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REVIEW

Lurasidone for the treatment of bipolar depression: an evidence-based review

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Rachel Franklin[1]
Sam Zorowitz[1]
Andrew K Corse[1]
Alik S Widge[2]
Thilo Deckersbach[1]

[1]Division of Neurotherapeutics, Department of Psychiatry, Massachusetts General Hospital, Harvard Medical School, Charlestown, [2]Picower Institute for Learning and Memory, Massachusetts Institute of Technology, Cambridge, MA, USA

Abstract: Bipolar disorder (BD) is a debilitating and difficult-to-treat psychiatric disease that presents a serious burden to patients' lives as well as health care systems around the world. The essential diagnostic criterion for BD is episodes of mania or hypomania; however, the patients report that the majority of their time is spent in a depressive phase. Current treatment options for this component of BD have yet to achieve satisfactory remission rates. Lurasidone is a drug in the benzisothiazole class approved by the US Food and Drug Administration in June 2013 for the acute treatment of bipolar depression. Its pharmacological profile features high-affinity antagonism at D_2, 5-HT_{2A}, and 5-HT_7 receptors; moderate-affinity antagonism at α_{2C}-adrenergic receptors; low- to very low-affinity antagonism at α_{1A}-adrenergic, α_{2A}-adrenergic, H_1, M_1, and 5-HT_{2C} receptors; and high-affinity partial agonism at 5-HT_{1A}. Preliminary findings from two recent double-blinded clinical trials suggest that lurasidone is efficacious in treating bipolar I depression, with clinical effects manifesting as early as the first 2–3 weeks of treatment (as measured by the Montgomery–Åsberg Depression Rating Scale and Clinical Global Impressions Scale for use in bipolar illness). Its therapeutic benefit appears to be comparable to the current US Food and Drug Administration-indicated treatments: quetiapine and olanzapine–fluoxetine, according to a measure of effect size known as number needed to treat. These studies reported relatively limited extrapyramidal and metabolic side effects as a result of treatment with lurasidone, with the most common side effect being nausea. Safety data drawn from these studies, as well as a more extensive body of schizophrenia research, indicate that in comparison with other atypical antipsychotics, treatment with lurasidone is less likely to result in metabolic side effects such as weight gain or disturbances of serum glucose or lipid levels. Lurasidone holds clinical potential as a novel, efficacious pharmacological treatment for bipolar depression. However, current data on its use for the treatment of BD are limited, and more extensive research, both longer in duration as well as independently conducted, is needed.

Keywords: lurasidone, bipolar depression, bipolar disorder, atypical antipsychotic

Introduction

Bipolar disorder (BD) is a chronic and often severely disabling psychiatric condition. Collectively, forms of BD (type I, type II, or not otherwise specified) are estimated to affect approximately 4.4% of Americans or about 12.7 million people.[1,2] Worldwide, BD was ranked 18th by the World Health Organization in worldwide causes of years lived with disability, surpassing all forms of cancer.[3] The economic burden in terms of cost of health care for patients with BD is estimated to be four times greater than that for patients without mental disorders.[4] Overall, the total economic burden of BD to the US economy is difficult to estimate, but one 24-year-old study approximated the figure to be nearly $45 billion,[5] adjusted for inflation; in 2015, the estimate will be closer to $78 billion.[6]

The essential diagnostic criterion for BD is episodes of elevated/irritable mood, usually either mania (type I) or hypomania (type II).[7] Despite this, BD patients have

Correspondence: Thilo Deckersbach
Room 2628, Building 149, 13th Street, Division of Neurotherapeutics, Department of Psychiatry, Massachusetts General Hospital, Harvard Medical School, Charlestown, MA, USA
Tel +1 617 724 6300
Fax +1 617 726 4078
Email tdeckersbach@partners.org

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reported through surveys and clinical status ratings that they spend the majority of their time in a depressive phase[8] and that these episodes are more disruptive to their functioning than mania.[9] Bipolar depression is notably distinct from unipolar depression in that its phenomenological features more commonly include psychosis, depressive mixed state, anxiety, agitation, anergic depression, irritability, and anger attacks.[10] Moreover, the increased risk of suicide in patients with BD (whose rates of suicide are one of the highest among patients with psychiatric illness)[11,12] is observed predominantly during the depressive phase.[11,12]

