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Lurasidone for the treatment of acutely psychotic patients with schizophrenia: A 6-week, randomized, placebo-controlled study

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ABSTRACT

Despite the availability of established antipsychotic agents for the treatment of schizophrenia, continued unmet needs exist for effective medications with lower adverse-effect burden. The present study evaluated the efficacy, safety, and tolerability of treatment with the atypical antipsychotic lurasidone for patients with an acute exacerbation of schizophrenia. Patients were randomized to 6 weeks of double-blind treatment with lurasidone 40 mg/day, 80 mg/day, or 120 mg/day, or placebo. Changes in Positive and Negative Syndrome Scale (PANSS) scores were evaluated using mixed-model repeated-measures (MMRM) analysis. Vital signs, laboratory parameters, extrapyramidal symptoms, and electrocardiogram were assessed. Treatment with lurasidone 80 mg/day resulted in significantly greater improvement in PANSS total score compared with placebo (−23.4 versus −17.0; $p < 0.05$) at study endpoint (MMRM); lurasidone 40 mg/day and 120 mg/day achieved clinically meaningful overall PANSS score reductions from baseline (−19.2 and −20.5), but not significant separation from placebo. Differences between all lurasidone groups and placebo for changes in laboratory parameters and electrocardiographic measures were minimal. Weight gain ≥7% occurred in 8.2% of patients receiving lurasidone and 3.2% receiving placebo. Modest increases in prolactin (median increase, 0.7 ng/mL) and extrapyramidal symptoms were observed following treatment with lurasidone compared with placebo. Akathisia was the most commonly reported adverse event with lurasidone (17.6%, versus 3.1% with placebo). In this study, in which a large placebo response was observed, lurasidone 80 mg/day, but not 40 mg/day or 120 mg/day, was statistically superior to placebo in treating acute exacerbation of chronic schizophrenia. All lurasidone doses were generally well tolerated.

1. Introduction

Schizophrenia is a chronic, debilitating psychiatric disorder affecting between 0.5% and 1.1% of adults worldwide (Regier et al., 1993; Saha et al., 2005). Several illness characteristics contribute to the substantial personal and socioeconomic burden imposed by schizophrenia, including onset in early adulthood, the persistence of symptoms despite treatment, and the disabling nature of those symptoms, which often impair patients' social and vocational functioning, including the ability to live independently (Saha et al., 2005).

Second-generation or "atypical" antipsychotics were developed to provide a more favorable benefit–risk profile than first-generation antipsychotics for the treatment of schizophrenia (Arranz and de Leon, 2007). The risk of movement disorders such as extrapyramidal symptoms (EPS) and tardive dyskinesia is lower during treatment with atypical antipsychotics compared with first-generation agents (Correll et al., 2004; Tenback et al., 2005; Leucht et al., 2009). However, several atypical antipsychotics have been associated with metabolic changes, including weight gain, metabolic syndrome, diabetes, and atherogenic dyslipidemia, that increase cardiovascular risk (American Diabetes Association et al., 2004; Henderson et al., 2005; Koro et al., 2002; Newcomer, 2007). Limitations of treatment with well-established antipsychotics were evident in findings from the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE): 74% of patients discontinued treatment with the initially prescribed agent within 18 months because of lack of efficacy, adverse events, or personal preference. Moreover, the agent deemed most effective (olanzapine) was associated with the greatest weight gain and unfavorable changes in glucose and lipid metabolism (Lieberman et al., 2005).

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Thus, unmet needs remain for effective, more tolerable treatment options for patients with schizophrenia.

Lurasidone is an atypical antipsychotic agent approved by the US Food and Drug Administration for the treatment of adult patients with schizophrenia (Latuda PI, May 2012). Lurasidone acts as an antagonist with high affinity for dopamine D_2, 5-hydroxytryptamine $(5\text{-HT})_{2A}$, and 5-HT_7 receptors, and as a partial agonist with moderate to high affinity for 5-HT_{1A} receptors (Ishibashi et al., 2010). In placebo-controlled clinical studies, fixed daily doses of lurasidone 40 mg, 80 mg, 120 mg, and 160 mg have demonstrated efficacy for patients with acute psychotic episodes associated with chronic schizophrenia (Loebel et al., in press; Meltzer et al., 2011; Nakamura et al., 2009; Ogasa et al., 2012). In these studies, treatment with lurasidone was not associated with clinically relevant adverse-effects on metabolic parameters, weight, or electrocardiographic (ECG) parameters and was associated with modest elevations in prolactin level and low propensity for EPS (Loebel et al., in press; Meltzer et al., 2011; Nakamura et al., 2009; Ogasa et al., 2012).

The objective of the present study was to further evaluate the efficacy, safety, and tolerability of treatment with lurasidone (40, 80, or 120 mg/day) for patients with an acute exacerbation of schizophrenia.

2. Materials and methods

This randomized, fixed-dose, double-blind, placebo-controlled, multiregional, parallel-group, 6-week study was conducted between October 2007 and December 2008 at 48 centers in the United States ($n = 21$), Russia ($n = 7$), India ($n = 6$), Ukraine ($n = 6$), Romania ($n = 5$), Malaysia ($n = 2$), and France ($n = 1$).

