

Lurasidone as a potential therapy for bipolar disorder

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Abstract: Lurasidone is a benzisothiazol derivative and an atypical antipsychotic approved by the US Food and Drug Administration for the acute treatment of adults with schizophrenia (October 2010) and bipolar I depression (June 2013). Lurasidone has a strong antagonistic property at the D_2 , serotonin ($5-HT_{2A}$), and $5-HT_7$ receptors, and partial agonistic property at the $5-HT_{1A}$ receptor. Lurasidone also has lower binding affinity for the α_{2C} and $5-HT_{2C}$ receptor. Lurasidone is rapidly absorbed (time to maximum plasma concentration: 1–3 hours), metabolized mainly by CYP3A4 and eliminated by hepatic metabolism. In two large, well-designed, 6-week trials in adult patients with bipolar I depression, lurasidone monotherapy and adjunctive therapy with mood stabilizers were significantly more effective than placebo at improving depressive symptoms assessed using the Montgomery–Åsberg Depression Rating Scale total score. In both trials, lurasidone also reduced the Clinical Global Impression–Bipolar Severity depression score to a greater extent than placebo. In these two trials, discontinuation rates due to adverse events in the lurasidone group were small (<7%) and were not different from those of the placebo group. The most common adverse events in the lurasidone group were headache, nausea, somnolence, and akathisia. The changes in lipid profiles, weight, and parameters of glycemic control were minimal, and these findings were in line with those observed in schizophrenia trials. Further active comparator trials and long-term tolerability and safety data in bipolar patients are required. Lurasidone may be an option for the management of depressive symptoms in patients with bipolar I disorder, and it may be considered as a treatment alternative for patients who are at high risk for metabolic abnormalities.

Keywords: lurasidone, bipolar disorder, acute depression, metabolic

Introduction

Bipolar disorder is a chronic and recurrent psychiatric disorder.¹ Findings from recent studies generally indicate an overall lifetime prevalence of bipolar disorder of 1%–2.5%;^{2–4} however, using broadened diagnostic criteria, recent studies reported much higher lifetime prevalence rates ranging from 4.5%–10.9%.⁵ Moreover, these rates for bipolar spectrum disorders may be underestimated because they do not include patients with highly recurrent major depression – some of whom may fall within the bipolar spectrum.⁶

The natural course of bipolar disorder is variable; however, remission – the goal of treatment in bipolar disorder – is not easily achieved. The remission rate after acute treatment for mania is in the range of 40%–50%, and for depression is 25%–60%.⁷ In a recent large cohort study, only 60% of patients achieved remission during a 2-year follow-up period.⁸ Chronic persistence of symptoms can be expected

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in about 20% of cases, and social incapacity in about 30%.⁶ Judd et al⁹ carried out a follow-up study over 13 years and reported that bipolar patients were symptomatic during about half of the follow-up period. Specifically, the frequent occurrence of subsyndromal symptoms has been noted in longitudinal studies.^{10–12} Subsyndromal symptoms have been associated with significant functional disability,^{13,14} and with an increased risk of relapse.^{15,16} Moreover, recurrence is not an exception rather than the rule. Almost all bipolar patients experience relapse, given adequate observation time.¹⁷ More than 90% of patients who have a single manic episode will have future episodes;¹⁸ about half of patients recur within 12 months after a mood episode, and the recurrence rate at 5 years is about 85%.^{18,19}

Several treatments including antipsychotics, anticonvulsants, lithium, or electroconvulsive therapy have been reported to be efficacious and successful in the treatment of bipolar disorder. However, in reality, few drugs come close to being “true mood stabilizers” – agents that have acute efficacy in the treatment of manic, mixed, and depressive episodes – which are effective in preventing all types of episodes and residual symptoms.²⁰ Classic mood stabilizers or anticonvulsants, including lithium and valproate, have been used as first-line therapies for acute and maintenance treatment of patients with bipolar I disorder. However, there is the need for more effective pharmacotherapy for acute depression and for the maintenance phase because bipolar depression is less responsive to classic mood stabilizers,²¹ and outcomes after relapse have been generally reported as poor.^{18,22,23} During the past decade, atypical antipsychotics have been the class of agents most studied across various phases of bipolar disorder, and updated treatment guidelines reflect an expanded role for atypical antipsychotics in bipolar disorder treatment.

