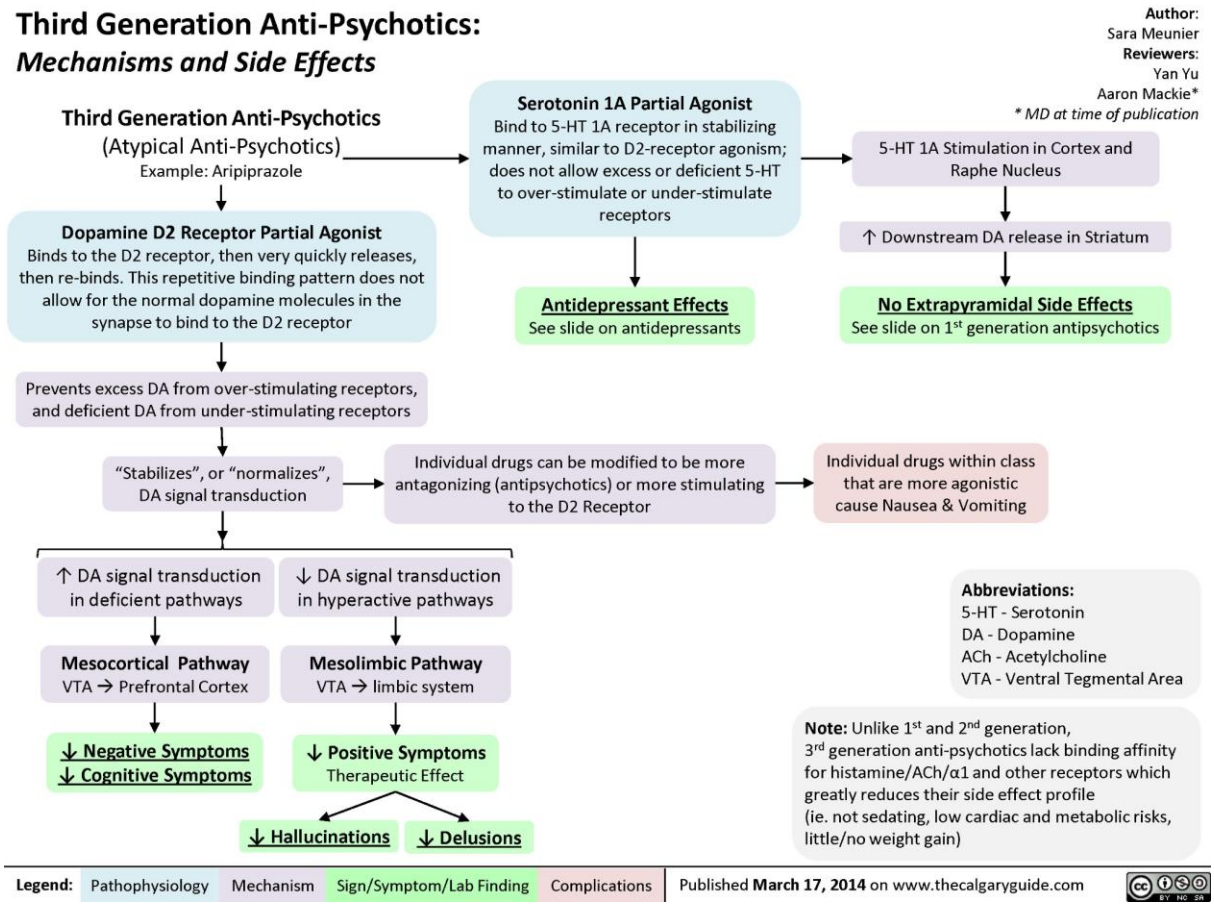

Figure 10 *Summary of TGAs (Meunier, 2014)*

Chapter 2: Novel Drug for Schizophrenia

2.1 Reasons for Developing New Drugs

- **Side Effects:** By and large, drugs used to treat schizophrenia have had many undesirable conclusions, especially akathisia and different other extrapyramidal incidental effects. Therefore, new drugs with novel mechanisms of action and significantly reduced side effect profiles, are needed to be introduced for the treatment of schizophrenia.
- **Metabolic Issues:** New medications are expected to treat various kinds of individuals because of the numerous ways they are processed. Different medications influence males and females distinctively due to their different science, while some are not reasonable for the grown-ups and small kids. As a result, several medications might be expected to treat people.
- **Minimal Expense Drugs:** More affordable medications are additionally expected for nations with less wealth who can not bear the cost of the more refined drugs. Since a disease may not be eradicated everywhere, less expensive medications are frequently required to treat people in less developed nations to prevent the reintroduction of diseases from other nations.
- **Drug Resistance:** The development of resistance is caused to some extent by the abuse of existing medications. So, newer treatments are needed (Trevelyan, 2021).

