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Switching to Lurasidone following 12 months of treatment with Risperidone: results of a 6-month, open-label study

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Abstract

Background: Patients with a diagnosis of schizophrenia are at an increased risk for developing metabolic syndrome, which is associated with greater cardiovascular morbidity and mortality. Treatment with some commonly used antipsychotic medications may increase the risk of developing metabolic syndrome. The aim of the study was to evaluate the safety of lurasidone in patients who continued lurasidone or switched from risperidone to lurasidone. A secondary aim was assessment of the effect of long term lurasidone on the Positive and Negative Syndrome Scale (PANSS).

Methods: The treatment sample in the current study consisted of clinically stable patients with schizophrenia ($N = 223$) who had completed a 12 month, double blind study of lurasidone vs. risperidone. In the current extension study, all patients received 6 months of open label treatment with lurasidone, either continuing lurasidone assigned during the preceding double blind trial, or switching from double blind risperidone to lurasidone. Safety and tolerability parameters included body weight, prolactin, and metabolic laboratory tests.

Results: Six months of OL treatment with lurasidone was generally well tolerated, with a low incidence of parkinsonism (4.5%) and akathisia (3.1%). Overall, few adverse events were rated as severe (4.9%), and discontinuation due to an adverse event was low in the lurasidone continuation vs. risperidone switch groups (3.7% vs. 6.9%). In the lurasidone continuation versus risperidone switch groups, change from OL baseline to 6 month endpoint (observed case) was observed in mean body weight (− 0.6 vs. 2.6 kg), median total cholesterol (− 4.0 vs. + 4.5 mg/dL), triglycerides (− 4.5 vs. 5.5 mg/dL), glucose (0.0 vs. 3.0 mg/dL) and prolactin (males, + 0.15 vs. 11.2 ng/mL; females, + 1.3 vs. 30.8 ng/mL). Improvement in PANSS total score was maintained, from OL baseline to endpoint in the continuation vs. switch groups (+ 1.0 vs. 1.0; OC).

Conclusions: In this 6 month extension study, lurasidone treatment was generally well tolerated and associated with minimal effects on weight, metabolic parameters, and prolactin levels. Patients who switched from risperidone to lurasidone experienced reductions in weight, metabolic parameters and prolactin levels commensurate with increases in these safety parameters experienced during the previous 12 months of treatment with risperidone.

Trial registration: ClinicalTrials.gov NCT00641745 (Date of Registration: March 24, 2008).

Keywords: Lurasidone, Antipsychotic agents, Schizophrenia, Adverse effects, Weight, Metabolic, Lipids, Prolactin

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Background

Non-response to treatment with an initial antipsychotic occurs in at least 50% of patients with first episode schizophrenia and increases as the illness becomes more chronic and recurrent [1, 2]. The recommended next-step treatment option in non-responders is switching to an alternative antipsychotic [3, 4]. In addition to lack of efficacy, problems with safety or tolerability frequently necessitate switching antipsychotics [5].

Lurasidone is an atypical antipsychotic agent that has demonstrated efficacy in short-term [6–9] and long-term studies [10–12] of patients with schizophrenia, with a safety profile indicating minimal effects on weight, metabolic parameters, and prolactin [13, 14].

Previously, the effectiveness of switching patients with schizophrenia or schizoaffective disorder to lurasidone using 3 different dosing strategies has been evaluated [15]. At the time of the switch, patients were in a non-acute phase of their illness and were being treated with a wide range of typical or atypical antipsychotics. This 6-week study demonstrated that switching patients to lurasidone was associated with good efficacy and tolerability and low rates of treatment failure (8%), regardless of switching strategy (rapid or slow titration of lurasidone). Initial improvement in weight and lipids was observed after 6 weeks of treatment. In a 6-month, open-label extension of this study, improvements in efficacy on lurasidone were maintained, with minimal long-term effects on weight, metabolic parameters, and prolactin [16].

The effect on safety parameters of switching patients with schizophrenia from olanzapine to lurasidone has also been evaluated in a 6-month, open-label extension study in which patients who completed 6 weeks of double-blind, placebo-controlled treatment with olanzapine or lurasidone were switched to 6 months of open-label lurasidone 40–120 mg/d [17]. At 6-month endpoint, switching from olanzapine to lurasidone resulted in clinically meaningful (≥7%) reduction in weight in 29.0% of patients; and median reduction in lipid parameters, including total cholesterol (− 15.0 mg/dL) and triglycerides (− 28.0 mg/dL).

