Lurasidone: A Clinical Overview

John M. Kane, MD

Lurasidone is a new second-generation (atypical) antipsychotic approved for the treatment of schizophrenia in adults. The recommended dose is 40–80 mg given once daily, with no titration needed. Lurasidone should be taken with food. The tolerability profile of lurasidone is noteworthy in terms of a good weight and metabolic profile and no cardiovascular adverse effects such as orthostatic hypotension or prolongation of the QTc interval. Lurasidone is associated with some somnolence, akathisia, nausea, and parkinsonism, especially early in treatment. Its preclinical profile suggested it might be helpful for cognitive or depressive symptoms; early findings have shown some benefit in these areas, but additional studies are needed. Lurasidone may be particularly helpful for patients with schizophrenia who are overweight or have endocrine problems (diabetes, dyslipidemia) or comorbid cardiovascular conditions.

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OVERVIEW OF DEVELOPMENT

Lurasidone is a second-generation (atypical) antipsychotic indicated for the treatment of schizophrenia.[1] Developed by Dainippon Sumitomo Pharma (DSP) in Japan, it was approved for the treatment of schizophrenia by the US Food and Drug Administration (FDA) in October 2010. It is marketed in the United States by Sunovion Pharmaceuticals, the US subsidiary of DSP. Registration trials in bipolar depression and maintenance treatment of schizophrenia and bipolar disorder are under way.

PHARMACOLOGIC PROFILE

Lurasidone is a benzisothiazol derivative. Although its mechanism of action is unknown, it is hypothesized that its efficacy for schizophrenia is mediated by a combination of dopamine (D_2) and serotonin (5-HT_{2A}) antagonism.[1]

Pharmacokinetics

After oral administration, lurasidone reaches peak serum concentrations in 1–3 hours, with concentrations increasing in a dose-dependent fashion at doses of 20–160 mg. Following a 40-mg dose, mean elimination half-life was 18 hours. Food produces a 3-fold increase in the area under the curve of a 20-mg dose with no effect on T_{max},[1–3] so it is recommended that lurasidone be taken with food.

Lurasidone is mainly metabolized by CYP3A4, with 2 active metabolites and 2 inactive metabolites. When lurasidone is coadministered with a moderate CYP3A4 inhibitor (eg, diltiazem), the dose should not exceed 40 mg/d. Lurasidone should not be combined with strong CYP3A4 inhibitors (eg, ketoconazole) or inducers (eg, rifampin).[1] No drug interactions have been observed when lurasidone is coadministered with CYP3A4 substrates (eg, midazolam, oral contraceptives, lithium).[1,4]

Corresponding author: *John M. Kane, MD, The Zucker Hillside Hospital, 75-59 263rd St, Glen Oaks, NY (psychiatry@nshs.edu).*

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Pharmacodynamics

Lurasidone has potent binding affinity for D_2, 5-HT_{2A}, and 5-HT_7 receptors and moderate affinity for 5-HT_{1A} and α_{2C}-noradrenergic receptors. It has weak affinity for α_1-adrenergic and 5-HT_{2C} receptors and negligible affinity for histamine H_1 and muscarinic M_1 receptors, suggesting reduced potential for orthostasis, weight gain, sedation, and negative cognitive effects.[2,3] Lurasidone acts as an antagonist at D_2 and 5-HT_7 receptors and as a partial agonist at 5-HT_{1A} receptors. It has the highest affinity for 5-HT_7 receptors among the atypical antipsychotics. Experimental data suggest that affinity for 5-HT_7 receptors may influence memory and mood regulation,[2,5] while affinity for 5-HT_{1A} receptors may have a positive effect on memory and mood.[3] Given lurasidone's affinity for 5-HT_7, 5-HT_{1A}, and α_{2C} receptors, it was hypothesized that lurasidone might have favorable effects on cognition and also possess anxiolytic and antidepressant properties.[2,3,5]

EFFICACY

Short-Term Trials

The efficacy and tolerability of lurasidone in the treatment of acute schizophrenia was evaluated in six 6-week, double-blind, placebo- and active comparator–controlled, randomized studies, 4 of which formed the basis for the approval of the drug by the FDA.[6]