2.2 Lumateperone

A new antipsychotic that has been approved by the Food and Drug Administration (FDA) which has been ensured to provide to adults suffering from schizophrenia. Intra-Cell Treatments delivered

Caplyta (lumateperone) to the general population in March 2020. Caplyta is otherwise called ITI-007 in examinations, working through the process of antipsychotic drugs which ties at the receptors of serotonin as well as dopamine.

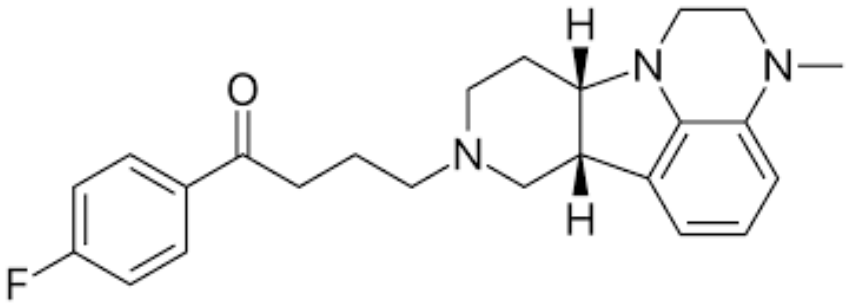

Figure 11 *Structure of lumateperone*

Figure 12 *Dosage form of lumateperone (Caplyta)*

As indicated by the FDA, lumateperone ought to be managed as a 42 mg oral measurement, once a day with food. The capsule has a blue cap and is opaque white with the label "ITI-007 42 mg."

