Lurasidone in the Treatment of Acute Schizophrenia: A Double-Blind, Placebo-Controlled Trial

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Objective: Lurasidone is a novel psychotropic agent with high affinity for D_2 and 5-HT_{2A} receptors, as well as for receptors implicated in the enhancement of cognition and mood and the reduction of negative symptoms (5-HT_7, 5-HT_{1A}, and α_{2c}). The objective of the study was to evaluate the safety and efficacy of lurasidone in patients hospitalized for an acute exacerbation of DSM-IV–defined schizophrenia.

Method: Patients were randomly assigned to 6 weeks of double-blind treatment with a fixed dose of lurasidone 80 mg (N = 90, 75.6% male, mean age = 39.7 years, mean baseline score on the Brief Psychiatric Rating Scale derived from the Positive and Negative Syndrome Scale [BPRSd] = 55.1) or placebo (N = 90, 77.8% male, mean age = 41.9 years, mean BPRSd score = 56.1). The primary efficacy measure was the BPRSd. The study was conducted from May to December 2004.

Results: At day 42, last-observation-carried-forward endpoint, treatment with lurasidone was associated with significant improvement compared to placebo on the BPRSd (least squares mean ± SE = –8.9 ± 1.3 vs. –4.2 ± 1.4; p = .012), as well as on all secondary efficacy measures, including the PANSS total score (–14.1 ± 2.1 vs. –5.5 ± 2.2; p = .004) and the PANSS positive (–4.3 ± 0.7 vs. –1.7 ± 0.7; p = .006), negative (–2.9 ± 0.5 vs. –1.3 ± 0.5; p = .025), and general psychopathology (–7.0 ± 1.1 vs. –2.7 ± 1.2; p = .0061) subscales. Significant improvement was seen as early as day 3, based on BPRSd, PANSS, and Clinical Global Impressions-Severity of Illness assessments. Treatment with lurasidone was generally well tolerated and was not associated with adverse changes in metabolic or electrocardiogram parameters. There were no clinically significant differences between lurasidone and placebo in objective measures of extrapyramidal symptoms.

Conclusions: The results of this study suggest that the novel psychotropic agent lurasidone is a safe and effective treatment for patients with an acute exacerbation of schizophrenia.

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Lurasidone (SM-13496, (3a*R*,4*S*,7*R*,7a*S*)- 2-{(1*R*,2*R*)-2-[4-(1,2-benzisothiazol-3-yl) piperazin-1-ylmethyl] cyclohexylmethyl}hexahydro-4, 7-methano-2*H*-isoindole-1,3-dione hydrochloride) is a novel psychotropic agent discovered by Dainippon Sumitomo Pharma research laboratories in Japan. Lurasidone has a high affinity for dopamine D_2 and serotonin 5-HT_{2A} receptors. However, despite its potent D_2-antagonist activity, treatment with lurasidone is associated with minimal extrapyramidal side effects in animal models.[1]

Compared with other atypical antipsychotic agents, lurasidone has similar binding affinities for D_2 and 5-HT_{2A} receptor subtypes, but greater affinity for serotonin 5-HT_7, 5-HT_{1A}, and norepinephrine α_{2c} receptor subtypes.[1] Lurasidone has little affinity for norepinephrine α_1 and no affinity for histamine H_1 or cholinergic M_1 receptors.[1]

The pharmacologic and preclinical profile of lurasidone suggests that it may be an effective antipsychotic drug in humans, with a reduced potential for histamine H_1– and 5-HT_{2C}–mediated weight gain, histamine H_1– and cholinergic M_1–mediated central nervous system (CNS) depression, and α_1 adrenergic–mediated orthostatic hypotension.

The primary objective of the current study was to evaluate the efficacy of lurasidone in the treatment of patients suffering from an acute exacerbation of schizophrenia. The secondary objectives were to assess the safety and

tolerability of lurasidone and to evaluate the ability of lurasidone to improve secondary measures such as negative symptoms and depressive symptoms.

METHOD

Patients

Men and women between 18 and 64 years of age, inclusive, who were hospitalized for an acute exacerbation of schizophrenia meeting DSM-IV criteria[2] (disorganized, paranoid, or undifferentiated subtypes) based on the Structured Clinical Interview for DSM-IV Disorders-Clinician's Version (SCID-CV)[3] were enrolled. Patients were also required to have (1) a minimum illness duration of at least 1 year; (2) a Brief Psychiatric Rating Scale (BPRSd)[4] total score, extracted from the Positive and Negative Syndrome Scale (PANSS),[5] of at least 42, with a score of at least 4 on 2 or more positive symptom items; (3) a Clinical Global Impressions-Severity of Illness scale (CGI-S)[4] score ≥ 4 (illness of at least moderate severity); (4) a Simpson-Angus Scale (SAS)[6] score of < 2; and (5) an Abnormal Involuntary Movement Scale (AIMS)[7] score of < 3. Women were required to be at least 1 year postmenopausal, surgically sterilized, or using a medically reliable form of birth control. Patients were also excluded if their baseline BPRSd score was < 42, or if they had a ≥ 20% decrease from screen to baseline in their BPRSd score.

