



Efficacy and Safety of Lurasidone vs. Quetiapine XR in Acutely Psychotic Patients With Schizophrenia in Korea: A Randomized, Double-Blind, Active-Controlled Trial

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Objective This study was performed to evaluate the efficacy and safety of lurasidone (160 mg/day) compared to quetiapine XR (QXR; 600 mg/day) in the treatment of acutely psychotic patients with schizophrenia.

Methods Patients were randomly assigned to 6 weeks of double-blind treatment with lurasidone 160 mg/day (n=105) or QXR 600 mg/day (n=105). Primary efficacy measure was the change from baseline to week 6 in Positive and Negative Syndrome Scale (PANSS) total score and Clinical Global Impressions severity (CGI-S) score. Adverse events, body measurements, and laboratory parameters were assessed.

Results Lurasidone demonstrated non-inferiority to QXR on the PANSS total score. Adjusted mean±standard error change at week 6 on the PANSS total score was -26.42 ± 2.02 and -27.33 ± 2.01 in the lurasidone and QXR group, respectively. The mean difference score was -0.91 (95% confidence interval -6.35 – 4.53). The lurasidone group showed a greater reduction in PANSS total and negative subscale on week 1 and a greater reduction in end-point CGI-S score compared to the QXR group. Body weight, body mass index, and waist circumference in the lurasidone group were reduced, with significantly lower mean change compared to QXR. Endpoint changes in glucose, cholesterol, triglycerides, and low-density lipoprotein levels were also significantly lower. The most common adverse drug reactions with lurasidone were akathisia and nausea.

Conclusion Lurasidone 160 mg/day was found to be non-inferior to QXR 600 mg/day in the treatment of schizophrenia with comparable efficacy and tolerability. Adverse effects of lurasidone were generally tolerable, and beneficial effects on metabolic parameters can be expected.

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Keywords Lurasidone; Efficacy; Safety; Randomized clinical trial.

INTRODUCTION

Schizophrenia is a chronic illness with devastating course, and antipsychotic medication is the most effective treatment. Although novel antipsychotic agents have been introduced, according to a large-scale study, 70%–80% of schizophrenia outpatients discontinue antipsychotic treatment due to inadequate therapeutic effects or side effects.¹ In aspects of adverse effects of antipsychotics, second generation antipsychotics have benefits in reduced extrapyramidal side effects. However, they still pose safety and tolerability concerns such as weight gain and endocrine abnormalities.²

Lurasidone is a novel antipsychotic used for the treatment of schizophrenia. As a benzisothiazole derivative, lurasidone exhibits a distinct receptor profile that sets it apart from other antipsychotics, including phenothiazine, butyrophenone, or benzamide derivatives.³ Lurasidone exhibits high binding affinities to D₂ and 5-HT_{2A} receptors (antagonism) as well as other atypical antipsychotics, and has a high affinity for 5-HT₇ (antagonism), 5-HT_{1A} (partial agonism), and α_{2C} adrenergic receptors (antagonism).⁴ It has low affinity for α_1 receptors and has no affinity for H₁ and M₁ receptors, suggesting a potential to minimize adverse effects such as weight gain, sedation, and cognitive impairment.⁵ In addition, due to the property of 5-HT_{2A} blockade and 5-HT_{1A} agonism, attenuation of extrapyramidal symptoms (EPS) was anticipated.^{6,7} At a dose of 80–160 mg/day, lurasidone achieves D₂ receptor occupancy > 65%.⁸

Lurasidone has been subjected to over 80 related clinical trials conducted in the United States, Canada, Europe, Asia, Australia, and Central and South America. On October 28,

2010, the FDA had approved lurasidone for the treatment of adult schizophrenia patients. In particular, multiple well-controlled clinical trials have demonstrated the therapeutic effect of lurasidone in the acute exacerbation of psychotic symptoms in schizophrenia.^{9–15} It has been also approved for the treatment of depression in adult and pediatric (≥ 10 years of age) bipolar I disorder as well as adolescent schizophrenia patients aged 13 and above.^{16,17}

Previous clinical trials on lurasidone have reported few serious adverse events (SAEs).¹⁸ The most commonly reported adverse reactions included insomnia, akathisia, headache, nausea, and somnolence, which showed similar frequency compared to those reported with other atypical antipsychotic medications.¹⁸ Lurasidone was generally well tolerated with minimal impact on weight and metabolic parameters.^{9–12} Meta-analyses on antipsychotic-induced metabolic effects concluded that lurasidone had the lowest risk of weight gain and glucose changes compared to other antipsychotics.^{18,19}

Although previous studies have demonstrated the efficacy and the safety profiles of lurasidone in schizophrenia, lurasidone has not yet been introduced in Korea. The present study is a randomized, double-blind, active-controlled, multi-center clinical trial to examine the efficacy and safety of lurasidone in Korean patients with schizophrenia. The active controlled drug was quetiapine XR (QXR) to establish comparable efficacy and adverse events (AEs).