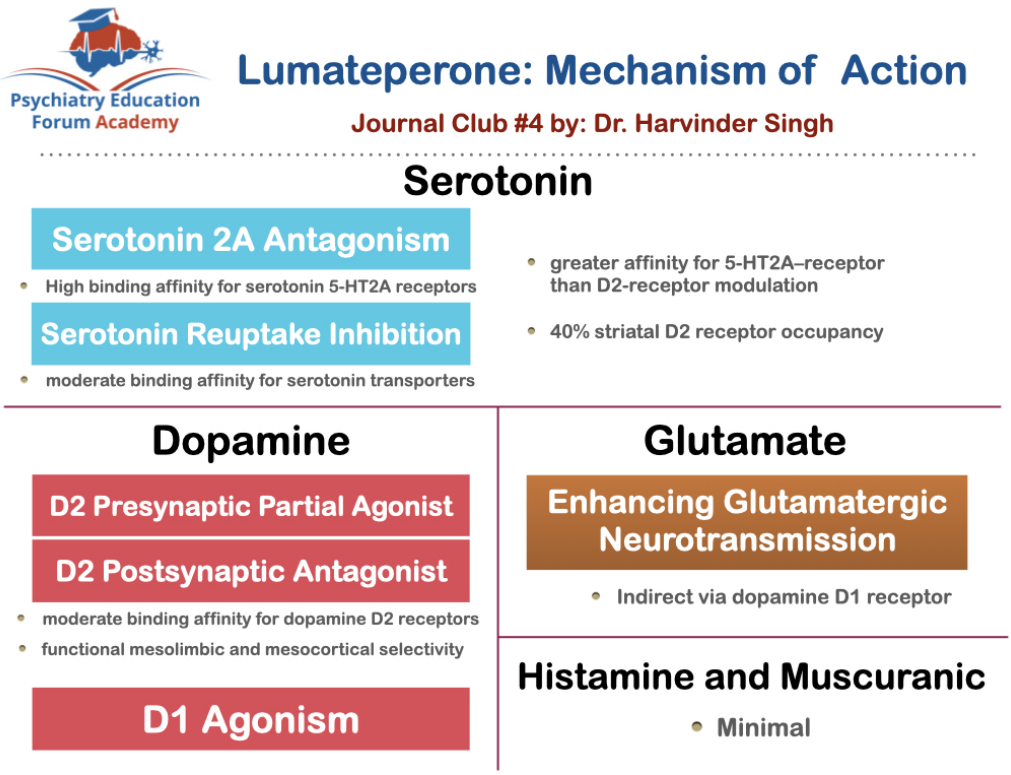

Figure 13 *The way lumateperone works (Singh, 2021)*

Right now, lumateperone is just shown for grown-ups and not recommended in the therapy of psychosis disorders like dementia. Not a single clinical examination noticed the safety and efficacy in paediatric or geriatric population, subsequently considered it to be in restriction for the people ageing between 18-65-year-old. Age, sex or race have not been found to have any effect differences in this population. On the label of lumateperone, there are a number of warnings and precautions to be aware of when prescribing the drug. Patients with moderate to extreme hepatic impairment are not recommended to take lumateperone. Additionally, awareness must be made among patients for the neuroleptic malignant syndrome, tardive dyskinesia, metabolic changes, leukopenia, orthostatic hypotension, falls and seizures that are potential side effects of lumateperone (Amber et al., 2020).

2.3 Aims and Objectives

This study is done through conducting clinical trials to determine whether lumateperone's short-term treatment of schizophrenia is safe and effective. Clinical studies show us what works and what does not in medication and medical services. These studies are intended to respond to a few significant inquiries-

- ➔ Does lumateperone work for individuals? Assuming it does, how well does it function
- ➔ Is it superior to the current treatment? If it is not, is it as great and causes less aftereffects?
- ➔ On the other hand, does it work in certain individuals where current medicines do not work?
- ➔ Is lumateperone safe?
- ➔ Do the advantages of this drug offset the dangers?
- ➔ Is this treatment better than the standard treatment given for schizophrenia?

Clinical studies show if another medication, treatment or another treatment mix works better compared to what is presently utilised. Responding to these inquiries, while giving few individuals an unknown treatment, frequently requires a few clinical studies in various stages. Each stage is intended to address specific inquiries while keeping the individuals safe in the participation. Results from these stages show if the new medication or treatment is sensibly safe and effective (Types and Phases of Clinical Trials, 2020).

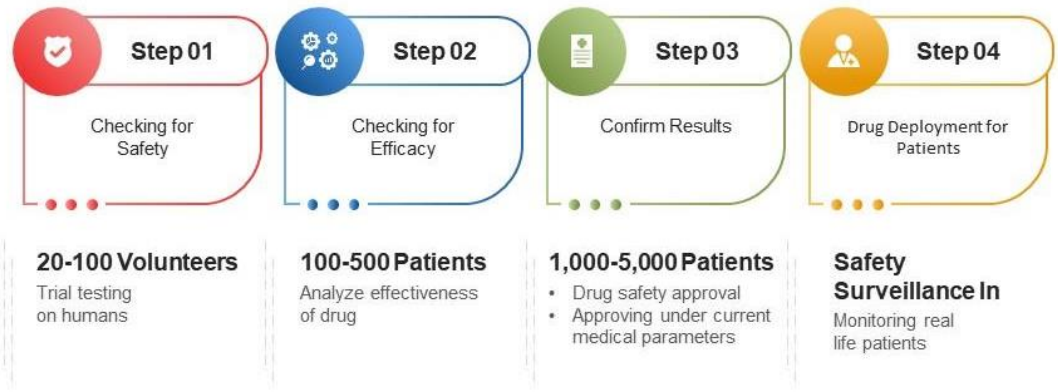

Figure 14 *Steps of how clinical trials take place (Types and Phases of Clinical Trials, 2020)*

Chapter 3: Methodology

3.1 Study Selection for Introduction

Table 1 *Study Selection*

Type	**Phase**	**Design**	**Condition**	**Intervention**
Interventional • Controlled trial • Double blinded • Placebo (Intervention Studies, n.d.)	Phase 3	Randomised	• Schizophrenia • Bipolar depression • Major depressive disorder.	• Lumateperone oral capsule • Placebo oral capsule (Clinical Trial Evaluating Lumateperone Monotherapy in the Treatment of Bipolar Depression or Major

				Depressive Disorder, 2023)