Key exclusion criteria included (1) DSM-IV diagnosis of schizophreniform disorder, schizoaffective disorder, or the catatonic or residual subtypes of schizophrenia; (2) no hospitalizations in the month prior to screening (the current hospitalization must have begun < 3 weeks prior to screening); (3) failure to respond to adequate trials of 2 or more antipsychotic agents from 2 different classes; (4) evidence of chronic neurologic disease, organic mental disorder, clinically significant medical illness, and/or laboratory or electrocardiogram (ECG) abnormality, or any condition that might interfere with the absorption, metabolism, or excretion of study medication; (5) prolactin level ≥ 200 ng/mL at screen or baseline; (6) use of depot neuroleptics within 1 standard treatment cycle, or use of antidepressants (including reversible monoamine oxidase inhibitors [MAOIs]) within 1 week of entry into washout (1 month for fluoxetine or irreversible MAOIs); or (7) positive urine drug screen or a history in the past 3 months of alcohol or substance abuse.

The protocol was approved by institutional review boards (ethics committees) at each of the 22 U.S. sites and conducted from May to December 2004. Study conduct was consistent with the Declaration of Helsinki. The study was explained to prospective participants, and written informed consent was obtained prior to study entry from either the patient or the patient's legal guardian.

Study Design and Treatment

This was a multicenter, parallel-group trial in which eligible patients completed a 7- to 14-day screening period. Patients who continued to meet study entry criteria were hospitalized for a single-blind, 3- to 7-day placebo washout period before being randomly assigned, in a 1:1 ratio, to 6 weeks of double-blind treatment with a once-daily morning dose of lurasidone 80 mg or placebo taken with or immediately following breakfast. Patients remained in the hospital until the day 28 assessment time point. After day 28, patients could be discharged to the outpatient setting or could remain in the hospital at the discretion of the investigator.

During the placebo washout period, patients were not permitted to take any CNS medication other than benztropine mesylate, lorazepam, zolpidem, or temazepam on an as-needed basis until 8 hours prior to baseline efficacy assessments. As-needed use of these concomitant medications was also permitted during the double-blind phase, until 8 hours prior to any efficacy assessment.

Assessments

Efficacy. The primary efficacy measure was the BPRSd extracted from the PANSS. The secondary efficacy measures included the PANSS total and positive, negative, general psychopathology, and cognitive subscales[8]; the CGI-S; and the 10-item, clinician-rated Montgomery-Asberg Depression Rating Scale (MADRS).[9] The PANSS was completed at screen, baseline, and double-blind treatment days 3, 7, 14, 21, 28, 35, and 42 (or on early termination). The CGI-S was omitted at the screening visit, but otherwise was completed at the same time points. The MADRS was completed at baseline and day 42 (or on early termination). Patients were evaluated in the inpatient setting from the screen assessment to the day 28 assessment. Weekly evaluations were conducted on an outpatient basis after day 28 for those patients released from the hospital. After release from the hospital, compliance with study treatment was assessed by weekly pill counts.

Investigators received expert training, prior to the start of the study and again at the midpoint in the study, in the use of the SCID-CV and the PANSS and in the assessment of extrapyramidal symptoms.

Safety and tolerability. All adverse events volunteered or observed during the study were recorded, together with their severity, duration, and the investigator's assessment of the possible causative relationship to study drug. Movement disorders were assessed using the 10-item SAS to measure extrapyramidal symptoms (0 = normal to 4 = most severe),[6] the Barnes Akathisia Scale to evaluate akathisia (0 = normal to 5 = most severe),[10] and the AIMS to evaluate tardive dyskinesia (0 = normal to 4 = most severe).[7] These 3 scales were assessed at screen, baseline, and days 3, 7, 14, 21, 28, 35, and 42 (or on early termination). A 12-lead ECG was done at screen, baseline, day 1

(predose and 1.5 hours postdose), and days 7, 14, and 42 at approximately 1.5 hours postdose. Supine and standing vital signs and weight were obtained at every assessment visit. Clinical laboratory tests (blood chemistry, hematology, prolactin, urine pregnancy) were obtained at screen, baseline, and days 21 and 42 (or on early termination). A physical examination was performed at screen, baseline, and day 42 (or on early termination). Urine pregnancy and drug screening was performed at each assessment visit after discharge from the hospital.