METHODS

The present study is a randomized, double-blind, active-

controlled study over a 6-week period to evaluate the efficacy and safety of lurasidone (160 mg/day) compared to QXR (600 mg/day) in patients with acute psychotic symptoms of schizophrenia. This study was conducted between 9 April 2018 and 26 May 2022 and randomized a total of 210 subjects at 35 sites in the Republic of Korea. Prior to proceeding with the trial procedures, the participants provided informed consent to participate in the clinical trial. The study protocol was approved by the Institutional Review Board (IRB) of SMG-SNU Boramae Medical Center (IRB No. 30-2017-34). The study was conducted in accordance with the International Conference on Harmonization Good Clinical Practice guideline E6 (R2) and with the ethical principles of the Declaration of Helsinki.

Inclusion and exclusion criteria

Patients aged 19–75 years with a diagnosis of schizophrenia determined based on the diagnostic statistical manual-5 criteria were enrolled. Key inclusion criteria were to have an illness duration ≥ 1 year and to be currently at a state of acute exacerbation of psychotic symptoms, lasting ≤ 2 months.

On both screening and baseline visits, patients were required to have a Clinical Global Impressions Severity (CGI-S)²⁰ score ≥ 4 (moderate or greater) and a Positive and Negative Syndrome Scale (PANSS)²¹ total score ≥ 80 , including a score ≥ 4 (moderate or greater) on two or more of the following PANSS items: delusions, conceptual disorganization, hallucinations, and unusual thought content. The following cases were excluded from the study: 1) Subjects who had used quetiapine for the treatment of schizophrenia, bipolar disorder, or mood symptoms, or doses exceeding 50 mg/day for any reason within 30 days prior to screening, or had a history of inadequate response or intolerability to quetiapine. 2) Individuals with treatment-resistant schizophrenia, defined as a failure to respond to ≥ 2 marketed antipsychotic agents from two different classes, given at an adequate dose for at least 6 weeks. 3) Subjects who had received long-acting injectable antipsychotics, unless the last injection was administered at least 1 treatment cycle before randomization. In addition, patients having medical or neurological conditions determined that can affect the health risk or imminent risk of suicide were excluded.

Study design

Following a screening period of up to 14 days, the previous administration of psychotropic medications was appropriately tapered off. Participants who met the selection criteria and did not meet any exclusion criteria underwent a placebo washout period of 3–7 days. Subsequently, the eligible participants were randomly assigned in a 1:1 ratio to one of the two double-blind treatment groups— lurasidone 160 mg/day or

QXR 600 mg/day. Randomization of participants was performed using the Interactive Web Response System. After the baseline evaluation, participants underwent 6 weeks of the trial. The follow-up (week 7) visit took place 1 week after the participants' last dose of the study medication. Outpatient participants were allowed to be hospitalized during the entire study period, including the placebo washout period, based on the investigator's judgment.

Study medication

The washout period ranged from a minimum of 3 days to a maximum of 7 days, during which the subjects were given a placebo. Following the washout period, each medication was titrated from the initial dose to the target dose (lurasidone 160 mg/day and QXR 600 mg/day). Dose increase was determined by each investigator's judgment based on the condition of the individual patients at each visit during the first 2 weeks of the trial. The sequential dose increase schedule is as follows; lurasidone was started with an initial dose of 80 mg/day, which was sequentially increased to 120 mg/day, and then 160 mg/day; QXR was started at a dose of 300 mg/day, which was sequentially increased to 450 mg/day followed by 600 mg/day. From week 2, the dose was maintained until the end of the trial as long as there were no safety concerns. The medication for the clinical trial was administered orally, once daily in the evening with a meal or within 30 minutes after a meal. All study medications were identical in shape and weight, with a total of 4 tablets per day in both treatment groups. The investigational product was provided to the trial participants by designated pharmacist or authorized personnel at each institution, referred to as a designated pharmacist or equivalent.

Assessments

As a primary outcome, efficacy was assessed as the mean change in the total score of PANSS.^{21,22} Secondary outcomes included the mean changes in PANSS positive, negative, and general psychopathology subscale scores, along with the mean change in CGI-S score. For these parameters, weekly changes from baseline to week 6 were evaluated. Efficacy evaluation was conducted for both the per-protocol (PP) set and the intent-to-treat (ITT) set population, and the primary analysis was based on the PP set.

Safety evaluations included subject-reported AEs, physical examination, vital signs, weight, body mass index (BMI), and waist circumference. Laboratory tests including serum concentration of glucose, lipid panel, and prolactin were also conducted, along with a 12-lead electrocardiogram (ECG). In addition, the drug-induced extrapyramidal symptoms scale (DIEPSS)^{23,24} was used to evaluate the extrapyramidal side effects, and the Columbia suicide severity rating scale

(C-SSRS)^{25,26} was used to evaluate the suicidal ideation and behavior. Any new physical or mental complaint was recorded as AEs^{27,28} at each visit. SAEs^{27,28} resulting in significant hazard were also separately collected.