Lurasidone was approved by the US Food and Drug Administration (FDA) in July 2013 for the treatment of bipolar depression as monotherapy, or in combination with lithium or valproate. However, at the time of writing this review (July 2013), we did not identify any clinical studies written on bipolar disorder and lurasidone that had been published in peer reviewed journals. There were only two Phase III studies noted, of which, the results were reported as poster presentations during international conferences.^{32,33} In this review, we will summarize the study results from these two Phase III bipolar depression studies, as well as present the results of preclinical and clinical trials of lurasidone from subjects with schizophrenia.

Review of the pharmacology, mode of action, and pharmacokinetics of lurasidone

Lurasidone is a chemical of the benzisothiazol class. It has full antagonistic properties at the dopamine (D)₂ and serotonin 2A (5-HT_{2A}) receptors like other second-generation antipsychotics.²⁴ Lurasidone shows high selectivity at the D₂ receptor when compared to the D₁, D₃, and D₄ subtypes.²⁵ Lurasidone also has partial agonistic properties of high affinity at the 5-HT_{1A} receptor.²⁴ Lurasidone has much greater binding affinity at the 5-HT₇ receptor compared to other second-generation antipsychotics, and the blockade of this receptor subtype is also thought to contribute to lurasidone's antipsychotic actions.^{24,26} There have also been several studies that suggested the positive impacts of 5-HT₇ antagonistic effects on memory²⁷ and affective symptoms.²⁸ Lurasidone has weak affinity for norepinephrine α_{2C} and the 5-HT_{2C} receptor.²⁹ The weak affinity for α_{2C} suggests a low probability of causing orthostatic hypotension, and the weak affinity for the 5-HT_{2C} receptor suggests a low propensity of causing weight gain.²⁴ Lurasidone poses negligible affinity at the muscarinic receptors and the histamine H₁ receptors, which are associated with weight gain and sedation.^{24,30} The receptor profiles possessed by lurasidone mentioned above have been expected to explain lurasidone's efficacy, not only against positive and negative symptoms, but also for affective symptoms.²⁹

After oral administration of lurasidone, it is rapidly absorbed. The time to maximum plasma concentration (T_{max}), is about 1 hour to 3 hours. The bioavailability is from 9% to 19%;²⁹ however, pharmacokinetic studies showed that lurasidone absorption is influenced by food consumption.²⁵ If administered with food, the exposure of lurasidone showed a twofold increase; the maximum concentration (C_{max}) also increased by threefold. The T_{max} is shown to increase by 0.5–1.5 hours with food.²⁵ However, fat content in food and caloric intake did not seem to have an influence on the overall effect observed when taking lurasidone with food.^{25,29} Considering the significant food effect on the bioavailability of lurasidone, lurasidone is recommended to be administered once daily with at least 350 calories of food.²⁶

After absorption of lurasidone distributes extensively in tissues.²⁴ It showed a dose-dependent increase in the occupancy of the D₂ receptor until a dose of 60 mg of lurasidone was reached (77.4%–84.3%); however, after 80 mg, it showed no further increase in the D₂ receptor occupancy at the T_{max} among healthy subjects.³¹ D₂ occupancy among healthy male subjects was 63.1%–67.5%, 77.4%–84.3%, and

72.9%–89.9% after a single administration of 40 mg, 60 mg, and 80 mg, respectively.²⁵ Lurasidone showed 99.5% protein binding, and it also binds to α_1 glycoprotein and albumin.³¹

Lurasidone is metabolized primarily by CYP3A4 into several metabolites, including the hydroxylated derivative ID-20220, the acidic derivative ID-20219, ID-14326, ID-11614 (BITP), and ID-14283. Both ID-20219 and ID-20220 have been found to have negligible affinity at the 5-HT_{1A}, 5-HT_{2A}, and 5-HT₇ receptor subtypes.²⁴ ID-11614 also has low affinity at the 5-HT₂ receptor and the D₂ receptor, and it does not have antipsychotic action in preclinical tests.²⁴ Conversely, both ID-14283 and ID-14326 have binding affinity at the D₂ and 5-HT_{2A} receptors, which is similar to lurasidone. They also have high binding affinity at 5-HA_{1A} and 5-HT₇, which is comparable to lurasidone. Both metabolites, especially ID-14283, seem to contribute to the antipsychotic action of lurasidone.^{24,26} The T_{max} of ID-14283 is 1.6 hours to 1.8 hours, and its half-life ($T_{1/2}$) is 7.48–10 hours.^{26,31}