In the first US phase 2 trial, 145 participants with acute schizophrenia were randomized to lurasidone 40 or 120 mg/d or placebo for 6 weeks.[7,8] Both lurasidone groups showed statistically significant improvement in total scores on the Brief Psychiatric Rating Scale derived from the Positive and Negative Syndrome Scale (BPRSd) and in Clinical Global Impressions severity (CGI-S) and improvement (CGI-I) scores compared with placebo. Lurasidone 120 mg was also superior to placebo on total Positive and Negative Syndrome Scale (PANSS) scores and on the response measure of 20% improvement from baseline in PANSS total score.[7,8]

In the second double-blind US trial,[9] 180 hospitalized patients with an acute exacerbation of schizophrenia were randomized to lurasidone 80 mg/d or placebo for 6 weeks.

Discontinuation rates were 42% for lurasidone and 48% for placebo, with significantly higher rates of discontinuation due to lack of efficacy in the placebo (32%) rather than the lurasidone (10%) group. Lurasidone produced statistically significant improvement compared with placebo on the BPRSd as early as day 3, which continued for the rest of the 6-week trial (Figure 1). Lurasidone also produced significantly greater improvement than placebo on total PANSS score; PANSS positive, negative, cognitive, and general psychopathology subscales; and the Montgomery Asberg Depression Rating Scale. A significantly higher percentage of patients receiving lurasidone (44%) than placebo (27%) were responders (at least 20% improvement in PANSS score).

The third trial, which involved lurasidone 20, 40, and 80 mg; haloperidol; and placebo, failed to demonstrate superiority of any active treatment over placebo and was deemed a failed trial.[4,7,8]

In an international multicenter phase 3 trial, 478 hospitalized patients with an acute exacerbation of schizophrenia were randomized to lurasidone 40 or 120 mg/d, olanzapine 15 mg/d, or placebo for 6 weeks.[10] Completion rates were 64% for lurasidone 40 mg, 56% for lurasidone 120 mg, 68% for olanzapine, and 61% for placebo. Patients receiving lurasidone 40 and 120 mg and olanzapine had significantly better total PANSS scores than those receiving placebo, with significant superiority over placebo observed at week 1 for lurasidone 40 mg and olanzapine and at week 3 for lurasidone 120 mg (Figure 2). Both doses of lurasidone and olanzapine were also superior to placebo on the PANSS positive, negative, and general psychopathology subscales; in post hoc analyses of the modified PANSS cognitive subscale score; and on CGI-S scores. Olanzapine, but neither of the lurasidone doses, was superior to placebo on the endpoint responder rate (20% improvement on PANSS).

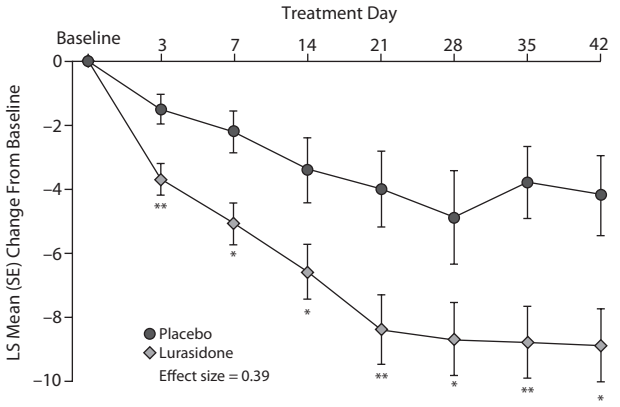
In the fourth 6-week study on which approval was based, 496 patients were randomized to 40, 80, or 120 mg/d of lurasidone or placebo. In this study, lurasidone 80 mg/d, but not 40 or 120 mg/d, was statistically significantly superior to placebo on PANSS total score and CGI-S rating.[7,8]

In a 6-week phase 3 trial completed after the New Drug Application was submitted, 488 patients with acute schizophrenia were randomized to 80 or 160 mg/d of lurasidone, quetiapine XR 600 mg/d, or placebo, dosed once a day in the evening.[8,11] Both doses of lurasidone and quetiapine produced significantly greater improvement in PANSS total scores and CGI-S scores than placebo. Significant improvement in PANSS total scores was found at day 4 and all subsequent study visits for both lurasidone groups.