Treatment of BD aims for remission of symptoms, both manic and depressive. Efficacious treatment, however, is not easy to achieve; the remission rate for bipolar mania and depression after acute treatment is reported to be approximately 40%–50% and 25%–60%, respectively.[13,14] (This estimate is possibly misrepresentative of long-term remission, as a common feature of BD depression is insensitivity to acute treatment).[10] Factors complicating treatment include tolerance to medications and significant likelihood of relapse,[15] even with continual pharmacological maintenance.

Pharmacotherapy options for BD are typically grouped by the targeted symptoms. Lithium, first- and second-generation antipsychotics, valproate, and carbamazepine are usually prescribed for the treatment of acute mania, while quetiapine, olanzapine–fluoxetine, lamotrigine (maintenance), and antidepressants in conjunction with an antimanic agent (acute) are usually prescribed for the treatment of depressive symptoms.[16,17] Currently, only quetiapine, olanzapine–fluoxetine combination, and lurasidone are approved by the Food and Drug Administration (FDA) to treat bipolar depression. Further treatment options are greatly needed, as bipolar depression, the most prevalent and fatal feature of BD, is often not well covered by these regimens and nonresponse to first-line options is perhaps as high as 40%.[18] In a review of therapeutic options for treatment-resistant BD depression, Sienaert et al found that although promising, current research for this diagnosis is scarce.[18] In this review, we aim to summarize recent available literature regarding the compound lurasidone and its role in the treatment of bipolar depression.

Pharmacology and pharmacokinetics

The biological basis of BD depression remains unknown: one current theory, developed by Fountoulakis et al[19] postulates that unlike unipolar depression, norepinephrine reuptake and 5-HT_{1A} agonism are heavily implicated as core deficits. Pharmacologically, lurasidone is appropriate to treat these features, though long-term clinical data in conjunction with neurobiological models remain to be established.

Lurasidone or (3aR,4S,7R,7aS)-2-{(1R,2R)-2-[4-(1,2-benzisothiazol-3-yl)piperazin-1-ylmethyl]cyclohexylmethyl}hexahydro-4,7-methano-2H-isoindole-1,3-dione hydrochloride[20] (as it is known chemically) (Figure 1 for 3D chemical structure) is a chemical in the benzisothiazole class, structurally related to perospirone and ziprasidone, as well as the benzisoxazole derivative risperidone.[21] In vitro assays have demonstrated that lurasidone is a full antagonist at D_2 (K_i=1.68 nM)[22] (Table 1) and 5-HT_{2A} (K_i=2.03 nM) receptor subtypes, a property shared by other atypical antipsychotics such as risperidone, olanzapine, quetiapine, clozapine, and aripiprazole.[22] In comparison to similar drugs, lurasidone has the highest binding affinity for the 5-HT_7 receptor (K_i=0.5 nM).[22] Other notable pharmacological properties include moderate-affinity α_{2C}-adrenergic antagonism, partial agonism at the 5-HT_{1A} receptor, and low affinity for the muscarinic (M_1), histamine (H_1) (both K_i values >1,000 nM), 5-HT_{2C} (415 nM), α_{1A} (47.9 nM), and α_{2A} (40.7 nM) adrenergic receptors.[23] Table 1 shows the pharmacological profile of lurasidone.

There is limited evidence that lurasidone may provide cognitive benefits due to several properties of its binding profile. Blocking activity at the 5-HT_7 receptor (K_i=0.5 nM) may contribute to therapeutic benefits as suggested by a study of the drug's effect on learning when given in conjunction with an *N*-methyl-D-aspartate blocker.[22] Ishiyama et al found that rats were prevented from learning a passive-avoidance shock response when administered with *N*-methyl-D-aspartate receptor antagonist dizocilpine; this inhibition, however, was dose dependently reversed when the animals were given lurasidone, regardless of pre- or post-training administration.