Lurasidone is eliminated mainly by hepatic metabolism.²⁶ Among schizophrenia patients, the $T_{1/2}$ ranges from 28.8–37.4 hours after administration of a single dose with 120 mg/day to 160 mg/day. Among healthy volunteers, however, the $T_{1/2}$ is 12.2 hours to 18.3 hours after single-dose administration of 100 mg or less. However, the $T_{1/2}$ increases up to 36 hours on the 9th day after continuous dose administration.²⁶ A steady state was reached within 7 days.²⁶

Lurasidone exposure between older adults with psychosis and younger patients was comparable after the administration of 20 mg/day of lurasidone. Thus, like other atypical antipsychotics, dose adjustment in the elderly is not necessary. So far, the pharmacokinetics of lurasidone have not been investigated among adolescent and pediatric patients.²⁴ Renal impairment is known to cause an increase in exposure to lurasidone. Compared to healthy controls, mild, moderate, and severe kidney disease caused a mean C_{max} increase of 40%, 92%, and 54%, respectively. It also caused a mean increase in plasma exposure, which was calculated using area under the curve (AUC), of 53%, 91%, and 100%, respectively. With an increased severity of kidney impairment the $T_{1/2}$ was prolonged. Thus, taken together, the manufacturer recommended that the doses of lurasidone should not exceed 40 mg among moderate to severe cases of renal impairment. In addition, 40 mg should not be exceeded among patients with moderate to severe hepatic impairment. In comparison to healthy controls, it was found that mild, moderate, and severe hepatic impairment caused a mean increase in C_{max} of 1.3 times, 1.2 times, and 1.3 times, respectively. Mild, moderate, and severe hepatic impairment also caused an increase in the mean AUC

of 1.5 times, 1.7 times, and three times higher, respectively. The mean $T_{1/2}$ among patients with hepatic impairment of moderate severity was greater than among healthy controls (112 hours versus 93 hours); however, there have been no data regarding the $T_{1/2}$ among severe hepatic impairment.²⁴

Lurasidone should be used with caution when coadministered with CYP3A4 inhibitors or inducers.²⁴ A moderate CYP3A4 inhibitor appeared to double the C_{max} and AUC of lurasidone and its metabolite, ID-14283, in healthy adults; whereas, rifampin (600 mg/day) (the CYP3A4 inducer) was shown to reduce lurasidone exposure by 85% after a single-dose administration of 40 mg of lurasidone among healthy adults.²⁴

Therapeutic efficacy

The efficacy of lurasidone in the treatment of depressive episodes in adults with bipolar disorder has been investigated in two Phase III randomized, double-blind trials,^{32,33} and lurasidone was recommended as a second-line treatment for bipolar I depression in a recently published treatment guideline (Table 1).³⁴ The results from the two Phase III studies are not yet published in peer reviewed journals; thus, this review is largely based on two abstracts that were not peer reviewed.

One of these trials (the Program to Evaluate Antidepressant Impact of Lurasidone [PREVAIL]-1 study³²) evaluated the efficacy and safety of adjunctive lurasidone in patients with bipolar I depression. During a 6-week double-blind treatment, 20–120 mg/day of lurasidone (number [N] = 183) or placebo (N = 165) was added to lithium or valproate. This trial enrolled adults with a *Diagnostic and Statistical Manual of Mental Disorders, 4th Edition, Text Revision* diagnosis of bipolar I disorder and who remained symptomatic (with a Montgomery–Åsberg Depression Rating Scale [MADRS] score ≥ 20) following at least 4 weeks of treatment with either lithium or valproate, two commonly used mood stabilizers.³²

As adjunctive therapy, lurasidone with lithium or valproate improved depressive symptoms in bipolar I disorder. MADRS scores reduced from baseline to 6 weeks to a significantly greater extent than placebo. At baseline, the MADRS scores were similar for lurasidone (30.6) and placebo (30.8). The MADRS score reduction in the lurasidone group was –17.1 and was significantly greater than that of the placebo group (–13.5; $P < 0.01$) at week 6. Adjunctive lurasidone also reduced the Clinical Global Impression–Bipolar Severity (CGI-BP-S) depression score by –2.0 points versus –1.5 points for placebo ($P < 0.01$). At the end of the 6-week

