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A REVIEW ON LUMATEPERONE ANTI-PSYCHOTIC DRUG

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Abstract:

Limitations of the study include the exclusion of patients with treatment-resistant illness, imminent suicidal risk, rapid cycling, or serious comorbid psychiatric or medical illnesses, which may limit the generalizability of the findings. This study only assessed lumateperone at 42 mg/day, so dose-response characteristics cannot be established, and it did not include an active treatment arm, so comparisons with other therapies are historical. Lastly, the safety data in this study are for short-term exposure; additional studies are needed to examine long-term safety in patients with bipolar disorder. Of note, lumateperone had a favorable safety and tolerability profile in a 1-year study in patients with stable schizophrenia

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INTRODUCTION:

Lumateperone is a medication used to manage and treat schizophrenia and other neuropsychiatric disorders. It is a second-generation atypical antipsychotic medication that exhibits a novel mechanism of action. Lumateperone's mechanism of action involves simultaneous modulation of dopaminergic, serotonergic and glutamatergic neurotransmission. This activity describes the indications, mechanism of action, and administration of lumateperone as a valuable treatment of schizophrenia. This activity will highlight the mechanism of action, adverse effect profile, and other key factors such as dosage and interactions for the interdisciplinary healthcare team responsible for treating individuals with schizophrenia and other neuropsychiatric disorders.

FIG-1

Drug Discovery:

The discovery of the role of 5HT-2A receptor antagonism in reducing the adverse motor effects caused by D2 receptor blockade has significantly improved treatment options available for those with schizophrenia. However, even with the repertoire of antipsychotics introduced in the past few decades, they have generally been more effective against positive symptoms rather than negative symptoms of schizophrenia. Additionally, they are associated with an increased incidence of adverse metabolic effects, such as weight gain and hyperprolactinemia. As a result, an antipsychotic with decreased incidence of side effects and a broader range of efficacy against schizophrenia would provide a valuable addition to current treatments.

One such medication, lumateperone, is a recently FDA-approved antipsychotic that provides a unique mechanism of action for treating schizophrenia. Clinical trials have found placebo-level metabolic adverse effects, a very low incidence of extrapyramidal symptoms, and potentially improved coverage of negative symptoms of schizophrenia. Its current indication is for managing acute schizophrenia, with clinical studies underway to determine its long-term safety and efficacy for this condition.

In addition to its favourable side effect profile, lumateperone demonstrates a unique pharmacodynamic profile not found in other second-generation atypical antipsychotics in that it interacts with glutamatergic pathways in addition to dopaminergic and serotonergic pathways. As a result, it provides a distinctive mechanism of action to treat schizophrenia.

Lumateperone effectiveness in treating acutely exacerbated schizophrenia has shown to be statistically significant vs. placebo in a four-week Phase II and Phase III clinical trial at 42 mg/day as well as a 6-week phase III trial.

There are also suggestions that patients currently stable on an antipsychotic may show symptomatic improvement when adding lumateperone as an adjunctive treatment.

Lumateperone has been studied for bipolar depression with positive outcomes in one trial, and in the other trial, lumateperone did not separate itself from the placebo.[9] A trial with lumateperone for agitation in patients with dementia was terminated; researchers determined that the trial would not meet the primary endpoints.

Lumateperone is currently approved for the treatment of schizophrenia in adults. In addition, it has also been approved as either a monotherapy or an adjunctive treatment with lithium or valproate for treating bipolar depression associated with bipolar I and II disorder.

New approaches in drug discovery:

Schizophrenia is a serious mental disorder with a lifelong prevalence of approximately 1% and a peak age of onset of 23-34 years in women and the early twenties in men. It is a very complex syndrome that involves widespread brain multi-dysconnectivity. It is characterized by cognitive, behavioural, and emotional dysfunctions. To fulfil the diagnostic criteria for schizophrenia, patients must exhibit two or more negative, disorganized, or positive symptoms that persist for a minimum of six months, and at least one symptom must be disorganized speech or a positive symptom. Positive symptoms include hallucinations and delusions; negative symptoms are

characterized by deficits in normal behaviour, including asociality, alogia, anhedonia, blunted affect, and avolition. There is a wide range of treatment possibilities; however, the effectiveness and/or adverse effects of antipsychotics with different pharmacological profiles vary. Successful treatment of schizophrenia is complicated by noncompliance and pharmacoresistance. The prevalence of pharmacoresistant schizophrenia is estimated to range from 12.9% to 48%.It has been estimated that approximately 20% of patients with schizophrenia receive combination treatment and/or antipsychotic polypharmacy. Augmentation strategies used in clinical practice include the addition of another antipsychotic, concurrent administration of benzodiazepines or mood stabilizers, repetitive transcranial magnetic stimulation, or electroconvulsive therapy.

The pathophysiological mechanism of the onset and progression of schizophrenia, the diagnostic neuropathology, and sensitive and specific biomarkers have not yet been identified. Several different hypotheses have been proposed to explain the neuropathology of schizophrenia that focus on environmental, genetic, neurodevelopment, and neurochemical effects. Research and development in imaging methods and in preclinical studies have led to the improvement of these theories. Positron emission tomography (PET) and single photon emission computer tomography enable *in vivo* quantification of dopaminergic functions in the brain and dopamine synthesis, release, and availability in postsynaptic dopaminergic neurons and transporters.

The targeting of existing and new drugs is based primarily on the dopamine and glutamate hypotheses of schizophrenia. All current antipsychotics modulate the function of the dopamine D_2 receptor. A nonlinear relationship between D_2 receptor occupancy, clinical response, and adverse effects of current antipsychotics was found. A small response to antipsychotic treatment appears at 50% dopamine receptor occupancy; as receptor occupancy increases, the response increases as well as the risk of extra pyramidal adverse effects. These findings were proven in a double-blind study in patients with first episode schizophrenia; 65% occupancy of D_2 receptors was the borderline between responders and non responders. Recently, research has focused on the prodromal phase of schizophrenia. Dopamine synthesis increases during the acute phase of the disease. Stress and other risk factors affect the dopamine systems, leading to their dysregulation and consequently to the development of psychotic disorder.

Excitatory glutamate neurotransmission occurs though ion tropic and metabotropic glutamate receptors. The glutamate hypothesis of schizophrenia is based on the dysfunction of the N-methyl-D-aspartate (NMDA) receptor. Currently, the effects of ketamine on brain function in healthy volunteers are being examined; studies are focused on glutamate concentrations in the brains of patients with prodromal symptoms during the first episode and other episodes of schizophrenia. Dysfunction of both NMDA receptors and presynaptic synthesis of dopamine has been implicated in the clinical symptoms of schizophrenia. Relationships between presynaptic dopamine dysfunction and positive symptoms and between glutamate dysfunction and negative and cognitive symptoms are expected.

To improve the diagnosis of schizophrenia, predict the therapeutic response to antipsychotics, develop new drugs, and personalize treatment, it is necessary to identify new specific and sensitive biomarkers of the disease. Blood-based biomarkers are regarded as a feasible option because the dysregulation of gene expression, epigenetic patterns, protein quantities, and metabolic and inflammatory molecules in peripheral blood have been shown to have distinct patterns in patients with schizophrenia. The aim of this review is to provide the newest insights into the pathophysiology and risk factors of schizophrenia and novel approaches to antipsychotic treatment.

GENETICS AND SCHIZOPHRENIA:

Schizophrenia is closely linked to genetic factors, including small nucleotide polymorphisms (SNPs), copy number variations and changes in gene expression. Combinations of different pathogenic mechanisms, including aberrant DNA methylation, altered histone code, dysregulated long noncoding RNA (lncRNA)-dependent tethering of epigenetic complexes to DNA, aberrant polyadenylation of pre-mRNAs, and mis-splicing, have been reported to play a role in schizophrenia development. The hereditary burden of schizophrenia is estimated to be approximately 80%. Genome-wide association studies (GWAS) have identified more than 100 loci, many of which contain multiple genes that are significantly associated with schizophrenia. The assessment of polygenic scores allows us to determine the risk of schizophrenia based on the number of risk alleles weighted by the odds ratio of each allele.

DNA methylation, an epigenetic process that produces 5-methylcytosine, is mediated by DNA methyltransferases and has a key role in several processes, such as imprinting, inactivation of the X-chromosome, silencing of transposons or regulation of genomic stability and chromatin structure. Schizophrenia is linked to pathophysiological DNA methylation of several genes, including those encoding reelin, catechol-O-methyltransferase (COMT), monoamine oxidase A, serotonin receptor 2A, the transcription factor SOX-10, and others. Unfortunately, no schizophrenia-specific "methylation panel" has been proposed, and it has not yet been clarified whether these changes represent causes or consequences of schizophrenia development.