2.1. Patients

Adult inpatients, aged 18–75 years, were eligible for study enrollment if they met *Diagnostic and Statistical Manual of Mental Disorders, 4th Edition* (DSM-IV) criteria for a primary diagnosis of schizophrenia (American Psychiatric Association, 1994), as established by structured clinical interview using the Mini-International Neuropsychiatric Interview (MINI) Plus (Sheehan et al., 1998), had received a diagnosis of schizophrenia ≥1 year previously, and were currently experiencing an acute exacerbation of psychotic symptoms (lasting ≤2 months). Additional criteria for eligibility included a Clinical Global Impression of Severity (CGI-S) score ≥4 (moderate or greater) and a Positive and Negative Syndrome Scale (PANSS) total score ≥80, including a score ≥4 (moderate) on two or more of the following five items: delusions, conceptual disorganization, hallucinations, unusual thought content, and suspiciousness. Patients were excluded if they had an acute or unstable medical condition, evidence of any other chronic disease of the central nervous system, history of resistance to treatment with neuroleptics (failure to respond to two or more marketed antipsychotic agents from two different classes in the past year), alcohol or other drug abuse/dependence within the past 6 months, or evidence of a severe chronic movement disorder. Patients were also excluded if they had been treated with clozapine during the 4 months prior to enrollment or had received depot neuroleptics, unless the last injection was at least one treatment cycle prior to randomization.

Eligible patients were tapered off psychotropic medications prior to a 3- to 7-day, single-blind, placebo run-in period. Patients who continued to meet entry criteria were then randomly assigned via an interactive voice response system in a 1:1:1:1 ratio to one of the three fixed-dose lurasidone treatment arms or placebo at each site: lurasidone 40 mg/day, lurasidone 80 mg/day, lurasidone 120 mg/day, or placebo. Patients were eligible for hospital discharge after 21 days of treatment if they were judged by the investigator to be clinically stable and had achieved a CGI-S score of 3 (mildly ill) or lower.

All patients provided written informed consent prior to enrollment. The study protocol was approved by an Institutional Review Board for Human Research associated with each study center. Study conduct was consistent with the Declaration of Helsinki (2000) and Good Clinical Practice guidelines.

2.2. Study medication

Study medication comprised lurasidone 40 mg tablets and matching placebo. All patients received 3 identical tablets daily, which were taken together in the morning ≤30 min after a meal. Depending on treatment assignment, patients received lurasidone 40 mg/day, 80 mg/day, or 120 mg/day or placebo. For example, patients randomized to lurasidone 40 mg/day received 1 tablet of lurasidone and 2 matching placebo tablets. Patients randomized to receive lurasidone 40 mg/day and 80 mg/day started treatment at the target dose; patients randomized to receive lurasidone 120 mg/day received 80 mg/day for 3 days before increasing to 120 mg/day.

Concomitant administration of benzodiazepines (lorazepam ≤6 mg/day orally, or 4 mg/day intramuscular administration for agitation and/or temazepam up to 30 mg/day for sleep) was permitted for severe anxiety, agitation, or insomnia. Medications administered for movement disorders were tapered and discontinued prior to randomization; treatment with benztropine (≤6 mg/day), biperiden (≤16 mg/day), trihexyphenidyl (≤15 mg/day), or diphenhydramine (≤100 mg/day) was then permitted on an as-needed basis if EPS-related symptoms emerged during the study. Treatment with propranolol (≤120 mg/day) or amantadine (≤300 mg/day) was permitted as needed for akathisia. Anticholinergic or other agents that could cause sedation were not administered within 6 h of scheduled assessments. Use of potent inducers or inhibitors of cytochrome P450 isoenzyme 3A4 (e.g., ketoconazole, rifampin) was prohibited.

2.3. Assessments

Efficacy was assessed using the PANSS total score as the primary outcome (Kay et al., 1987) and the CGI-S as the key secondary outcome (Guy, 1976). Other outcomes included PANSS subscale scores (positive symptoms, negative symptoms, general psychopathology) and assessment of change in depressive symptoms using the Montgomery-Åsberg Depression Rating Scale (MADRS) (Montgomery and Åsberg, 1979). PANSS and CGI-S evaluations were performed at the screening and baseline visits and weekly during the 6-week study period. The MADRS was administered at screening, baseline, and Weeks 3 and 6.

Neurologic, metabolic, and other adverse events were also assessed throughout the study period. The presence and severity of EPS was assessed at every study visit using the Simpson-Angus Scale (SAS), the Barnes Akathisia Rating Scale (BAS), and the Abnormal Involuntary Movements Scale (AIMS) (Simpson and Angus, 1970; Barnes, 1989; Guy, 1976). On the SAS, an abnormal score was defined as a mean item score >0.3. The BAS Global Clinical Assessment of Akathisia provides ratings of intensity from absent to severe (Barnes, 1989). On the AIMS, an abnormal score was defined as a rating of "mild" or worse on at least two items or a rating of "moderate" or worse on at least one item.

Other safety evaluations included vital signs, fasting glucose, fasting lipid panel, glycosylated hemoglobin [HbA1c], prolactin), weight, body mass index (BMI), and 12-lead ECG, as well as standard blood chemistry and hematology panels.