Table 1 Completed trials with lurasidone in bipolar depression

Title	Criteria	Intervention	Results	Safety
<p>Phase III</p> <p>A randomized, 6-week, double-blind, placebo-controlled, flexible-dose, parallel group study of lurasidone adjunctive to lithium or divalproex for the treatment of bipolar I depression: PREVAIL-1, NCT00868452³⁶</p>	<p>Bipolar I disorder; most recent depressed episode; age: 18–75 years; have a lifetime history of at least one bipolar manic or mixed episode; taking lithium or divalproex at least 28 days prior to screening; MADRS score ≥ 20 and YMRS score ≤ 12</p>	<p>Lurasidone 20–120 mg/day or placebo adjunctive to lithium or valproate</p>	<p>Lurasidone treatment showed significantly greater MADRS score reduction at week 6 in the lurasidone group (–17.1) versus the placebo group (–13.5)</p> <p>Lurasidone treatment significantly reduced the CGI-BP-S depression score by –2.0 versus –1.5 for placebo</p> <p>Responder rates were significantly higher for the lurasidone group (57%) than for the placebo group (42%)</p> <p>Significant improvement when compared to placebo was observed for quality of life, as assessed by Q-LES-Q-SF (+22.2 in the lurasidone group and +15.9 in the placebo group)</p>	<p>Study completion rates were 78% (143/183) in the lurasidone group and 83% (136/163) in the placebo group</p> <p>The discontinuation rate due to adverse events for the lurasidone group (6%) was similar to that of the placebo group (8%)</p> <p>Most frequently reported adverse events were nausea, headache, and somnolence</p>
<p>Phase III</p> <p>A randomized, 6-week, double-blind, placebo-controlled, fixed-flexible dose, parallel-group study of lurasidone for the treatment of bipolar I depression: PREVAIL-2, NCT00868699³⁷</p>	<p>Bipolar I disorder; most recent depressed episode; age: 18–75 years; have a lifetime history of at least one bipolar manic or mixed episode; MADRS score ≥ 20 and YMRS score ≤ 12</p>	<p>Lurasidone 20–60 mg/day, lurasidone 80–120 mg/day, or placebo</p>	<p>Lurasidone treatment showed significantly greater MADRS score reduction at week 6 for both the lurasidone 20–60 mg group (–15.4) and the lurasidone 80–120 mg group (–15.4) versus the placebo group (–10.7)</p> <p>Both the lurasidone 20–60 mg group and the lurasidone 80–120 mg group differed significantly from the placebo group from week 2 onward</p> <p>Both the lurasidone 20–60 mg group (–1.8) and the lurasidone 80–120 mg group (–1.7) showed significant reductions in CGI-BP-S depression scores versus the placebo group (–1.1)</p> <p>Responder rates were significantly higher for the lurasidone 20–60 mg group (53%) and the lurasidone 80–120 mg group (51%) when compared with the placebo group (30%)</p> <p>Both the lurasidone 20–60 mg (+19.3) and lurasidone 80–120 mg (+19.8) groups showed significant improvements versus the placebo group (+12.8) on the Q-LES-Q-SF score</p>	<p>Study completion rates were 74.1% (123/166) in the lurasidone 20–60 mg group, 73.4% (124/169) in the lurasidone 80–120 mg group, and 74.7% (127/170) in the placebo group</p> <p>Discontinuation rates due to adverse events for the lurasidone 20–60 mg group (7%) and the lurasidone 80–120 mg group (6%) were similar to that of the placebo group (6%)</p> <p>Changes in weight, lipids, and measures of glycemic control were minimal</p> <p>Most frequently reported adverse events were nausea, headache, and akathisia</p>

Abbreviations: MADRS, Montgomery–Åsberg Depression Rating Scale; YMRS, Young Mania Rating Scale; CGI-BP-S, Clinical Global Impression–Bipolar Severity; Q-LES-Q-SF, Quality of Life, Enjoyment, and Satisfaction scale short form.

study period, when compared to placebo, lurasidone recipients achieved significantly higher MADRS response (57% versus 42%; $P < 0.01$).

