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Lurasidone adjunctive with lithium or valproate for bipolar depression: A placebo-controlled trial utilizing prospective and retrospective enrolment cohorts

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ABSTRACT

In this study, designed to evaluate the efficacy of lurasidone as adjunctive therapy with lithium or valproate, patients with bipolar I depression were randomized to 6 weeks of double-blind treatment with lurasidone (N = 180) or placebo (N = 176), added to background treatment with lithium or valproate. All patients were treated with lithium or valproate for a minimum of 4 weeks prior to screening. This was confirmed either by prospective treatment after study enrolment (run-in cohort), or retrospectively, with blood levels of lithium and valproate at screening (non-run-in cohort). Primary and key secondary endpoints were change from baseline to week 6 on the Montgomery-Åsberg Depression Rating Scale (MADRS) and depression severity score on the Clinical Global Impressions scale for use in bipolar illness (CGI-BP-S), respectively. Treatment with lurasidone was associated with non-significant improvement at week 6 vs. placebo for the MADRS total score (−11.8 vs −10.4; P = 0.176), and the CGI-BP-S score (−1.36 vs −1.13; P = 0.095). Significant separation from placebo was observed from weeks 2–5 for the MADRS and weeks 3–5 for the CGI-BP-S. Improvement in the placebo-subtracted MADRS total score was notably larger at week 6 for the non-run-in cohort compared to the run-in cohort (LS mean difference in endpoint change scores, −4.6; P = 0.009). Adverse events most frequently reported for lurasidone were akathisia, somnolence, and extrapyramidal side effects. In conclusion, lurasidone adjunctive with lithium or valproate demonstrated significant improvement in depressive symptoms based on the MADRS from weeks 2–5 but not at the primary week 6 endpoint.

1. Introduction

Medications for the treatment of bipolar depression are often used in combination. Multiple large scale surveys of prescribing practices indicate that more than 75% of patients with bipolar depression receive at least 2 medications, and more than one-third receive 3 or more (Goldberg et al., 2009; Haeberle et al., 2012; Greil et al., 2012). Over the past decade there has been a marked increase in the use of atypical antipsychotics for the treatment of bipolar depression. Up to 60% of patients treated with atypical antipsychotics for bipolar depression are on adjunctive therapy, most commonly with either mood stabilizers or standard antidepressants (Goldberg et al., 2009; Haeberle et al., 2012; Greil et al., 2012; Hooshmand et al., 2014; Ketter et al., 2015).

Although combination treatment is common in patients with bipolar depression, few controlled trials have been reported to support such use. The limited availability of evidence-based options for the acute treatment of patients with bipolar depression (Ostacher et al., 2015) is reflected in the lack of consensus in many treatment guidelines which recommend as first-line treatment a wide range of both monotherapies (e.g., quetiapine, lithium, lamotrigine) and combination therapies (e.g., atypicals + mood stabilizers, atypicals + antidepressants, antidepressants + mood stabilizers; Nivoli et al., 2011; Pacchiarotti et al., 2013).

Lurasidone is the only psychotropic agent that has demonstrated efficacy as an adjunctive therapy, with lithium or valproate, for the acute treatment of bipolar depression, based on positive results from a placebo-controlled trial (Loebel et al., 2014a). In

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contrast, previous controlled trials of atypicals combined with mood stabilizers in bipolar depression have been negative (Thase et al., 2008; Sachs et al., 2011).

The aim of the current study was to further evaluate the short-term efficacy and safety of lurasidone as adjunctive therapy with lithium or valproate in patients with bipolar depression. In both lurasidone bipolar depression adjunctive treatment studies, patients were required to have failed at least 4 weeks of adequate treatment with either lithium or valproate prior to randomization. The current study established inadequate response to mood stabilizer treatment based on either prospective treatment with lithium or valproate after study enrolment (run-in cohort), or retrospectively using several confirmatory methods (non-run-in cohort), allowing for a pre-planned secondary analysis of within-study comparison of the impact of these case ascertainment approaches.

2. Methods

2.1. Patients

This multiregional study enrolled outpatients, 18–75 years of age (inclusive), diagnosed with bipolar I disorder who were experiencing a major depressive episode (DSM-IV-TR criteria, ≥4 weeks and <12 months in duration), with a history of at least one lifetime bipolar manic or mixed manic episode either with rapid cycling (limited to <8 episodes in the past 12 months) or without rapid cycling, and without psychotic features. Diagnosis was confirmed by the Mini International Neuropsychiatric Interview (Sheehan et al., 1998) and the Bipolarity Index (Sachs, 2004). A Montgomery-Åsberg Depression Rating Scale (MADRS; Montgomery and Åsberg, 1979) score ≥20 and a Young Mania Rating Scale (YMRS; Young et al., 1978) score ≤12 were required at both screening and baseline.