Statistical analysis

For the efficacy measure, changes from baseline in PANSS score and CGI-S score at week 6 were assessed using a mixed-model repeated-measures (MMRM) analysis. The changes from baseline were presented as least squares mean (LS mean)±standard error (SE). The treatment group, visit time point, and the interaction effect between them were considered as fixed effects, and the baseline score and trial site were considered as covariates in the MMRM analysis. An unstructured covariance matrix was employed, estimating variance parameters through the restricted maximum likelihood method. The significance of fixed effects was assessed using the Kenward-Rogers method to calculate the degrees of freedom. The 95% two-sided confidence interval (i.e., 97.5% one-sided confidence interval) for the difference in score change was estimated to determine the non-inferiority of lurasidone to QXR, which would be verified if the lower limit of the confidence interval does not exceed the non-inferiority margin of -8.99.

Categorical data including safety parameters was presented as frequencies and proportions. The comparison of categorical data between treatment groups was performed using the chi-square test or Fisher's exact test, and the comparison of

the changes before and after the administration of the study drug within each treatment group was analyzed with McNemar's test. To compare the means between groups, the student's t-test or Wilcoxon rank sum test was conducted, and the paired t-test or Wilcoxon signed-rank test was used for the comparison of means within each treatment group.

RESULTS

A total of 284 subjects were screened and enrolled in the washout period, of whom 210 were randomly assigned to 6 weeks of double-blind treatment. Among 210 subjects, total 206 who took the study drugs at least once after enrollment were included as test subjects (safety set; Figure 1). Baseline demographic and clinical characteristics of safety set subjects were not significantly different between the two treatment groups (Table 1). At week 6 of completed treatment, 74.3% and 71.4% of subjects completed the trial in lurasidone and QXR groups, respectively, and dropout rates of both groups were not significantly different ($p=0.655$).

Efficacy

MMRM analysis was used to compare the LS mean change±SE from baseline to week 6 in the PANSS total score. In the primary efficacy analysis of the PP set, a significant reduction in PANSS total score at week 6 was observed in both lurasidone (-26.42 ± 2.02 , $p<0.001$) and QXR (-27.33 ± 2.01 , $p<0.001$)

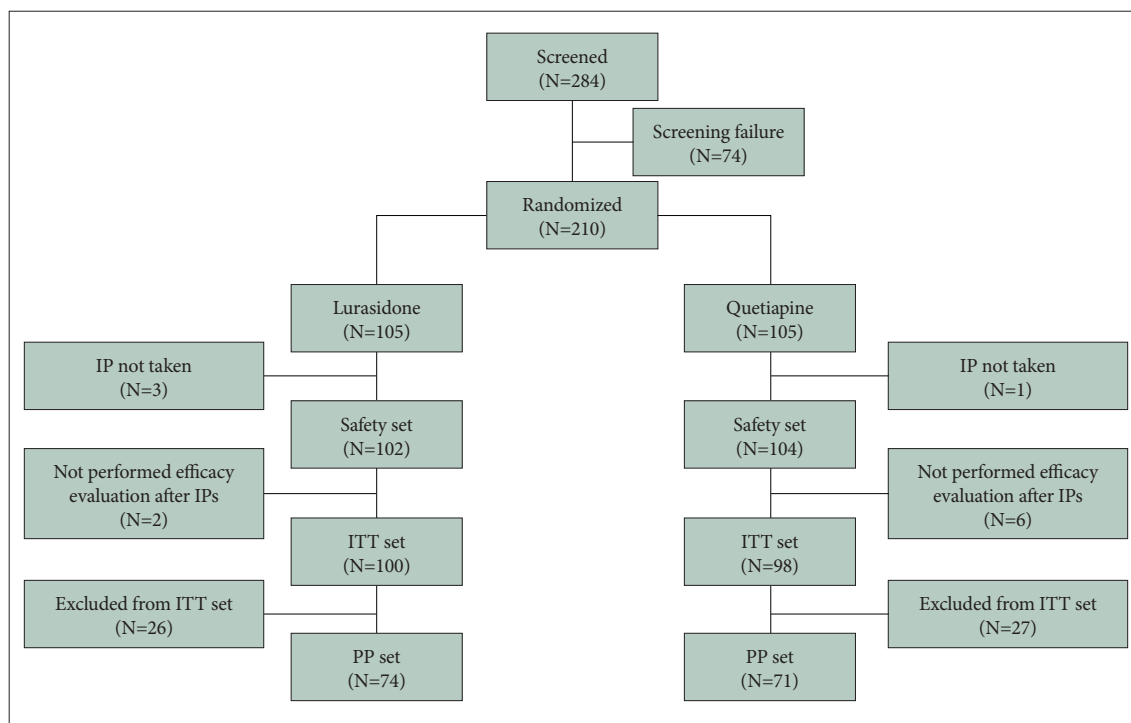


Figure 1. Flowchart describing the study flow and patient disposition. After screening, patients were randomized into either the lurasidone 160 mg/day group or the quetiapine XR 600 mg/day group. IP, Investigational product; ITT, intention-to-treat; PP, per-protocol.