Approximately 70%-80% of the genome is transcribed into noncoding transcripts, and the majority of schizophrenia-associated risk variants have been found in noncoding regions. LncRNAs can interact with DNA, RNA, and proteins, influencing transcription and posttranscriptional processes such as splicing, polyadenylation and/or regulation of transcript stability. MicroRNAs (miRNAs) are small noncoding RNAs that regulate more than 50% of protein-coding genes by acting as promoter or enhancer elements; miRNAs might participate in histone, DNA, or chromatin methylation and modification. Both lncRNAs and miRNAs can be affected by different genetic variants, especially SNPs, which could increase the risk of schizophrenia onset.

Microdeletions in chromosomal region 22q11.2 are one of the well-established genetic risk factors for schizophrenia and increase the risk of schizophrenia development to 30%-40%. COMT is a major dopamine catabolic enzyme, and its gene is located in this microdeletion region. In addition, a functional COMT polymorphism [valine/methionine (VAL/MET) substitution at codon 108] causes differences in its catabolic activity, dopamine baselines and stress-induced cortical dopamine release. The MET version of the allele is not as stable as the VAL version, causing decreased COMT activity and an increase in dopamine levels, especially in the prefrontal cortex.

The major histocompatibility complex (MHC) locus located on chromosome 6, which contains genes encoding proteins essential for adaptive immunity, has one of the strongest links to schizophrenia. Specifically, there was increased expression of complement component 4A (C4A). Sex differences in the *C4* gene could explain the higher male susceptibility to schizophrenia. Schizophrenia patients with higher C4 Levels were characterized as low responders or nonresponse's to antipsychotic medication. The expression of the genes encoding CSMD1 and CSMD2, which are important regulators of C4, has been found to be decreased in schizophrenia and connected with reduced cognition and executive function. Other immune receptors, including toll-like receptors (TLRs), which take part in microbe-derived molecular signalling, early brain development, synaptic plasticity, and neurogenesis, have been identified as schizophrenia susceptibility genes by GWAS. Both TLR2 and TLR4 were altered in the blood and brain tissue of schizophrenic patients.

The genes encoding for neuregulin 1 and neuregulin 3 are candidate schizophrenia genes and produce several possible proteins that influence neuronal differentiation and migration. The role of neuregulin 1 in schizophrenia is not well known, but increased neuregulin 1 signalling led to NMDA receptor hypo function (in accordance with the glutamate hypo function hypothesis of schizophrenia). There is no evidence of hyper expression of neuregulin 1 itself; however, the possibility of mutations causing the production of proteins with enhanced function is still present. Neuregulin 3 is a ligand for receptor tyrosine-protein kinase erbB-4 (ErbB4), and different genetic variants of the neuregulin 3 gene, especially the rs10748842 allele, relate to higher schizophrenia risk and cognitive impairment. Mutant mice with ErbB4 deletion from fast-spiking interneurons exhibited increased cortical excitability and oscillatory activity and desynchronized neurons in the cortical region probably caused by the disruption of the proper function of inhibitory GABA circuits in interneurons. These functional changes manifested in increased locomotion, impaired social and emotional behaviour, and cognitive dysfunction, which are common symptoms of schizophrenia.

The gene encoding dystrobrevin-binding protein 1 (also referred to as dysbindin or DTNBP1) has been identified as a gene associated with schizophrenia; however, no specific protein coding mutations increasing the risk of schizophrenia have been identified. Decreased dysbindin expression has been found in the brains of schizophrenia patients, and dysbindin risk haplotypes have been associated with increased negative symptomatology in schizophrenia.

The gene most closely linked to schizophrenia is probably the gene encoding the protein disrupted in schizophrenia 1 (DISC1), which has been associated with schizophrenia mainly due to a mutation causing a translocation between exons 8 and 9. The molecular mechanism of this mutation is not known, but the shortened mutant DISC1 protein is incapable of dimerization, and it may interact with other proteins. DISC1 expression is especially high during neurodevelopment in the late fetal and early postnatal phases, during which it participates in hippocampal development; however, DISC1 expression continues into adulthood. In schizophrenia pathophysiology, not only DISC1 itself but also its binding and interaction partners, such as microtubule-associated protein 1A, glycogen synthase kinase 3β, phosphodiesterase 4 and fasciculation and elongation protein zeta-1, might play a crucial role.

The synaptosomal-associated protein SNAP25 is involved in synaptic vesicle docking and fusion during neurotransmitter release. The promoter variant rs6039769 with the C risk allele caused an increase in SNAP25 expression, probably causing a larger amygdala and greater functional connectivity between the amygdala and ventromedial prefrontal cortex in male schizophrenic patients. This modulation in the plasticity of the prefrontal cortex-limbic connection caused higher schizophrenia risk.

The gene encoding transcription factor 4 (TCF4) is another GWAS-confirmed gene associated with schizophrenia. It encodes class I basic helix-loop-helix transcription factors and plays a role in neurodevelopment. Altered expression of TCF4 in the forebrain of a transgenic mouse caused altered cognition and long-term depression increased the density of immature spines. Many other genes have been associated with schizophrenia diagnosis and have been reported in the literature; description of all schizophrenia-linked genes is beyond the scope of this review.

TRIGGERS AND RISK FACTORS:

Environmental model of schizophrenia

The onset and severity of schizophrenia are always modulated by an interplay between genetic and environmental risk factors. Many epidemiological studies have investigated putative environmental risk factors for schizophrenia and peripheral biomarkers of the disease. According to an umbrella review of meta-analyses on risk factors and peripheral biomarkers for schizophrenia, history of obstetric complications, exposure to stressful events in adulthood or to childhood adversity, cannabis use, and serum folate level showed robust evidence of association with schizophrenia.

The prenatal and perinatal periods are characterized by great neural vulnerability to environmental insults. A recent systematic review and meta-analysis of 152 studies revealed numerous prenatal and perinatal risk factors, calculated with odds ratios (ORs), that were statistically linked to schizophrenia onset. The biggest risk factors for schizophrenia onset are any familial psychopathology, especially maternal psychosis (OR: 7.61). Maternal infections (herpes simplex 2, OR: 1.35; unspecified infections, OR: 1.27), a suboptimal number of antenatal care visits (OR: 1.83), or maternal stress (OR: 2.4) can lead to a higher prevalence of obstetric events (OR: 1.52), which are the longest-studied and best replicated environmental risk factors for schizophrenia. Significantly relevant obstetric events include maternal hypertension (OR: 1.4), hypoxia (OR: 1.63), premature rupture of membranes (OR: 2.29) and polyhydramniosis (OR: 3.05). There is experimental and clinical evidence showing significant risks of prenatal infection and inflammation for the later development of schizophrenia. According to the viral model of schizophrenia, prenatal viral and bacterial infections, and inflammation play an important role in the development of schizophrenia.

Nutritional deficits or famine in pregnancy (OR: 1.4) or more than two pregnancies (OR: 1.3) can be associated with reduced allocation or lower socioeconomic status. Another risk factor is congenital malformations (OR: 2.35). The most relevant postnatal environmental risk factors are childhood trauma (OR: 2.87), urban living (OR: 2.19), migration (2.10) and cannabis use (OR: 5.17), and these stress factors lead to the sensitization of the subcortical dopamine system.

Many genes relevant to schizophrenia, especially immune genes, can be altered by air pollution. Children with greater exposure to traffic-related air pollution had increased levels of proinflammatory cytokines. It is not yet clear whether air pollution itself causes brain changes or inflammatory changes caused by air pollution contribute to the pathology of schizophrenia.

A study of the roles of both genetic and environmental influences on the development of schizophrenia is necessary to explain the fact that in approximately 40%-55% of cases, monozygotic twins do not share a

diagnosis of schizophrenia. How genetic and environmental factors interact and the related neurobiological mechanisms that induce schizophrenia are not yet known.

Stress and schizophrenia:

The vulnerability-stress model of schizophrenia proposes that when stress exceeds the vulnerability threshold, an individual is likely to develop a psychotic episode. Stressful life events or psychological stress, especially in key periods of neurodevelopment, increase the risk of schizophrenia. These events include physical or mental abuse, lower socioeconomic status, urban environment, and neglect. The molecular mechanisms connecting these stressful situations with schizophrenia remain unclear. It was proven that patients with schizophrenia have altered cortisol function, and its release is linked to the inflammatory response rather than the anti-inflammatory response. Observation of HPA axis activation and cortisol release because of stress events in individuals with schizophrenia has produced inconsistent results; however, HPA axis dysfunction has been observed.