3.2 Criterias

Table 2 *Criterias*

Inclusion Criteria	**Exclusion Criteria**
Male or female individuals from any nation or region, ageing between 18-75.	Pregnant or breast-feeding women.
Matches the Diagnostic and Statistical Manual of Mental Disorder, DSM-5 criteria for Major Depressive Disorder, MDD.	Those individuals who are tested to be medically unfit to participate in the study.
At least two weeks, but no more than six months, has passed since the beginning of the current major depressive episode.	Patients having serious tendency to commit suicide.
The current episode of major depression is causing clinically notable suffering in social, occupational or other significant areas of functioning.	Patients having a lifespan record of epilepsy, electroencephalogram, seizure, dementia, delirium, amnesia or other cognitive disorder (Clinical Trial Evaluating Lumateperone Monotherapy in the Treatment of Bipolar Depression or Major Depressive Disorder, 2023).

Chapter 4: Results and Discussion

4.1 Results

Table 3 *Results*

Patient No.	**Disease**	**Intervention**	**Dose**	**Primary/ Secondary Endpoints**	**Side Effects**	**References**
N/A	Schizophrenia	Lumateperone	20 mg and 60 mg	Reduction in PANSS total score from baseline when compared to placebo.	Mild side effects were observed.	(Amber et al., 2020)
366	Schizophrenia	Lumateperone Tosylate	40 mg	The LSMD from baseline to day 28 was −2.6 (95% CI, −6.2 to 1.1; P = .16; ES, −0.2) on the PANSS total score and −0.2 (95% CI, −0.5 to 0.0; P = .02; ES, −0.3) on the CGI-S.	Samnolence, constipation, fatigue and convulsion.	(Christoph et al., 2020)

188	Schizophrenia	Lumateperone	42 mg	On the 43rd day, there was greater improvement from baseline in MADRS score compared with placebo (least squares mean difference compared with placebo, -4.6 points; effect size=-0.56) and CGI-BP-S total score (least squares mean difference compared with placebo, -0.9; effect size=-0.46).	Extrapyramidal sympyom, nausea, samnolence and less changes in weight, metabolism, vital signs as well as endocrine system.	(Joseph et al., 2021)
311	Schizophrenia	Lumateperone Tosylate	120 mg	LS Mean (± SEM) Change From Baseline on Day 28- −8.3 ± 1.68,	Weight gain, dry mouth, nausea, dizziness,	(Jeffrey et al., 2015)

				LS Mean Difference From Placebo (Rounded)- −.9, p Value- .708, Effect Size- .07.	somnolence.	
N/A	Schizophrenia	Lumateperone	60 mg and 120 mg	On the 28th day, total PANNS decreased from baseline when compared to placebo [Least squares mean change (LSMC) −13.2 points vs. −7.4 points; p = 0.017].	No side effects were seen.	(Amber et al., 2020)

4.2 Discussion

For lumateperone 20 mg and 60 mg, it was a six-week long study with risperidone or placebo, for patients with schizophrenia. Like the first preliminaries, the primary endpoint was a decrease in PANSS complete score from baseline when contrasted with placebo. Neither the 20 mg nor 60 mg dose of lumateperone was fundamentally different from placebo in decreasing PANSS complete score, separating the outcomes from the earlier two preliminaries. The specialists hypothesise that the high placebo reaction seen was answerable for the results (Amber et al., 2020).

For lumateperone tosylate 40 mg, the review included 450 patients (mean [SD] age, 42.4 [10.2] years; 346 [77.1%] male; mean [SD] baseline PANSS score, 89.8 [10.3]; mean [SD] baseline CGI-S score, 4.8 [0.6]). In the prespecified changed aim to-treat efficacy analysis (n = 435), 42 mg of lumateperone met the primary and key secondary efficacy objectives, exhibiting a genuinely huge improvement vs placebo from baseline to day 28 on the PANSS total score (least-squares mean difference [LSMD], −4.2; 95% CI, −7.8 to −0.6; P = .02; effect size [ES], −0.3) and the CGI-S (LSMD, −0.3; 95% CI, −0.5 to −0.1; P = .003; ES, −0.4). For 28 mg of lumateperone, the LSMD from baseline to day 28 was −2.6 (95% CI, −6.2 to 1.1; P = .16; ES, −0.2) on the PANSS total score and −0.2 (95% CI, −0.5 to 0.0; P = .02; ES, −0.3) on the CGI-S. Both lumateperone portions were very much endured without clinically critical unfavorable impacts or changes in cardiometabolic or endocrine elements vs placebo (Christoph et al., 2020).

