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Lumateperone for the Management of Bipolar Depression

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ABSTRACT
Lumateperone is a new FDA-approved drug for the treatment of schizophrenia and depressive episodes ofbipolar I and II disorder. A literature review signifies that the lumateperone 42 mg once daily, administeredas a monotherapy or adjuvant therapy with lithium was helpful in managing the symptoms of schizophreniaand bipolar disorder. Clinical trials were used to evaluate the efficacy of lumateperone, by assessing theMontgomery- Aberg depression rating scale (MADRS) and clinical global impressions scale-bipolar versionseverity scale (CGI-BP-S). Safety assessment of lumateperone was assessed by adverse events andextrapyramidal symptoms. Extrapyramidal symptoms of lumateperone are low which is similar to that ofplacebo. According to the trials, this review concludes that the lumateperone 42mg was effective indepressive symptoms which are commonly associated with bipolar I and II disorder.

Keywords: CGI-BP-S, MADRS, schizophrenia, bipolar i and ii disorder, lumateperone

INTRODUCTION AND BACKGROUND

Periodic episodes of mania/hypomania and depression are characteristics of bipolar disorders, which arepsychiatric conditions. Bipolar I, II, and sub-threshold bipolar disorders affect 2 percent to 4 percent of thegeneral population on a lifetime basis [1]. Approximately 1-2% of people have this condition. Bipolar IIseems to be more prevalent in women, although bipolar I affect both men and women. Bipolar disorders aredivided into several subgroups based on the intensity and frequency of episodes. Rapid cycling (four or moreepisodes of mania, sadness, hypomania, or mixed mood in one year) and cyclothymia are additionalsubtypes of bipolar disease besides bipolar I and bipolar II (hypomanic and sub-depressive symptoms overtwo years)[2]. Increased morbidity and mortality are linked to bipolar depression episodes. Therefore,recognizing an acute depressive episode early and treating it well not only lowers treatment costs but alsosaves lives. When severe Anxiety symptoms are present throughout preadolescence and usually appearbefore the onset of depression [3]. Comorbid anxiety symptoms and anxiety disorders are linked to seriousdepression. Furthermore, bipolar disorder patients experience one or more severe depressed episodes beforedeveloping hypomanic or manic symptoms. Major depression can occur alongside bipolar disorder [4].Bipolar I disorder, which is characterized by periodic manic and depressive episodes, is expected to have a12-month prevalence ranging from 0.6% to 2.8%. Major depression and anxiety disorders are more prevalentin women during their reproductive years [5]. Table 1 lists the most often recommended medicines forbipolar I and II disorders based on WHO standards. Lumateperone is a new FDA-approved atypicalantipsychotic medication. That is licensed for the treatment of schizophrenia and bipolar depression. Itworks in a variety of ways, including by binding to D1, D2, and D4 receptors, functioning as a 5-HT2Areceptor antagonist, and inhibiting certain serotonin transporters. The most prevalent side effects at anFDA-approved dosage of 42mg/day include somnolence, drowsiness, lethargy, and constipation [6].Thisreview focuses on clinical studies to assess the efficacy of lumateperone in bipolar I and II disorders, as therehave been more evaluations that have examined its usage in schizophrenia.

Table 1: Treatment for bipolar I and II disorder

CLASS	GENERIC NAME	DOSE	SIDE EFFECTS
Mood stabilizes	Lithium Carbonate	300mg TID- QID Maximum dose:900-2400mg/day	Tremors, polyuria/ polydipsia, WeightGain, Hypothyroidism.
Anticonvulsants	Lamotrigine	25 OD up to 200 mg/D over 5weeks	Rash, SJS, blurred Vision.
	Valproic acid, divalproexsodium	250mg BD-QID.	GI upset, Tremors, Weight Gain, alopecia.
Antipsychotics	Aripiprazole	10-15 mg, to a maximum of 30mg/d	Insomnia, fatigue, nausea.
	Quetiapine	300mg/d	Tremor, weight gain
	Ziprasidone	40-160mg/d BID	EPS, rashes.
Atypical Antipsychotics	Lurasidone	20-120mg/d	EPS, Somnolence.
	Lumateperone (newly approved drug)	42mg/d, ideal at bedtime.	Weight gain, diabetes.
Antipsychotic/ Antidepressant combination	Olanzapine/Fluoxetine	6/12mg – 25/50mg OD	Xerostomia, Edema.

Pharmacokinetic Parameters

The pharmacokinetics parameter includes absorption by the body, distributed throughout the body,metabolized via liver and eliminated through bowel movements and urine.

Absorption

The Tmax of the drug is about 3-4 hours. The steady-state concentration is achieved after 5 days of regularconsumption once daily [7].