Neurons are extremely sensitive to redox imbalance during neurodevelopment and differentiation, mostly because of their high lipid content and metabolic rate. Increased reactive oxygen species (ROS) production and/or lowered antioxidant system capacity are considered risk factors for schizophrenia development. Increased protein and lipid oxidation and lowered levels of vitamin C and E, catalase, glutathione peroxidase and superoxide dismutase have been detected in schizophrenia patients. A study revealed that participants with low vitamin D3 Levels in the first year of life were at two times higher risk of schizophrenia. Glutamate-cysteine ligase is the rate-limiting biosynthetic enzyme of glutathione. One allelic variant of the GCLC gene is linked to the decreased activity of glutamate-cysteine ligase and schizophrenia. NMDA receptors are regulated by the redox state, and glutathione deficiency induces NMDA receptor hypofunction, which leads to cortical oxidative stress and glutathione decrease.

Neurodevelopmental model:

The neurodevelopmental model postulates that an increased risk of schizophrenia development is the result of abnormal brain neurodevelopment caused by genetic and environmental factors years before the onset of the disease. The hypothesis is based on clinical, epidemiological, brain imaging, and genetic studies. Schizophrenia is supposed to be a developmental disorder of the brain, and changes in brain neuroplasticity are involved. The disconnection hypothesis presumes the involvement of abnormal synaptic connections in the pathophysiology of schizophrenia. Impaired synaptic plasticity and synaptic efficacy, mainly in areas of the brain responsible for learning, memory, and emotion, participate in schizophrenia pathophysiology. Modulation of ascending neurotransmitter systems and consolidation of synaptic connections during learning are implicated in schizophrenia neuropsychology, especially in impaired adaptive behaviour and disintegrative aspects.

The unitary hypothesis of schizophrenia includes different types of pathophysiological models according to the hypothesis, early brain insults can lead to dysplasia of selective neural circuits, which is responsible for premorbid cognitive and psychosocial dysfunction in patients with schizophrenia. The onset of psychosis in adolescence may be associated with the excessive elimination of synapses with subsequent dopaminergic over activity. Decreased glutamatergic neurotransmission can predispose the brain to these processes. After the onset of the disease, these neurochemical changes can lead to further neurodegenerative processes. Brain plasticity includes both synaptic and nonsynaptic plasticity. The dysplastic model of schizophrenia suggests that impaired neuroplasticity during brain development may underlie cognitive and deficit symptoms and may lead to reorganization in other neuronal circuits, which may lead to affective and psychotic symptoms.

The multiple hit theory of schizophrenia presumes that schizophrenia can be conceptualized as a process involving multiple vulnerability factors across numerous neurodevelopment windows in which some hits are applied prenatally, in childhood, in adolescence, and in adulthood. Thus, the development of schizophrenia is driven by the interactions between genetic vulnerability and environmental influences (including prenatal vitamin D, nutrition, childhood trauma, viral infections, IQ, smoking, cannabis use, and social defeat), which are cumulative and interact with each other. The neurodevelopment phase involves changes in synaptogenesis, synaptic enhancement, and myelination, leading to excessive elimination of synapses and loss of neuroplasticity.

An extension of the neurodevelopment model proposes that the abnormal formation and maturation of connectomes (an extensive network of interconnected neurons) is central to the etiology of the disease. That is, abnormal anatomical architecture and

functional organization of the connective may be a final common pathway leading to the manifestation of schizophrenia symptoms. To further refine the developmental hypothesis of schizophrenia, progress in our understanding of brain connectivity during development and dysconnectivity resulting from genetic and environmental factors is necessary.

Oxidative stress and apoptosis:

Disconnection of the prefrontal cortex in schizophrenic patients is associated with abnormalities in white matter, oligodendrocytes, and myelin. Myelin is produced by mature oligodendrocytes, and oligodendrocyte precursor cells are extremely sensitive to oxidative stress. A redox-induced prefrontal oligodendrocyte precursor cell-dysfunctioning hypothesis of cognitive symptomatology in schizophrenia has been proposed. According to this hypothesis, the combination of environmental factors and genetic predisposition causes oxidative stress due to the excessive generation of ROS and reactive nitrogen species in oligodendrocyte precursor cells. Oxidative stress can lead to the down regulation of myelin-related genes in oligodendrocytes, decreased expression of myelin basic protein, and a reduced number of oligodendrocytes in the rat brain. During adolescence, a high concentration of ROS impairs the proliferation and differentiation of oligodendrocytes and their precursors. This leads to their dysfunction and hypomyelination and consequently to the disruption of connectivity in the prefrontal cortex. The resulting cognitive symptoms coincide with the onset of schizophrenia.

Additionally, oxidative stress induces dysregulation of the immune system and favours a proinflammatory response. Inflammation and disruption of immunity are other factors contributing to the pathogenesis of schizophrenia, as described in the following sections.

Mitochondria play a major role in cellular bioenergetics, oxidative stress, and apoptosis. According to the mitochondrial hypothesis of schizophrenia, mitochondrial dysfunction leads to distorted neuronal activity and plasticity, causing imbalanced brain circuitry and finally abnormal behaviour. Massive loss of white matter oligodendrocytes is a hallmark of schizophrenia. Therefore, it has been hypothesized that mitophagy is increased in oligodendrocytes in schizophrenia, which contributes to disease-related white matter neuropathology.

The intrinsic pathway of apoptosis is activated by intracellular signals generated during cellular stress and is triggered by the release of proapoptotic factors from mitochondria. Thus, consistent with the mitochondrial hypothesis, the apoptotic hypothesis postulates that apoptosis contributes to the pathophysiology of schizophrenia. The data indicate a dysregulation of apoptosis in several cortical areas in schizophrenia. The potential involvement of nonlethal localized apoptosis in the early stages of the disease is presumed.

NEUROCHEMICAL HYPOTHESES:

Dopamine hypotheses:

According to the classic (receptor) dopamine hypothesis of schizophrenia, psychotic symptoms are related to dopaminergic hyperactivity in the brain. Hyperactivity of dopaminergic systems during schizophrenia is the result of increased sensitivity and density of dopamine 2 (D_2) receptors. This increased activity can be localized in specific brain regions. The dopamine hypothesis does not assume that dopamine hyperactivity fully explains schizophrenia. Over activation of D_2 receptors appears to be only one effect of the overall dysregulation of chemical synapses in this disease.

The modified dopamine hypothesis assumes that schizophrenia is characterized by abnormally low prefrontal dopamine activity (causing negative symptoms) that leads to excessive dopamine activity in mesolimbic dopamine neurons (causing positive symptoms). Thus, this hypothesis presumes the co-occurrence of high and low dopamine activity in different neuronal circuits, which could explain the concurrent presence of positive and negative symptoms.

The unifying dopamine hypothesis of schizophrenia, called "the final common pathway", proposes that multiple environmental, genetic, and other risk factors (such as stress, drugs, or frontotemporal dysfunction) interact and result in striatal dopamine dysregulation, which alters signal transmission and leads to psychosis. This hypothesis combines dopamine dysfunction with other risk factors, including pregnancy and obstetric complications, stress and trauma, drug abuse, genetic predisposition and environment–gene interactions, with both increased presynaptic striatal dopaminergic function and other brain functions that underlie negative and cognitive symptoms.

A model has been presented of how genes and environmental factors may sensitize the dopamine system so that it is vulnerable to acute stress, leading to progressive dysregulation and the onset of psychosis. The main steps of this model are as follows: genetic risk factors lead to impaired glutamatergic regulation, followed by increased striatal dopamine release, aberrant salience, and psychotic symptoms. Acute psychosocial stress can activate increased striatal dopamine release both directly and indirectly *via* blunted cortical dopamine release and impaired glutamatergic regulation. The dopaminergic system interacts also with muscarinic cholinergic system and closely related muscarinic hypothesis of schizophrenia.

Glutamate hypotheses:

The glutamate hypothesis assumes that schizophrenia is caused by developmental abnormalities in glutamate synapse formation at specific sites, particularly at GABA interneurons in the cerebral cortex. These abnormalities may lead to subsequent excessive glutamate signaling to the ventral tegmental area (VTA), and excessive activation of this pathway may result in an excess of dopamine in the ventral striatum *via* the mesolimbic pathway. The role of dysregulation of glutamatergic neurotransmission in the pathophysiology of schizophrenia is supported by evidence from genetics, pharmacological, postmortem, and brain imaging studies. The convergence of GABA impairment and glutamate neurotransmission in the dorsolateral prefrontal cortex could explain the impairment of certain cognitive functions in schizophrenia.