Patients were excluded if they demonstrated a reduction of ≥25% in MADRS total score between screening and baseline; scored ≥4 on MADRS item 10 (suicidal thoughts) at screening or baseline; were judged to be at imminent risk of suicide or injury to self or others; had been hospitalized for a manic or mixed episode within the 60 days prior to randomization; had received treatment with antidepressants within 3 days, fluoxetine within 28 days, an MAO inhibitor within 21 days of randomization, or clozapine within 120 days of randomization; had an acute or unstable medical condition; had a history of alcohol or substance abuse (past 3 months) or dependence (12 months); or had a history of non-response to ≥3 adequate (6-week) trials of an antidepressant (with or without mood stabilizers) during the current depressive episode.

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 Practices guidelines and with the ethical principles of the Declaration of Helsinki. All patients who entered the study reviewed and signed an informed consent document explaining study procedures and potential risks before study entry. An independent data and safety monitoring board reviewed and monitored subject data throughout the study.

2.2. Study cohorts

All patients were required to have been treated for at least 28 days with lithium or valproate prior to screening, based on interview of the patient and a reliable informant, chart records, and documented blood levels within the protocol-specified therapeutic range at the time of screening (0.6–1.2 mEq/L for Li; 50–125 μg/mL for VPA). A variable length (but ≤8 weeks), prospective run-in period was utilized for all patients not meeting these criteria at initial screening. Patients with less than 28 days of treatment with lithium or valproate at initial screening were required to complete the missing days of treatment in a prospective run-in period (run-in cohort). Patients with lithium or valproate blood levels above or below the protocol-specified therapeutic range at the time of screening were required to achieve these levels at least once during the run-in period. Patients meeting all entry criteria at screening were permitted to be randomized without further run-in treatment (non-run-in cohort).

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. Study design

A total of 356 patients were randomized (currently treated cohort, n = 137; run-in treatment cohort, n = 219) at 71 sites in Europe (n = 106), North America (n = 162), Asia (n = 52), and South America (n = 36). This study was conducted between December 2010 and August 2012.

Patients underwent stratified randomization, based on treatment with lithium or VPA, to either adjunctive lurasidone 20–120 mg/day or placebo in a 1:1 ratio via an Interactive Voice Response System. A central randomization center used a computer-generated list of random numbers to allocate study treatments. None of the investigators, study staff or patients had access to the randomization codes or list. Study medication was provided in blister packs as identically matched tablets containing placebo, or 20 mg or 40 mg of lurasidone.

Lurasidone treatment was initiated at 20 mg/day on days 1–3, increased to 40 mg/day on days 4–6, and then 60 mg/day on day 7. After the first week, lurasidone could be adjusted within the dose range of 20–120 mg/day at weekly intervals, in 20 mg increments or decrements, based on investigator judgment. Lurasidone (or placebo) was taken once daily in the evening, with a meal or within 30 min after eating. The dose of mood stabilizer was adjusted to maintain a serum level in the range of 0.6–1.2 mEq/L for lithium or 50–125 μg/mL for valproate throughout the study.

2.4. Concomitant medications

Treatment with anticholinergic agents, propranolol or amantidine, was permitted as needed for movement disorders. As needed treatment with lorazepam (≤2 mg/d) for anxiety, or with eszopiclone (≤3 mg/d), temazepam (≤30 mg/d), or zolpidem (≤12.5 mg/d; for sleep) was permitted. Concomitant treatment for movement disorders, anxiety or insomnia was not permitted within 8 h prior to any psychiatric assessments.

2.5. Efficacy assessments

Efficacy assessments were obtained at baseline and weekly intervals. The primary efficacy endpoint was mean change from baseline to week 6 in MADRS total score. The MADRS, a 10-item scale with a total score that ranges from 0 to 60 (Montgomery and Åsberg, 1979), was assessed at each study visit by a qualified site-based rater; a second MADRS assessment was administered and scored by computer as part of a quality control process (Concordant Rater Systems, Boston, MA). The key secondary efficacy endpoint was mean change from baseline to week 6 in the Clinical Global Impression-Bipolar Severity (CGI-BP-S) assessment,