We now report results of an open-label extension study in which patients with schizophrenia who completed a double-blind, 12-month study of lurasidone versus risperidone [18] either continued lurasidone or switched from risperidone to lurasidone for an additional 6 months of open-label treatment. Notable safety results for lurasidone vs. risperidone at endpoint of the initial double-blind study included: mean reduction in weight (− 1.0 vs. + 1.5 kg) and waist circumference (− 0.6 vs. + 1.6 cm); smaller mean increases in prolactin for females (+ 34.9 vs. 53.3 ng/mL) but similar increases for males (13.5 vs. 14.1 ng/mL).

The primary objective of this study was to evaluate the long-term safety, tolerability and overall effectiveness of lurasidone in both the continuation and risperidone switch groups.

Methods

Study design

Detailed methods for the initial 12-month, double-blind study have been previously reported [18]. Briefly, clinically stable outpatients, ages 18–75 years, with a diagnosis of schizophrenia or schizoaffective disorder, were randomly assigned in a 2:1 ratio to receive lurasidone (flexibly dosed, 40–120 mg/d) or risperidone (flexibly dosed, 2–6 mg/d). Study completers were eligible to continue into the current 6-month, open-label extension study that was conducted from March 2009 to January 2011 at sites in the United States ($n = 40$), South Africa ($n = 7$), Argentina ($n = 5$), Chile ($n = 5$), Brazil ($n = 4$), Croatia ($n = 3$), Thailand ($n = 3$), and Israel ($n = 1$). To maintain the double-blind in the initial 12-month study, all patients entering the current open-label study received 3 days of single-blind placebo washout followed by 7 days of lurasidone 80 mg/d. After 7 days, the lurasidone dose could be titrated, based on the judgment of the investigator, in the range of 40–120 mg/d.

The study was conducted in accordance with the Good Clinical Practice Guidelines of the International Conference on Harmonisation and with the ethical principles of the Declaration of Helsinki. The study was approved by an institutional review board or independent ethics committee at each study site, and all patients provided written informed consent prior to initiation of study procedures. No important changes in study design or methodology were made after the study was initiated.

Assessments

Assessment visits occurred at baseline of the open-label extension study and monthly thereafter. Adverse events were based on patient self-report in response to an open-ended question or were based on investigator observation of changes in the patient during examination. Movement disorder symptoms were evaluated with the Simpson-Angus Scale (SAS) [19], Barnes Akathisia Rating Scale (BARS) [20], and Abnormal Involuntary Movement Scale (AIMS) [21]. Safety assessments included laboratory tests (chemistry and hematology panels, lipid panel, glycosylated hemoglobin [HbA1c], bone alkaline phosphatase, N-telopeptide, osteocalcin, parathyroid hormone, prolactin, and testosterone), electrocardiograms (ECG), physical examinations, and vital sign measurements. In a subset of patients (at selected US sites), bone mineral density assessments were performed (BMD, using dual-energy x-ray absorptiometry [DXA]). T-scores were calculated ([patient's BMD − mean BMD of sex-matched young adults] / 1-SD of young adults), and standard criteria

were used to determine BMD category (normal vs. osteopenia vs. osteoporosis) [22]. Ophthalmologic examinations, including dilated funduscopic and slit lamp eye examinations, were also performed.

Efficacy was assessed using the Positive and Negative Syndrome Scale (PANSS) [23], Clinical Global Impression, Severity scale [21], and the Montgomery-Åsberg Depression Rating Scale (MADRS) [24]. Training and certification of raters at each investigational site on study assessments was provided prior to initiation of the double-blind study.

Statistical analysis

The primary safety analysis population consisted of all patients who received at least one dose of lurasidone during the 6-month open-label extension study. All safety and efficacy outcomes were pre-specified and were analyzed for the overall treatment sample, and for 2 patient subgroups: patients who received lurasidone in the double-blind study, and patients who received risperidone in the double-blind study. Change scores were calculated from double-blind baseline to open-label study endpoint and from open-label baseline to open-label study endpoint (month 6). Observed cases (OC) and last observation carried forward (LOCF-endpoint) analyses were performed.

Results

Patient disposition and study treatment

Of the 236 patients who completed the initial 12-month double-blind study, 223 (94.5%) continued into the current open-label extension study. Overall, 90.1% of patients completed at least 3 months of open-label treatment with lurasidone, and 174/223 (78.0%) completed 6 months of treatment. Reasons for premature discontinuation included adverse events (11/223; 4.9%), withdrew consent (11/223; 4.9%), lost to follow-up (10/223; 4.5%), insufficient clinical response (8/223; 3.6%), and miscellaneous other reasons (9/223; 4.0%). Figure 1 summarizes patient disposition for the two pre-specified patient subgroups (based on double-blind treatment assignment in the initial double-blind study.