The NMDA receptor hypofunction hypothesis assumes that genetic and other risk factors induce epigenetic alterations leading to NMDA receptor hypofunction in schizophrenia. NMDA receptor hypofunction induces a cascade of downstream disturbances in neuronal activity, calcium entry, and epigenetic machinery, leading to abnormal synaptic development and dopaminergic and GABAergic dysfunction. These changes in neurotransmission result in the cognitive and social deficits found in schizophrenia. According to this hypothesis, changes in the dopamine system are secondary to NMDA receptor hypofunction.

Antagonists of NMDA receptors (*e.g.*, phencyclidine) have been shown to cause symptoms similar to the positive and negative symptoms and cognitive defects in schizophrenia. According to increasing evidence, deficits in NMDA transmission are linked to cognitive defects and negative symptomatology.

Serotonin hypothesis:

There are 3 interconnected pathways hypothetically associated with hallucinations and delusions: (1) Dopamine hyperactivity at D_2 dopamine receptors in the mesolimbic pathway, which extends from the VTA to the ventral striatum; (2) NMDA receptor hypoactivity on GABAergic interneurons in the prefrontal cortex; and (3) Serotonin (5-HT) hyperactivity of 5-HT_{2A} receptors on glutamate neurons in the cerebral cortex. All 3 pathways can lead to hyperactivity of the mesolimbic dopamine pathway.

According to the serotonin hypothesis. the basic cause of schizophrenia is stress-induced serotonergic hyperfunction in the cerebral cortex, especially in the anterior cingulate cortex and the dorsolateral frontal lobe. The serotonin hypothesis assumes hyperfunction of 5-HT_{2A} receptors on glutamate neurons in the cerebral cortex. This overactivation of 5-HT_{2A} receptors may be due to an excess of serotonin, upregulation of 5-HT_{2A} receptors, or the effects of 5-HT_{2A} receptor agonists. Subsequent release of glutamate in the VTA may activate the mesolimbic pathway, resulting in excess dopamine in the ventral striatum.

Cannabinoid hypothesis:

According to the cannabinoid hypothesis, changes in the endocannabinoid system may contribute to the pathogenesis of schizophrenia. This hypothesis proposes that increased activation of the endocannabinoid system through CB_1 receptors on GABAergic interneurons in the ventral tegmental area, basolateral amygdala, and medial prefrontal cortex may lead to a hyperdopaminergic and hypoglutamatergic status, which may cause schizophrenia. The hypothesis was supported by evidence that cannabis use in adolescence is an independent risk factor for schizophrenia development (OR: 3.90) and by the confirmation of interactions between the cannabinoid and dopamine systems that may be related to the processes associated with drug addiction or schizophrenia.

CPCSEA GUIDELINES FOR THE CARE AND USE OF LABORATORY ANIMALS:

GOAL:

The goal of these Guidelines is to promote the humane care of animals used in biomedical and behavioural

research and testing with the basic objective of providing specifications that will enhance animal well-being, quality in the pursuit of advancement of biological knowledge that is relevant to humans and animals.

VETERINARY CARE:

Adequate veterinary care must be provided and is the responsibility of a veterinarian or a person who has training or experience in laboratory animal sciences and medicine. Daily observation of animals can be accomplished by someone other than a veterinarian; however, mechanism of direct and frequent communication should be adopted so that timely and accurate information on problems in animal health, behaviour, and well-being is conveyed to the attending veterinarian. The veterinarian can also contribute to the establishment of appropriate policies and procedures for ancillary aspects of veterinary care, such as reviewing protocols and proposals, animal husbandry and animal welfare; monitoring occupational health hazards containment, and zoonosis control programs and supervising animal nutrition and sanitation. Institutional requirements will determine the need for full-time or part-time or consultative veterinary services.

QUARANTINE, STABILIZATION AND SEPARATION:

Quarantine is the separation of newly received animals from those already in the facility until the health and possibly the microbial status of the newly received animals have been determined. An effective quarantine minimizes the chance for introduction of pathogens into an established colony. A minimum duration of quarantine for small lab animals is one week and large animals is 6 weeks (cat, dog and monkey) Effective quarantine procedures should be used for non-human primates to help limit exposure of human's zoonotic infections. Regardless of the duration of quarantine, newly received animals should be given a period for physiologic, psychological and nutritional stabilization before their use. The length of time stabilization will depend on the type and duration of animal transportation, the species involved and the intended use of the animals. Physical separation of animals by species is recommended to prevent interspecies disease physiological and behavioural changes due to interspecies conflict. Such separation is usually accomplished by housing different species in separate rooms; however, cubicles, laminar-flow units, cages that have filtered air or separate ventilation, and isolators shall be suitable alternatives. In some instances, it shall be acceptable to house different species in the same room, for example, if two species have a similar pathogen status and are behaviourally compatible.

SURVEILLANCE, DIAGNOSIS, TREATMENT AND CONTROL OF DISEASE:

All animals should be observed for signs of illness, injury, or abnormal behaviour by animal house staff. As a rule, this should occur daily, but more-frequent observations might be warranted, such as during postoperative recovery or when animals are ill or have a physical deficit. It is imperative that appropriate methods be in place for disease surveillance and diagnosis (Annexure 1 and 2). Unexpected deaths and signs of illness, distress, or other deviations from normal health condition in animals should be reported promptly to ensure appropriate and timely delivery of veterinary medical care. Animals that show signs of a contagious disease should be isolated from healthy animals in the colony. If an entire room of animals is known or believed to be exposed to an infectious agent (e.g. Mycobacterium Tuberculosis in non-human primates), the group should be kept intact and isolated during the process of diagnosis, treatment, and control. Diagnostic clinical laboratory may be made available.

ANIMAL EXPERIMENTATION INVOLVING HAZARDOUS AGENTS:

Institutions should have policies governing experimentation with hazardous agents. Institutional Bio safety Committee whose members are knowledgeable about hazardous agents are in place in most of the higher level education, research institutes and in many pharmaceutical industries for safety issues.

This committee shall also examine the proposal on animal experiments involving hazardous agents in addition to its existing functions (Annexure– 8).Since the use of animals in such studies requires special consideration, the procedures and the facilities to be used must be reviewed by both the Institutional Bio safety Committee and Institutional Animal Ethics Committee (IAEC).

DURATIONS OF EXPERIMENTS:

No animal should be used for experimentation for more than 3 years unless adequate justification is provided.

PHYSICAL RESTRAINT:

Brief physical restraint of animals for examination, collection of samples, and a variety of other clinical and experimental manipulations can be accomplished manually or with devices be suitable in size and design for the animal being held and operated properly to

minimize stress and avoid injury to the animal. Prolonged restraint of any animal, including the chairing of non-human primates, should be avoided unless essential to research objectives. Less restrictive systems, such as the tether system or the pole and collar system, should be used when compatible with research objectives. The following are important guidelines for the use of restraint equipments: Restraint devices cannot be used simply as a convenience in handling or managing animals. The period of restraint should be the minimum required to accomplish the research objectives. Animals to be placed in restraint devices should be given training to adapt to the equipment. Provision should be made for observation of the animal at appropriate intervals. Veterinary care should be provided if lesions or illness associated with restraint are observed. The presence of lesions, illness, or severe behavioral change should be dealt with by the temporary or permanent removal of the animal from restraint.

PHYSICAL FACILITIES:

(a) **Building materials**: should be selected to facilitate efficient and hygienic operation of animal facilities. Durable, moisture-proof, fire-resistant, seamless materials are most desirable for interior surfaces including vermin and pest resistance.

(b) Corridor(s): should be wide enough to facilitate the movement of personnel as well as equipment's and should be kept clean.

(c) Utilities: such as water lines, drain pipes and electrical connections should preferably be accessible through service panels or shafts in corridors outside the animal rooms. (d) Animal room: doors should be rust, vermin and dust proof. They should fit properly within their frames and provided with an observation window. Door closures may also be provided. Rodent barriers can be provided in the doors of the small animal facilities.

(e) Exterior windows: Windows are not recommended for small animal facilities. However, where power failures are frequent and backup power is not available, they may be necessary to provide alternate sources of light and ventilation. In primate rooms, windows can be provided.