Statistical Analysis

The intent-to-treat population consisted of all randomly assigned patients who received at least 1 dose of study medication and had at least 1 postrandomization efficacy assessment during the double-blind treatment phase.

Allowing for a 10% attrition rate prior to the first on-drug assessment, and assuming a BPRSd change score standard deviation of 10.5, it was estimated that 80 patients per dosage group would provide at least 90% power to detect a 6-point difference between lurasidone and placebo on a 2-sided t test at an α level of .050.

Descriptive statistics were calculated for baseline demographic and clinical characteristics of each treatment group.

For efficacy measures, descriptive statistics were calculated for the actual value and the change from baseline value. Efficacy analyses were performed using a 2-way analysis of covariance model with the baseline to day 42 last-observation-carried-forward (LOCF) endpoint change score for each efficacy measure as the dependent variable and with treatment group and study center as main effects and baseline score on each efficacy measure as a covariate. No evidence of treatment-by-center or treatment-by-baseline interaction was found on an exploratory analysis. Day 42 LOCF endpoint analyses were performed, as well as an observed case analysis of patients available at each study visit. Analyses of covariance of change scores were performed on the BPRSd and PANSS total scores, the PANSS subscales (positive and negative symptom, general psychopathology, and cognitive [consisting of the following 5 items: P2, N5, G5, G10, and G11]), the MADRS total score, and the CGI-S score. The Cohen d effect size was calculated for day 42 efficacy measures as the between-treatment difference score divided by the pooled standard deviation.

Patients achieving a $\geq 20\%$ reduction from baseline in PANSS score were classified as responders, and the proportion was compared using the Cochran-Mantel-Haenszel test, controlling for center.

For adverse events, number needed to harm (NNH) was calculated as 1 divided by the difference in the risk of an event for lurasidone versus placebo. From a clinical standpoint, NNH represents the number of patients who need to be given the experimental treatment for 1 more patient to experience the event than would be expected to experience the event with placebo.

The NNH is the number of patients who need to be treated with the first treatment rather than with the second treatment of the given treatment contrast in order for 1 additional patient to be harmed. The NNH was calculated as $NNH = 1/(Pt - Pc)$. Pt is the probability risk of the study treatment, and Pc is the probability risk of the comparator (placebo).

RESULTS

A total of 180 patients (79.6%), out of 226 screened, met study entry criteria at the end of the single-blind placebo washout and were randomly assigned to double-blind treatment (Figure 1). At pretreatment baseline, the 2 treatment groups were similar across key demographic and clinical characteristics (Table 1). Patients were predominantly male and between the ages of 30 and 50 years. Paranoid was the most common schizophrenia subtype.

Study Treatment

The mean ± SD duration of study treatment was similar among patients randomly assigned to lurasidone 80 mg (30.1 ± 15.3 days) and placebo (32.3 ± 12.9 days). During the 4 weeks of inpatient treatment, compliance rates were > 99% for both lurasidone and placebo. Mean medication compliance among outpatients in the study was similar for both lurasidone and placebo (92.3% vs. 88.2%).

The overall discontinuation rate was slightly higher in the placebo group (47.8%) compared with the lurasidone group (42.2%; Figure 1). Discontinuation due to lack of efficacy was significantly higher in the placebo group compared to the lurasidone group (32.2% vs. 10.0%; 2-sided Fisher exact test; $p < .001$). Discontinuation due to withdrawal of consent (20.0% vs. 10.0%; 2-sided Fisher exact test; $p = .094$) and adverse events (6.7% vs. 1.1%; 2-sided Fisher exact test; $p = .118$) were both marginally higher in the lurasidone compared to the placebo group.

Efficacy

Treatment with lurasidone 80 mg was associated with statistically significantly greater improvement than placebo on the primary efficacy measure, day 42 LOCF endpoint change in BPRSd (Table 2). The onset of improvement on lurasidone was rapid, achieving statistical significance compared to placebo by day 3, and continued at a significant level throughout the 6 weeks of study treatment (Figure 2A). The PANSS total score and CGI-S showed a similar pattern of statistically significant early and sustained improvement with lurasidone (Figure 2B, Figure 2C).