Patient characteristics were similar at open-label baseline in both the lurasidone continuation subgroup, and the risperidone-to-lurasidone switch subgroup (Table 1). The mean daily dose of lurasidone during open-label extension was 81.1 mg. Twenty-nine percent of patients ($n = 65$) received at least one concomitant medication, most commonly anxiolytics (22%), hypnotics/sedatives (18%), antidepressants (15%), and anticholinergics (13%).

Safety

Adverse events

The most commonly reported adverse events were headache (6.3%), psychotic disorder (5.4%), and parkinsonism

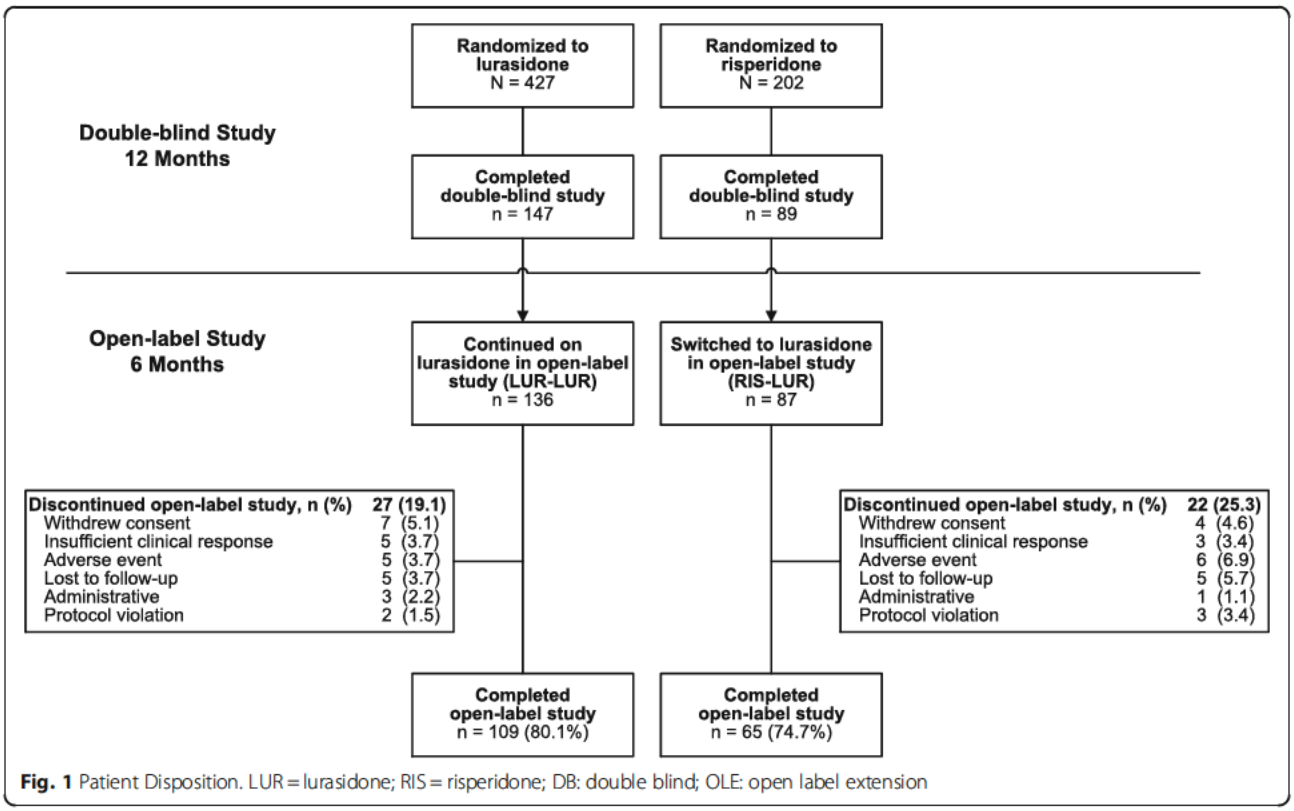

Fig. 1 Patient Disposition. LUR = lurasidone; RIS = risperidone; DB: double blind; OLE: open label extension

(4.5%; Table 2), with minimal differences between the lurasidone continuation versus risperidone switch groups. For both groups combined, a total of 11 patients (4.9%) experienced an adverse event rated as severe; and 10 patients (4.5%) experienced a serious adverse event, consisting of schizophrenia ($n = 3$), psychotic disorder ($n = 3$), ankle fracture ($n = 1$), lung carcinoma ($n = 1$), possible seizure ($n = 1$), attempted suicide ($n = 1$; patient recovered and completed the study), and a completed suicide ($n = 1$; on open-label day 22 in a patient who had previously received 12 months of double-blind lurasidone, and who was experiencing recurrent psychotic symptoms).