The monotherapy trial (PREVAIL-2 study³³) enrolled patients with a *Diagnostic and Statistical Manual of Mental Disorders, 4th Edition, Text Revision* diagnoses of bipolar 1 disorder and who were currently experiencing a depressed episode, with or without rapid cycling, and who had a MADRS score ≥ 20 and who had a Young Mania Rating Scale score ≤ 12 . Eligible patients were randomized to 6 weeks of a once-daily, double-blind treatment with either lurasidone (20–60 mg; $N = 166$), lurasidone (80–120 mg; $N = 169$), or placebo ($N = 170$).³³ Monotherapy with lurasidone for both the 20–60 mg group and the 80–120 mg group improved depressive symptoms in bipolar 1 patients, reducing the MADRS total scores from baseline to 6 weeks to a significantly greater extent than placebo. At the end of the 6-week trial, mean changes from baseline in the MADRS total score were -15.4 ($P < 0.001$) in the lurasidone 20–60 mg group and -15.4 ($P < 0.001$) in the lurasidone 80–120 mg group; these results were significantly greater than that of the placebo group (-10.7). With respect to monotherapy, improvements in the MADRS score were significant from week 2 onwards in both of the lurasidone dose groups. Lurasidone treatment resulted in significantly greater CGI-BP-S depression scores for both the lurasidone 20–60 mg group (-1.8 ; $P < 0.001$) and the lurasidone 80–120 mg group (-1.7 ; $P < 0.001$) when compared with the placebo group (-1.1). MADRS response rates observed in the lurasidone 20–60 mg group (53%; $P < 0.001$) and in the lurasidone 80–120 mg group (51%; $P < 0.001$) were significantly greater than that of the placebo group (30%) at week 6.³³

In an analysis of anxiety symptoms among the PREVAIL-1 and PREVAIL-2 study populations,³⁵ lurasidone also improved anxiety symptoms in bipolar depression, whether used adjunctively to mood stabilizers or as monotherapy. In the PREVAIL-1 trial, adjunctive treatment with lurasidone significantly reduced anxiety symptoms when compared with placebo, as indicated by the greater Hamilton Anxiety Rating Scale (HAMA) total score. Reduction of the HAMA total score in the lurasidone group was -8.0 , and -6.0 in the placebo group ($P = 0.003$). One hundred and eight patients (31.8%) in this study met the criteria for moderate to severe anxiety (HAMA ≥ 18) at baseline. The CGI-BP-S score was significantly higher in this subgroup (4.7) compared with patients with lower anxiety burden (4.4; $P < 0.001$). The response rate (a $\geq 50\%$ reduction in HAMA scores) in the moderate-to-severe anxiety subgroup was significantly higher among the lurasidone group (68.8%) than among the

placebo group (47.1%; $P = 0.016$). In the PREVAIL-2 trial, when compared with placebo, both of the lurasidone dose groups demonstrated significant reductions in anxiety levels at the end of week 6; HAMA score reductions were -6.8 in the lurasidone 20–60 mg group ($P = 0.001$ versus placebo), -6.3 in the lurasidone 80–120 mg group ($P = 0.015$ versus placebo), and -4.6 in the placebo group. One hundred sixty five patients (34.0%) met the criteria for moderate to severe anxiety (HAMA ≥ 18) at baseline. Similar to the findings from the PREVAIL-1 study, the reported general severity of illness reflected by the CGI-BP-S score of this subgroup (4.7) in the PREVAIL-2 was significantly higher compared to patients with lower anxiety at baseline (4.5; $P < 0.001$). More lurasidone patients with moderate to severe anxiety at baseline (52.0%) met anxiety treatment-responder criteria than patients with placebo (37.3%), but the difference did not reach statistical significance ($P = 0.102$).³⁵

To date, there is no published clinical trial regarding the efficacy of lurasidone in the treatment of bipolar mania or maintenance. Phase III trials in bipolar maintenance treatment are under way.

Safety and tolerability

There were no clinical studies on lurasidone and bipolar disorder published in peer reviewed journals so far. Thus, we will discuss the safety of lurasidone based on the results of previous studies conducted on schizophrenia or schizoaffective disorder that were published in peer reviewed journals, and we will address preliminary findings regarding its safety in bipolar disorder, as reported in several abstracts.

