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# Management of bipolar I depression: clinical utility of lurasidone

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**Abstract:** Lurasidone is a benzisothiazol derivative second-generation antipsychotic. It has been approved in the United States and Europe for treatment of acute schizophrenia and bipolar depression. In type I bipolar subjects, treatment with lurasidone monotherapy of adjunctive therapy to lithium or valproic acid with doses of 20 to 120 mg once daily with food, results in statistically and clinically significant reduction of depressive symptoms. Patients experience relatively few side effects, which include somnolence, akathisia, nausea, and other gastrointestinal upset. Dopamine related side effects, such as Parkinsonism and elevated prolactin, are rare and mild. Longer term safety data obtained in 6 months long, open continuation observation periods, suggest that metabolic related elevations in weight, glucose, and lipids are absent or minimal. The mechanism of action of lurasidone is not known, but the data are compatible with antagonism of the serotonin 7 receptor. Lurasidone is a new option for the treatment of bipolar depression with relatively few side effects.

**Keywords:** lurasidone, bipolar disorder, bipolar depression, adjunctive therapy

## Introduction

The treatment of depression in patients diagnosed with bipolar disorder presents considerable challenges to the clinician. Depression is a key feature of bipolar disorder, and the total number of depressive episodes may be present in up to a third or half of a patient's life.<sup>1-4</sup> These depressive episodes have a variety of clinical presentations; for example, the symptoms may meet full diagnostic criteria for a major depressive episode, or may be subsyndromal. Alternatively, the symptoms may be a manifestation of the commonly comorbid dysthymic disorder.<sup>2,3,5,6</sup> Additionally, depressive symptoms frequently occur due to comorbid medical conditions that are common in patients with bipolar illness. These include sleep apnea, thyroid disease, diabetes, cardiac disease, and other chronic medical conditions.<sup>7-12</sup>

Pharmacologic treatment of depression in bipolar illness is complicated by a dearth of efficacy and safety data. While the current use of antidepressants in bipolar disorder has declined to as low as 34% of patients,<sup>13</sup> their use in this population remains controversial.<sup>14</sup> Some reviews report that antidepressants are safe and effective;<sup>15</sup> however, others report that antidepressants are ineffective and potentially harmful.<sup>16</sup> Current reports on efficacy suggest that antidepressants appear to be effective in bipolar depression when used alone<sup>17,18</sup> or when added to an antipsychotic,<sup>19</sup> but are ineffective in placebo-controlled trials in which they are added to a mood stabilizer.<sup>20-22</sup> Furthermore, while much research has focused on the problem of induction of a manic state due to the use of antidepressants, research suggests that antidepressants can induce at least three distinct problems in bipolar patients. Antidepressants can indeed increase the likelihood of a manic switch,<sup>21</sup>

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or any switch by accelerating cycling,<sup>4,23</sup> and increase the likelihood of both acute and chronic depression in rapid cycling patients.<sup>24,25</sup>

Thus, clinicians are often presented with a quandary in clinical practice when their patients with bipolar disorder present with depression since the evidence-based options available for treating such a patient are limited.<sup>26</sup> However, clinical research increasingly supports the use of anti-psychotic medications as an effective treatment option for depression in bipolar disorder.<sup>27,28</sup> For example, lurasidone, a second-generation antipsychotic that is already approved for the treatment of schizophrenia,<sup>29,30</sup> has been approved by the United States Food and Drug Administration (FDA) for the treatment of bipolar depression.<sup>31,32</sup> The agent has demonstrated efficacy and safety in this population. Its presumed mechanism of action appears to be unique. This paper will review the available information about lurasidone for the management of bipolar depression.

## Pharmacokinetics, pharmacodynamics, and pharmacology

Lurasidone is a benzisothiazol derivative second-generation antipsychotic. It has a complex multi-ring structure that is minimally soluble in water. It is supplied as lurasidone hydrochloride in unscored 20, 40, 60, 80, and 120 mg tablets.