For lumateperone 42 mg, at day 43, it was related with essentially more prominent improvement from baseline in MADRS score contrasted with placebo (least squares mean difference compared with placebo, -4.6 points; effect size=-0.56) and CGI-BP-S total score (least squares mean difference compared with placebo, -0.9; effect size=-0.46). In both bipolar I and bipolar

II patients, lumateperone outperformed placebo by a significant MADRS margin. The only treatment-emergent adverse events that occurred at a rate that was clinically significant higher with lumateperone than with placebo were somnolence and nausea. The frequency of extrapyramidal side effect related treatment-developing unfriendly occasions was low and like the placebo. Weight, vital signs and metabolic or endocrine assessments all changed little (Joseph et al., 2021).

For lumateperone tosylate 120 mg, (p = .017, impact size = .4) exhibited antipsychotic efficacy predominance over placebo on the primary end point. It improved negative and depressive symptoms, according to secondary analyses. It was very much endured in the patient population, as proven by low discontinuation and adverse event rates and was related to a harmless metabolic profile as confirmed by fundamentally lower levels of prolactin, fasting glucose, total cholesterol and fatty substances. LS mean (± SEM) changed from baseline on day 28- −8.3 ± 1.68, LS mean difference from placebo (rounded)- −.9, p value- .708, effect size- .07. Side effects were weight gain, dry mouth, nausea, dizziness and somnolence (Jeffrey et al., 2015).
For lumateperone 60 mg and 120 mg, on day 28, it fundamentally diminished total PANNS from baseline when compared to placebo [Least squares mean change (LSMC) −13.2 points vs. −7.4 points; p = 0.017]. In patients with depression at baseline, 60 mg lumateperone was displayed to fundamentally decrease both the PANSS sub-score, with a more prominent Effect Size (E.S.) (E.S. = 1.13) than risperidone (E.S. = 0.6) when contrasted to baseline. This outcome was reiterated in the CDSS score when contrasted to baseline (Lumateperone EF = .99; Risperidone E.F. = −0.46). 60 mg lumateperone was more effective than risperidone at reducing the PANNS negative subscale (E.F. =.34) in patients with severe negative symptoms. Outstandingly, 60 mg lumateperone likewise altogether decreased PANSS prosocial factor (E.F. = 0.6), demonstrating improved friendly way of behaving, while risperidone had a lower E.F. (E.F. = 0.4). For safety data, patients in the 60 and 120 mg lumateperone arms encountered

no serious treatment-emergent adverse events (TEAEs). There was no link between lumateperone and EPS or significant weight gain. Also, when contrasted with risperidone, lumateperone had fundamentally 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, $p = 0.023$) (Amber et al., 2020).

4.3 Comparison between Lumateperone and Standard Treatment

Table 4 *Comparison*

Lumateperone	**Standard Treatment**
Prescribed for bipolar disorder and schizophrenia (Comparing Caplyta vs Risperdal, n.d.).	Prescribed for autism, asperger syndrome, bipolar disorder, schizoaffective disorder, schizophrenia and mania.
Side effects are seen in higher doses.	Side effects are seen in lower doses.
Less effects on body weight.	Significant effects on body weight.
Metabolic variation is not common.	Metabolic changes are seen frequently.
Motoric function stays stable.	Moving capability is hampered.
Should not be taken with grapefruit, grapefruit juice or alcohol. These increase the chances of side effects.	Should not be taken with tea or cola. These increase the chances of side effects.
Prolactin is seen to be at a normal level.	Prolactin levels are imbalanced (Leslie, 2023).

Drug-drug interaction is high.	Drug-drug interaction is low.
Generic drugs are costly.	Generic drugs are found at affordable prices.
Disease interactions are low.	Disease interactions are high.

