

Lurasidone in the Treatment of Bipolar Depression

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Received: February 19, 2021; **Published:** March 27, 2021

Abstract

Context: Depression is the most frequent manifestation of Bipolar Affective Disorder and its treatment remains controversial, mainly dealing with the role of antidepressants.

Objective: To investigate the use of lurasidone in the treatment of bipolar depression.

Methods: Literature review of scientific productions in the textual modality of articles, indexed in the database of the Online Medical Literature Search and Analysis System, using the free search tool PUBMED. The search was carried out in September 2020, using the keywords selected according to Medical Subject Headings: "Lurasidone and depression disorder", resulting in 8 eligible publications for this study.

Results: The investigated studies proved the efficacy, safety and tolerability of lurasidone in treating bipolar depression by reducing depressive symptoms and improving life quality. The results were verified for children, teenagers, adults and the elderly. Lurasidone has mild effects on altering body weight and other metabolic parameters.

Conclusion: Since 2018, the Canadian Network for Mood and Anxiety Treatments recommends using lurasidone as the first-line treatment to the acute depressive episode of bipolar disorder in monotherapy or therapy combined with lithium or divalproate. The use of lurasidone decreased the recurrence of mood swings episodes, improved cognition and reduced anxiety.

Keywords: Antipsychotic; Bipolar Depression; Bipolar Disorder; Lurasidone

Introduction

Bipolar Affective Disorder (BPAD) is a severe and chronic mood disorder, defined by recurrent episodes of mania, hypomania and depression, interspersed with short euthymia intervals, which vary from days, weeks, to long months or years [1]. The BPAD Type I is specified in the DSM-V as a manic episode, followed by hypomanic and major depressant episodes. On the other hand, the BPAD Type II is defined by a current or previous hypomanic episode, followed by a current or previous major depressant episode [2].

It was estimated that 2.4% of the human population has BPAD. It was identified as a severe and chronic mental disorder, being the sixth largest cause of disability-adjusted life years in the world among the 15 to 44 age group [1].

Kapczinski advises that the initial BPAD stages are characterized by few previous mood episodes and functional recuperation during the euthymia break. The final stages are remarkable by chronic cognitive and functional worsening, such as impaired working and visual memories, which are more likely to be remitted during euthymia. Even during mood states' remission, difficulties in executive functioning, verbal and selective memory may be presented [1].

Citation: Hélida de Souza Valadão and César Augusto Trinta Weber. "Lurasidone in the Treatment of Bipolar Depression". *EC Psychology and Psychiatry* 10.4 (2021): 03-10.

The BPAD global charge embraces the chronicity and a wide range of medical and psychiatric comorbid conditions. It also includes the neurocognitive degeneration, which has been more prevalently reported in patients with BPAD than in healthy people [1].

The life perspective of people who have BPAD is smaller when comparing to the general population. It is related to the high level of suicide among them, which is 9 times higher than the general population. 30% of patients who present suicidal attempts during the life have it during the disorder depressive phase. Also, the smaller life perspective is due to the clinical comorbidities occasioned by BPAD [3].

Depression is the most constant manifestation of BPAD. Its diagnosis is not always simple, requiring a detailed and careful investigation about the previous history of manic and hypomanic symptoms, allowing the differentiation between the bipolar and unipolar depression [3].

Through a classical prospective study, with an average follow-up of 12 years, Judd, *et al.* [4] demonstrated that BPAD I patients had 3 times more depressive than manic symptoms throughout life. In contrast, the BPAD II patients had 37 times more depressive than hypomanic symptoms, reinforcing the notion of depression as the most predominant manifestation of bipolarity.

Although the recent advances in psychopharmacology for BPAD, the available therapeutic drug arsenal has proved to be difficult to choose for doctors and patients [5-7].

The treatment of bipolar depression remains polemic, mainly dealing with the role of antidepressants [8]. Diverse authors, such as Licht, *et al.* [9] and Wong [10] warn about the use of antidepressants to bipolar depression, which is generally not recommended because patients can do manic, hypomanic or cycle acceleration.