It is likely that lurasidone is absorbed in the stomach. For this reason, it is more effectively absorbed when taken with food.<sup>33</sup> This effect is similar to that observed with ziprasidone.<sup>34,35</sup> In both cases a meal of approximately 350 calories for lurasidone and 500 calories for ziprasidone, maximizes and stabilizes absorption of the drug.<sup>34,35</sup> Fat content of the meal does not alter the absorption. Absorption is increased approximately two to three times, and maximal serum concentration is increased about three fold.<sup>33</sup> Once absorbed, lurasidone is highly plasma protein bound (99.8% is bound to albumin and  $\alpha$ -1-glycoprotein).<sup>36</sup>

It is metabolized predominantly by the cytochrome P450 isozyme 3A4. It is broken down by oxidative N-dealkylation, hydroxylation of norbornane ring, and S-oxidation. There are two active metabolites (ID-14283 and ID-14326) and three inactive metabolites (ID-20219, ID-20220, and ID-11614).<sup>33</sup> The active metabolites comprise only about 28% of the breakdown products of lurasidone, and have a shorter half-life, thus most of the action is believed to be due to the parent drug.<sup>36</sup> The half-life of lurasidone is 18 hours for a 40 mg oral dose, so it can be taken once daily. Steady state is achieved within 5 to 7 days.<sup>33,36</sup> Because lurasidone

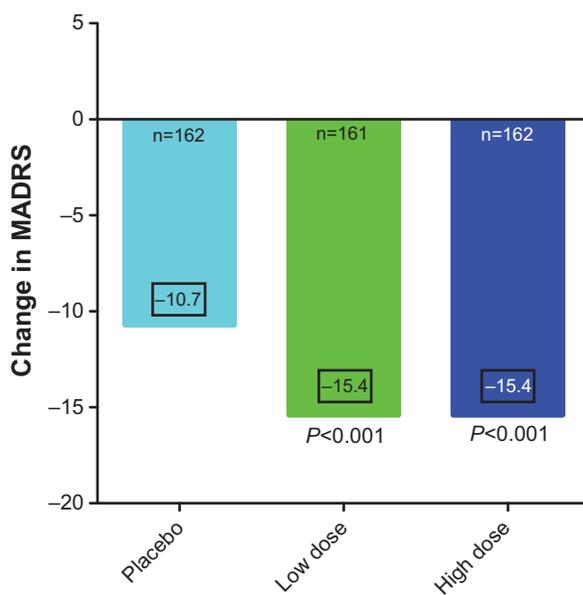
is not a substrate for CYP1A2, smoking does not alter metabolism. The majority of the metabolic remnants of lurasidone end up in the feces (80%), with a small fraction in the urine (9%).

Lurasidone interacts with many receptors, and is antagonistic at most of them. The principal ones are dopamine D<sub>2</sub> (K<sub>i</sub> = 1.68 nM), serotonin 5HT<sub>7</sub> (K<sub>i</sub> = 0.5 nM), 5HT<sub>2A</sub> (K<sub>i</sub> = 0.5 nM in human and 2.0 nM in rat), and 5HT<sub>1A</sub> (K<sub>i</sub> = 6.4 nM in human and 6.8 nM in rat).<sup>36</sup> For the 5HT<sub>1A</sub> receptor, lurasidone is classified as a partial agonist; but the partial agonist effect is only 33% that of serotonin.<sup>37</sup> At higher doses it may interact with the adrenergic  $\alpha$ <sub>2A</sub> (K<sub>i</sub> = 40.7 nM), and  $\alpha$ <sub>2C</sub> (K<sub>i</sub> = 10.8 nM). It does not interact with the histamine H<sub>1</sub> or muscarinic M<sub>1</sub> (K<sub>i</sub> > 1,000 nM for both).<sup>36</sup> Receptor binding in humans as measured by positron emission tomography (PET) reveals that doses below 40 mg do not achieve adequate D<sub>2</sub> binding for an antipsychotic effect (41%–43% for 10 mg, and 51%–55% for 20 mg).<sup>38,39</sup> With a 40 mg dose the D<sub>2</sub> binding is 63%–67%, and increases to 77%–79% with 60 mg. Interestingly, higher doses do not increase receptor occupancy (73%–79% with 80 mg dose).<sup>39</sup> This observation may explain why Parkinsonism and elevated prolactin are uncommon with lurasidone in these studies, particularly with lower doses.<sup>31</sup> However, D<sub>2</sub> receptor occupancy is more closely related to blood levels than to dosage of lurasidone, because of the significant variability in drug concentrations across individuals.<sup>40</sup>