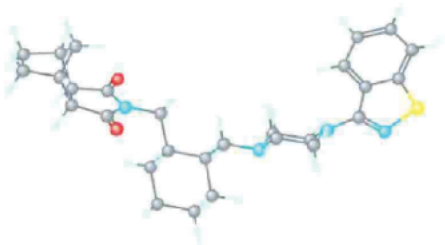

Figure 1 Three-dimensional structure of lurasidone, also known as (3aR,4S,7R,7aS)-2-{(1R,2R)-2-[4-(1,2-benzisothiazol-3-yl)piperazin-1-ylmethyl]cyclohexylmethyl}hexahydro-4,7-methano-2H-isoindole-1,3-dione hydrochloride or Latuda.

Notes: Molecular weight is 529.13698 g/mol and molecular formula is $C_{28}H_{37}ClN_4O_2S$. Teal atoms represent hydrogen, gray atoms carbon, red atoms oxygen, blue atoms nitrogen, and the yellow atom a sulfur; the associated hydrogen chloride salt is not pictured.[18]

Table 1 Binding profile of the chemical lurasidone: endogenous neurotransmitter, characteristic activity type, and experimental K_i values associated with major receptors

Binding profile of lurasidone[a]			
Receptor	**Neurotransmitter**	**Activity**	**Binding affinity (K_i)[b] (nM)**
D_1	Dopamine	Antagonist	262
D_2	Dopamine	Antagonist	1.68±0.09[c]
5-HT_{1A}	Serotonin	Partial agonist	6.75±0.97
5-HT_{2A}	Serotonin	Antagonist	2.03±0.46
5-HT_{2C}	Serotonin	Antagonist	415
5-HT_7	Serotonin	Antagonist	0.495±0.090
α_{1A}	Norepinephrine	Antagonist	47.9±7.8
α_{2A}	Norepinephrine	Antagonist	40.7±7.7
α_{2C}	Norepinephrine	Antagonist	10.8±0.64
H_1	Histamine	Antagonist	>1,000
M_1	Acetylcholine	Antagonist	>1,000

Notes: [a]Experimental values reported by Ishibashi et al.[22] [b]The equilibrium dissociation constant, decreased value indicated increased affinity. [c]Values are means ± standard error of the mean of three or more separate experiments.

This effect suggests that lurasidone may contribute to restoration of the memory consolidation process and may therefore have benefits in reducing the cognitive impairments observed in bipolar depression.[23]

Additionally, the drug acts with moderate binding affinity as an antagonist at α_{2C}-adrenergic receptor (K_i=10.8 nM), overexpression of which has been shown to increase impairment in the Morris water maze,[24] further lending support to possible procognitive effects of lurasidone.

Lurasidone also interacts as a partial agonist at the 5-HT_{1A} receptor (K_i=6.75 nM),[22] activation of which has been shown to increase adult neuronal proliferation in the dentate gyrus of the hippocampus.[25] This influence in neurogenesis may be of cognitive therapeutic benefit, as demonstrated by pilot clinical studies using antipsychotics with adjunct 5-HT_{1A} agonists.[26]

Overall, based on neurobiological evidence, lurasidone may provide advantages in learning and memory via high-affinity 5-HT_7 and moderate-affinity α_{2C}-adrenergic antagonism, as well as partial agonism at the 5-HT_{1A} receptor.[22,23,27]

The 5-HT_7 receptor-blocking activity of lurasidone may also underlie antidepressant properties of the drug. Selective antagonists and experiments in 5-HT_7 gene knockout animals have demonstrated anxiolytic-like and antidepressant-like effects in rodents, which demonstrated improvement on the Vogel drinking, elevated plus-maze, four-plate test, forced swimming, and tail suspension tests.[28,29] It is far from proven that these tests translate well to human depression, unipolar or bipolar, but they may be useful screens. These mood effects may be mediated by a cortical and hippocampal dopamine efflux caused by activity at the 5-HT_7 and 5-HT_{1A} receptors.[30]

Similarly, lurasidone injected subcutaneously in adolescent rats modulates levels of brain-derived neurotrophic factor by preventing adult decreases in brain-derived neurotrophic factor expression normally seen in animals exposed to prenatal stress.[31] This effect provides support for the neurotrophic hypothesis of depression[32] and further implicates lurasidone as a potentially beneficial therapy for bipolar depression.