4.4 Why is Lumateperone better than the Standard Treatment?

Lumateperone effectively reduces dopaminergic signalling by acting as an agonist which works partially at the presynaptic receptor and an antagonist at the postsynaptic receptor, in contrast to old antipsychotic drugs, which works as antagonists to pre- and postsynaptic receptors of dopamine. Lumateperone likewise has been displayed to tie at the receptor of serotonin with an excessive partiality. As a result, this drug is mostly focused on treating schizophrenia. Additionally, it has flexibility over available doses. For example, a patient will only suffer from its adverse effects only if he/she takes a large amount of this particular drug. Smaller amounts do not cause harm to the body. So, it is safe in moderate doses. The efficacy profile of lumateperone is like those of most other first-line antipsychotics but it is remarkable in not being related with clinically significant consequences for body weight, metabolic factors, motoric capability or prolactin levels. All things considered, drugs utilised to medicate schizophrenia previously had a large number of undesirable end products, especially akathisia, the ECG QT span and different other extrapyramidal side effects. Lumateperone's introduction to the consumers develops an inventive source to handle schizophrenia highlighting both a proper process of activity and a notably diminished aftereffect profile. Furthermore, certain medication intake is possible while taking lumateperone since the drug-drug interaction level is very low. Consequently, it will not cause unwanted reactions in the body. Also, if a schizophrenic patient has another medical condition, it will not worsen the issue because

lumateperone is known to have low disease interactions. Moreover, this drug has been displayed to actually decrease both the positive and negative symptoms of schizophrenia. In comparison to other available treatments, such as risperidone, lumateperone is additionally known to reduce two of the groups of symptoms in a number of studies. All in all, lumateperone has been demonstrated to be ok for an expansive crowd and not for serious treatment-emergent adverse events (TEAEs) (Amber et al., 2020).

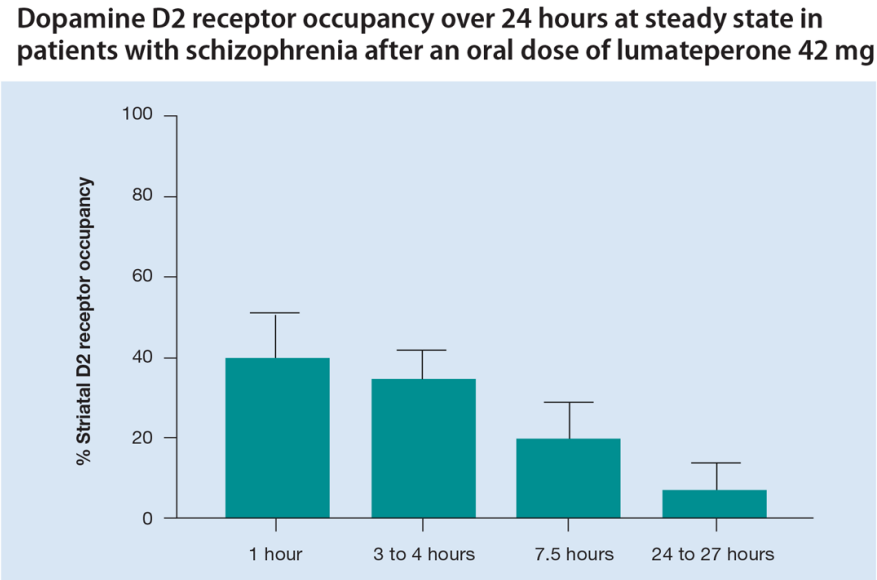

Figure 15 *Lumateperone for the treatment of schizophrenia (Meyer, 2020)*

Chapter 5: Conclusion

5.1 Future Studies

Orally managed antipsychotic drugs are the first-line treatment for psychotic issues, like schizophrenia and bipolar problems. However, adverse drug effects put clinical outcomes in jeopardy, leading to patient noncompliance. The plan detailing techniques for improving drug delivery systems to the brain has been a significant test, primarily because of the prohibitive characteristics of the blood–brain barrier. In any case, in vivo tests related to pharmacokinetic and pharmacodynamic processes affirmed the benefit of the intranasal route when contrasted with oral and intravenous administration, as it allows direct nose-to-frontal cortex drug transport through neuronal pathways, diminishing fundamental delayed consequences and helping remedial outcomes. Moreover, the administration of antipsychotic meds into nanosystems, for instance, polymeric nanoparticles, polymeric mixed micelles, solid lipid nanoparticles, nanostructured lipid carriers, nanoemulsions, nanoemulgel, nanosuspensions, niosomes and spanlastics have shown to ensure therapeutic value. The made nanosystems, having a bit and homogeneous particle size (ideal for nose-to-frontal cortex conveyance), high encapsulation proficiency and great solidness, turned out to have better brain bioavailability and therapeutic impacts in animal models. Subsequently, in spite of the fact that it is vital to proceed with research in this field, the intranasal delivery of nanosystems for the treatment of schizophrenia, bipolar disease and other related issues has shown to be very encouraging, opening a way for future treatments with higher viability (Ferreira et al., 2023).