The interaction with 5HT<sub>7</sub> is believed to be particularly important for the antidepressant effect in bipolar illness. Blockade of this receptor with selective 5HT<sub>7</sub> antagonists or knocking out the 5HT<sub>7</sub> gene, improve symptoms of “depression” in animal models of depression.<sup>41–43</sup> A pure 5HT<sub>7</sub> antagonist reduced depressive symptoms in a preclinical rodent study, but did not separate from placebo due to a high placebo response rate.<sup>44</sup> Testing in animal models of depression and anxiety with lurasidone demonstrates that it is effective in reducing depressive symptoms in animals.<sup>45</sup> Part of this effect may be due to an increase in dopamine efflux in the frontal cortex that is induced by lurasidone blockade of 5HT<sub>7</sub>.<sup>46,47</sup> This effect is also believed to mediate the pro-cognition effect of lurasidone.<sup>48–51</sup> Additionally, lurasidone appears to modulate the reductions in brain-derived neurotrophic factor and promote neuroplasticity in animal models of stress and depression.<sup>52,53</sup> A positive effect on brain-derived neurotrophic factor appears to be a marker for effective antidepressant agents.<sup>54</sup> None of these potential mechanisms of action have been demonstrated as being central in human studies.

## Efficacy of lurasidone in bipolar depression

Two randomized, double-blinded controlled clinical trials have examined the efficacy of lurasidone in the treatment of bipolar I depression (Figures 1 and 2).<sup>31,32</sup> Lurasidone was tested as monotherapy at 20–60 mg/day (N=166) and 80–120 mg/day (N=169), with a placebo comparison (N=170) (Figure 1). Findings indicated that after 6 weeks, scores on the Montgomery–Åsberg Depression Scale (MADRS) were equally and significantly decreased in both the 20–60 mg/day group (–15.4) and in the 80–120 mg/day group (–15.4), compared to placebo (–10.7) (Figure 1). Response, defined as >50% improvement on the MADRS, was achieved by 53% of those receiving the low dose, and 51% of those receiving the high dose, compared to 30% of those receiving placebo. The number needed to treat (NNT) was 5 for both groups. Similarly, remission, defined as a MADRS score of ≤12, was achieved by 42% in the low dose group and 40% in the high dose group, compared to 25% on placebo. The NNT for remission was 6 in the low dose group and 7 in the high dose group. In addition, both treatment groups showed significantly greater endpoint decreases in depression severity scores on the Clinical Global Impressions Scale for Bipolar Illness compared to placebo. Endpoint decreases were –1.8 for the 20–60 mg/day group, –1.7 for the 80–120 mg/day group, and –1.1 for the placebo group.

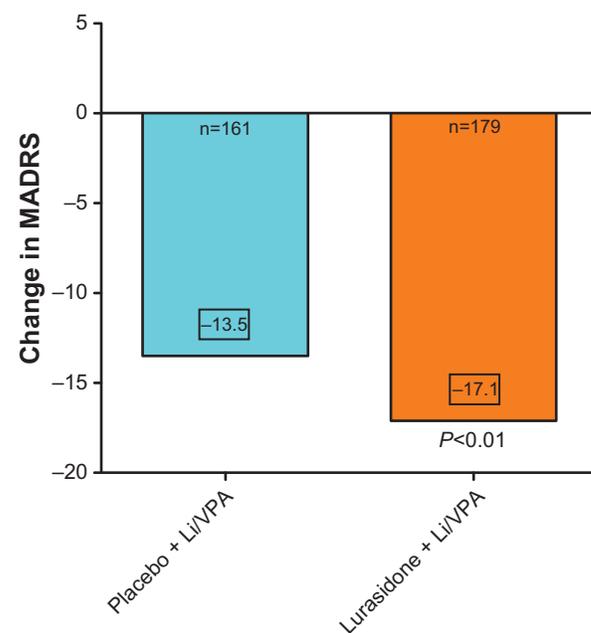


**Figure 1** The efficacy outcome at the end of 6 weeks of treatment of acutely depressed type I bipolar patients treated with placebo, or monotherapy with lurasidone 20–60 mg/day, or lurasidone 80–120 mg/day.