Figure 1. Flow Diagram for a 6-Week Study of Lurasidone Versus Placebo in Acute Schizophrenia

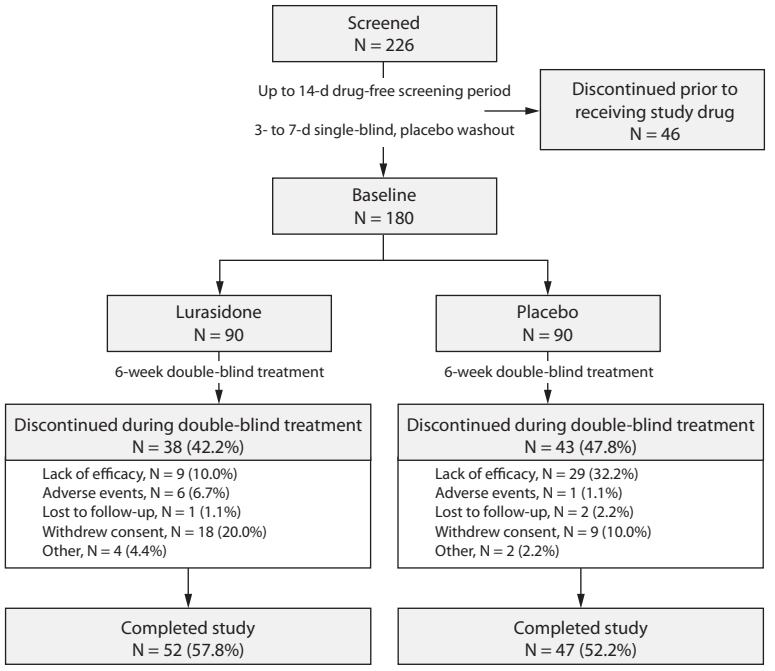


Table 1. Patient Characteristics at Baseline, Safety Sample

Parameter	Lurasidone (N = 90)	Placebo (N = 90)
Sex, male, N (%)	68 (75.6)	70 (77.8)
Race, N (%)		
White	35 (38.9)	26 (28.9)
Black	47 (52.2)	56 (62.2)
Other	8 (8.9)	8 (8.9)
Age, y		
Mean (SD)	39.7 (9.9)	41.9 (9.8)
Range	22–62	21–63
BMI, kg/m^2, mean (SD)	30.7 (8.5)	31.2 (7.7)
Tobacco use, yes, N (%)	73 (81.1)	68 (75.6)
DSM-IV schizophrenia subtype, N (%)		
Paranoid	73 (81.1)	72 (80.0)
Undifferentiated	13 (14.4)	14 (15.6)
Disorganized	4 (4.4)	4 (4.4)
Prior medications, N (%)		
Antipsychotics		
Atypical	68 (75.6)	71 (78.9)
Typical	6 (6.7)	12 (13.3)
Benzodiazepines	24 (26.7)	25 (27.8)
Antidepressants	24 (26.7)	24 (26.7)
BPRSd score, mean (SD)	55.1 (6.0)	56.1 (6.8)
PANSS score, mean (SD)		
Total score	94.4 (10.9)	96.0 (11.6)
Positive symptoms	24.0 (3.8)	25.0 (4.2)
Negative symptoms	23.4 (4.8)	23.5 (4.4)
General psychopathology	47.0 (6.3)	47.5 (6.3)
Cognitive	14.5 (3.5)	15.2 (4.1)
MADRS score, mean (SD)	14.2 (8.0)	14.5 (8.3)
CGI-S score, mean (SD)	4.8 (0.7)	4.8 (0.7)

Abbreviations: BMI = body mass index, BPRSd = Brief Psychiatric Rating Scale (extracted from PANSS), CGI-S = Clinical Global Impressions-Severity of Illness scale, MADRS = Montgomery-Asberg Depression Rating Scale, PANSS = Positive and Negative Syndrome Scale.

Treatment with lurasidone also demonstrated significant efficacy compared to placebo on all other secondary measures (Table 2), including the PANSS positive (least squares mean ± SE = –4.3 ± 0.7 vs. –1.7 ± 0.7; p = .006), negative (–2.9 ± 0.5 vs. –1.3 ± 0.5; p = .025), cognitive (–2.1 ± 0.4 vs. –0.5 ± 0.4; p = .0015), and general psychopathology (–7.0 ± 1.1 vs. –2.7 ± 1.2; p = .0061) subscales.

The Cohen d effect sizes were 0.39, 0.44, and 0.41 for the BPRSd, PANSS total score, and CGI-S score, respectively. Cohen d effect sizes were 0.42, 0.34, and 0.49 for the PANSS positive, negative, and cognitive subscales, respectively.

With ≥ 20% improvement in PANSS score used as the criterion to define treatment response, the proportion of responders was significantly higher with lurasidone compared to placebo on the day 42 LOCF endpoint analysis (44.4% vs. 26.7%; p = .007).