Extrapyramidal symptoms

In the combined patient groups, the proportion who reported an extrapyramidal symptom (EPS)-related adverse event during the extension study was 7.6%, and the proportion with akathisia was 3.1%. EPS-related adverse events reported in more than 1 patient were parkinsonism (4.5%) and dystonia (1.3%). The incidence of an EPS-related adverse event was similar in the lurasidone continuation versus risperidone switch groups (Table 2). No patient discontinued due to an EPS-related adverse event or akathisia. Mean change from open-label baseline to study endpoint (LOCF) was 0.0 on the Simpson-Angus Scale, 0.0 on the Barnes Akathisia Rating Scale global clinical assessment of akathisia, and + 0.3 on the Abnormal Involuntary Movement Scale total score.

Table 1 Patient Characteristics (Open-Label Baseline, Safety Population)

Characteristic	LUR LUR[a] (*N* = 136)	RIS LUR[b] (*N* = 87)
Male, n (%)	102 (75.0)	58 (66.7)
Age, mean (SD), y	43.9 (10.7)	42.8 (10.8)
Race, n (%)		
White	50 (36.8)	39 (44.8)
Black	67 (49.3)	40 (46.0)
Asian	6 (4.4)	1 (1.1)
Other	13 (9.6)	7 (8.0)
Ethnicity, Hispanic/Latino, n (%)	36 (26.5)	25 (28.7)
Duration of illness, mean (SD), y	16.9 (10.7)	17.6 (11.9)
≥4 hospitalizations, n (%)	30 (22.1)	25 (28.8)
PANSS total score, mean (SD)	55.4 (13.6)	55.5 (11.2)
CGI S score, mean (SD)	2.8 (0.8)	2.9 (0.8)
MADRS score, mean (SD)	5.1 (5.6)	4.3 (4.4)

CGI S Clinical Global Impression Severity Scale, *LUR* lurasidone, *MADRS* Montgomery Åsberg Depression Rating Scale, *PANSS* Positive and Negative Syndrome Scale, *RIS* risperidone, *SD* standard deviation
[a] Patients who received lurasidone in both double blind and open label studies
[b] Patients who received risperidone during the double blind study and were switched to lurasidone in the open label study

Table 2 Adverse Events Reported in ≥2% of Patients During Open-Label Treatment With Lurasidone

Adverse Event, n (%)	LUR LUR[a] (*N* = 136)	RIS LUR[b] (*N* = 87)
≥1 adverse event	80 (58.8)	51 (58.6)
Headache	7 (5.1)	7 (8.0)
Psychotic disorder	6 (4.4)	6 (6.9)
Parkinsonism	5 (3.7)	5 (5.7)
Anxiety	2 (1.5)	6 (6.9)
Blood creatine phosphokinase increased	5 (3.7)	3 (3.4)
Insomnia	3 (2.2)	5 (5.7)
Nasopharyngitis	5 (3.7)	3 (3.4)
Akathisia	5 (3.7)	2 (2.3)
Somnolence	5 (3.7)	2 (2.3)
Influenza	6 (4.4)	1 (1.1)
Nausea	3 (2.2)	3 (3.4)
Upper respiratory infection	6 (4.4)	0 (0)
Vomiting	3 (2.2)	3 (3.4)
Back pain	2 (1.5)	3 (3.4)
Decreased appetite	3 (2.2)	2 (2.3)
Weight decreased	4 (2.9)	1 (1.1)

LUR lurasidone, *RIS* risperidone
[a] Patients who received lurasidone in both double blind and open label studies
[b] Patients who received risperidone during the double blind study and were switched to lurasidone in the open label study

Body weight, BMI, waist circumference

Mean weight, BMI, and waist circumference were reduced, from double-blind to open-label baseline, in patients who received 12 months of treatment with lurasidone (– 1.1 kg, – 0.55 kg/m^2, and – 0.4 cm, respectively), and were increased in patients who received 12 months of treatment with risperidone (+ 2.4 kg, + 2.1 kg/m^2, + 2.8 cm, respectively; Table 3; Fig. 2).

