Lurasidone in combination with lithium or valproate for the maintenance treatment of bipolar I disorder

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Abstract
Lurasidone (DS-RAn) has demonstrated efficacy in the acute treatment of bipolar depression, both as monotherapy, and as combination therapy with lithium or valproate. To evaluate the recurrence prevention efficacy of lurasidone for the maintenance treatment of bipolar I disorder, patients received up to 20 weeks of open-label lurasidone (20–80 mg/d) combined with lithium or valproate during an initial stabilization phase. A total of 496 patients met stabilization criteria and were randomized to 28 weeks of double-blind treatment with lurasidone (20–80 mg/d) or placebo, in combination with lithium or valproate. Based on a Cox proportional hazard model, treatment with lurasidone reduced the probability of recurrence of any mood episode by 29% (primary endpoint), however, the reduction did not achieve statistical significance. Probability of recurrence on lurasidone was significantly lower in patients with an index episode of depression (HR, 0.57; P = 0.039), in patients with any index episode who were not rapid-cycling (HR, 0.69; P = 0.046), and when recurrence was based on MADRS, YMRS, or CGI-BP-S severity criteria (HR, 0.53; P = 0.025; sensitivity analysis). Long-term treatment with lurasidone combined with lithium or valproate was found to be safe and well-tolerated, with minimal effects on weight or metabolic parameters.

1. Introduction
Bipolar disorder is a chronic illness with a high rate of recurrence that is frequently associated with reduced quality of life and impairment in functioning (Judd et al., 2002).
2.1. Patient population

Patients who met DSM-IV-TR criteria (APA, 2000) for bipolar I disorder were enrolled if they had \( \geq 1 \) manic, mixed manic, or depressed episode in the past 2 years (with or without rapid cycling or psychotic features), and a current Young Mania Rating Scale (YMRS; Young et al., 2011) or Montgomery-Åsberg Rating Scale (MADRS; Montgomery and Åsberg, 1979) total score \( \geq 14 \) (if treated with lithium or valproate at the time of the screen visit), or \( \geq 18 \) (if not on lithium or valproate). Patients treated with lithium or valproate with YMRS and/or MADRS scores \( \geq 14 \) were judged to be partial responders, and therefore the addition of lurasidone was considered to be warranted. Reasons for exclusion included substance dependence or abuse, clinically significant acute and/or unstable medical condition, concomitant use of a potent cytochrome P450 3A4 inhibitor or inducer, history of non-response to \( \geq 3 \) adequate trials of antidepressants, antipsychotics or mood stabilizers, or currently an imminent suicide risk (as judged by the investigator).

2.2. Study design

Patients first completed 12-20 weeks of open-label treatment with lurasidone plus lithium or valproate. For patients not currently being treated with lithium or valproate, mood stabilizer treatment was initiated as described below. Patients who met clinical stability criteria after at least 12 weeks of open-label treatment were then randomized (in a 1:1 ratio) to 28 weeks of double-blind treatment with lurasidone or placebo, in combination with lithium or valproate. The study was conducted at 26 sites in the United States (\( n = 468 \) patients), 10 sites in South America (\( n = 76 \) patients), 48 sites in Europe (\( n = 391 \) patients), and 10 sites in Asia (\( n = 25 \) patients) between September 2011 and October 2014. The study was approved by an Institutional Review Board at each investigational site and was conducted in accordance with the International Conference on Harmonisation Good Clinical Practice guidelines and with the ethical principles of the Declaration of Helsinki. An independent data and safety monitoring board reviewed and monitored patient data throughout the study.

2.3. Clinical stability criteria

Qualified patients were randomized to the 28-week double-blind phase if they achieved clinical stability during open-label treatment with lurasidone, defined as MADRS and YMRS total scores \( \leq 12 \) for \( \geq 12 \) weeks. Clinical worsening at up to two visits was permitted (YMRS \( \geq 13 \) and/or MADRS \( \geq 14 \)), except during the last 4 weeks prior to randomization.

2.4. Study medication

Patients who met entry criteria began open-label treatment with lurasidone 20 mg/d on days 1-3, 40 mg/d on days 4-7, and received flexible dosing thereafter in the range of 20-80 mg/d, with dose adjustments permitted in 20 mg increments/decrements per week. Following the 12-20-week open-label phase, patients who met clinical stability criteria were randomly assigned (in a 1:1 ratio) to receive either lurasidone 20-80 mg/day (flexibly dosed) or matching placebo in a double-blind manner; randomization was stratified based on which mood stabilizer was being used. Doses of lithium and valproate were adjusted throughout the study, as needed, to maintain serum trough concentrations of 0.4-1.2 mEq/L and 50-125 μg/mL, respectively. All country-approved formulations of lithium or valproate (including extended-release and controlled-release formulations) were permitted, with the exception of lithium orotate and magnesium valproate. For patients not
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