Despite relatively low baseline MADRS scores (mean score of 14), lurasidone also demonstrated significant efficacy compared to placebo on the MADRS (LS mean ± SE = –2.9 ± 0.8 vs. –0.1 ± 0.9; p = .019; Cohen d effect size, 0.37). In a post hoc analysis of the subgroup of patients (combined subgroup N = 113; 62.8% of total intent-to-treat population) with elevated levels of depressive symptomatology (baseline MADRS ≥ 12; mean = 18.7), the effect size was 0.44 (LS mean ± SE MADRS change at day 42 LOCF endpoint, –6.1 ± 1.2 vs. –2.7 ± 1.2; p = .033).

Safety and Tolerability

The incidence of at least 1 adverse event was nonsignificantly higher with lurasidone compared to placebo (76.7% vs. 68.9%; Table 3). The most frequent adverse events were gastrointestinal (nausea, constipation, vomiting, dyspepsia; Table 3). However, only nausea was significantly more frequent in the lurasidone group compared to placebo (16.7% vs. 3.3%; p = .005; NNH = 7.5). The incidence of adverse events rated as severe was low in both the lurasidone group and the placebo group (N = 7 vs. N = 5). Among adverse events in the lurasidone group with an incidence ≥ 5%, 4 were rated as severe: insomnia (N = 2) and anxiety and akathisia (1 event each).

Treatment-emergent adverse events leading to discontinuation of study treatment occurred in 6 patients in the lurasidone group: 1 patient reported nausea, dyskinesia, and akathisia; 1 reported dystonia and akathisia; 1 reported anxiety and insomnia; and 1 each reported facial

Table 2. Endpoint Change in Primary and Secondary Efficacy Measures[a]

Parameter	N	LS Mean (SE) Change	95% CI	p Value
BPRSd				
Lurasidone	90	–8.9 (1.3)	–11.5 to –6.2	.0118
Placebo	90	–4.2 (1.4)	–6.9 to –1.5	
PANSS total				
Lurasidone	90	–14.1 (2.1)	–18.3 to –9.9	.0040
Placebo	90	–5.5 (2.2)	–9.8 to –1.2	
PANSS positive symptoms				
Lurasidone	90	–4.3 (0.7)	–5.7 to –3.0	.0060
Placebo	90	–1.7 (0.7)	–3.1 to –0.3	
PANSS negative symptoms				
Lurasidone	90	–2.9 (0.5)	–3.9 to –1.8	.0250
Placebo	90	–1.3 (0.5)	–2.3 to –0.2	
PANSS general psychopathology				
Lurasidone	90	–7.0 (1.1)	–9.3 to –4.8	.0061
Placebo	90	–2.7 (1.2)	–5.0 to –0.4	
PANSS cognitive				
Lurasidone	90	–2.1 (0.4)	–2.8 to –1.4	.0015
Placebo	90	–0.5 (0.4)	–1.2 to 0.2	
CGI-S				
Lurasidone	90	–0.6 (0.1)	–0.8 to –0.4	.0072
Placebo	90	–0.2 (0.1)	–0.4 to 0.0	
MADRS				
Lurasidone	86	–2.9 (0.8)	–4.6 to –1.3	.0187
Placebo	83	–0.1 (0.9)	–1.9 to 1.6	

[a]Analysis of covariance model based on LOCF endpoint data including treatment, center, and baseline terms.

Abbreviations: BPRSd = Brief Psychiatric Rating Scale (extracted from PANSS), CGI-S = Clinical Global Impressions-Severity of Illness scale, LOCF = last observation carried forward, LS = least squares, MADRS = Montgomery-Asberg Depression Rating Scale, PANSS = Positive and Negative Syndrome Scale.

swelling, headache, and increased liver enzymes (alanine aminotransferase and aspartate aminotransferase). Adverse events leading to study discontinuation occurred in 1 placebo-treated patient, who reported psychotic disorder and had an increase in blood creatine phosphokinase levels. None of the patients who discontinued due to withdrawal of consent had a severe adverse event.

Physical examination and vital signs. There were no clinically significant, treatment-emergent changes with either lurasidone or placebo in physical examination findings (including fundoscopy), heart rate, or systolic or diastolic blood pressure.