Mean changes in mean weight, BMI, and waist circumference at 6-month open-label endpoint (OC analysis) were minimal in the lurasidone continuation subgroup; in contrast, notable reductions were observed in the subgroup that switched from risperidone to lurasidone (– 2.9 kg, – 1.0 kg/m^2, – 1.6 cm, respectively; [OC]); and the proportion of patients who experienced ≥7% weight loss was 19.7%; Table 3).

Metabolic parameters

Median total cholesterol, triglycerides, and glucose were reduced, from double-blind to open-label baseline, in patients who received 12 months of treatment with lurasidone (– 8.5 mg/dL, – 13.0 mg/dL, – 1.0 mg/dL, respectively); and in patients who received 12 months of treatment with risperidone, median triglycerides and glucose were minimally increased (+ 1.0 mg/dL, + 3.0 mg/dL, respectively), while total

Table 3 Change From Double-blind Baseline in Safety Parameters After 12-months of Treatment With Lurasidone or Risperidone, Followed by 6-months of Open-label Treatment With Lurasidone (OC analysis)

Parameter	LUR LUR	RIS LUR
Weight, kg	***n* = 109**[a]	***n* = 66**[a]
DB Baseline mean (SD)	81.1 (18.25)	82.9 (18.65)
Mean change to OL Baseline (after 12 mo DB Tx)	1.1	+ 2.4
Mean change from OL Baseline to Month 6 OL	0.6	2.9
≥ 7% weight increase from DB Baseline, %	12.8	13.6
≥ 7% weight decrease from DB Baseline, %	28.4	18.2
≥ 7% weight increase from OL Baseline, %	1.8	3.0
≥ 7% weight decrease from OL Baseline, %	6.4	19.7
Body mass index, kg/m^2	***n* = 109**	***n* = 66**
DB Baseline mean (SD)	27.7 (5.3)	28.8 (5.6)
Mean change to OL Baseline (after 12 mo DB Tx)	0.55	+ 2.1
Mean change from OL Baseline to Month 6 OL	0.2	1.0
Waist circumference, cm	***n* = 104**	***n* = 62**
DB Baseline mean (SD)	93.8 (14.1)	97.5 (14.3)
Mean change to OL Baseline (after 12 mo DB Tx)	0.4	+ 2.8
Mean change from OL Baseline to Month 6 OL	0.9	1.6
Total cholesterol, mg/dL	***n* = 108**	***n* = 64**
DB Baseline mean (SD)	196.4 (45.4)	188.0 (49.0)
Median change to OL Baseline (after 12 mo DB Tx)	8.5	9.0
Median change from OL Baseline to Month 6 OL	4.0	+ 4.5
Triglycerides, mg/dL	***n* = 108**	***n* = 64**
DB Baseline mean (SD)	127.5 (57.7)	125.5 (88.8)
Median change to OL Baseline (after 12 mo DB Tx)	13.0	+ 1.0
Median change from OL Baseline to Month 6 OL	4.5	5.5
Glucose, mg/dL	***n* = 105**	***n* = 63**
DB Baseline mean (SD)	95.1 (14.5)	94.6 (13.7)
Median change to OL Baseline (after 12 mo DB Tx)	1.0	+ 3.0
Median change from OL Baseline to Month 6 OL	0.0	3.0
Hemoglobin A1c, %	***n* = 103**	***n* = 63**
DB Baseline mean (SD)	5.7 (0.4)	5.6 (0.4)
Median change to OL Baseline (after 12 mo DB Tx)	0.0	0.0
Median change from OL Baseline to Month 6 OL	0.0	0.0
Bone alkaline phosphatase, mcg/L	***n* = 106**	***n* = 61**
DB Baseline mean (SD)	13.6 (5.2)	13.9 (4.3)
Median change to OL Baseline (after 12 mo DB Tx)	0.9	0.3
Median change from OL Baseline to Month 6 OL	+ 1.5	0
N telopeptide (urine), nmol BCE/mmol creatinine	***n* = 104**	***n* = 62**
DB Baseline mean (SD)	41.2 (120.3)	37.0 (35.8)
Median change to OL Baseline (after 12 mo DB Tx)	+ 1.5	4.0
Median change from OL Baseline to Month 6 OL	1.0	+ 0.5
Osteocalcin, ng/mL	***n* = 104**	***n* = 61**
DB Baseline mean (SD)	5.25 (3.38)	5.70 (4.36)
Median change to OL Baseline (after 12 mo DB Tx)	0.85	1.0

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