(f) Floors: Floors should be smooth, moisture proof, non-absorbent, skid-proof, resistant to wear, acid, solvents, adverse effects of detergents and disinfectants. They should be capable of supporting racks, equipment, and stored items without becoming gouged, cracked, or pitted, with minimum number of joints. A continuous moisture-proof membrane might be needed. If sills are installed at the entrance to a room, they should be designed to allow for convenient passage of equipment.

(g) Drains: Floor drains are not essential in all rooms used exclusively for housing rodents. Floor in such rooms can be maintained satisfactorily by wet vacuuming or mopping with appropriate disinfectants or cleaning compounds. Where floor drains are used, the floors should be sloped and drain taps kept filled with water or corrosion free mesh. To prevent high humidity, drainage must be adequate to allow rapid removal of water and drying of surfaces.

(h) Walls and ceilings: Walls should be free of cracks, unsealed utility penetrations, or imperfect junctions with doors, ceilings, floors and corners. Surface materials should be capable of withstanding scrubbing with detergents and disinfectants and the impact of water under high pressure

PRECLINICAL STUDIES:

Bipolar I and bipolar II disorders are serious mental illnesses associated with a wide array of debilitating symptoms, including episodes of mania, hypomania, and depression .Depressive episodes in bipolar I and II disorders (bipolar depression) are more prevalent than episodes of mania or hypomania in most patients and are associated with greater disability and decreased quality of life. Currently, the second-generation antipsychotics cariprazine, quetiapine(and extended-release quetiapine), lurasidone, and olanza-pine in combination with fluoxetine are approved for the treatment of depressive episodes in bipolar I disorder .Treatment options for depression associated with bipolar IIdisorder are even more limited, with only quetiapine (and extended-release quetiapine) approved for treatment .Approved antipsychotics for bipolar depression are associated with a range of undesirable side effects, including cardiometabolic disturbances, motor impairments, and hyperprolactinemia .

These adverse effects are a major contributor to nonadherence with antipsychotic treatment. In addition, the use of psychotropic medications for bipolar disorder, including antidepressants and antipsychotics, is associated with increased risk for type 2 diabetes mellitus , metabolic syndrome , cardiovascular dis-ease , obesity, and movement and seizure disorders ,which exacerbate the already increased risk of cardiovascular disease, coronary heart disease, and cerebrovascular dis-ease associated with severe mental illness . The use of antidepressants in depressed patients with bipolar disorders of uncertain value and is associated with potential switch-in gintomaniain bipolar I disorder. Thus, antitreatment option that is effective for depressive episodes in both bipolar I and bipolar II disorders and has a more benign and favourable safety profile could improve patient outcomes, with lower morbidity and a

higher quality of life. Lumateperone (lumateperone tosylate), a mechanistically novel antipsychotic, is approved by the U.S. Food and Drug Administration (FDA) for the treatment of schizophrenia. Lumateperone simultaneously modulates serotonin, dopamine, and glutamate neurotransmission, the key neuro-transmitters implicated in serious mental illnesses .Lumateperone functions as a potent serotonin 5-HT2Areceptor antagonist, a dopamine D2receptor presynaptic partial agonist and postsynaptic antagonist, a D1receptor–dependent modulator of glutamate, and a serotonin reuptake inhibitor .

These properties, combined with lack of interaction with receptors that contribute to cardiometabolicside effects associated with other antipsychotic medications, make lumateperone an attractive candidate for the treatment of mood disorders. In late-phase controlled clinical trials in schizophrenia, lumateperone treatment for up to4 weeks was effective without significant extrapyramidal, cardiometabolic, or endocrine side effects compared with placebo. The favorable safety profile of 42 mg/day of lumateperone in schizophrenia was confirmed for up to1 year of treatment in an open-label clinical trial .In this multinational randomized double-blind placebo-controlled phase 3 study, we evaluated the efficacy andsafety of lumateperone for the treatment of major depressive episodes associated with bipolar I and bipolar II disorders.

METHODS:

Patients

Eligible participants were 18 to 75 years old, with a confirmed diagnosis of bipolar I or bipolar II disorder according toDSM-5, who were experiencing a major depressive episode. Patients were required to have depression of at least moder-ate severity, with a total score$20 on the Montgomery-Åsberg Depression Rating Scale (MADRS) and scores$4 on the depression and overall bipolar illness subscales of the Clinical Global Impressions Scale–Bipolar Version severity scale (CGI-BP-S) at screening and baseline.

The duration of the major depressive episode must have been at least2 weeks but less than 6 months before screening, and symptoms must have caused clinically significant distress or functional impairment. Patients were required to have a score#12 on the Young Mania Rating Scale (YMRS) at screening and baseline. Patients were recruited from the clinical practices of participating investigators or via institutional review board–approved recruitment materials to identify potential participants in their catchment areas.

Patients were excluded if they had a decrease$25% in MADRS score between screening and baseline, had a significant risk for suicidal behaviour, or had been diagnosed with apsychiatric illness other than bipolar disorder within 12months of screening. Additional inclusion and exclusion criteria are listed in the online supplement. All patients provided written informed consent as approved by the responsible institutional review board or independent ethics committee before participating in any study-related activities. Study Design, Intervention, and Randomization This was a 6-week multicenter randomized double-blind placebo-controlled outpatient study (NCT03249376) conducted at 54 clinical sites in six countries: the United States (14sites), Bulgaria (10 sites), Colombia (three sites), the Russian Federation (11 sites), Serbia (five sites), and Ukraine (11 sites).During a screening period of up to 2 weeks, patients eligiblefor participation discontinued their current antidepressant or other psychotropic treatment. At baseline, patients stratified by bipolar I or bipolar II diagnosis were randomized in a 1:1ratio to receive treatment with either 42 mg/day of lumateperone (equivalent to 60 mg/day of lumateperone tosylate)or placebo.

Patients were randomized using an interactive voice or web response system. Independent biostatistics personnel not participating in the conduct of the study generated permuted block randomization schedule for the interactive system, linking sequential patient randomization numbers to treatment codes. Lumateperone was administered via capsule, with or without food, once daily in the evening for 6weeks. Safety and efficacy assessments were conducted at weekly clinic visits (days 8, 15, 22, 29, 36, and 43) and at a final safety follow-up visit approximately 2 weeks after the last dose of study medication. Study medication adherence was calculated as the percentage of adherent days during the treatment period.

Adherent days were defined as days during the treatment period on which a patient took one capsule of study medication. This study was performed in accordance with the principles outlined in the Declaration of Helsinki and in compliance with Good Clinical Practice guidelines.

Measures and Procedures:

The primary and key secondary endpoints were the efficacy of 42 mg/day of lumateperone compared with placebo, measured by mean change from baseline to

day 43 in MADRS total score and CGI-BP-S total score, respectively.

CGI-BP-S total score was calculated as the sum of the CGI-BP-S sub-scores for depression, mania, and overall bipolar illness; the individual CGI-BP-S sub scores were also evaluated. Additional efficacy measures included response to treatment(defined as a decrease$50% in MADRS score), remission(defined as a MADRS score#12), improvement in MADRS. And CGI-BP-S scores by week of treatment, and percent score on the Quality of Life Enjoyment and Satisfaction Questionnaire–Short Form (Q-LES-Q-SF) . Safety was assessed by incidence of treatment-emergent adverse events(coded according to the Medical Dictionary for Regulatory Activities, version 20.1), clinical laboratory evaluations, ECG ,physical and neurological examination, and vital sign measurements. Extra pyramidal symptoms were assessed by the Simpson-Angus Scale, the Barnes Akathisia Rating Scale, and the Abnormal Involuntary Movement Scale.

Mania was monitored using the YMRS, and sociality was evaluated with the Columbia–Suicide Severity Rating Scale

Statistical Analysis:

Treatment effects on primary and key secondary efficacy end points were evaluated using a mixed-effects model for repeated measures in the prespecified modified intent-to-treat population, defined as all patients who received at least one dose of study medication and had a valid baseline MADRS assessment and at least one valid post baseline MADRS assessment. The model included visit, treatment group, site, and bipolar disorder stratification (bipolar I or bipolar II disorder)as factors. The patient term was included as a random effect, and baseline score was included as a covariate, with interaction terms for treatment group-by-visit and visit-by-baseline score. An unstructured covariance matrix was used to estimate the correlation of repeated measurements within a patient.

Sensitivity analyses for primary and key secondary end points used an analysis of covariance (ANCOVA), with missing data imputed using the last observation carried for-ward. To control the type I error rate for multiple comparisons of the primary and key secondary efficacy parameters, a fixed-sequence hierarchical gate keeping strategy with a two-sided significance level of 0.05 was used. Safety parameters were summarized descriptively by treatment group and visit in the safety population, defined as patients receiving at least one dose of study drug. Laboratory assessment summaries included by-visit and change from baseline values and incidence of patients meeting markedly abnormal criteria.