Table 1. Baseline demographic and clinical characteristics (N=206)

	Lurasidone (N=102)	Quetiapine XR (N=104)	P
Age (yr)			0.214*
Mean±SD	40.64±14.93	42.84±14.68	
Min–Max	19.00–75.00	20.00–75.00	
Sex, n (%)			0.494†
Male	40 (39.22)	36 (34.62)	
Female	62 (60.78)	68 (65.38)	
Weight (kg)			0.187*
Mean±SD	66.46±12.34	64.92±15.24	
Min–Max	43.40–99.50	40.90–110.50	
BMI (kg/m ²)			0.221*
Mean±SD	24.87±3.95	24.37±4.36	
Min–Max	18.60–34.20	17.60–36.30	
PANSS total score			0.605*
Mean±SD	99.93±13.95	100.03±16.27	
Min–Max	81.00–157.00	80.00–155.00	
CGI-S score			0.801*
Mean±SD	4.91±0.71	4.90±0.78	
Min–Max	4.00–6.00	4.00–7.00	
Duration of illness (yr), n (%)			0.536†
≥1, <5	41 (40.20)	47 (45.19)	
≥5, <10	19 (18.63)	22 (21.15)	
≥10	42 (41.18)	35 (33.65)	

*Wilcoxon rank sum test; †chi-square test. BMI, body mass index; PANSS, Positive and Negative Syndrome Scale; CGI-S, Clinical Global Impressions severity; SD, standard deviation

group. The difference in PANSS total score change between groups was -0.91 (95% confidence interval -6.35–4.53). Since the lower limit of the confidence interval did not exceed the pre-defined non-inferiority margin of -8.99 in this clinical trial, the non-inferiority of lurasidone compared to QXR was verified. When compared weekly, the PANSS total score showed a significantly greater reduction from baseline by week 1 in the lurasidone group (-8.48 vs. QXR, -5.20; p=0.010) (Figure 2). Analysis using ITT set also showed similar pattern of changes in PANSS total score demonstrating the non-inferiority of lurasidone compared to QXR (Supplementary Figure 1 in the online-only Data Supplement).

For the secondary efficacy parameters, weekly pairwise comparison using the MMRM analysis was conducted to assess the differences in PANSS subscale scores (positive, negative, and general psychopathology subscale) and CGI-S scores between the two groups. In the PP set population, significant reductions from baseline at the efficacy parameters were observed in all three PANSS subscale scores for both the lurasidone and QXR groups (all p<0.001) (Figure 3). No significant differences were found between the two treatment groups in terms of PANSS subscale scores at the efficacy parameters. However, the lurasidone group showed a greater reduction in PANSS negative subscale score on week 1 (lurasidone, -1.76±0.42; QXR, -0.63±0.39, p=0.025). CGI-S scores also showed a significant reduction from baseline to week 6 in both the lurasidone and QXR groups. Throughout the 6-week period, the lurasidone group exhibited a more favorable CGI-S score, particularly with a statistically significant reduction observed at week 4 (lurasidone, -1.33±0.10; QXR, -1.03±0.10, p=0.019) and week 6 (lurasidone, -1.57±0.11; QXR, -1.25±0.11, p=0.036). At baseline, the CGI-S scores measured in both groups were around an average of 5 (lurasidone, 4.89±0.67; QXR, 4.97±0.77), indicating a “marked” severity. After administering the drug in the investigation for 6 weeks, both groups showed average scores around 3 (lurasidone, 3.31±1.07; QXR, 3.66±1.12), indicating a severity of “slightly to moderately ill” level. The analysis of the ITT set population for all efficacy evaluation measures was similar to that of the PP set (Supplementary Figure 2 in the online-only Data Supplement).