**Notes:** The effect size for the low dose arm is 0.61, and for the high dose arm 0.50; these are considered medium in size. *P*-values are versus placebo arm.  
**Abbreviation:** MADRS, Montgomery–Åsberg Depression Rating Scale.

For both treatment groups, significant improvements were seen on several domains of the MADRS, including in reported and apparent sadness, inner tension, “inability to feel”, lassitude, and pessimistic thoughts. The lurasidone 20–60 mg/day group showed significant improvements in sleep, and the 80–120 mg/day group showed significant improvements in concentration. No significant changes were seen in appetite or suicidal ideation in either treatment group compared to placebo. Both treatment groups also reported significant reductions in anxiety compared to placebo, as measured by the Hamilton Anxiety Rating Scale. Findings from this study further indicate that participants in both treatment groups reported significantly improved quality of life and life satisfaction, along with significantly reduced disability.<sup>32</sup>

A second randomized, controlled trial examined the effectiveness of lurasidone as an adjunct to lithium or valproate in the treatment of bipolar I depression.<sup>32</sup> All patients met criteria for a moderate major depression despite documented therapeutic levels of lithium or valproate. The treatment group (N=183) was started on lurasidone at 20 mg, which was increased to 60 mg by the end of the first week of the study. After the first week, dosages could be adjusted within a range of 20–120 mg/day at weekly intervals, with increases or decreases of 20 mg, based on clinical judgment.<sup>32</sup>



**Figure 2** The efficacy outcome at the end of 6 weeks of treatment of acutely depressed type I bipolar patients treated with lithium or valproate to which either placebo was added or lurasidone 20–80 mg/day.

**Notes:** The effect size is 0.34. *P*-values are versus placebo arm.

**Abbreviations:** Li, lithium; VPA, valproate; MADRS, Montgomery–Åsberg Depression Rating Scale.

The control group (N=165) received placebo added to the lithium or valproate.

Depression, anxiety, quality of life, life satisfaction, and disability were measured at baseline and at 6 weeks. Findings indicate that the group treated with lurasidone + lithium/valproate had significantly improved depression, as measured by the MADRS (Figure 2). The least squares mean change of the MADRS score for the lurasidone + lithium/valproate group was -17.1, compared to -13.5 for the placebo group. In addition, significantly shorter time to remission was seen in the lurasidone + lithium/valproate group (35 days) compared to the placebo group (43 days). Response was achieved by 57% of patients receiving lurasidone + lithium/valproate compared to 42% of those on placebo + lithium/valproate. The NNT was 7. Remission rates were 50% in the lurasidone + mood stabilizer group, versus 35% in the placebo + mood stabilizer group; with an NNT of 7.

Several domains of the MADRS showed significant improvement in the lurasidone + lithium/valproate group compared to placebo, including reported and apparent sadness, sleep, lassitude, inability to feel, and pessimistic thoughts. However, no significant differences were seen in inner tension, appetite, concentration difficulties, and suicidal ideation. In addition, the lurasidone + lithium/valproate group reported significant reductions in anxiety and disability, along with significant improvements in quality of life, enjoyment, and life satisfaction, compared to the placebo group.

A separate adjunctive, placebo-controlled study failed to separate from placebo. This study had a design similar to the previous study, while improvement was noted in the lurasidone arm, it did not separate from placebo. The safety data (see the "Lurasidone Safety and tolerability" section) includes patients from this unpublished failed study.