Exploratory analysis com-pared differences in prespecified clinical chemistry parameters between the lumateperone and placebo groups. In each treatment arm, 163 patients were expected to have evaluable data. The study was designed to have 85%power to demonstrate a clinically relevant treatment difference from placebo of 3 points in MADRS score, with a common standard deviation of 9.0, at a two-sided significancelevelof0.05. Statistical analyses were perform with SAS.

RESULTS:

Patient Population

Of the 546 patients screened for eligibility, 381 were ran-domized (lumateperone, N5191; placebo, N5190), and 377 received treatment and were included in the safety population (see Figure S1 in the online supplement). The average time from screening to randomization was 14.5 days(SD55.18). There were 376 patients in the modified intent-to-treat efficacy population (lumateperone, N5188; placebo, N5188); 333 patients completed the 6-week treatment period (lumateperone, N5167; placebo, N5166). The most common causes of discontinuation from treatment were adverse events (lumateperone, 5.8%; placebo, 2.6%) and patient withdrawal of consent (1.6% and 4.7%, respectively)(see Figure S1).Baseline demographic and clinical characteristics were similar between the lumateperone and placebo treatment groups

(Table 1).

Characteristic	Lumateperone group(N=188)		Placebo Group (N=189)	
	Mean	**SD**	**Mean**	**SD**
Age (Years)	46	14.1	44	12.9
	N	%	N	%
Male	18	47.3	69	36.5
Race				
White	173	92.0	171	90.5
Black	14	7.4	15	7.9
Asian	1	0.5	0	0.0
Other	0	0.0	3	1.6
Hispanic or Latino ethnicity	18	9.6	21	11.1
Bipolar disorder diagnosis				
Bipolar I disorder	150	79.8	151	19.0
Bipolar II disorder	38	2.0.2	38	20.1
Number of life time depressive episodes				
1-9	166	88.3	168	88.9
10-20	21	11.2	19	10.1
>20	1	0.5	2	1.1
	Mean	**SD**	**Mean**	**SD**
Age at first bipolar disorder diagnosis (years)	32.2	11.97	32.0	11.50
MADRS Total score	30.8	4.92	30.2	4.65
CGI-BP-S				
Total score	10.3	1.12	10.2	1.08
Mania sub score	1.1	0.25	1.1	0.28
Depression sub score	4.6	0.56	4.6	0.52
Overall bipolar illness sub score	4.6	0.55	4.5	0.52
Q-LES-Q-SF	37.0	12.53	38.6	12.25

Efficacy:

The majority of patients were White(91.2%) and had bipolar I disorder (79.8%). The overall population had moderate to severe depression symptoms at baseline, as indicated by a mean baseline MADRS score of30.5 and a mean CGI-BP-S depression sub score of 4.6 (30).The mean age at first bipolar diagnosis was 32.6 years(range, 5–63 years).

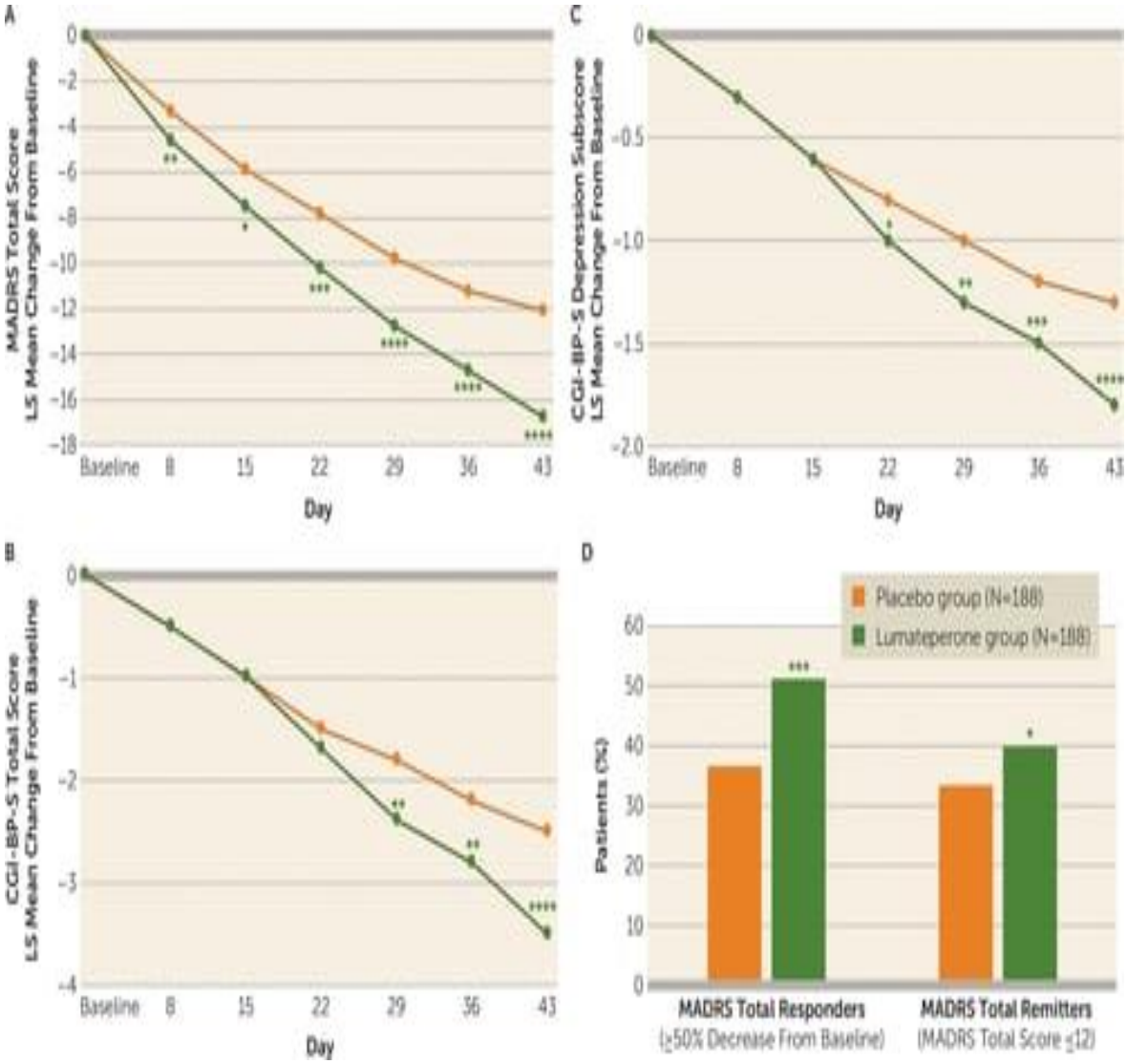
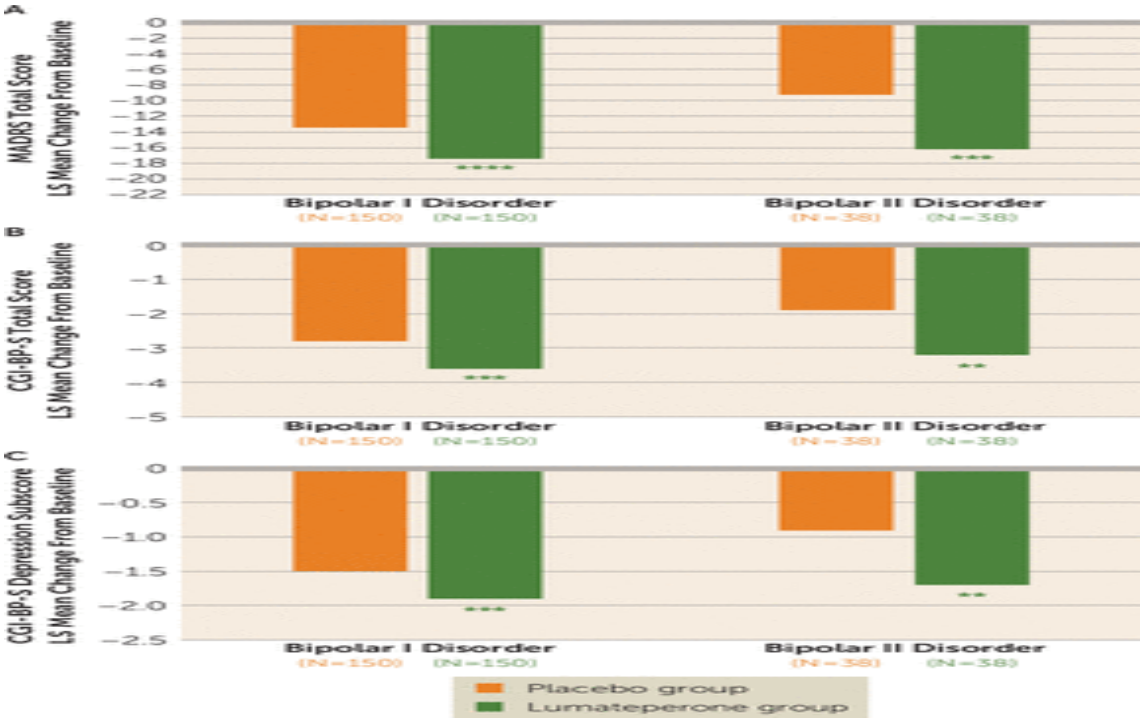