Clinically, one of the most promising features of lurasidone is its low affinity for muscarinic (M_1), histamine (H_1) (both K_i values >1,000 nM), 5-HT_{2C} (415 nM), α_{1A}-(47.9 nM), and α_{2A}-(40.7 nM) adrenergic receptors.[33] Well-known side effects of many antipsychotics, such as sedation, weight gain, and negative cognitive symptoms, have been only minimally observed in both animal and human trials of lurasidone (see "Safety and tolerability" section). This is thought to be due to the low levels of activity of lurasidone at H_1[34] and 5-HT_{2C}[35] receptors.[22] Decreased interaction with muscarinic and α-1 adrenergic receptors may prevent negative cognitive and cardiovascular side effects.[36]

Despite being a high-affinity D_2 receptor antagonist, historically a harbinger of severe neurological side effects,[33] in vivo studies of lurasidone to date have observed fewer central nervous system's depressive effects, extrapyramidal symptoms, and anticholinergic side effects (such as dry mouth or amnesia)[22] than other typical and even other atypical antipsychotics. This may be explained in part by the drug's receptor saturation point. A study of lurasidone's dopamine D_2 receptor binding in healthy males using positron emission tomography demonstrated that doses less than 40 mg did not achieve adequate binding to reach antipsychotic effect;[37] however, increasing the dose from 60 mg to 80 mg did

not effectively change receptor occupancy (77%–84% and 73%–79%, respectively). This curve may explain, in part, why incidents of parkinsonism are infrequently seen, as there appears to be a dopamine receptor saturation point well below the threshold for extrapyramidal symptomology.

Lurasidone is primarily metabolized by CYP3A4, with the most common pathways being oxidative *N*-dealkylation, hydroxylation of the norbornane ring, and *S*-oxidation. The half-life, described in the product label as 18 hours, has been reported in some studies to be as long as 37 hours, given repeated oral doses at steady state.[33] Several known pharmacologically active metabolites have been described such as ID-14283, ID-14326, and ID-11614 (25%, 3%, and <1% of parent exposure, respectively).[33] In vitro studies demonstrated that both ID-14283 and ID-14236 showed affinity for D_2 and 5-HT_{2A}, as well as partial agonism at 5-HT_{1A} and antagonism at 5-HT_7. ID-14283 may contribute to the parent compound's efficacy, but has a shorter half-life (7 hours).[21]

Therapeutic efficacy

Though there now exists a growing body of literature detailing the pharmacokinetic properties of lurasidone, a complementary body of literature documenting its efficacy for the treatment of bipolar I disorder is comparatively less due to the short time since initial approval.[38] At the time of writing, only two controlled clinical trials have begun to investigate lurasidone as a treatment for bipolar I depression: as a monotherapy[39] and as an adjunct treatment with lithium or valproate.[40]

The first of the two clinical trials was a randomized, double-blind, placebo-controlled, fixed-flexible dose study investigating the efficacy of lurasidone as a monotherapy treatment for bipolar I depression. Patients were randomly assigned to a 6-week treatment group of 20–60 mg/day of lurasidone (N=166; mean daily dose =31.8 mg), 80–120 mg/day of lurasidone (N=169; mean daily dose =82.0 mg), or a placebo (N=170). The primary outcome measure was the change between baseline and week 6 scores on the Montgomery–Åsberg Depression Rating Scale (MADRS); a secondary outcome measure was the change in the depression severity score on the Clinical Global Impressions Scale for use in bipolar illness (CGI-BP).