Distribution

Lumateperone is highly permeable along with bidirectional permeability through multidrug resistanceprotein 1 (MDR 1). It is a lipophilic at 7.4 pH. The medication passes both the small intestinal tract and thebarrier between the blood and the brain.

Metabolism

The liver breaks down Lumateperone around 20 metabolites. These metabolites have mechanisms by bothprolong and extend the action of lumateperone.

Excretion

Lumateperone having a half-life of 13 hrs. Around 58% of the compound is excreted in the urine, <1% inunchanged form. About 29% of the drug is excreted in feces.

Contraindications

Lumateperone should be avoided in patients with increased risk of stroke and other transient ischemicattacks. Due to its high sedative property, it should be avoided in patients consuming alcohol and otherrelated agents. Lumateperone is not advised for patients with symptoms of dementia in acute psychosis [8].To avoid unwanted drug-drug interactions, it should be avoided in patients taking inducers of CYP3A4 andinhibitors of CYP3A4 enzymes. It should be avoided in women who are or may become pregnant orbreastfeed [9].

Warnings

Lumateperone should be used with caution in patients with moderate to severe hepatic impairment.Patients ought to be cautious of the following side effects: brain tumors, tardy dyskinesia, metabolic2 of 5abnormalities, anemia, orthostatic hypotension, tumbles, and epilepsy.

Mechanism of lumateperone

Lumateperone's mechanism encompasses the connection and activation of glutaminergic neurotransmissionvia serotonergic, dopaminergic, and NMDA receptors [10]. Lumateperone's dopaminergic activity is uniqueto D2 receptors, having distinct intrinsic actions at pre- and post-synaptic terminals. The D2 receptor isactive in mesolimbic and mesocortical circuits, but has a lesser affinity for nigrostriatal pathways [11].Lumateperone

inhibits 5HT2A receptors with a binding affinity 60 times greater than D2 receptors [12].Lumateperone also exhibits serotonergic modulatory action, which leads to the suppression of SERT,resulting in potential antidepressant activity and effectiveness against schizophrenia's negative symptoms(i.e., depression) [13]. Lumateperone regulates glutaminergic signaling in the PFC by increasing both NMDAand AMPA receptor activation. While NMDA-receptor activity is regarded as insufficient in schizophreniapatientsthis activity might have been a significant component of its antidepressant and antidepressanteffects [14]. Figure 1 illustrates the Lumateperone short mechanism.