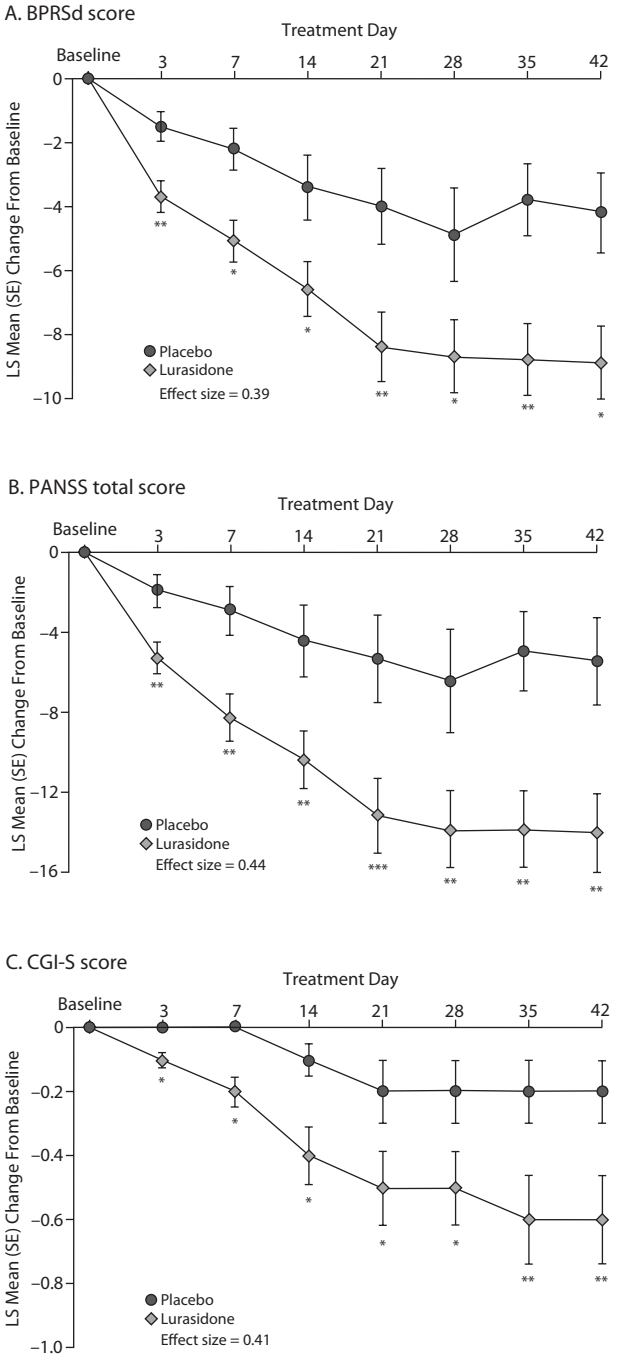
Extrapyramidal symptoms. Mean ± SD endpoint change from baseline was comparable for the lurasidone and placebo groups, respectively, on the AIMS (+0.3 ± 2.1 vs. +0.5 ± 2.5; p = .61) and the SAS (+0.2 ± 1.4 vs. +0.1 ± 1.3; p = .58). However, there was a modest but significant between-group difference at endpoint on the BAS (+0.2 ± 0.9 vs. –0.1 ± 0.7; p = .03). In addition, treatment with lurasidone and placebo was associated with similar rates of use of benztropine (12.2% vs. 8.9%) and β-adrenoceptor antagonists (2.2% vs. 4.4%). Use of as-needed lorazepam and benzodiazepine hypnotics was also similar for both lurasidone and placebo (87.8% vs. 85.6%).

Body weight. Median change from baseline in weight was 0.9 kg for lurasidone (N = 89) and 0.5 kg for placebo (N = 90). The incidence of clinically significant weight gain (≥ 7% increase from baseline) was 6.7% with lurasidone versus 7.8% with placebo. The incidence of clinically significant weight gain was slightly lower among patients treated with lurasidone compared to placebo in all body mass index (BMI) subgroups, including individuals with BMI > 27 (3.8% vs. 4.8%).

Metabolic laboratory tests. There were no significant differences between lurasidone and placebo in endpoint change in cholesterol, triglycerides, high-density lipoprotein, low-density lipoprotein, or fasting blood glucose (Figure 3). Mean serum cholesterol and triglycerides decreased with lurasidone treatment during the course of the study. There was a statistically significant difference between treatment groups in glycosylated hemoglobin (HbA1c) levels (mean increase of 0.1% with lurasidone vs. a mean change of 0.0% with placebo; p < .05), but this difference was not clinically significant.