The investigators reported significantly greater decreases in MADRS scores in both the 20–60 mg/day group (−15.4) and in the 80–120 mg/day group (−15.4) as compared to the placebo group (−10.7) (Figure 2A). Moreover, a significantly greater reduction in core depressive symptoms (MADRS-6 subscale score) between baseline and week 6 was also observed for the lurasidone 20–60 mg group (−10.4) and the lurasidone 80–120 mg group (−10.4) as compared to the placebo group (−6.9). A similar pattern was found in the CGI-BP scores for the 20–60 mg/day group (−1.8) and the 80–120 mg/day group (−1.7) as compared to placebo (−1.1). Notably, these statistically significant decreases in MADRS and CGI-BP scores were observed in both dosage groups early in the course of treatment; differences between the groups in reported MADRS scores began at week 2, whereas

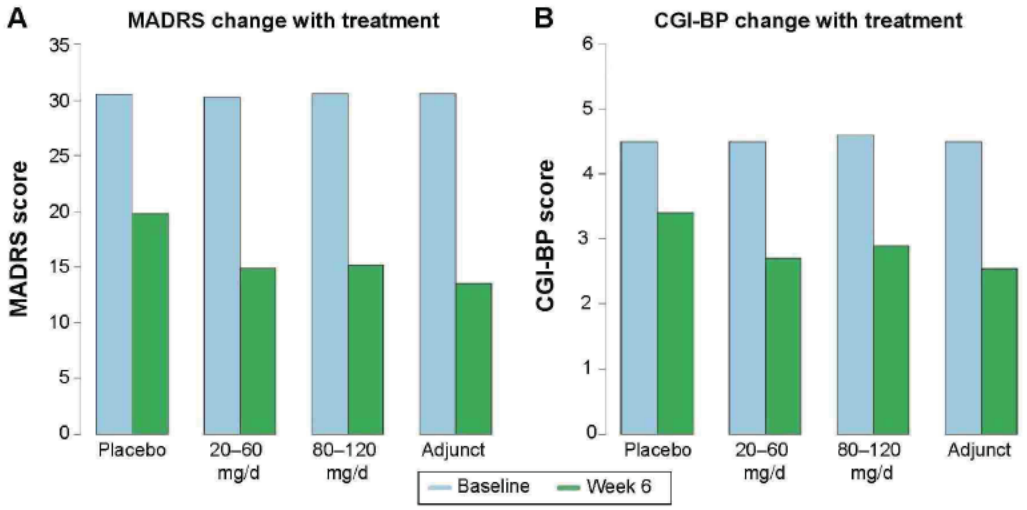

Figure 2 Differences among behavioral outcomes by lurasidone treatment regimen between baseline and Week 6 as measured by MADRS score and CGI-BP score.
Notes: (**A**) Mean change in MADRS from baseline to week 6 across different treatments in patients with bipolar I depression. (**B**) The mean change in depression severity score on the CGI scale from baseline to week 6 for the same treatment groups. Placebo, 20–60 mg/day and 80–120 mg/day values reported in Loebel's monotherapy study;[39] adjunct experimental values from Loebel et al's investigation of lurasidone as adjunctive treatment with lithium and valproate.[40]
Abbreviations: MADRS, Montgomery–Åsberg Depression Rating Scale; CGI-BP, Clinical Global Impressions Scale for use in bipolar illness; d, day.

differences in reported CGI-BP scores began at week 1 for the 80–120 mg group and week 2 for the 20–60 mg group. Caution is warranted, however, in interpreting these results as the authors included neither standard deviations nor confidence intervals in the differences in MADRS or CGI-BP scores. Nonetheless 53% and 51% of subjects met response criteria (defined as ≥50% reduction from baseline in MADRS total) after 6 weeks of treatment with lurasidone 20–60 mg and lurasidone 80–120 mg, respectively, as compared to only 30% in the placebo group. Finally, the lurasidone 20–60 mg and lurasidone 80–120 mg groups both showed proportionately higher remission rates (42%; 40%) than did the placebo group (25%).