Two additional short-term trials in schizophrenia have been completed.

A 21-day, double-blind study evaluated the safety and efficacy of lurasidone 120 mg/d versus ziprasidone 80 mg bid in 301 clinically stable outpatients with schizophrenia or schizoaffective disorder.[12,13] The percentage of patients discontinuing treatment due to adverse events was similar in both groups (lurasidone 10.4%, ziprasidone 11.2%). Similar improvement on PANSS total score was seen for both agents

Figure 1. Change From Baseline to Day 42 in Mean BPRSd Score[a]



[a]Reprinted with permission from Nakamura et al.[9]
*P < .05; **P < .01.
Abbreviations: BPRSd = Brief Psychiatric Rating Scale derived from the Positive and Negative Syndrome Scale, LS = least squares.

at weeks 1, 2, and 3, with similar proportions of patients completing the study (lurasidone 67.5%, ziprasidone 69.3%). Given lurasidone's pharmacodynamic profile and preclinical studies suggesting potential for positive cognitive effects,[14,15] and findings of efficacy on the PANSS cognitive subscale in an earlier study,[9] patients in this study[12,13] were assessed with tests from the Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) Consensus Cognitive Battery (MCCB) and the Schizophrenia Cognition Rating Scale (SCoRS). No between-group differences were found on the MCCB or the SCoRS ratings. However, in exploratory analyses, the lurasidone group demonstrated significant within-group improvement from baseline on the MCCB composite score (P = .026) and on the SCoRS (P < .001), while the ziprasidone group did not improve on either the MCCB composite (P = .254) or the SCoRS (P = .185). At endpoint, there was a statistical trend (P = .058) for lurasidone to demonstrate greater improvement from baseline than ziprasidone in SCoRS ratings. Further studies designed for this purpose are needed to evaluate the cognitive effects of lurasidone.

Finally, an 8-week randomized dose-response study in 195 patients found that 40- and 80-mg/d doses of lurasidone were associated with significant improvements from baseline in PANSS and BPRS scores and were significantly better than a 20-mg/d dose.[16]

Longer Trials

Subjects who successfully completed the 6-week, double-blind, olanzapine-controlled study[10] had the option to continue into a 6-month, open-label extension phase.[17] In this longer-term study, subjects maintained improvement, as measured by PANSS total score, for up to 8 months with flexible doses of lurasidone (40–120 mg/d).

A 12-month study evaluated the long-term safety and tolerability of lurasidone 40–120 mg/d (n = 427) and risperidone 2–6 mg/d (n = 202) in clinically stable outpatients with

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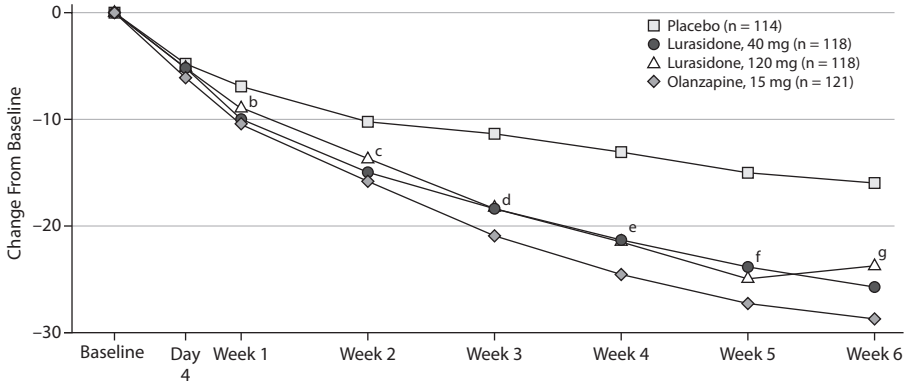
Figure 2. Change From Baseline to Day 42 in Mean Score on the Positive and Negative Syndrome Scale (PANSS)[a]