Prolactin and other laboratory tests. Treatment with lurasidone was associated with a small but significant median increase in prolactin levels at endpoint compared to placebo (+2.4 vs. –0.3 ng/mL; p < .05). There was a gender difference in the effect of lurasidone on prolactin, with larger median increases observed in the small group of women (N = 19; +9.2 ng/mL) compared to men (N = 57; +1.4 ng/mL). None had any prolactin-related adverse events (i.e., galactorrhea, menstrual disturbances, sexual dysfunction). The Pearson correlation coefficient between serum lurasidone concentrations and prolactin levels was

Figure 2. Efficacy Measures During Treatment With Lurasidone (N = 90) or Placebo (N = 90)[a]



[a]Analysis of covariance with treatment, center, and baseline terms. Analysis sample consists of last-observation-carried-forward data at each assessment timepoint.
*p < .05.
**p < .01.
*** p < .001.
Abbreviations: BPRSd = Brief Psychiatric Rating Scale (extracted from PANSS), CGI-S = Clinical Global Impressions-Severity of Illness scale, LS = least squares, PANSS = Positive and Negative Syndrome Scale.

Table 3. Treatment-Emergent Adverse Events Occurring With an Incidence ≥ 5% (all-causality)[a]

Adverse Event	Lurasidone (N = 90)	Placebo (N = 90)
Nausea	15 (16.7)*	3 (3.3)
Headache	10 (11.1)	9 (10.0)
Constipation	10 (11.1)	5 (5.6)
Vomiting NOS	10 (11.1)	5 (5.6)
Dyspepsia	10 (11.1)	3 (3.3)
Somnolence	10 (11.1)	3 (3.3)
Insomnia	9 (10.0)	3 (3.3)
Sedation	9 (10.0)	4 (4.4)
Akathisia	8 (8.9)	3 (3.3)
Anxiety	6 (6.7)	1 (1.1)
Toothache	5 (5.6)	3 (3.3)
Upper respiratory tract infection NOS	3 (3.3)	6 (6.7)
Back pain	3 (3.3)	5 (5.6)
At least 1 adverse event	69 (76.7)	62 (68.9)
No. of adverse events rated as severe	7	5

[a]Data shown as number (percentage) of patients experiencing events, except in the last row, which shows number of events.
*p = .005.
Abbreviation: NOS = not otherwise specified.

0.39, suggesting a moderate correlation. Three patients treated with lurasidone (2 male, 1 female) had treatment-emergent prolactin concentrations at day 42 LOCF endpoint between 50 and 100 ng/mL.

There were no clinically significant, treatment-emergent changes in hematology or chemistry results with lurasidone when compared to placebo.

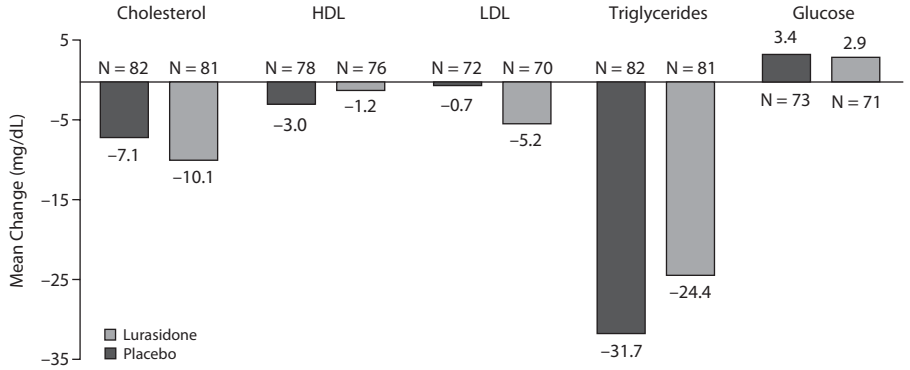
Electrocardiogram. Treatment with lurasidone was not associated with any significant treatment-emergent ECG abnormalities. Mean ± SD QTc (Fridericia) change was –1.2 ± 17.3 and +0.9 ± 16.7 ms for lurasidone and placebo, respectively. No subjects in either group experienced a QTc change > 500 ms during the study.

DISCUSSION

This is the first reported double-blind, placebo-controlled clinical trial evaluating the efficacy of the novel psychotropic lurasidone in the treatment of patients with an acute exacerbation of schizophrenia. The results demonstrate consistent antipsychotic efficacy in all primary and secondary efficacy measures, including the BPRSd, the CGI-S, and the PANSS total and subscale scores, across all study visits through the 6-week primary endpoint.

Notably, significant improvement in BPRSd, PANSS total, and CGI-S scores was observed by day 3 of lurasidone treatment, suggesting an early onset of treatment effect. While antipsychotics have traditionally been thought to have a delayed onset of action, several meta-analyses[11,12] suggest that significant improvement may occur within the first week of treatment. Early onset has not always been measured in previous trials; therefore, the consistency of this finding for individual atypical

Figure 3. Change From Baseline in Metabolic Parameters With Lurasidone or Placebo



Abbreviations: HDL = high-density lipoprotein, LDL = low-density lipoprotein.

drugs remains to be determined. Due to the absence of adverse event–limiting α_1 adrenergic and antihistaminergic effects, treatment with lurasidone can be initiated at a therapeutically effective dose, which may contribute to the potential for rapid onset of efficacy.