The second of the two clinical trials was also double blinded, but investigated lurasidone as an adjunct to lithium or valproate in the treatment of bipolar I depression. Inclusion criteria required that patients should not have exhibited a response to a 28-day minimum trial of either lithium or valproate, prescribed at therapeutic levels, as determined by a health care professional. Qualifying patients were then randomly assigned to receive 6 weeks of lurasidone (N=183) or placebo (N=165) in addition to continuing their previously prescribed medication. Patients receiving lurasidone were initially administered a dosage of 60 mg; with each week after the first, health care professionals were allowed to adjust lurasidone doses by increments of 20 mg within a range of 20–120 mg/day (the mean daily dose was 66.3 mg). As in the monotherapy study, the primary and secondary outcomes of interest were changes in the MADRS and CGI-BP scores, respectively, between baseline and week 6 of the trial.

Similar to the results of the monotherapy trial, significantly greater decreases in MADRS and CGI-BP scores were observed for the adjunct lurasidone group (−17.1; −1.96) than for the placebo group (−13.5; −1.51) (Figure 2B). These differences were first observed beginning at week 3 for the MADRS as well as at week 2 for the CGI-BP, and remained reliably different for the remainder of the trial. As mentioned earlier, caution is again warranted in interpreting these results as the authors included neither standard deviations nor confidence intervals in the differences in MADRS or CGI-BP scores. Finally, greater proportions of patients met response criteria (≥50% reduction from baseline in MADRS total) and remission (57%; 50%) than were observed in the placebo group (42%; 35%).

Although promising, these preliminary results regarding the therapeutic efficacy of lurasidone for the treatment of bipolar I depression should be considered with respect to the efficacy of preexisting treatments, specifically quetiapine and olanzapine–fluoxetine combination. Recently, Citrome et al[41] compared the benefits of these three treatments using the number needed to treat (NNT) measure.[42] As an indicator of effect size, NNT measures how many patients would need to be treated with one medication, on average, to observe one additional beneficial outcome of interest. Low NNTs are indicative of large effect sizes, with an example NNT of 2 indicating that on average, one of every two patients treated with a medication would receive the desired clinical benefit.

Citrome et al calculated the NNT for clinical response and remission for lurasidone based on the above two clinical trials, as well as the NNT for quetiapine (immediate and extended release) and olanzapine–fluoxetine combination based on published 8-week trials and product labeling (see article for details).[43] Of the three reviewed quetiapine studies, two studies set dosing levels at 300 mg/day and 600 mg/day;[43,44] the other prescribed quetiapine studies set dosing levels at 400 mg/day and 800 mg/day.[45] In the two reviewed olanzapine–fluoxetine combination studies, the dosing levels were set at 6/25 mg/day, 6/50 mg/day, or 12/50 mg/day.[46,47] Clinical response was defined as a ≥50% reduction from baseline on the MADRS, whereas remission was defined as a final MADRS score of ≤12. For clinical response, NNT values of 5 (95% CI 3–8) and 5 (95% CI 4–11) were found for patients prescribed monotherapy lurasidone at low (20–60 mg/day) or high (80–120 mg/day) doses; an NNT value of 7 (95%, 4–24) was found for adjunct lurasidone (20–120 mg/day). In comparison, NNT values of 6 and 5 were found for quetiapine and olanzapine–fluoxetine combination in clinical response, respectively. For clinical remission, an NNT value of 6 (95%, 4–14) was found for patients with a low dose (20–60 mg/day) of monotherapy lurasidone; an NNT value of 7 (95%, 4–21) was found for patients with a high dose (80–120 mg/day) of monotherapy lurasidone; and an NNT value of 7 (95%, 4–23) was found for patients with 20–120 mg/day adjunct dose of lurasidone. In comparison, NNT values of 6 and 4 were found for quetiapine and olanzapine–fluoxetine combination in clinical response, respectively.[41,42] It is worth noting that 95% confidence intervals were similarly not reported for the NNT values of the comparative treatments. Perhaps related to this, Citrome et al offer a conservative conclusion regarding the therapeutic efficacy of lurasidone relative to its predecessors, stating only that it yielded comparable benefits for treatment.

In summary, preliminary findings from two recent double-blinded clinical trials suggest that lurasidone is efficacious in treating bipolar I depression, with clinical effects manifesting as early as the first 2–3 weeks of treatment (as measured by MADRS and CGI-BP). Its therapeutic benefit, however,

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