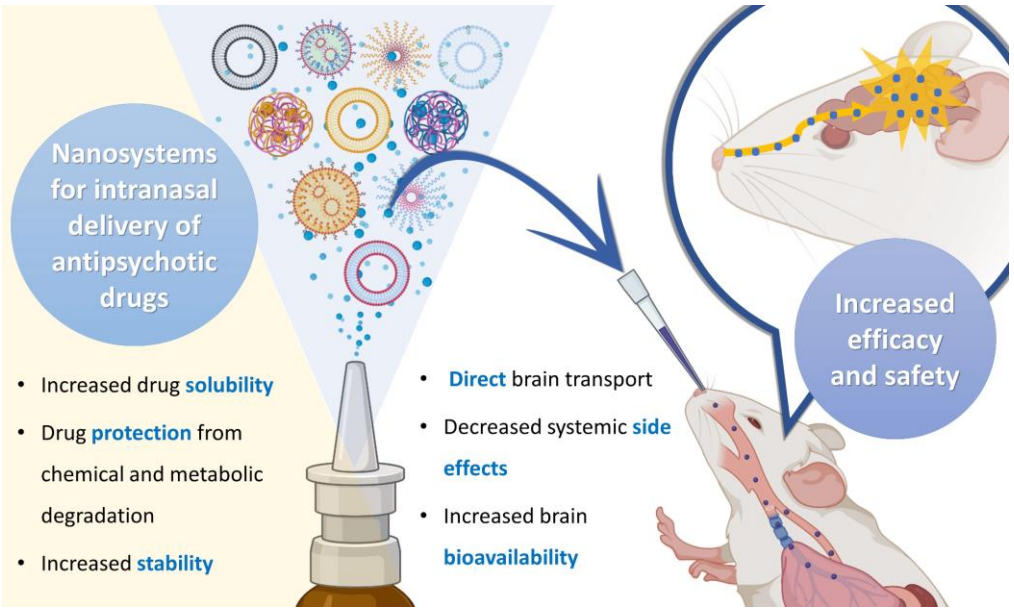

Figure 16 *How nanosystems work to target brain in case of antipsychotic drugs to ensure improved bioavailability and therapeutic efficacy (Ferreira et al., 2023)*