Lurasidone's safety, so far, has been assessed in short-term clinical trials and in a few long-term trials of lurasidone among schizophrenia or schizoaffective disorder patients.^{36–40} The clinical trials among bipolar disorder patients are currently being completed; however, limited evidence exists regarding the safety of lurasidone among these populations.²⁴ Preliminary findings based on several short-term studies among schizophrenia patients suggest that lurasidone is tolerable and safe with a low discontinuation rate.²⁴ Pooled analyses reported that about 8% of the subjects treated with lurasidone and 4% of the subjects treated with placebo discontinued their treatment prematurely because of adverse events.⁴¹ The most common adverse events reported in schizophrenia trials included somnolence, nausea, akathisia, parkinsonism, and sedation.^{24,42} A few long-term studies also suggested that long-term treatment of lurasidone is well tolerated and safe among schizophrenia populations.^{39,40}

Regarding extrapyramidal symptoms (EPS), short-term studies reported that EPS are more common in the subjects treated with lurasidone than in subjects treated with placebo (14.7% in the lurasidone group versus 5.1% in the placebo group).⁴³ Akathisia was reported more frequently in the lurasidone group (15%) as compared to the placebo group (3.3%).⁴³ Dystonia was observed in 4.7% of the lurasidone group compared with 0.7% of the placebo group.⁴³ The changes from baseline to the end of study period, however, were comparable for EPS (including for akathisia) between the lurasidone group and the placebo group.^{41,43,44}

Regarding adverse events related to weight gain, lurasidone is known to cause minimal effects on body weight among schizophrenia populations.²⁴ The short-term clinical trials reported a mean increase of body weight of 0.75 kg in the subjects treated with lurasidone compared with 0.26 kg in the subjects treated with placebo.^{24,43} The percentages of the subjects who showed a weight gain of 7% or more was 5.6% in the lurasidone group compared with 4% in the placebo group;⁴³ the weight gain did not seem to be dose related.²⁴ Potkin et al³⁶ found that mean weight changes were comparable between the lurasidone group and the ziprasidone group (−0.29 kg versus −0.16 kg). The evidence regarding the long-term effect of lurasidone on weight gain is limited, however, lurasidone showed a favorable effect on body weight compared with quetiapine extended release (XR) or risperidone in two long-term schizophrenia trials.^{39,40}

Lurasidone does not appear to influence clinically significant changes in glucose levels, or across other metabolic parameters.^{29,45} The pooled data analysis from short-term schizophrenia studies showed that the mean increases of fasting glucose levels were 1.4 mg/dL in subjects treated with lurasidone and 0.6 mg/dL in subjects treated with placebo; this difference was not statistically significant.⁴³ The adverse events related to fasting glucose level did not appear to be dose related.⁴³ A comparison trial with ziprasidone³⁶ showed similar changes in fasting glucose levels between the lurasidone group and the ziprasidone group (+4.7 mg/dL versus +4.8 mg/dL). In a long-term study comparing lurasidone with risperidone,⁴⁰ the median change of fasting glucose levels in the lurasidone group was −0.5 mg/dL, while that of the risperidone group was 3.0 mg/dL. Another long-term study comparing lurasidone with quetiapine XR³⁹ showed that lurasidone does not have a negative influence on glucose level when administered for a long-term period.

Regarding the adverse events related to dyslipidemia, there were no increases in the level of total cholesterol, low-density lipoprotein (LDL) cholesterol, and triglycerides reported

in short-term studies.^{41,43} Furthermore, Potkin et al³⁶ found that lurasidone appeared to be associated with a decrease in triglycerides (−2.6 mg/dL) when compared to an increase (+22.4 mg/dL) in the ziprasidone-treated group. The pooled data from five short-term studies showed that mean changes in triglycerides and total cholesterol of the lurasidone group (−5.0 mg/dL and −8.0 mg/dL) were comparable to those of haloperidol (−3.0 mg/dL and −8.0 mg/dL) and placebo (−7.0 mg/dL and −10.0 mg/dL).⁴¹ In a long-term comparison study with risperidone, the median change of triglyceride and LDL cholesterol levels in the lurasidone group were −3.5 mg/dL and −2.0 mg/dL, respectively.⁴⁰ Another long-term study among schizophrenia patients that compared lurasidone with quetiapine XR also confirmed that long-term treatment of lurasidone does not have any adverse influence on measures of triglyceride levels, or on total and LDL cholesterol levels.³⁹