A 6 months open observation period was performed for patients in both of these studies who wished to remain in the study. Patients on placebo were switched to active medication. The study has not yet been published and symptom data are not available for this review.

## Lurasidone safety and tolerability in bipolar depression

The FDA approved lurasidone for schizophrenia in 2010 and subsequently in 2013 for bipolar depression.<sup>55</sup> It is considered as safe, well-tolerated, and efficacious in these conditions.<sup>31,32,56,57</sup> In a systematic review of the literature from June 2009 to February 2014, lurasidone, compared to other recently approved second-generation atypical antipsychotics such as paliperidone, iloperidone, and asenapine,

was considered by researchers to be less likely to produce the metabolic side effects of weight gain, hyperlipidemia, hypercholesterolemia, and hyperglycemia, and was not linked to significant electrocardiogram (ECG) abnormalities.<sup>58-61</sup>

Among a total of eleven articles found that described the safety and tolerability of lurasidone in the treatment of schizophrenia or major depressive episodes associated with bipolar I disorder, four were peer-reviewed, double-blind, placebo-controlled studies,<sup>31,32,56,57</sup> and another was a meta-analysis.<sup>62</sup> Two of the peer-reviewed studies examined the use of lurasidone in the treatment of bipolar I disorder.<sup>31,32</sup>

In the monotherapy study, 505 adults 18-75 years of age were recruited.<sup>31</sup> The three study groups comprised of patients receiving 6 weeks of lurasidone flexible daily oral doses in the ranges of either 20-60 mg or 80-120 mg, or placebo.<sup>31</sup> The majority of adverse events were rated as mild to moderate and  $\leq 10\%$  ranked as severe across groups.<sup>31</sup> Dropout rates due to adverse events were similar across groups (5.9%-6.6%). There was no statistically or clinically-significant change in weight, lipid, cholesterol, or prolactin levels, glycemic control, waist circumference, or ECG readings.<sup>31</sup> The proportion of patients with  $\geq 7\%$  increase in weight from baseline was 4.2% in the 20-60 mg group, 0.7% in both the 80-120 mg and placebo groups.<sup>31</sup> The high dose group experienced more adverse effects with a modest occurrence of the incidence of nausea (N=29, 17.4%), akathisia (N=18, 10.8%), somnolence (N=11, 13.8%), sedation (N=12, 7.2%), vomiting (N=10, 6.0%) and extrapyramidal side effects (N=15, 9.0%) (Table 1). Females experienced a higher mean increase in prolactin (7.5 ng/mL) compared to males (2.6 ng/mL).<sup>31</sup> Treatment-emergent mania did not differ across the groups. There were low rates of serious adverse events across groups with no deaths, suicidal behaviors or suicides during the study.<sup>31</sup>

In the trial comparing the safety and efficacy of lurasidone added to stable doses of lithium or valproate versus placebo added to lithium or valproate in depressed bipolar I patients, 348 adults 18-65 years of age were studied.<sup>32</sup> The lurasidone + lithium/valproate group most commonly experienced the adverse events of nausea (17.5%), somnolence (8.7%), tremor (8.2%), akathisia (7.7%), insomnia (7.1%), and Parkinsonism (15.3%). Discontinuation rates due to adverse events were 6% in this group versus 7.9% in the placebo + lithium/valproate group. Additionally, lurasidone did not significantly increase body weight, lipids, glucose, or prolactin levels.<sup>32</sup>

In both bipolar I studies, overall adverse events with lurasidone versus placebo included extrapyramidal events 24% versus 13%, akathisia 11% versus 5%, and Parkinsonism

**Table 1** Spontaneously reported adverse events (AEs) in the three registrational trials for lurasidone

Event	Low dose (n=164)	High dose (n=167)	Placebo (n=168)	Li/VPA + lurasidone (n=360)	Li/VPA + placebo (n=334)
Tremor				18.2%	4.3%
Nausea	10.4%	17.4%	7.7%	17.5%	11.0%
Somnolence	7.3%	13.8%	6.5%	8.7%	4.3%
Headache				10.4%	12.3%
Akathisia	7.9%	10.8%	2.4%		
Insomnia				7.1%	5.5%
Dry mouth	6.1%	3.6%	4.2%		
Diarrhea	4.9%	3.0%	1.8%	4.4%	6.7%
Discontinuation due to AE	7.0%	6.0%	6.0%	7.9%	6.0%