Table2

Measure	Lumateperone Group(N=188)		Placebo Group (N=188)		Comparison with Placebo			
	LS mean change	SE	LS mean change	SE	LS mean differ-rence	95% CI	Effect size	P
Primary efficacy measure: MADRS total score								
MMRM	-16.7	0.69	-12.1	0.68	-4.6	-6.342-2.83	-0.56	<0.0001
ANCOVA, last observation carried forward	-16.0	0.81	-11.3	0.78	-4.7	-6.402-2.95	-0.55	<0.001
Key secondary efficacy measure : CGI-BP-S total score								
MMRM	-3.5	0.17	-2.5	0.17	-0.9	-1.372-0.54	-0.46	<0.0001
ANCOVA, last observation carried forward	-3.2	0.20	-2.2	0.19	-1.0	-1.462-0.61	-0.49	<0.001
Other efficacy measure								
CGI-BP-S mania sub score (MMRM)	0.0	0.02	0.0	0.02	-0.0	-0.08-0.04	-0.08	0.448
CGI-BP-S depression sub score (MMRM)	-1.8	0.09	-1.3	0.09	-0.5	-0.75-0.30	-0.50	<0.0001
CGI-BP-S overall bipolar illness sub score (MMRM)	-1.7	0.08	-1.3	0.08	-0.4	-0.65-0.22	-0.43	<0.0001

Prior to treatment with study drug, 49.9% of patients were being treated with antipsychotics, antidepressants, and/or mood stabilizers; 50.1% of patients were not treated with these prior medications. In the modified intent-to-treat population, treatment adherence was99.7% for both groups, and none of the patients were nonadherent, defined as,80% or.120% adherence. EfficacyLumateperone treatment was associated with a statistically significant greater reduction in MADRS score from baseline to day 43 compared with placebo (least squares [LS].
Mean change,216.7; LSmeandifference comparedwithplacebo,24.6, 95% CI526.34, 22.83; effect size 520.56, p,0.0001)(Figure 1A).



Lumateperone significantly improved MADRS score compared with placebo as early as day 8, with continuing improvement throughout the study (Figure 1A). Improvement in MADRS score at day 43 with lumateperone was supported by an ANCOVA last-observation-carried-forward sensitivity analysis (LS mean difference,24.7, 95% CI526.4,23.0; effect size520.55, p,0.001, Table 2). Treatment with lumateperone resulted in significantly greater rates of response at day 43 compared with placebo (51.1% and 36.7%,respectively; p,0.001). Remission rates were also significantly higher at day 43 in the lumateperone group compared with the placebo group (39.9% and 33.5%, respectively; p50.018).There was significant improvement in the key secondary efficacy endpoint, change from baseline to day 43 in CGI-BP-S total score for the lumateperone group compared with the placebo group (LS mean change,23.5; LS meandifference,20.9, 95% CI521.37,20.51; effect size520.46,p,0.0001) (Figure 1B). ANCOVA last-observation-carried-forward sensitivity analysis of CGI-BP-S total score sup-ported the robustness of the primary analysis (LS meandifference,21.0, 95% CI521.46,20.61; effect size520.49,p,0.001) (Table 2). At day 43, lumateperone treatment compared with place bowasalso associated with significantly improved CGI-BP-S subscores for depression (LS mean dif-ference,20.5, 95% CI520.75,20.30; effect size520.50,p,0.0001) (Figure 1C) and for overall bipolar illness (LS mean difference,20.4, 95% CI520.65,20.22; effectsize520.43, p,0.0001) (Table 2). Change from baseline today 43 in CGI-BP-S mania subscore was minimal and similar to placebo (LS mean change, 0.0; LS mean difference,20.0, 95% CI520.08, 0.04; effect size520.08, p50.4). The Q-LES-Q-SF percent score was also significantly improved at day 43 in the lumateperone group compared with the placebo group (ANCOVA LS mean difference, 4.6, 95%CI51.42, 7.69; effect size50.31, p50.005).

Significant improvement in MADRS score in the lumateperone group compared with the placebo group at day 43was observed bothin patients with bipolar disorder (LSmean difference,24.0, 95% CI525.92,21.99; effectsize520.49, p,0.0001) and in those with bipolar II disorder (LS mean

difference,27.0, 95% CI5210.92,23.16;effect size520.81, p,0.001) (Figure 2A). There was also significant improvement in CGI-BP-S total score compared with placebo at day 43 in patients with bipolar I disorder(LS mean difference,20.9, 95% CI521.34,20.37; p,0.001)and bipolar II disorder (LS mean difference,21.3, 95%CI522.25,20.34; p,0.01) (Figure 2B). Significant improvement in CGI-BP-S depression subscore compared with placebo at day 43 was also observed in patients with bipolar I disorder (LS mean difference,20.5, 95% CI520.72,20.21;p,0.001) and bipolar II disorder (LS mean difference,20.8,95% CI521.25,20.26; p,0.01) . Consistent treatment effects were observed for MADRS score and CGI-BP-S total score in subgroups of sex, age (#40 years and.40 years), and age at illness onset (, 22 years and$22years).

Significant improvements in MADRS score in patientsin the lumateperone group compared with the placebo group were observed at clinical sites located both in the United States (LS mean difference,23.4, 95% CI526.83,20.02;p,0.05) and outside the United States (LS mean difference,25.2, 95% CI527.25,23.09; p,0.001).

Safety:

The rate of treatment-emergent adverse events occurring with lumateperone (54.8%) was similar to the rate with placebo (50.3%). Drug-related treatment emergent adverse events occurred in 41.5% of the lumateperone group and31.2% of the placebo group. The only treatment emergent adverse events occurring in the lumateperone group in atleast 5% of patients and at more than twice the rate of the placebo group were somnolence (lumateperone, 8.5%; placebo, 1.1%) and nausea (lumateperone, 6.4%; placebo, 2.1%).The majority of treatment-emergent adverse events were mild to moderate in severity, with four patients (2.1%) in the lumateperone group experiencing severe treatment-emergent adverse events, including insomnia (two patients, 1.1%), head-ache (one patient, 0.5%), and somnolence (one patient, 0.5%).

Treatment-emergent adverse events led to discontinuation of 11 patients (5.9%) in the lumateperone group and four patients (2.1%) in the placebo group. Treatment-emergent adverse events that led to discontinuation of at least one patient were mania (two patients [1.1%] in each group) and insomnia (two patients [1.1%] in the lumateperone group).The proportion of patients experiencing mania was low in both groups (lumateperone, 1.1%; placebo, 2.1%). Additionally, there was one case of hypomania (0.5%) in each group. There was one treatment-emergent serious adverse event of mania in the lumateperone group, which led to discontinuation. There was no worsening of mania in either group as measured by mean change from baseline to day 43 in YMRS score (lumateperone,21.4; placebo,20.9). Nine patients (2.4%)had a YMRS score$15 at any point during the study, with a similar proportion between groups (lumateperone, four patients [2.1%]; placebo, five patients [2.7%]).There was no suicidal behaviour in either group during treatment, as assessed with the C-SSRS. Baseline C-SSRS suicidal ideation was reported in 4.3% of patients in the lumateperone group and 7.9% of patients in the placebo group. C-SSRS–assessed suicidal ideation at any time during treatment was reported in 5.3% of patients in the lumateperone group and 10.1% of patients in the placebo group.

No patients died during the study. In the modified intent-to-treat population, as-needed zolpidem treatment for insomnia was reported in 1.6% of the lumateperone group and 3.2%of the placebo group.