Lurasidone does not appear to cause clinically significant changes in the QT interval on electrocardiogram findings.^{29,42} There have been no studies that reported increases in QTc intervals of more than 500 ms, and that reported clinically significant electrocardiographic findings.^{37,43,44} Comparisons with olanzapine and placebo in Meltzer et al's study³⁸ showed that mean changes in the QTc interval for 40 mg and 80 mg of lurasidone were +5.1 ms and +4.5 ms, which were comparable to those of placebo (+3.8 ms) and olanzapine (+4.4 ms).³⁸ In long-term studies, there were no reports of clinically significant electrocardiogram abnormalities or significant increases in the QT interval.^{39,40}

Short-term studies showed that lurasidone was associated with significant increases in prolactin levels.²⁴ The pooled data from five short-term studies reported that the mean changes of prolactin levels were 1.1 ng/mL in the lurasidone group and −0.6 ng/mL in the placebo group.⁴¹ However, the potential of lurasidone to cause an increase in prolactin levels seems to be lower than that of haloperidol.⁴⁴ The mean changes in prolactin levels were greater among the haloperidol treatment group (+8.5 ng/mL), followed by olanzapine (+3.7 ng/mL), lurasidone (+1.1 ng/mL), and placebo (−0.5 ng/mL).⁴⁴ In comparison with ziprasidone, it was shown that those in the lurasidone group demonstrated a greater increase in prolactin level than those in the ziprasidone group (3.0 ng/mL versus 2.0 ng/mL).³⁶ A long-term study comparing lurasidone with risperidone showed that the median changes of prolactin levels in the lurasidone group were 0 ng/mL among male subjects and 0.95 ng/mL among female subjects; these levels were lower than those of the risperidone group (7.50 ng/mL in males and 26.40 ng/mL in females).⁴⁰ Another long-term study showed that the median change of prolactin levels in the

lurasidone group was +0.6 ng/mL, while that of the quetiapine XR group was −0.7 ng/mL.³⁹

So far, there have not been any published articles in peer reviewed journals, except for several abstracts, regarding the safety and tolerability of lurasidone among bipolar disorder patients. However, we think that it is worth discussing the preliminary findings of two studies among bipolar patients. Calabrese et al³² performed a 6-week, placebo-controlled, double-blind study (PREVAIL-1) to examine the efficacy and safety of lurasidone adjunctive therapy among patients with bipolar 1 depression who showed inadequate response to either valproate or lithium therapy. In this study, the discontinuation rates due to drug-related adverse events among the 346 subjects randomized were 6% in the lurasidone group and 8% in the placebo group. The common adverse events included nausea (17.5% in lurasidone group versus 11.0% in the placebo group), headache (10.4% in the lurasidone group versus 12.3% in the placebo group), and somnolence (8.7% in the lurasidone group versus 4.3% in the placebo group).³² Loebel et al³³ examined the effectiveness and tolerability of lurasidone monotherapy among the subjects with nonpsychotic bipolar 1 depression in a 6-week, placebo-controlled, double-blind study (PREVAIL-2). Among a total of 505 subjects randomized, the discontinuation rates were 25.9% (43/166) in the lurasidone 20–60 mg group, 26.6% (45/169) in the lurasidone 80–120 mg group, and 25.3% (43/170) in the placebo group. The discontinuation rates due to adverse events were 7% in the lurasidone 20–60 mg group, 6% in the lurasidone 80–120 mg group, and 6% in the placebo group. The most common adverse events in the lurasidone 20–60 mg group were headache (14.0%), nausea (10.4%), and akathisia (7.9%). The common adverse events in the lurasidone 80–120 mg group were nausea (17.4%), akathisia (10.8%), and headache (9.0%). The changes in lipid profiles, weight, and parameters of glycemic control were minimal. The findings of these two bipolar disorder studies were in line with those observed in schizophrenia trials, suggesting that lurasidone could also be safely used among bipolar disorder populations both as a monotherapy agent and as an adjunctive therapy.⁴⁶