[a]Reprinted with permission from Meltzer et al.[10] Statistical significance was computed on the basis of a repeated-measures linear regression model of the change from baseline score, with fixed effects for pooled site, assessment visit as a categorical variable, baseline score, treatment, and treatment-by-assessment visit interaction, assuming an unstructured covariance matrix; *P* values are unadjusted, and only significant *P* values are noted.
[b]Week 1 comparison with placebo: $P = .022$ for lurasidone 40 mg; $P = .008$ for olanzapine.
[c]Week 2 comparison with placebo: $P = .008$ for lurasidone 40 mg; $P = .002$ for olanzapine.
[d]Week 3 comparison with placebo: $P = .002$ for lurasidone 40 mg; $P = .004$ for lurasidone 120 mg; $P < .001$ for olanzapine.
[e]Week 4 comparison with placebo: $P < .001$ for lurasidone 40 mg; $P < .001$ for lurasidone 120 mg; $P < .001$ for olanzapine.
[f]Week 5 comparison with placebo: $P = .001$ for lurasidone 40 mg; $P < .001$ for lurasidone 120 mg; $P < .001$ for olanzapine.
[g]Week 6 comparison with placebo: $P < .001$ for lurasidone 40 mg; $P = .011$ for lurasidone 120 mg; $P < .001$ for olanzapine.

schizophrenia, with efficacy a secondary outcome; this study found comparable efficacy with both agents.[18]

SAFETY AND TOLERABILITY

Overview of Adverse Effect Profile

Change in weight. In the short-term trials, mean weight change from baseline was +0.75 kg with lurasidone (+0.67, +1.14, and +0.69 kg in patients receiving 40, 80, and 120 mg/d, respectively) compared with +0.26 kg with placebo.[1] The proportion of patients who gained at least 7% of their baseline body weight was 5.6% with lurasidone and 4.0% with placebo.[1] In uncontrolled longer studies, mean change in weight was −0.38 kg at 24 weeks, −0.47 at 36 weeks, and −0.71 at 52 weeks.[1] The 6-month open-label extension study found no evidence of sustained change in weight, lipids, or glucose over 8 months of lurasidone treatment, and subjects who were switched from olanzapine to lurasidone showed marked sustained decreases in weight and lipid levels.[17] In the 12-month double-blind study, lurasidone had minimal effects on weight at endpoint (−0.97 ± 5.06 kg) compared with risperidone (1.47 ± 5.03 kg); 9.3% of patients treated with lurasidone reported increased weight as an adverse effect and 7% had more than a 7% endpoint increase in weight compared with 19.8% and 14%, respectively, of those treated with risperidone.[18] A pooled analysis of weight and metabolic data found that lurasidone was associated with minimal increases in weight and BMI in short-term trials (N = 1,508, 20–160 mg/d), small decreases in weight and BMI in longer-term trials (N = 2,905, 40–120 mg/d), and a decrease in mean total and low-density lipoprotein cholesterol and triglycerides during both short- and longer-term treatment.[19]

Extrapyramidal symptoms (EPS). No significant differences were found between lurasidone and placebo on measures of EPS or tardive dyskinesia, except for a modest but significant difference in scores on the Barnes Akathisia Rating Scale at endpoint.[1] In short-term trials, akathisia was reported in 15% of patients receiving lurasidone and 3% of those receiving placebo and appeared to be dose-related.[1]

Glucose and lipid levels. No significant differences were found between lurasidone and placebo on any metabolic laboratory tests, including blood glucose, cholesterol, and triglyceride levels, in short-term trials, nor were any significant changes in these levels observed in longer-term open-label extension studies.[1] In the 12-month study, lurasidone was associated with minimal effects on glucose and a small reduction in total cholesterol and triglycerides, suggesting a low metabolic risk, compared with median increases in glucose and insulin levels with risperidone.[18]