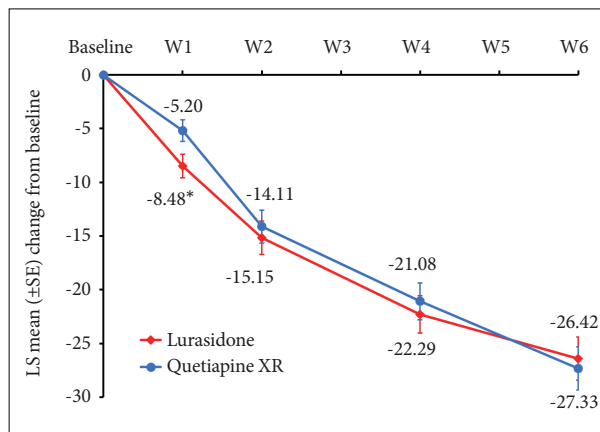


Figure 2. Change in Positive and Negative Syndrome Scale (PANSS) total score from baseline. Mixed-model repeated-measures analysis results showing the change in PANSS total score for lurasidone 160 mg/day and quetiapine XR 600 mg/day (per-protocol set). Results are shown as weekly least squares mean (LS mean)±standard error during 6 weeks of the double-blind trial period. *p<0.05 vs. quetiapine XR. W 1–6, week 1–6.

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AEs

The safety analysis was evaluated in the safety set that includes all subjects who received the study drug at least once after randomization. AEs were recorded with severity classification. Among a total of 516 cases of treatment-emergent AEs, the majority of the cases were rated as mild events in both the lurasidone (n=230, 87.1%) and QXR (n=213, 84.5%) groups. Severe cases were less than 1% in both treatment group (lurasidone, n=2, 0.98%; QXR, n=2, 0.96%). The proportion of