Lurasidone's lack of affinity for muscarinic M_1 and histamine H_1 receptors, and high affinity for 5-HT_7, 5-HT_{1A}, α_{2C} receptors,[1] suggests the potential for enhancement of cognitive function.[13] Consistent with this receptor binding profile, lurasidone demonstrated significant improvement in a group of items that comprise a proposed cognition subscale,[14] including conceptual disorganization, poor attention, and difficulty in abstract thinking. This preliminary result is consistent with preclinical findings that lurasidone reverses scopolamine- and MK-801–induced impairment in learning and memory in the passive-avoidance test in rats.[15–17] However, since the PANSS cognitive symptom subscale has not consistently demonstrated good validity as a measure of neurocognitive change,[18] a more definitive characterization of the cognitive effects of lurasidone awaits completion of ongoing clinical trials.

Clinically significant depressive symptoms occur in one quarter or more of patients with schizophrenia[19,20] and have been shown to be more responsive to selected second-generation compared to first-generation antipsychotics, although the number of well-designed, adequately powered clinical trials is limited.[21,22] Treatment with lurasidone significantly improved mean MADRS scores when compared to placebo, with the largest effect observed among the subgroup of patients (62.8%) with clinically significant depressive symptoms (baseline MADRS ≥ 12; mean = 18.7).

Lurasidone was well tolerated in the current study. The percentage of patients reporting at least 1 adverse event was nonsignificantly higher (7.8%) in the lurasidone group compared to the placebo group. Only 1 adverse event (nausea; NNH = 7.5) was significantly more frequent in the lurasidone group. Overall, the most frequent adverse events were gastrointestinal (nausea, constipation, vomiting, dyspepsia). The incidence of adverse events rated as severe was low in both the lurasidone and placebo groups (N = 7 vs. N = 5). Only 3 adverse events were considered serious in the lurasidone group, compared to 4 categorized as serious in the placebo group. All 3 serious adverse events in the lurasidone group were due to exacerbation of preexisting schizophrenia, and none were judged by the investigator to be due to lurasidone. Adverse events leading to discontinuation were more frequent in the lurasidone group, but the absolute frequency was low (6.7%) and in the range reported for short-term trials of other atypical antipsychotics.

No clinically significant differences were seen between lurasidone and placebo in any of the 3 extrapyramidal symptom score scales. Furthermore, use of antiparkinsonian medication was similarly low in both the lurasidone group (12.2%) and the placebo group (8.9%).

Although lurasidone was associated with a small (0.5 kg) placebo-adjusted increase in weight, there were no clinically significant differences between lurasidone and placebo in laboratory parameters, including metabolic assessments (cholesterol, triglycerides, HDL, LDL, fasting blood glucose). A minor observed increase in HbA1c levels (+0.1) was not regarded as clinically significant and may have been due to nonspecific measurement variation.

Several possible study limitations should be noted. First, the use of a single fixed dose of lurasidone did not permit us to evaluate dose-response effects and may have reduced the tolerability of the drug. Second, the absence of an atypical antipsychotic comparator group limits our ability to draw inferences regarding the comparative efficacy and tolerability of lurasidone. Finally, the relatively high discontinuation rate (42%) in the current study, while typical of double-blind, placebo-controlled trials in schizophrenia, nonetheless complicates the analysis of the data.

In conclusion, the results of this study indicate that lurasidone is an effective treatment for patients with an acute exacerbation of schizophrenia. This study utilized a fixed daily dose of 80 mg. The full dose range of lurasidone will be characterized in further studies. Significant improvement occurred early, by day 3, and was consistent across all primary and secondary efficacy measures, including positive and negative symptoms as well as assessments of depressed mood and cognitive impairment. Treatment with lurasidone was well tolerated and was not associated with adverse changes in metabolic or ECG parameters. Further research is underway to fully characterize the antipsychotic effects of lurasidone in patients with schizophrenia, as well as its potential for enhancement of cognitive deficits and improvement in other schizophrenic psychopathology beyond the core psychotic syndrome.

Drug names: benztropine mesylate (Cogentin and others), fluoxetine (Prozac and others), lorazepam (Ativan and others), temazepam (Restoril and others), zolpidem (Zolpimist, Ambien, and others).

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