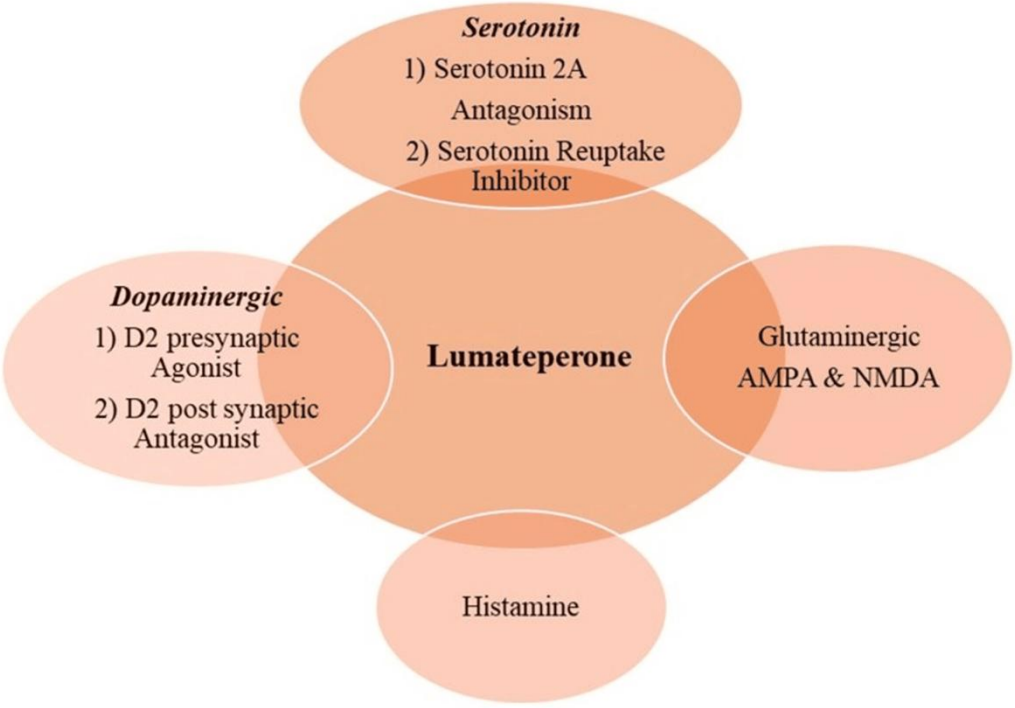

Figure 1: Mechanism of Lumateperone

DISCUSSION

An overall safety profile has been determined by newer atypical antipsychotics. Lumaterperone relatively hasa lower side effect that include weight gain, Parkinsonism and akathisia.A 6-week study conducted by joseph calabrese et al, in 2021 with a sample size of 377, Patients wererandomly randomized to receive 42 mg/day of lumateperone (N=188) or a placebo (N=189) orally once dailyin the evening. The study's results were evaluated using the MADRS and CGI-BP scores. The study wasconcluded that the lumateperone significantly reduced Depressive symptoms in patients with bipolar 1 and2 disorders [15].The first and second-generation psychotropic drugs function as antagonists to the presynaptic andpostsynaptic dopamine receptors, whereas lumateperone acts as partial agonist in the presynaptic receptors,and at the postsynaptic receptor, it acts as an antagonist that effectively reduce the dopaminergic signaling.The extra-pyramidal side effects are reduced when lumateperone binds at the serotonin 5-HT2A receptor[16]. There is no evidence of clinical research on the safety and efficacy of this medication in pediatric(under 18 years) or geriatric (over 65 years) populations, hence it is only available for those aged 18-65.The primary objective is to control any severe and increasing psychotic episodes, and pharmaceuticaltherapy plays a vital part. The enhancement of lumateperone for the future can be determined Long-termefficacy studies will use more precise behavioral measures, such as the Scale for the Assessment of NegativeSymptoms and the Scale for the Assessment of Positive Symptoms, as well as molecular imaging to targetthe dopamine D1 and D2, serotonin 5-HT2A, glutamate GluN2B receptors, and serotonin transporters.3 of 5A 6- week clinical trial conducted with a dose of 40 mg shows promising results by improving the depressivesymptoms in both bipolar I and II disorder when compared with placebo [17]. With a reduced risk ofextrapyramidal side effects and cardio metabolic side effects, lumateperone is well tolerated and alsomaintains the symptoms. Those patients who oppose the use of current antipsychotics due to their extra-pyramidal side effects and cardio-metabolic effects, lumateperone is proven to be a better choice ofmedication as it is not associated with such side effects. Double-blind randomized trial in bipolar depressivesymptoms is listed in Table 2.

Table 2: Double-blind randomized trial in bipolar depressive symptoms.

Study	Duration	Treatment	Results and Findings	Conclusion
Joseph Calabrese et al. (2021)	6 weeks	Lumateperone 42 mg or Placebo	When lumateperone is compared to placebo, itshows significant improvement from baseline in MADRS score (least-squares mean difference,-4.6 points; effect size=-0.56) and CGI-BP-S totalscore (least-squares mean difference, -0.9; effect size=-0.46).	Depressive symptoms weresignificantly improved in thelumateperone (42mg/day) group and is also well-tolerated in majordepressive episodes in patients involved with bipolar I and II disorders.
Intra-Cellular Therapies (2020)	6 weeks	Lumateperone 40 mg or Placebo	Lumateperone (40mg) significantly reduceddepressive symptoms when compared withplacebo in bipolar I and II disorder patients ($p<0.0001$, E.S.= 0.49) and ($p<0.001$, E.S.=0.81).	In patients with BPD I and BPD II, 40mg of lumateperone is effective intreating depressive symptoms. It helpsthese patients manage their bipolar symptoms.
ClinicalTrials.gov Identifier: NCT04285515	-	Lumateperone 42 mg oralcapsules orPlacebo capsules	Ongoing Investigation	Ongoing Investigation

The literature that are available is limited thereby the use of the studies and their statistical statements toargue the negative results of some clinical studies. Also, some clinical trials are limited only to abstracts andposters as their original articles have not been published with the required findings.

CONCLUSIONS

Lumateperone represents a significant advancement in the treatment of bipolar I and II disorders,characterized by its innovative mechanism of action that modulates serotonin, dopamine, and glutamatepathways. It also shows serotonergic modulatory action, which suppresses SERT, resulting in potentialantidepressant activity and effectiveness against schizophrenia's negative symptoms. Lumateperone has apromising efficacy and safety profile by alleviating depressive symptoms and reducing the incidence ofhyperglycemia, extrapyramidal symptoms, weight gain, and dyslipidemia compared totraditional antipsychotics. This evidence makes lumateperone a preferred option for patients whoare particularly sensitive to the adverse effects of existing treatments. However, the current evidenceprimarily focusses on the adult population, necessitating further research, particularly in pediatric andgeriatric populations. Future studies, which should incorporate more detailed behavioral assessments andadvanced molecular imaging techniques, are necessary to understand lumateperone's potential and ensureits long-term safety. Despite these areas requiring further exploration, lumateperone remains a valuable andpromising addition to the therapeutic options available for managing bipolar disorder.