These risks can be decreased by combining an antidepressant with a mood stabilizer. However, it may lead to a reduced efficacy and tolerability, limiting their utilization [9,10].

In this context, only the association of olanzapine, fluoxetine and quetiapine were approved to treat bipolar depression, both in standard preparation and extended-release.

In July 2013, lurasidone was approved for treating bipolar depression in monotherapy or combined with lithium and valproate by the Food and Drug Administration (FDA) of United States. These are the only drugs with extended FDA approval for acute treatment of bipolar depression in adults [11].

Muneer [11], Bawa, Scarff [12] reported efficacy in treating bipolar depression using lurasidone combined with lithium and valproate, classified as safe and well-tolerated, with mild effects on body weight or alteration other metabolic parameters.

Aim of the Study

In this context, this work aims to investigate the use of lurasidone in the treatment of bipolar depression.

Methods

Literature review of scientific productions in the textual modality of articles, indexed in the Medical Literature Search and Analysis System Online (MEDLINE) database, using the free search tool PUBMED. The search was carried out in September 2020, using the selected keywords according to the Medical Subject Headings (MeSH Terms), coordinated by the National Library of Medicine of United States (US NLM), in English: Lurasidone; Bipolar Depression.

The preliminary search resulted in 163 articles for screening according to the following research details: lurasidone [MeSH Terms] AND bipolar disorder [MeSH Terms].

In a second search, the followed selection filters were activated as inclusion criterium: Article types: Clinical Trial; Publication dates: (“2015/01/01”[PDat]: “2020/09/09”[PDat]); Species: Humans; Text availability: Full text. 11 articles were selected for abstract reading from this search, aiming to analyze each work’s contents.

As an exclusion criterium, the inadequacy of the main subject to this study’s objective was adopted, resulting in 3 articles excluded. A total of 8 articles were eligible for this revision.

The methodology for searching and selecting articles for this review is illustrated in the flowchart shown in figure 1.

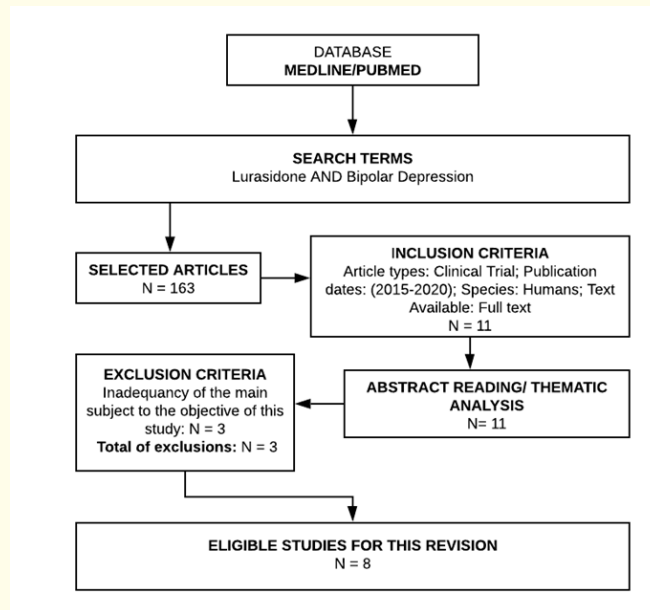


Figure 1: Flowchart of the method for searching and selecting articles.

Results

The studies selected for this review are shown in table 1. They are summarized in a chronological crescent order, referring to the month and year of publication. When identical publication dates (year and/or month) occurred among the selected studies, the criterium adopted for the presentation order followed the alphabetical order of the initial letter of the first author’s last name.