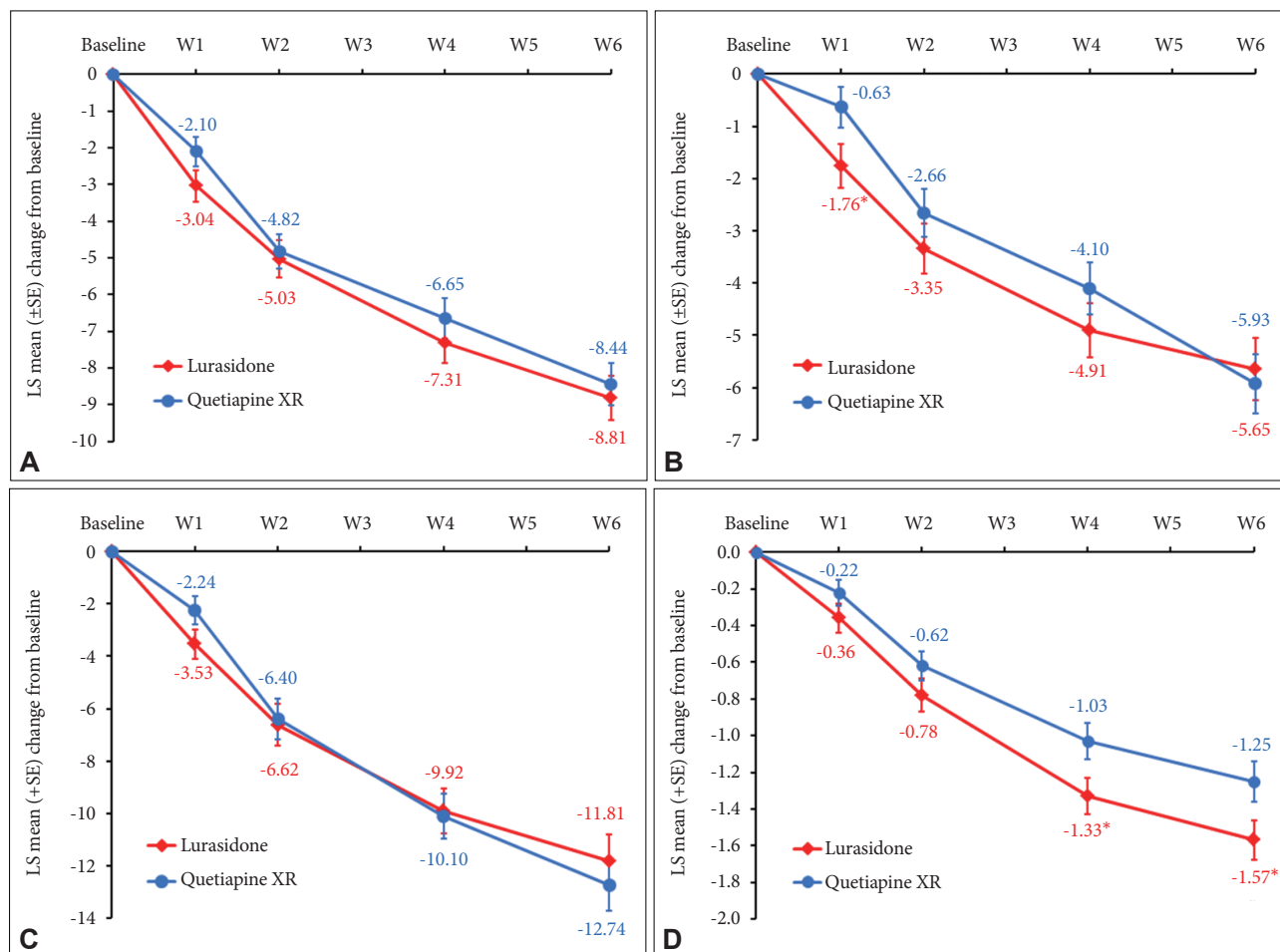


Figure 3. Change in Positive and Negative Syndrome Scale (PANSS) subscale scores and Clinical Global Impressions severity (CGI-S) score from baseline. Mixed-model repeated-measures analysis results showing the change in PANSS sub-scores (positive, negative, and general psychopathology) and CGI-S score for lurasidone 160 mg/day and quetiapine XR 600 mg/day (per-protocol set). Results are shown as weekly least squares mean (LS mean)±standard error during 6 weeks of the double-blind trial period. A: PANSS positive subscore. B: PANSS negative subscore. C: PANSS general psychopathology subscore. D: CGI-S score. * $p < 0.05$ vs. quetiapine XR. W 1–6, week 1–6.

the severity of the AEs did not differ between two groups ($p=0.104$).

SAEs occurred in 5 cases including the psychiatric symptoms and the gastrointestinal symptoms throughout the 6 weeks of trial; 2 cases in the lurasidone group (anxiety and enteritis) and 3 cases in the QXR group (two for psychotic symptoms, one for auditory hallucination). All of them were rated as mild or moderate, and the causality was considered ‘not related’ or ‘unlikely’ except for a case with ‘possible’ causality for moderate psychotic symptoms in the QXR group. All of the SAEs were recovered.

The incidence of the reported adverse drug reaction was 59.8% (61/102) in the lurasidone group, which was not significantly different from the incidence in the QXR group, 58.7% (61/104, $p=0.867$). The most common adverse drug reactions in the lurasidone group were akathisia (22.6%), followed by nausea (16.7%), increased blood prolactin level (7.8%), trem-

or (6.9%), and anxiety (6.9%). In the QXR group, akathisia was also the most common adverse reaction (15.4%), followed by constipation (9.62%), dizziness (8.7%), and somnolence (7.7%). Nausea ($p=0.001$) and prolactin increase ($p=0.048$) occurred more frequently in the lurasidone group compared to the QXR group. The adverse drug reactions occurring more than 5% of subjects are listed in Table 2.

Metabolic parameters

Mean changes in body weight, BMI, and waist circumference from baseline to week 6 were compared between the two groups (Table 3). While the QXR group showed increased body weight, BMI, and waist circumference after 6 weeks of treatment, the lurasidone group, on the contrary, showed a mild decrease in all three measures. The difference of mean change between the two groups regarding weight (lurasidone, -0.24 vs. QXR, 1.65; $p < 0.001$), BMI (lurasidone, -0.08 vs. QXR,

Table 2. Adverse drug reactions occurring more than 5% of subjects (N=206)

	Lurasidone (N=102)	Quetiapine XR (N=104)	p
Nervous system disorders			
Akathisia	23 (22.55)	16 (15.38)	0.189
Dizziness	3 (2.94)	9 (8.65)	0.080
Somnolence	2 (1.96)	8 (7.69)	0.056
Tremor	7 (6.86)	3 (2.88)	0.184
Gastrointestinal disorders			
Nausea	17 (16.67)	3 (2.88)	0.001*
Constipation	5 (4.90)	10 (9.62)	0.193
Psychiatric disorders			
Anxiety	7 (6.86)	3 (2.88)	0.184
Blood prolactin increased	8 (7.84)	2 (1.92)	0.048*
Musculoskeletal and connective tissue disorders			
Muscle rigidity	6 (5.88)	1 (0.96)	0.051

Data are presented as N (%). *p<0.05

0.63; p<0.001), and waist circumference (lurasidone, -0.97 vs. QXR, 1.64; p<0.001) were statistically significant.

Changes in serum glucose levels were significantly lower in the lurasidone group compared to the QXR group (lurasidone, 1.69 vs. QXR, 2.77; p<0.001). Among lipid levels, the changes in serum cholesterol (lurasidone, -3.92 vs. QXR, 11.13; p=0.040), low-density lipoprotein (LDL) cholesterol (lurasidone, -4.84 vs. QXR, 5.32; p=0.032), and triglyceride level (lurasidone, 0.63 vs. QXR, 24.21; p=0.033) were also significantly lower in the lurasidone group. High-density lipoprotein cholesterol level change showed no significant difference (Table 3).

Prolactin and other laboratory values

At week 6, the percentage of subjects with increased serum prolactin levels was 14.3% (11/77) in the lurasidone group and 2.7% (2/75) in the QXR group, which showed significant differences between the two groups (p=0.049). Other blood and urine laboratory test results did not show significant differences in terms of the incidence of abnormal values at week 6. At 1 week after the last administration of the study drugs (week 7), there were also no significant differences in laboratory parameters between the two groups.