Patient focused perspective

A secondary analysis on quality of life (QoL) and functioning in patients with bipolar 1 depression was performed for the PREVAIL-1 and PREVAIL-2 studies.⁴⁷ Functioning was assessed in the secondary analyses using the Sheehan Disability Scale (SDS) total score and subscores. QoL was assessed using the Quality of Life, Enjoyment, and Satisfaction

scale short form (Q-LES-Q-sf). In PREVAIL-1, lurasidone adjunctive therapy resulted in significantly greater improvement in function, as demonstrated by an SDS total score change of −9.5 for lurasidone versus −7.0 for placebo ($P = 0.012$). Functional improvement was also observed in subscales of SDS; the SDS-social life subscore ($P = 0.003$) and the SDS-family life/home responsibilities subscore ($P = 0.003$) were improved significantly when compared with the placebo group, and there was a nonsignificant trend towards improvement on the SDS-work/school subscore ($P = 0.068$).

QoL assessed by the Q-LES-Q-sf total score was also significantly improved by lurasidone treatment (+22.2) when compared to placebo (+15.9; $P = 0.003$) during the 6-week study period. Also, a significantly higher proportion of subjects shifted from below normal to normal (≥ 52.3) Q-LES-Q-sf scores ([lurasidone group] 64.3% versus [placebo group] 44.1%; $P = 0.001$). In the PREVAIL-2 trial, both lurasidone dose groups showed significant improvements in function at week 6. A reduction in the total SDS score exhibited a reduction for both the lurasidone 20–60 mg group (−9.5; $P = 0.003$) and the lurasidone 80–120 mg group (−9.8; $P < 0.001$); these results were significantly greater than that of the placebo group (−6.3). Changes in the Q-LES-Q-sf total score in the placebo group was +12.8, and that was significantly different from both the lurasidone 20–60 mg group (+19.3; $P = 0.001$) and the lurasidone 80–120 mg group (+19.8; $P = 0.001$). The proportion of patients who shifted from below normal to normal QLES-Q-sf scores were 55.3% in the lurasidone 20–60 mg group ($P < 0.001$) and 54.2% in the lurasidone 80–120 mg group ($P < 0.001$); these results were significantly different from the proportion of patients from the placebo group (32.9%) who demonstrated this change.⁴⁷

Conclusion

Lurasidone is an atypical antipsychotic agent that was most recently approved by the FDA for schizophrenia and bipolar depression treatment. Lurasidone belongs to the benzisothiazol class, and exerts full antagonism at the D_2 and $5-HT_{2A}$ receptors, like other second-generation antipsychotics. It has a partially agonistic effect among $5-HT_{1A}$ subtypes, and poses stronger binding affinity at the $5-HT_7$ receptor and weak binding affinity at the α_{2C} and $5-HT_{2C}$ receptor.^{24,29} The receptor profiles of lurasidone suggest the beneficial effects of lurasidone over affective symptoms, as well as lurasidone's favorable side effects, including low potential of sedation and weight gain. The bioavailability of lurasidone is increased with food; thus, it is recommended that lurasidone be administered with food. Lurasidone is metabolized

primarily by CYP3A4; thus, it should be used with caution when coadministered with CYP3A4 inducers or inhibitors. For patients with renal and hepatic impairments, dose adjustment of lurasidone is necessary.

Lurasidone is established as an effective agent in the acute treatment of bipolar I depression as either a monotherapy or an adjunctive therapy used with lithium or valproate. The overall effect of lurasidone in reducing depressive severity, as measured by the MADRS, is not dissimilar from any other atypical antipsychotics approved by the FDA for bipolar depression treatment. Lurasidone was also effective in the treatment of anxiety symptoms in bipolar depression, and it improved quality of life and functioning. Moreover, although mainly based on the findings from schizophrenia studies, lurasidone appears to cause minimal effects on body weight, and it does not cause significant changes across metabolic parameters. Olanzapine (combined with fluoxetine) and quetiapine, the only two agents approved by the FDA for the treatment of bipolar depression, have been frequently related to changes both in body composition and on metabolic parameters; therefore, these unique properties of lurasidone can be beneficial in the treatment of bipolar depression.

Disclosure

The authors report no conflicts of interest in this work.

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