QTc interval. Lurasidone does not have a significant effect on the QTc interval. No patient experienced an increase in QTc greater than 60 milliseconds or an absolute value greater than 500 milliseconds, even at doses of 120 and 600 mg/d tested in a QT interval study in clinically stable patients with schizophrenia.[1]

Orthostatic hypotension. Lurasidone is not associated with clinically significant orthostatic hypotension.[1] In short-term trials, the frequency of orthostatic hypotension was 0.8%, 1.4%, and 1.7% in patients taking lurasidone 40, 80, and 120 mg/d, respectively, compared to 0.9% with placebo.[1]

Prolactin levels. Short-term trials found small dose- and gender-related effects on prolactin levels, with a median change from baseline to endpoint of 1.1 ng/mL with lurasidone (0.3 ng/mL with 40 mg/d, 1.1 ng/mL with 80 mg/d, and 3.3 ng/mL with 120 mg/d) and −0.6 ng/mL with placebo, with female patients more likely to show prolactin increases.[1] However, in uncontrolled, longer studies,[1] lurasidone was associated with decreases in prolactin levels (−1.9 ng/mL at 24 weeks, −5.4 ng/mL at 36 weeks, and −3.3 ng/mL at 52 weeks). The 12-month study found minimal effects on prolactin levels with lurasidone, but median increases in these levels with risperidone.[18]

Table 1. Spontaneously Reported Adverse Events in Short-Term Trials of Lurasidone for the Acute Treatment of Schizophrenia With Incidence ≥ 5% and 2-Fold Greater Than Placebo[a]

		Lurasidone 40–120 mg/d	
Adverse Event	Placebo Rate[b]	Rate[b]	NNH[c]
Somnolence[d]	10%	22%	9
Akathisia	3%	15%	9
Nausea	6%	12%	17
Parkinsonism[e]	5%	11%	17
Agitation	3%	6%	31

[a]Adverse event rates from Latuda prescribing information.[1]
[b]Percentage of patients reporting reaction.
[c]Number needed to harm (NNH) for lurasidone versus placebo. NNH is used to denote how many patients one would need to treat with 1 intervention versus another in order to encounter 1 additional adverse outcome.[20] The higher the NNH, the less likely that the event will be encountered with lurasidone versus the comparator, in this case placebo.
[d]Includes hypersomnia, hypersomnolence, sedation, and somnolence.
[e]Includes bradykinesia, cogwheel rigidity, drooling, extrapyramidal disorder, hypokinesia, muscle rigidity, parkinsonism, psychomotor retardation, and tremor.

Table 2. Percentage of Subjects Reporting Selected Adverse Events in Short-Term Clinical Trials of Lurasidone[a]

		Lurasidone			
Adverse Event	Placebo	20 mg/d	40 mg/d	80 mg/d	120 mg/d
Akathisia	3%	6%	11%	15%	22%
Somnolence	10%	15%	19%	23%	26%
Parkinsonism	5%	6%	10%	7%	17%
Dystonia	1%	0%	4%	5%	7%

[a]Adverse event rates from Latuda prescribing information.[1]

Tolerability. In the international, multicenter, olanzapine-controlled trial,[4,10] discontinuation due to adverse events occurred in 7% of the lurasidone 40-mg and olanzapine 15-mg groups, 12% of the lurasidone 120-mg group, and 9% of the placebo group. Overall, rates of discontinuation due to adverse events in short-term trials were 9.4% with lurasidone and 5.9% with placebo. There were no discontinuations due to adverse reactions that occurred in at least 2% of patients or at twice the rate as in placebo.

Adverse Effects in Short-Term Clinical Trials

The most frequent adverse effects in the short-term clinical trials were gastrointestinal; however, only nausea occurred significantly more often with lurasidone than placebo.[1] The most commonly reported adverse events in the lurasidone short-term trials were somnolence, akathisia, nausea, parkinsonism, agitation, anxiety, and dystonia (Table 1).[1] Both somnolence and akathisia appeared to be dose-related, and the greatest frequency of parkinsonism and dystonia also occurred with the highest doses of lurasidone (Table 2).