Vitality signs

Diastolic blood pressure (BP) levels measured at week 2–6 were significantly lower compared to baseline values in the lurasidone group; albeit still within the normal range. In the QXR group, there was no significant change during the study

Table 3. Changes from baseline to week 6 in metabolic parameters

	Lurasidone	Quetiapine XR	p†
Body weight (kg)	N=78	N=75	<0.001*
Mean±SD	-0.24±2.43	1.65±2.64	
Min-Max	-6.70-4.40	-7.50-11.00	
BMI (kg/m ²)	N=78	N=75	<0.001*
Mean±SD	-0.08±0.88	0.63±1.01	
Min-Max	-2.30-1.60	-2.80-3.60	
Waist circumference (cm)	N=76	N=74	<0.001*
Mean±SD	-0.97±4.18	1.64±4.19	
Min-Max	-18.00-9.00	-9.00-12.00	
Glucose (mg/dL)	N=77	N=75	<0.001*
Mean±SD	1.69±17.10	2.77±19.28	
Min-Max	-36.00-95.00	-77.00-114.00	
Total cholesterol (mg/dL)	N=77	N=75	0.040*
Mean±SD	-3.92±27.05	11.13±31.68	
Min-Max	-91.00-46.00	-71.00-113.00	
HDL-C (mg/dL)	N=77	N=75	0.248
Mean±SD	0.06±8.39	-0.68±8.77	
Min-Max	-24.10-20.00	-18.00-34.00	
LDL-C (mg/dL)	N=77	N=75	0.032*
Mean±SD	-4.84±23.82	5.32±25.74	
Min-Max	-100.00-40.00	-80.00-61.00	
Triglyceride (mg/dL)	N=77	N=75	0.033*
Mean±SD	0.63±53.20	24.21±87.08	
Min-Max	-172.00-166.00	-312.00-248.00	

*p<0.05; †Wilcoxon rank sum test. BMI, body mass index; HDL-C, high-density lipoprotein-cholesterol; LDL-C, low-density lipoprotein-cholesterol; SD, standard deviation

period. Change in diastolic BP was significantly lower in the lurasidone group compared to the QXR group at week 5 (lurasidone, -3.55 vs. QXR, 0.49; p=0.029). Change in systolic BP did not show significant differences between the two groups. A Significant increase in heart rate was observed at week 6 in the QXR group, but not in the lurasidone group, compared to baseline level, leading to significant between-group differences in heart rate changes at week 6 (all p<0.05).

ECG

There were no subjects showing abnormal ECG findings at baseline, week 6, and week 7 in both treatment groups. In the lurasidone group, Bazett's corrected QT interval (QTc) did not show significant changes at weeks 6 and 7 compared to baseline, while a significant increase was observed at week 6 (p<0.001) and week 7 (p=0.009) in the QXR group. Chang-

es in Bazett's corrected QTc interval from baseline to week 6 were significantly different between the two groups (lurasidone, -0.29 ± 20.51 msec; QXR, 15.68 ± 23.46 msec, $p < 0.001$). The prevalence of the subjects showing Bazett's corrected QTc > 450 msec was significantly lower ($p = 0.006$) in the lurasidone group ($n = 11/101$, 12.4%) than in the QXR group ($n = 26/99$, 29.2%) at week 6.

EPS

The extrapyramidal side effects were evaluated weekly using the DIEPSS scale. The change from baseline in DIEPSS total score did not show a significant difference between the treatment groups at week 6 (lurasidone, 0.47 vs. QXR, -0.05; $p = 0.180$).

Suicidal ideation and behavior

The suicidal ideation and behavior were assessed with C-SSRS. The scores related to suicidal ideation and behavior did not change at week 6 compared to baseline in both groups, and there were no differences between the two groups in terms of changes in scores of suicidal ideation and behavior. One case of suicidal behavior after study initiation was reported in lurasidone group at week 4, which was rated as "no physical damage or very minor physical damage/behavior not likely to result in injury" in lethality score of C-SSRS.

DISCUSSION

The efficacy and safety of lurasidone 160 mg/day were evaluated by comparing to QXR 600 mg/day in Korean patients with schizophrenia presenting acutely psychotic symptoms. Treatment with lurasidone and quetiapine both showed significant improvement at week 6 compared to baseline in terms of PANSS total, positive, negative, and general psychopathology subscale scores, as well as CGI-S score. PANSS total and negative subscale scores were more prominently reduced at week 1 in the lurasidone group compared to the QXR group. The reduction of CGI-S scores at week 4 and 6 was significantly larger in the lurasidone group. Body weight, BMI, and waist circumference were significantly lower at week 6 compared to baseline in the lurasidone group, resulting in significant differences of changes between the two treatment groups. Endpoint changes in levels of glucose, cholesterol, triglycerides, and LDL were also significantly lower in the lurasidone group than in the QXR group. There were no prominent changes in ECG parameters by lurasidone.