| Author/Year | Objectives | N | Results/Conclusion |
|--|---|-----|--|
| Chapel, Chiu, Hsu, Cucchiaro, Loebel, 2015 [13] | Characterize the dose-response profile of lurasidone in patients with bipolar depression | 825 | The effect of lurasidone was significant (P< 0.001), and a positive drug response was detected. The modeling analysis of dose-response supports a linear positive response to 20-120 mg of lurasidone in treating patients with bipolar depression as monotherapy or adjuvant therapy with lithium or valproate. |
| Rajagopalan, Bacci, Ng-Mak, Wyrwich, Pikalov, Loebel, 2016 [14] | Examine the direct and indirect effects of lurasidone in improving patients’ health-related quality of life (HRQoL). The evaluation was carried out mediating the improvement of depression symptoms. | 818 | Lurasidone demonstrated efficacy in monotherapy and adjuvant therapy. The results were statistically significant. The drug decreased depressive symptoms associated with bipolar disorder. |
| Sajatovic, Forester, Tsai, Kroger, Pikalov, Cucchiaro., et al. 2016 [15] | Evaluate the lurasidone’s efficacy in 55-year-old patients or older with bipolar depression. | 505 | Lurasidone was significantly effective, safe, and well-tolerated in elderly adults. |
| Suppes, Kroger, Pikalov, Loebel, 2016 [16] | Evaluate the lurasidone’s efficacy as an adjuvant therapy with lithium or valproate in patients with bipolar depression I. | 288 | Lurasidone combined with lithium or valproate significantly improved the depressive symptoms, according to the MADRS scale. |

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|--|--|------|--|
| Calabrese, Pikalov, Stricher, Cucchiario, Mao, Loebel, 2017 [17] | Evaluate the lurasidone’s efficacy combined with lithium or valproate to the maintenance treatment of bipolar disorder type I. | 960 | Lurasidone has efficacy in treating bipolar depression. Combined with lithium or valproate, lurasidone demonstrated efficacy, safety and was well-tolerated, showing minimum effects in body weight or metabolic parameters. |
| DelBello, Goldman, Phillips, Deng, Cucchiario, Loebel, 2017 [18] | Evaluate the efficacy and safety of lurasidone in treating bipolar depression of children and teenagers. | 318 | Lurasidone has efficacy as monotherapy, in the dose of 20 to 80 mg/day. It significantly decreased the depressive symptoms of children and teenagers with bipolar depression. It was well-tolerated, with minimum effects on body weight and metabolic parameters. |
| Fornaro, De Bernardis, Perna, Solmi, Veronese, Orsolini, Buonaguro., <i>et al.</i> 2017 [19] | Evaluate the evidence of lurasidone in treating bipolar depression. | 1678 | A promisor profile of efficacy was suggested, along with the safety and tolerability of lurasidone. The drug has efficacy in the acute treatment of bipolar depression type I. |
| Kishi, Yoshimura, Sakuma, Okuya, Iwata, 2020 [20] | Evaluate the efficacy and safety profile of lurasidone, comparing to olanzapine and quetiapine XR to treat bipolar depression. | 1223 | Although the three drugs showed similar efficacy, there was a difference in the safety profile among the second-generation antipsychotics. |

Discussion

The studies evaluated in this review focused on the utilization of lurasidone in treating patients with bipolar depression. Different disease stages were approached, as the acute or maintenance, the search for syndromic recovery, or the relapse prevention. The studies also comprised the utilization of lurasidone in monotherapy or combined therapy.

Lurasidone has an increased absorption when combined with a meal of at least 350 calories, leading to an availability 2 times greater than fasting. The half-life is 18 hours, with a serum peak between 1 and 3 hours. Its metabolism is hepatic and occurs by cytochrome P450 and the isoenzyme 3A4 (CYP3A4). Excretion occurs via feces (80%) and urine (9%). The protein binding of lurasidone is about 99% [8].

The pharmacokinetics of lurasidone is illustrated by its hepatic metabolism via CYP3A4. Consequently, its use is contraindicated in the presence of strong CYP3A4 inducers and inhibitors. The recommended starting dose of lurasidone is 20 mg, while the maximum dose is 120 mg, both as monotherapy and in combination with lithium or divalproate [8].

The essential pharmacodynamic of lurasidone is related to being this drug antagonist of dopamine and serotonin receptors. Lurasidone is classified as an atypical antipsychotic of second-generation, from benzoyls thiazoles’ class [8], also acting as a potent mood stabilizer [21].