The only extra pyramidal symptom related treatment-emergent adverse event was one case (0.5%) of mild dyskinesia in the lumateperone group, which started on day 43and was considered drug-related by the investigator. Per protocol, the final dose of lumateperone was on day 42. This patient had a history of tardive dyskinesia. There were no significant changes from baseline in Barnes Akathisia Rating Scale, Abnormal Involuntary Movement Scale, or Simpson-Angus Scale scores in either group. Concomitant benzodiazepine use was permitted and was reported in four patient in the lumateperone group(2.1%)and10patientsinthepla-cebo group (5.3%) during the study. Minimal changes in weight and body morphology were observed in both groups (Table 3). Potentially clinically significant weight decrease ($7% decrease from baseline)occurred in 1.1% of patients in the lumateperone group and in none of the patients in the placebo group.

In both treatment groups, 1.1% of patients had potentially clinically significant weight increase ($7% increase from baseline).There were no notable changes in cardio metabolic parameters, including in fasting levels of glucose, total cholesterol ,high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, triglycerides, and insulin (Table 3). There were no notable changes in endocrine parameters and no increases in prolactin in either treatment group (Table 3).No patients had a QTc (Fridericia corrected) interval.500ms at any time; rates of an increase of$60 ms from base-line were low and

were similar between the lumateperone(one patient, 0.6%) and placebo (three patients, 1.8%) groups.

Table3

	Lumateperone Group (N=188)				Placebo Group (N=189)			
Measure	**Mean at Baseline**	**SD**	**Mean change**	**SE**	**Mean at Baseline**	**SD**	**Mean change**	**SE**
Weight (Kg)	77.7	13.5	0.11	0.1	80.5	14.5	0.03	0.1
Body mass index	26.6	4.2	0.04	0.0	27.6	4.1	0.00	0.0
Waist circumference ((cm)	90.5	13.2	-0.47	0.5	93.1	14.9	-0.08	0.2
Cholesterol (mg/dl)								
Total	187.9	41.0	3.7	3.1	195.4	47.9	-1.0	2.8
LDL	111.9	35.0	3.7	2.6	116.8	39.4	-1.1	2.4
HDL	49.7	13.8	0.2	0.8	49.7	13.6	-0.2	0.9
Triglycerides (mg/dL)	136.6	73.0	-5.7	5.3	143.6	98.8	-3.7	5.9
Glucose (mg/dL)	96.7	17.6	-0.5	1.2	95.7	12.7	1.0	1.3
Insulin (mIU/L)	14.51	14.5	-0.06	1.4	17.44	21.0	-0.1	1.9
Prolactin (mg/L)	13.7	13.7	-0.8	1.1	15.1	15.8	1.7	1.3

DISCUSSION:

In this multinational randomized double-blind placebo-controlled study, treatment with lumateperone mono therapy at 42 mg/day was significantly associated with improved symptoms in major depressive episodes in patients with bipolar I or bipolar II disorder. Treatment with lumateperone was associated with a rapid and significant improvement in MADRS score by week 1 (at the first post dose assessment), with continuing improvements throughout the6-week study. The efficacy of lumateperone on MADRS score, the primary endpoint, was supported by improvements in CGI-BP-S total score, the key secondary endpoint. Sensitivity analyses based on ANCOVA with last observation carried forward confirmed the robustness of the mixed-effects model for repeated measures approach for MADRS score, and no demographic subgroup appeared to drive the overall efficacy. Significant improvement in MADRS score was observed in patients treated both at U.S. study sites and at sites in other countries. The efficacy of lumateperone in improvement of depression symptoms is similar to that of approved antipsychotic therapies for bipolar I and bipolar II depression. The overall reduction and the placebo-adjusted reduction in MADRS score for lumateperone treatment (mean change,216.7; LSmean difference,24.6) was similar to that reported in trials of approved monotherapies for bipolar disorder (mean change range,213.7 to219.6; LS mean difference range,22.5 to24.8) . The MADRS score effect size for lumateperone treatment compared with placebo was favorable at day 43 (20.56).Patient-level improvements supported the clinical relevance of lumateperone treatment. MADRS response rates for lumateperone (51.1%) were comparable to those reported for other FDA-approved treatments (MADRS response rate range, 39% to 65%). Significantly greater remission rates for lumateperone compared with placebo further sup-port the clinical efficacy of lumateperone. The significant improvements measured by MADRS score were also accompanied by clinically meaningful improvements in quality of life as measured by the Q-LES-Q-SF, which includes assessment of family and social relationships as well as overall.

Lumateperone treatment was effective in patients with both bipolar I and bipolar II disorders (MADRS score effect sizes, . in bipolar I disorder . In patients with bipolar II disorder, the MADRS score effect size with lumateperone treatment compared favourably with that of quetiapine treatment . Improvements in patients with bipolar II disorder were supported by significant improvements in CGI-BP-S total score and CGI-BP-S depression subscore. While this initial study of lumateperone had a relatively small number of participants with bipolar II disorder (38 per treatment group), improvements with lumateperone are notable, as quetiapine (and its extended-release formulation) is the only antipsychotic currently approved as a mono therapy for depressive episodes associated with bipolar II disorder.

However, quetiapine is also associated with a high burden of side effects, including extrapyramidal symptoms, moderate weight gain, sedation, and risk of metabolic syndrome. Treatment with 42 mg/day of

lumateperone for 6 weeks in patients with bipolar I or bipolar II disorder with an associated major depressive episode was well tolerated. In this study, treatment-emergent adverse events were predominantly mild to moderate in severity. Somnolence and nausea were the only adverse events in the lumateperone group that occurred at a clinically meaningful rate. There were no differences between the lumateperone and placebo groups in the incidence of either treatment-emergent mania or suicidal ideation, with a single serious adverse event of mania during treatment. No new safety signals were detected in patients with bipolar disorder. This safety profile is consistent with that of lumateperone at 42 mg/day for the treatment of schizophrenia in both short- and long-term clinical trials.While lack of tolerability, often due to extrapyramidal symptoms and weight gain, is cited as a major driver of anti-psychotic non adherence , lumateperone was not associated with extrapyramidal symptoms. There was only one case of mild dyskinesia, in a patient who had a history of extrapyramidal symptoms and oral dyskinesia, with exacer-bation of dyskinesia and exacerbation of extrapyramidal symptoms reported after completion of day 42 of lumateperone treatment. There was no significant increase from base-line with lumateperone treatment in Barnes Akathisia Rating Scale, Abnormal Involuntary Movement Scale, and Simpson-Angus Scale scores at day 43. In comparison to no incidences of akathisia reported for lumateperone in this study, higher rates of akathisia have been reported with quetiapine (1.5%–4%), lursidone (8%–11%), and cariprazine(6%–10%) (4–7) in clinical bipolar depression trials. Weight, waist circumference, and body mass index were also stable for the duration of this short-term study of lumateperone treatment.

As patients with bipolar disorder are vulnerable to cardiovascular disease and metabolic syndrome, the cardio metabolic profile of lumateperone is an important consideration when selecting treatment. The lumateperone treatment group in this study had no meaningful increases in levels of triglycerides, cholesterol, insulin, or glucose, suggesting that it is not associated with an increased risk of metabolic syndrome. Additionally, there was no evidence of hyper prolactinemia in the study, which are associated withmany second-generation antipsychotics. The safety pro-file of lumateperone may be due to its unique mechanism of action, with minimal binding to histaminergic or muscarinic receptors, which have been associated with cardio metabolic effects and other tolerability issues of existing antipsychotics.

Limitations of the study include the exclusion of patients with treatment-resistant illness, imminent suicidal risk, rapid cycling, or serious comorbid psychiatric or medical illnesses, which may limit the generalizability of the findings. This study only assessed lumateperone at 42 mg/day, so dose-response characteristics cannot be established, and it did not include an active treatment arm, so comparisons with other therapies are historical. Lastly, the safety data in this study are for short-term exposure; additional studies are needed to examine long-term safety in patients with bipolar disorder. Of note, lumateperone had a favorable safety and tolerability profile in a 1-year study in patients with stable schizophrenia

In summary, 42 mg/day of lumateperone significantly improved depression in patients with bipolar I or bipolar II disorder experiencing an acute major depressive episode. Six-week treatment with lumateperone was generally well tolerated, with low risk for extrapyramidal symptoms and minimal adverse effects on metabolic parameters, prolactin, or weight. Lumateperone's clinical profile indicates that it is a promising treatment option for major depressive episodes associated with bipolar I or bipolar II disorder.

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