As the primary efficacy assessment, the PANSS total score significantly decreased from baseline to week 6 in the patients treated with lurasidone 160 mg/day, which showed non-infe-

riority of lurasidone compared to the QXR group. The primary finding demonstrates the efficacy of lurasidone in Korean patients with schizophrenia in an acutely psychotic state. In terms of the PANSS subscale, acute efficacy was demonstrated not only in the positive subscale but also negative and general psychopathology subscales. The findings indicate a clinically meaningful improvement in the overall severity of psychopathology. Along with the previous studies performed in other countries showing the effectiveness of lurasidone in schizophrenia,^{9,11,12,29} the present study re-confirmed the acute efficacy of lurasidone in Korea.

Lurasidone showed a more favorable response at week 1 compared to QXR in terms of PANSS total and negative subscale scores. Earlier response to antipsychotics could be associated with better long-term outcomes.^{30,31} A recent study conducted in Japan³² demonstrated that early improvement by week 2 could predict later favorable treatment response in lurasidone treatment. The CGI-S score, but not PANSS total and subscale scores, was more significantly reduced in the lurasidone group than in the QXR group at week 4 and 6. The finding could suggest that lurasidone showed greater overall improvement beyond psychotic symptoms over 6 weeks. It might be related to the earlier improvement of lurasidone in PANSS scores. Further investigations will be required to examine the possibility of early response to lurasidone and the related subsequent benefits.

The overall safety evaluation results did not show statistically significant differences between the treatment groups, including treatment-emergent AEs, drug-related adverse reactions, serious adverse reactions, or discontinuations due to AEs (lurasidone 3.92% vs. QXR 2.88%). Akathisia was the most frequently reported adverse reaction in lurasidone (22.6%), which was similar to the previous reports regarding the incidence of lurasidone-related akathisia in schizophrenia.^{33,34} Higher serum prolactin level at week 6 was observed in 14.3% of the lurasidone group. The incidence observed in the present study was higher than that reported by previous studies.³⁵ The increase in prolactin levels with lurasidone is dose-dependent, reported to occur typically at doses exceeding 120 mg/day.³⁶ The use of a higher dose of 160 mg/day may have attributed to the higher incidence in the present study.

In terms of the parameters related to metabolic risk, lurasidone demonstrated more favorable results compared to QXR. In the lurasidone group, body weight, BMI, waist circumference, serum cholesterol, serum LDL, and diastolic BP were reduced at the endpoint compared to baseline. Lurasidone was suggested to be an antipsychotic agent showing the lowest weight gain potential.¹⁹ A recent observational study has also reported that lurasidone significantly reduced body

weight, BMI, serum alanine amino transaminase level, and fasting blood glucose.³⁷ Moreover, a higher dose of lurasidone was correlated with lowering fasting blood level suggesting that lurasidone may normalize glucose homeostasis.³⁷ Nagamine and Nakamura³⁸ suggested that reduced blood glucose by lurasidone may be associated with improvement in psychiatric symptoms as well. It might be associated with the lurasidone's effects on central catecholamine regulation including a moderate affinity for the 5HT_{1A} receptor.³⁹ Prolongation of QTc interval increases the risk of arrhythmia and can be associated with cardiovascular risk and sudden death.^{40,41} Lurasidone induced a decrease in the corrected QT interval leading to the significant difference compared to the QXR group. In addition to the beneficial effects on metabolic parameters, lurasidone was also shown to have a favorable cardiac profile.

In conclusion, in this 6-week randomized double-blind clinical trial with acutely psychotic schizophrenia patients, lurasidone 160 mg/day demonstrated non-inferiority to QXR 600 mg/day in the treatment of schizophrenia with comparable efficacy in PANSS score and CGI-S score. Adverse effects were generally tolerable and limited and beneficial effects on metabolic and cardiac parameters could be expected. Taken together, in conjunction with previous research findings, lurasidone can be considered a viable option for the treatment of schizophrenia patients with acute psychotic symptoms, with favorable efficacy and tolerability.

Supplementary Materials

The online-only Data Supplement is available with this article at <https://doi.org/10.30773/pi.2024.0052>.

Availability of Data and Material

The datasets generated or analyzed during the study are not publicly available due to the confidentiality issue related to the clinical trial research results but could be available from the corresponding author on reasonable request.

Conflicts of Interest

Sung Won Roh, Jong-Woo Paik, and Euitae Kim a contributing editor of the *Psychiatry Investigation*, was not involved in the editorial evaluation or decision to publish this article. All remaining authors have declared no conflicts of interest.

Author Contributions

Conceptualization: Hee Yeon Jung. Data curation and formal analysis: Se Hyun Kim, Nuree Kang, Hee Yeon Jung. Investigation: all authors. Writing—original draft: Se Hyun Kim, Nuree Kang, Hee Yeon Jung. Writing—review: all authors.

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