Theoretically, this drug suggests being lesser prone to cognitive deficit induction, weight gain, or sedation than other agents with similar properties. This fact is attributed to the absence of potent actions of dopamine D1 receptors, muscarinic M1 and histamine H1 [21].

Lurasidone works by blocking dopamine D2 receptors, reducing the psychosis positive symptoms and stabilizing affective symptoms. It blocks the serotonin receptor 5HT2a, increasing the release of dopamine in specific brain regions. In this sense, it reduces the motor side effects and improves cognition and affective symptoms [21].

Moreover, lurasidone potentially blocks the serotonin 5HT7 receptors, benefiting the mood, sleep, cognitive deficit and the negative symptoms of schizophrenia, bipolar and major depressive disorders. It acts as a partial agonist at 5HT1A receptors and causes antagonistic actions at 5HT7, alpha-2a and alpha-2c serotonin receptors. In this way, it may improve mood and cognition and reduces anxiety in various disorders [21]. Lurasidone has a binding profile to 5HT7 receptors, located in gabaergic interneurons, both in the raphe and in the prefrontal cortex. The blockage of 5HT7 receptors in gabaergic interneurons at raphe increases the serotonin release in the prefrontal cortex. The blockage of 5HT7 receptors in gabaergic interneurons at the prefrontal cortex enhances the glutamate release by pyramidal neurons. It partially explains the antidepressant efficacy and improvement of cognition caused by lurasidone.

The amino acids glutamate and glycine are the main excitatory neurotransmitters in the CNS. These amino acids bind to sites associated with the N-methyl-D-aspartate (NMDA) receptor. An excess of glutamatergic stimulation can cause neurotoxic effects. Significantly, there is a high concentration of NMDA receptors in the hippocampus. The glutamate can operate combined with hypercortisolemia causing central disorders to mediate the harmful neurocognitive effects of severe recurrent depression. Among the central disorders, it can be emphasized the decreased serotonin inhibitory tone, increased norepinephrine impulse, acetylcholine-ACh or corticotrophin-releasing hormone CRH, or decreased inhibition of hippocampal feedback. Recent evidence indicates that antagonist agents to NMDA receptors have antidepressant effects [22].

In bipolar depression, aminobutyric acid (GABA) inhibits monoaminergic ascending pathways, particularly in the mesocortical and mesolimbic systems. Reductions in plasma levels have been observed in depression, such as reducing spinal and cerebral cerebrospinal fluid of GABA. Animal studies have shown that chronic stress can reduce and deplete GABA levels. GABA receptors suffer ascendants from antidepressants and some gabaergic drugs have weak antidepressant effects [22].

Therapeutic guidelines are documents based on scientific evidence that establish pharmacological criteria for the use of medicines. These criteria are classified into order categories of use according to the clinical condition. First-line treatments were defined as medications or interventions with proven efficacy based on meta-analyses or randomized clinical trials, which have shown superiority to placebo and superiority or equivalence to the established treatment [7].

The Canadian Network for Mood and Anxiety Treatments [23] (CANMAT) presents information to guide the treatment of bipolar disorder in acute episodes or prevention of any mood episode, based on scientific evidences. It considers the efficacy and the tolerability of each substance in the choosing the therapeutic plan. In this perspective, the CANMAT approved lurasidone in treating acute bipolar depression since 2018.

Lurasidone has a preclinical profile considered predictive of antipsychotics effects, antimanic, antidepressant and precognitive, compared to other second-generation antipsychotics. It also presents efficacy against negative symptoms of schizophrenia. In this sense, lurasidone proved to be effective in schizoaffective disorder and depressive episodes of BPAD. Moreover, higher remission rates were obtained to lurasidone than quetiapine in dealing with acute chronic schizophrenia [8].

For the pharmacologic treatment of mental disorders and bipolar depression, the equilibrium among the drug efficacy and drug tolerability plays a key role in choosing one or the other psychotropic drug [7].