**Notes:** Only AEs occurring at  $\geq 5\%$  are reported. The United States Food and Drug Administration does not perform statistical analysis on AEs. Low dose = lurasidone 20–60 mg/day; High dose = lurasidone 80–120 mg/day; Li/VPA + lurasidone = lurasidone 20–80 mg added to lithium or valproate; Li/VPA + placebo = placebo added to lithium or valproate.

**Abbreviations:** Li, lithium; VPA, valproate.

13% versus 8%.<sup>56</sup> Similarly, in the two studies examining the safety, tolerability, and efficacy of lurasidone in the treatment of acute schizophrenia, researchers generally found that the most commonly experienced side effects were akathisia, headache, gastrointestinal upset (nausea, vomiting, and dyspepsia), insomnia, somnolence, and sedation (Table 1).<sup>56,57</sup>

In the 6 months open observation study of patients receiving lurasidone monotherapy (N=130), there was no additional weight gain (0.0 kg).<sup>56</sup> Similarly fasting glucose increased by 1.2 mg/dL, total cholesterol dropped by 0.5 mg/dL, triglycerides dropped by 1.0 mg/dL, and prolactin dropped by 1.2 ng/dL.<sup>56</sup> Patients receiving lurasidone as adjunct (N=88) had more changes, but still quite modest. Over the 6 months period, weight increased by 1.3 kg, fasting glucose increased by 1.7 mg/dL, total cholesterol dropped by 0.9 mg/dL, triglycerides increased by 5.3 mg/dL, and prolactin dropped by 2.9 ng/dL.<sup>56</sup>

Lurasidone is metabolized primarily through the cytochrome P450 3A4, and it should be used with caution in combination with strong CYP3A4 inhibitors such as ketoconazole, clarithromycin, and voriconazole (the latter two no longer in the American market), or inducers such as rifampin, St John's Wort, phenytoin, and carbamazepine.<sup>56</sup> Dose adjustments are generally recommended in patients with renal and hepatic impairment.<sup>56</sup> Renal impairment may require initial dosing at 20 mg/day with a maximum dose of 80 mg/day for creatinine clearance  $< 50$  mg/min. However, since most of the deactivation of the drug is hepatic, these recommendations are precautionary. For hepatic impairment patients with a Child–Pugh Class B, starting dose is 20 mg/day with a maximum dose of 80 mg/day; Child–Pugh Class C patients should start at 20 mg/day with a maximum dose of 40 mg/day.<sup>56</sup>

Last, safety and tolerability in pediatric and geriatric populations diagnosed with either bipolar I disorder or schizophrenia has not been established.<sup>56</sup> However, in a review of the pharmacologic and clinical profile of lurasidone, according to industry data, no dose adjustment was needed in patients 65–85 years of age since no significant differences were found in concentrations of lurasidone among adult and geriatric patients diagnosed with schizophrenia.<sup>62</sup> Furthermore, because of improved cognition experienced in geriatric patients taking lurasidone and its lower potential for anticholinergic and hypotensive effects, further study is warranted in this age group.<sup>62</sup> It should be remembered that all antipsychotics carry an FDA class warning that death in severely demented, agitated patients with psychosis is nearly twice as common as in patients not receiving such medications.

## Conclusion

Lurasidone is a new second-generation antipsychotic that appears to have the desired property of antagonizing 5HT<sub>7</sub> receptors at relatively low doses. It is believed that this 5HT<sub>7</sub> blockade mediates the clinical improvement in depression. This effect occurs when lurasidone is administered alone or in combination with a mood stabilizer. The adverse effects seen in patients with bipolar illness receiving lurasidone are uncommon and generally mild. The effect on metabolic parameters is very favorable. Lurasidone is a new safe and effective option for the management of bipolar depression.

## Disclosure

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