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Recovery in bipolar depression: Post-hoc analysis of a placebo-controlled lurasidone trial followed by a long-term continuation study

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ABSTRACT

Background: In this post-hoc analysis, rates of remission and recovery were evaluated in patients with bipolar depression treated with lurasidone.
Methods: Outpatients meeting DSM-IV-TR criteria for bipolar I depression, were randomized to 6 weeks of once-daily, double-blind treatment with lurasidone 20–60 mg, lurasidone 80–120 mg or placebo, followed by a 6-month, open-label, flexible-dose, lurasidone continuation study. Recovery was defined as meeting criteria for combined symptomatic remission (Montgomery–Asberg Depression Rating Scale total score ≤ 12) and functional remission (all Sheehan Disability Scale domain scores ≤ 3) sustained for at least 3 months in the 6-month continuation study.
Results: A significantly higher proportion of lurasidone-treated patients met criteria for combined symptomatic remission and functional remission (33.3%, 91/273) compared to the placebo group (21.0%, 30/143, $p < 0.05$, NNT=9) at the 6-week study endpoint. In the 6-month continuation study, the proportion of lurasidone-treated patients achieving sustained recovery was 60.7% (85/140) and 44.9% (31/69), for patients who continued lurasidone treatment and who switched from placebo to lurasidone, respectively.
Limitations: The definition of recovery used has not been previously validated and the analysis was post hoc. Lack of a control group in the continuation study limits data interpretation.
Conclusions: Recovery in patients with bipolar depression was assessed based on rates of combined symptomatic and functional remission sustained over time. A majority of patients initially treated with lurasidone in the acute phase achieved recovery status in the continuation study. Treatment with lurasidone (vs. placebo) earlier in the course of the bipolar depressive episode increased the likelihood of subsequent recovery.

1. Introduction

Bipolar disorder is a persistent, serious psychiatric illness with an estimated prevalence of approximately 1% (Merikangas et al., 2007). Major depressive episodes constitute the most common symptomatic state associated with bipolar disorder (Judd et al., 2002; Calabrese et al., 2004; Kupka et al., 2007), imposing a large illness burden as well as substantial direct and indirect costs on patients, caregivers and society (Calabrese et al., 2004; Huxley and Baldessarini, 2007; Fagiolini et al., 2013; Kleine-Budde et al., 2014). In addition to the risks of suicide and poor symptomatic outcomes, poor functional outcomes are common (Huxley and Baldessarini 2007; Jamison 2000; Leverich et al., 2003; Wingo et al., 2010). Individuals with bipolar disorder are commonly unemployed or disabled, despite having at least some college or post-high school education (Wingo et al., 2010; Kupfer 2005; Simon 2003; Kogan et al., 2004). Difficulties with work adjustment and global outcome often persist after syndromic recovery from bipolar mood episode (Strakowski et al., 1998; Tohen et al., 2000). Although associated, functional recovery tends to lag substantially behind symptomatic remission (Tohen et al., 2003a; Goldberg et al., 2005; Sheehan and

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Sheehan, 2008; Sheehan et al., 2008; Mancini et al., 2012; Bijl and Ravelli, 2000; Simon et al., 2000).

Relatively little high-quality evidence exists to guide long-term maintenance treatment for bipolar depression. Long-term adjunctive antidepressant treatment was not superior to use of a mood stabilizer alone in a meta-analysis involving patients with bipolar disorder (Ghaemi et al., 2008). Long-term antidepressant treatment may increase the risks of treatment-emergent mania and rapid cycling in patients with bipolar disorder (Ghaemi et al., 2001; Strejilevich et al., 2011). Selected atypical antipsychotics have demonstrated efficacy in the treatment of acute bipolar depression, particularly quetiapine in both immediate (Calabrese et al., 2005; Thase et al., 2006) and extended-release formulations (Suppes et al., 2014), and the combination of olanzapine plus fluoxetine (Tohen et al., 2003b). In contrast, the other atypical antipsychotics aripiprazole and ziprasidone did not differentiate from placebo in randomized acute bipolar I depression trials (Thase et al., 2008; Lombardo et al., 2012; Sachs et al., 2011). More recently, lurasidone has demonstrated efficacy in improving depressive symptoms, and enhancing function and quality of life, both as monotherapy and adjunctive therapy to lithium or valproate, for the treatment of depressive episodes associated with bipolar disorder (Loebel et al., 2014a, 2014b; Citrome et al., 2014).