A dose-efficacy study [13] pointed to the significant improvement in the severity of depressive symptoms through the use of lurasidone, being indicated a therapeutic dose of 20 - 120 mg/day. The indication of higher doses of lurasidone in a bipolar depression episode is associated with a more significant improvement compared to lower doses. Lurasidone significantly improved the severity of depressive symptoms. The analysis also demonstrated the efficacy of lurasidone in treating bipolar depression as monotherapy or adjuvant therapy of lithium or valproate.

Rajagopalan, *et al.* [14] supported previous investigations that demonstrated a strong relation between bipolar depression and the damages caused in the work and visual memories due to neurocognitive degeneration, which reduces patients' life-quality. Lurasidone as monotherapy or adjuvant therapy to lithium or valproate shows efficacy in treating bipolar depression, improving the depressive symptoms and life quality.

A study [15] proved the efficacy of lurasidone as monotherapy, evaluating the efficacy and tolerability of lurasidone in treating bipolar depression in adults older than 55. On the other hand, it pointed that the lurasidone as adjuvant therapy did not achieve significant improvements. Both monotherapy and adjuvant therapy were verified as safe and well-tolerated in the elderly, with no significant clinical effects in the electrocardiogram (DCG), minimum effects in body weight, metabolic parameters and glycemic index. Lurasidone seems to be a promisor candidate in treating depressive episodes in the elderly population.

Suppes, *et al.* [16] carried out a controlled and short-term study using a placebo with patients with bipolar depression. A significant response of lurasidone was not verified, comparing to the placebo. In contrast, this study mentioned a previous study where lurasidone achieved a significant efficacy as adjuvant therapy with lithium or valproate.

Through a double-blind and placebo-controlling study, Calabrese, *et al.* [17] evidenced that lurasidone decreases the recurrence probability of any mood episode. It also evidenced a significant efficiency of lurasidone in treating bipolar depression both as monotherapy and adjuvant therapy.

The double-blind, randomized placebo-controlled study carried out by Bawa and Scarff [12] demonstrated that lurasidone improved depressive symptoms compared to the placebo. Comparable benefits and lower risk of damage than quetiapine and olanzapine-fluoxetine were obtained to lurasidone. In this study, lurasidone was considered safe and well-tolerated, with minimum effects on body weight and metabolic parameters.

Delbello, *et al.* [18] performed a study about the efficacy and safety of lurasidone in children and teenagers suffering from bipolar depression type I. These age groups are associated with high recurrence rates and psychiatric comorbidity, causing impairment in functioning and quality of life, increased risk and attempts of suicide and self-injurious behavior. The studied dose for children and teenagers (20 - 80 mg/day) was flexibly dosed and achieved a statistically significant improvement in depressive symptoms, anxiety, life-quality and global functioning. Lurasidone was well-tolerated in this age group, with minimum effects on body weight and metabolic parameters.

Fornaro, *et al.* [19] evaluated the efficacy, tolerability and safety of lurasidone in treating bipolar depression. They suggested further investigations of the dosage pattern to treat bipolar depression, depression with mixed characteristics, or major depression. This study proved the efficacy of lurasidone in treating bipolar depression type I.

Kishi, *et al.* [20] pointed out about the lurasidone dosage. In Japan, the approved lurasidone dose is about 20 - 60 mg/day to treat the second bipolar depressive episode. In other countries, this dose can reach up to 120 mg/day. According to the researchers, the lurasidone, olanzapine and quetiapine XR are the best drugs to treat the Japanese patients. The study also demonstrated that lurasidone, quetiapine XR and olanzapine are efficient in terms of the difference and the safety profile of the second-generation antipsychotics.

Conclusion

Since 2018, the CANMAT recommends using lurasidone as the first-line treatment to the acute depressive episode of bipolar disorder in monotherapy or therapy combined with lithium or divalproate. The use of lurasidone showed a reduced recurrence in mood swings, improved cognition and reduced anxiety, with evidence of greater effectiveness in the dosage range between 80 - 120 mg/day in treating bipolar depression.

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Volume 10 Issue 4 April 2021

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