Additional Information

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REFERENCES

1. Smith DJ, Whitham EA, Ghaemi SN. Bipolar disorder. In: Handbook of Clinical Neurology. Elsevier; 2012. p. 251–63. https://doi.org/10.1016/B978-0-444-52002-9.00015-2
2. Mazza M, Marano G, Traversi G, Carocci V, Romano B, Janiri L. Cariprazine in bipolar depression and mania: State of the art. CNS Neurol Disord Drug Targets . 2018;17(10):723–7. http://dx.doi.org/10.2174/1871527317666180828120256
3. Kalin NH. New insights into major depression and the treatment of bipolar depression. Am J Psychiatry . 2021;178(12):1071–4. http://dx.doi.org/10.1176/appi.ajp.2021.21101042
4. Akiskal HS. The prevalent clinical spectrum of bipolar disorders: Beyond DSM-IV. J Clin Psychopharmacol. 1996;16(SUPPLEMENT 1):4S-14S. http://dx.doi.org/10.1097/00004714-199604001-00002
5. Kessler RC, Petukhova M, Sampson NA, Zaslavsky AM, Wittchen H-U. Twelve-month and lifetime prevalence and lifetime morbid risk of anxiety and mood disorders in the United States. Int J Methods PsychiatrRes . 2012;21(3):169–84. http://dx.doi.org/10.1002/mpr.1359
6. Edinoff, A., Wu, N., deBoisblanc, C., Feltner, C. O., Norder, M., Tzoneva, V., Kaye, A. M., Cornett, E. M., Kaye, A. D., Viswanath, O., &Urits, I. Lumateperone for the Treatment of Schizophrenia. Psychopharmacology bulletin, 2020;50(4), 32–59. https://pubmed.ncbi.nlm.nih.gov/33012872
7. Blair HA. Lumateperone: First approval. Drugs . 2020;80(4):417–23. http://dx.doi.org/10.1007/s40265-020-01271-6
8. Ebied AM, Elmariah H, Cooper-DeHoff RM. New drugs approved in 2020. Am J Med . 2021;134(9):1096–100. http://dx.doi.org/10.1016/j.amjmed.2021.03.034
9. Greenwood J, Acharya RB, Marcellus V, Rey JA. Lumateperone: A novel antipsychotic for schizophrenia. Ann Pharmacother. 2021;55(1):98–104. http://dx.doi.org/10.1177/1060028020936597
10. Corponi F, Fabbri C, Bitter I, Montgomery S, Vieta E, Kasper S, et al. Novel antipsychotics specificity profile: A clinically oriented review of lurasidone, brexpiprazole, cariprazine and lumateperone. EurNeuropsychopharmacol. 2019;29(9):971–85. http://dx.doi.org/10.1016/j.euroneuro.2019.06.008
11. Vanover KE, Davis RE, Zhou Y, Ye W, Brašić JR, Gapasin L, et al. Dopamine D2 receptor occupancy of lumateperone (ITI-007): a Positron Emission Tomography Study in patients with schizophrenia. Neuropsychopharmacology . 2019;44(3):598–605. http://dx.doi.org/10.1038/s41386-018-0251-1
12. Kantrowitz JT. The potential role of lumateperone—something borrowed? Something new? JAMA Psychiatry . 2020;77(4):343. http://dx.doi.org/10.1001/jamapsychiatry.2019.4265
13. Vyas P, Hwang BJ, Brašić JR. An evaluation of lumateperonetosylate for the treatment of schizophrenia. Expert OpinPharmacother . 2020;21(2):139–45. http://dx.doi.org/10.1080/14656566.2019.1695778
14. Lumateperone . Prescriber's Guide. Cambridge University Press; 2020. p. 451–6. http://dx.doi.org/10.1017/9781108921275.077
15. Calabrese JR, Durgam S, Satlin A, Vanover KE, Davis RE, Chen R, et al. Efficacy and safety of lumateperone for major depressive episodes associated with bipolar I or bipolar II disorder: A phase 3 randomized placebo-controlled trial. Am J Psychiatry . 2021;178(12):1098–106. http://dx.doi.org/10.1176/appi.ajp.2021.20091339
16. Davis RE, Correll CU. ITI-007 in the treatment of schizophrenia: from novel pharmacology to clinical outcomes. Expert Rev Neurother . 2016;16(6):601–14. http://dx.doi.org/10.1080/14737175.2016.1174577
17. Intra-Cellular Therapies Announces U.S. FDA Approval of CAPLYTA® (lumateperone) for the Treatment of Bipolar Depression in Adults. Intra-Cellular Therapies Inc., (2022). https://ir.intracellulartherapies.com/news-releases/news-release-details/intra-cellular-therapies-announces-us-fda-approval-caplytar