Recovery in patients with serious mental illness has generally been defined as sustained improvement in both symptom control together with adequate global social/vocational functioning (Sheehan et al., 1996, 2008; Sheehan and Sheehan, 2008; Mancini et al., 2012; Frank et al., 1991; Robinson et al., 2004; Stahl et al., 2010). However, there are few reports that examine rates of combined symptomatic and functional remission in patients with bipolar disorder over extended time periods. In the past, recovery has been commonly conceptualized as sustained symptomatic (rather than functional or both symptomatic and functional) remission, as in the National Institute of Mental Health Collaborative Study of Depression (Keller et al., 1983), the McLean-Harvard First Episode project (Tohen et al., 2000, 2003a), and the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD) study (Perlis et al., 2006). Likewise, the International Society for Bipolar Disorders (ISBD) Task Force recommended recovery be defined on the basis of symptom status ("remission") and duration (Tohen et al., 2009), rather than functioning. Using these criteria, 72% of 166 patients in the McLean-Harvard First Episode project met symptomatic recovery criteria (Young Mania Rating Scale score <5 and Hamilton Depression Rating Scale score <8 for at least 8 weeks), as compared to only 43% achieving functional recovery (regaining both occupational level and residential status held during the pre-intake year based on information from patients, family members, and medical records) by 2 years after initial hospitalization for a DSM-IV manic or mixed episode. In the STEP-BD study, 58.4% met recovery criteria (two or fewer threshold-level symptoms of mood elevation, or depression for at least 8 weeks) within up to 2 years of follow-up (Perlis et al., 2006).

The primary objective of this post-hoc analysis was to evaluate rates of sustained (for at least 3 months) recovery in patients with bipolar depression treated with lurasidone for up to 6 months in an outpatient continuation study.

2. Methods

We conducted a *post hoc* analysis based on data from a previously reported double-blind, placebo-controlled trial in patients with bipolar depression (Loebel et al., 2014a), that was followed by a 24-week, flexible-dose, open-label continuation study of lurasidone (Ketter et al., in press); these studies were conducted between April 2009 and February 2013. The studies were approved by an institutional review board at each investigational site and were conducted in accordance with International Conference on Harmonization Good Clinical Practices guidelines and with ethical principles of the Declaration of Helsinki. All patients signed an informed consent document explaining study procedures and potential risks before study entry.

2.1. Participants

This multiregional study, conducted in the United States and 7 other countries, enrolled outpatients, 18–75 years, diagnosed with bipolar I disorder (with a history of at least one lifetime prior bipolar manic or mixed manic episode) who were currently experiencing a major depressive episode according to text revision of the fourth edition of the Diagnostic and Statistical Manual of Mental Disorders DSM-IV-TR criteria, of ≥ 4 weeks but <12 months duration, with or without rapid cycling, and without psychotic features. A Montgomery Asberg Depression Rating Scale (MADRS) score of ≥ 20 and a Young Mania Rating Scale (YMRS) score of ≤ 12 were required at both screening and baseline. A detailed summary of entry criteria and study design, as well as results, are provided in the primary report (Loebel et al., 2014a).

2.2. Interventions

Eligible patients were randomized to receive 6 weeks of double-blind treatment with lurasidone, at flexible daily doses of either 20–60 mg or 80–120 mg, or 6 weeks of placebo (PBO). Study medication was taken once daily in the evening, with a meal or within 30 min after eating. A total of 319 intent-to-treat patients enrolled in the open-label, continuation study of lurasidone. patients were started in the continuation study on open-label lurasidone 60 mg/day with subsequent flexible dosing to optimize effectiveness and tolerability (between 20 mg/d and 120 mg/d), as deemed clinically appropriate.

2.3. Outcomes

The MADRS is a ten-item clinician-rated assessment of severity of depression, with higher scores associated with greater depression severity (Montgomery and Asberg, 1979). The Clinical Global Impression of Bipolar Disorder-Severity (CGI-BP overall) is a single-item clinician-rated assessment of overall bipolar illness severity on a 7-point scale, with higher scores associated with greater illness severity. The Sheehan Disability Scale (SDS) (Sheehan et al., 1996) is a well-established, self-rated scale designed to assess level of functional impairment across three major functional domains, in which patients rate the extent to which (1) work, (2) social life or leisure activities, and (3) home life or family responsibilities are impaired by mood symptoms on 10-point visual analog scales (0=Not at all, 1–3=Mildly, 4–6=Moderately, 7–9=Markedly, and 10=Extremely), with higher scores reflecting greater functional impairment. For our main analysis, we analyzed MADRS, CGI-BP (overall), and SDS assessed at randomized acute baseline, (Day 0), week 6 (end of randomized acute study), and month 3 (week 19) and month 6 (week 32) of the continuation study.

We defined symptomatic remission as MADRS total score ≤ 12, and functional remission as all SDS domain scores <3 (and/or SDS mean domain score <3, representing no to at most mild functional impairment) (Sheehan et al., 1996). We defined "recovery" in the continuation study as meeting criteria for both symptomatic remission and functional remission sustained for at least 3 months (2 consecutive visits at months 3 and 6). Sensitivity analyses were performed using a MADRS score of <8 to assess rates of symptomatic remission at specific time points as well as recovery.