Long-Term Health Effects

The tolerability profile of lurasidone is encouraging, but more data are needed for a comprehensive understanding of its health effects. Lurasidone appears to have a low potential to cause substantial weight gain or metabolic adverse effects, although such effects might occur in individual patients. It is too soon to make meaningful estimates of the risk of tardive dyskinesia, but it also appears to be low. Lurasidone's very modest effects on prolactin have not been associated with any prolactin-related health effects.[4]

A post hoc analysis of data from 315 subjects over 30 years of age from the 6-week olanzapine-controlled study[10] found that lurasidone and placebo had similar acute effects on 10-year Framingham coronary heart disease (CHD) risk scores, while olanzapine was associated with higher risks than placebo in male patients.[21] At week 6, changes from baseline in overall 10-year CHD risk were significantly higher in men treated with olanzapine (going from 9.4% to 12%) than lurasidone (9.4% to 9.3%) or placebo (7.6% to 8.3%). Changes in CHD risk factors included 23 new diabetes cases (lurasidone 3.8%, olanzapine 14%, and placebo 6.8%), and significant elevations of hypertension risk and fasting total cholesterol levels in males treated with olanzapine compared with placebo.[21]

CLINICAL GUIDANCE

Clinicians treating patients with schizophrenia must make informed, and whenever possible, shared decisions with their patients about treatment choices. With a broad array of first- and second-generation antipsychotics now available, it is advantageous for physicians to evaluate each medication on its own merits rather than considering classes of drugs that do not necessarily share the same characteristics. In early-phase patients, there is no evidence that one particular class of drug or any specific drug is superior to others in efficacy against positive symptoms. Such differences may exist in more chronic patients who are likely to be poor or partial responders, and such differences certainly exist in patients with treatment-refractory illness.

Therefore, pharmacotherapeutic treatment decisions should be influenced more by issues related to tolerability, ease of administration, and adherence, particularly in early phases of schizophrenia. Lurasidone is another valuable option in terms of a good tolerability profile, once-daily dosing that can be administered in the evening, and ability to initiate treatment with a therapeutic dose. It should be taken with food (at least 350 calories).[1] Lurasidone can also cause sedation or akathisia in some patients, and large-scale experience in clinical populations is still lacking.

Although the current labeling for lurasidone recommends doses of 40–80 mg/d, additional data showing efficacy for the 160-mg/d dose from a recent study[8,11] are under review by the FDA.

Patients and families should be educated about the illness, its treatment, potential side effects, risks associated with discontinuing treatment, and the salient characteristics of the medication being prescribed, what it is expected to achieve, and areas that it is not likely to affect.

CONCLUSION

Lurasidone is the most recently approved new antipsychotic with demonstrated efficacy for acute exacerbations

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of schizophrenia in adults and positive clinical trial data concerning longer term continuation treatment. It is well tolerated, with a dropout rate for adverse effects similar to placebo. It has a good safety profile in terms of weight gain, metabolic effects, and potential cardiovascular adverse effects. It is associated with some somnolence, akathisia, nausea, and parkinsonism, especially early in treatment. There were no discontinuations due to adverse reactions that occurred in at least 2% of patients or at least twice the placebo rate. As with any new medication, it is important for clinicians to familiarize themselves with the package labeling and salient properties of this new agent in order to make an informed decision about its use. As new data emerge, these should also be reviewed and added to our knowledge base. Lurasidone appears to be a welcome addition to the options available for the treatment of schizophrenia. It is important that patients who will be expected to take medication for many years have options with good benefit-to-risk profiles.

Drug names: diltiazem (Cardizem, Taztia, and others), haloperidol (Haldol and others), lithium (Lithobid and others), ketoconazole (Nizoral and others), lurasidone (Latuda), olanzapine (Zyprexa), quetiapine (Seroquel), rifampin (Rifadin and others), risperidone (Risperdal and others), ziprasidone (Geodon).

Author affiliation: Department of Psychiatry, The Zucker Hillside Hospital, Glen Oaks, and Department of Psychiatry, Hofstra North Shore-LIJ School of Medicine, Hempstead, New York.

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