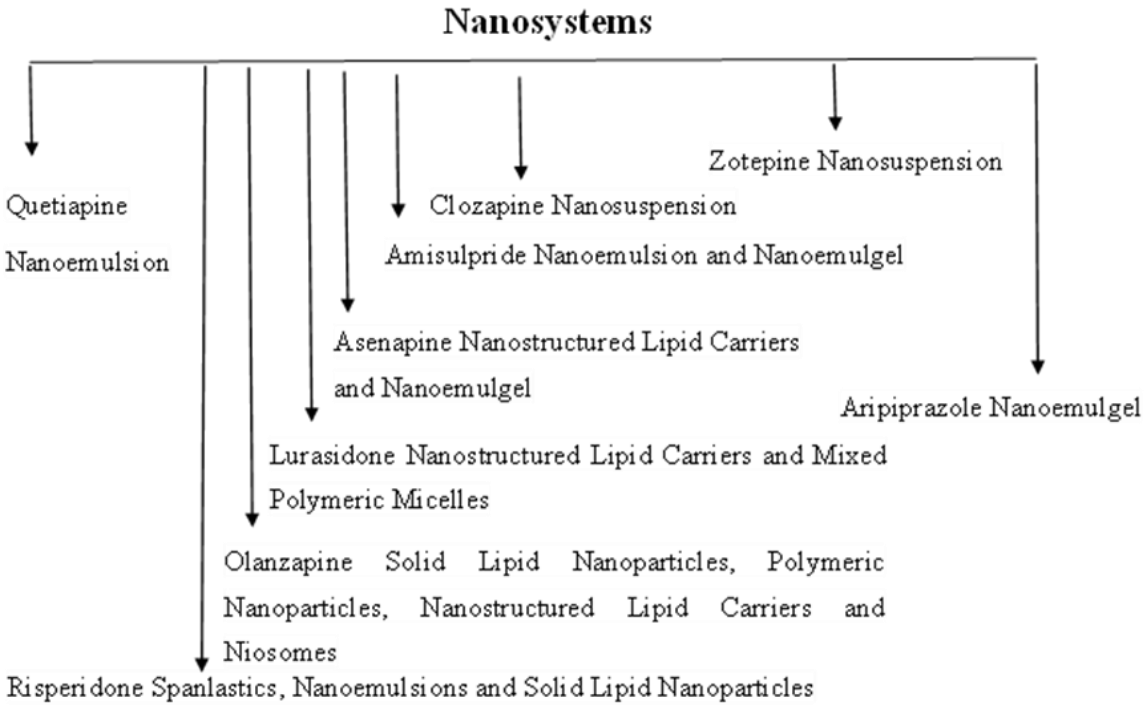

Figure 17 *Nanosystems for the existing antipsychotic drugs that proved to be therapeutic (Ferreira et al., 2023)*

5.2 Limitations of the Study

Firstly, no statistical analysis was done during the study. It is a qualitative research, fully based on real life situations. As a result, it has limited amounts of numerical data and mostly written in descriptions. Secondly, sample size variations are another limitation. In order to arrive at valid conclusions from a study, it is essential to have a large enough sample size. The bigger the example, the more exact the outcomes will be. Significant relationships in the data will be difficult to identify if the sample size is too small. Normally, statistical tests ask for a greater model size to ensure that the model is seen as illustrative of a populace and that the quantifiable result can be summarized to a greater populace. However, some clinical trials had smaller populations, leading to difficulty while comparing the results. Thirdly, certain resources could not be accessed. Since this study included assessing explicit people or affiliations, the issue of having limited availability to specific examination sources could be managed. However, as a result of this confined permission, there was a need to overhaul my investigation in another manner. Additionally, because of the lack of certain data, the scope of the study had to be restricted, which significantly hindered the process of finding some pattern. Furthermore, the limitation of methods to collect data was another barrier. Also, unreliable data made the study more complicated, leading to unpredictable and doubtful conclusions. So, the study was a little delayed. Finally, there were no similar endpoints which made it tough to compare between the results and come into a conclusion.

5.3 Conclusion

About 1% of people in general suffer from schizophrenia, a devastating condition that is often persistent. Based on the latest Global Burden of Disease study, it was found that out of 235 physical and mental health conditions, schizophrenia had the highest functional burden. While positive symptoms of schizophrenia, such as delusions and hallucinations, are frequently

improved by modern antipsychotic therapy, their effectiveness in treating negative symptoms, cognitive symtoms and social functioning is limited. To add to the already elevated morbidity and mortality linked to schizophrenia, current treatments are also linked to significant side effects, such as motor impairments, prolactin abnormalities, weight gain, metabolic disturbances and cardiovascular risk factors. An Investigational drug for schizophrenia that is mechanistically innovative is called lumetaperone (lumateperone tosylate, ITI-007). Lumateperone's mode of operation is distinct in that it modifies glutamate, dopamine and serotonin neurotransmission all at once, three important neurotransmitters linked to severe mental illness. Lumateperone specifically functions as a strong antagonist of the serotonin 5-HT2A receptor, a modulator of glutamate that is dependent on the D1 receptor, a postsynaptic partial agonist and agonist of the dopamine D2 receptor and an inhibitor of serotonin reuptake. This study included phase 3 clinical trial data which was randomized, double-blind and placebo-controlled. These trials assessed the safety and effectiveness of lumateperone therapy in individuals undergoing an acute exacerbation of schizophrenia. Thus, the study concludes that it is an effective medication for treating schizophrenia. Unlike other antipsychotics, it has a lower risk of causing adverse effects, especially at moderate doses. It does not significantly affect body weight, metabolic factors, motoric capability or prolactin levels. Lumateperone also has a minimal risk of drug interactions and does not worsen other medical conditions. Diminishing both the positive and negative side effects of schizophrenia, it has become a promising treatment option. Compared to other treatments like risperidone, lumateperone has demonstrated effectiveness in reducing symptoms. Overall, lumateperone is a safe and well-tolerated treatment for a wide range of patients.

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