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

Antony Loebela,d,n, Cynthia Siub, Krithika Rajagopalan a,d, Andrei Pikalova,d, Josephine Cucchiaroa,d, Terence A. Ketterc

a Sunovion Pharmaceuticals Inc., Marlborough, MA, USA
b COS and Associates Ltd., Hong Kong, Hong Kong
c Department of Psychiatry and Behavioral Sciences, Stanford University School of Medicine, Stanford, CA, USA
d Sunovion Pharmaceuticals Inc., Fort Lee, NJ, USA

**Article Info**

Article history:
Received 1 May 2015
Received in revised form 8 July 2015
Accepted 28 July 2015
Available online 5 August 2015

Keywords:
Recovery
Symptomatic remission
Functional remission
Bipolar depression
Lurasidone

**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 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.

© 2015 The Authors. Published by Elsevier B.V. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

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; Fagioli 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...
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 multicenter 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.
2.4. Statistical analyses

In this post-hoc analysis, a logistic regression model was applied to evaluate the effect of lurasidone on attaining symptomatic and functional remission and recovery. We built a parsimonious prediction function for the likelihood of achieving recovery (combined symptomatic and functional remission for at least 3 months), with respect to baseline and clinical characteristics, as well as initial treatment response from the 6-week acute phase. These characteristics included age, gender, duration of illness, baseline (week-0 of the randomized acute phase) symptom severity (CGI-BP overall), treatment received during the randomized acute phase, and remission status for MADRS symptoms or SDS function or both at week-6 of the randomized acute phase. The performance and predictive accuracy of this multivariate function was evaluated using c-statistics (D’Agostino et al., 2008).

3. Results

Patient disposition is depicted in Fig. 1. Demographic and clinical characteristics are summarized in Table 1. At week-6 (end of the 6-week acute randomized phase), a significantly higher proportion of lurasidone treated patients met criteria for combined symptomatic remission (MADRS total score ≤ 9) and functional remission (all SDS domain scores ≤ 3 representing no to at most mild functional impairment) (33.3%, 91/273 pooling the LUR20–60 and LUR80–120 groups) compared to the placebo group (21.0%, 30/143, p < 0.05, NNT = 10) (Fig. 2B). In a sensitivity analysis, rates of combined symptomatic and functional remission using a MADRS total score ≤ 8 and all SDS domain scores ≤ 3 were 24.9% (68/273) and 14.0% (20/143) for lurasidone and placebo patients, respectively, at the week-6 acute randomized phase endpoint (p < 0.05, NNT = 10) (Fig. 2B).

The proportion of lurasidone treated patients attaining symptomatic remission at week 6 of the acute randomized phase was significantly higher (40.9%, 132/323) compared to the placebo group (24.7%, 40/162, p < 0.01, NNT = 7). Likewise, the proportion of lurasidone treated patients attaining functional remission at week 6 was significantly higher (48.4%, 132/273) compared to the placebo group (31.5%, 45/143, p < 0.01, NNT = 6). Lurasidone was superior to placebo in achieving functional remission across the 3 SDS domains (SDS domain ≤ 3; Work/School, p < 0.05, NNT = 8; Social Life, p < 0.001, NNT = 6; Family Life, p < 0.001, NNT = 5) at week 6.

![Fig. 1. Patient disposition.](image)

![Fig. 2. Rates of combined symptomatic and functional remission at week 6 (LOCF). *p < 0.05 (Lurasidone vs. placebo).](image)

In the 6-month, open-label, continuation study, the proportions of lurasidone treated patients achieving recovery (meeting criteria for combined symptomatic remission and functional remission for at least 3 months), were 60.7% (85/140) and 44.9% (31/69), in the LUR–LUR and PBO–LUR groups, respectively (p = 0.03, NNT = 7) (Fig. 3A). There was also a significant increase in the rate of combined symptomatic and functional remission from week 6 (33.3% in the LUR–LUR group and 21.0% in the PBO–LUR group) to week 32 (74.8% in the LUR–LUR group and 64.9% in the PBO–LUR group at month 6 of the continuation study) (p < 0.001, trajectory over time), that was independent of the treatment groups (p = 0.798, treatment-by-time interaction).

### Table 1
Baseline demographic and clinical characteristics.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Acute, double-blind study phase</th>
<th>Continuation study phase</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Lurasidone (N=323)</td>
<td>Placebo (N=162)</td>
</tr>
<tr>
<td></td>
<td>N</td>
<td>%</td>
</tr>
<tr>
<td>Female</td>
<td>189</td>
<td>58.5</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>213</td>
<td>65.9</td>
</tr>
<tr>
<td>Black/African-American</td>
<td>46</td>
<td>14.2</td>
</tr>
<tr>
<td>Asian</td>
<td>46</td>
<td>14.2</td>
</tr>
<tr>
<td>Other</td>
<td>32</td>
<td>9.9</td>
</tr>
<tr>
<td>Age, years</td>
<td>Mean</td>
<td>SD</td>
</tr>
<tr>
<td></td>
<td>41.7</td>
<td>12.3</td>
</tr>
<tr>
<td>Age of onset of diagnosis, years</td>
<td>27.7</td>
<td>11.4</td>
</tr>
</tbody>
</table>

ITT = intent to treat; MADRS = Montgomery–Åsberg Depression Rating Scale; CGI-BP-S = Clinical Global Impression-Bipolar Version-Overall score.
Improvements in the SDS work/school, family life and social life

A 6-month continuation study (Fig. 4B, study in the LUR domain score for the work, social life and family life domains (SDS followed by lurasidone 20 mg/d flexibly dosed in the continuation study; PBO–LUR: placebo in the acute phase followed by lurasidone 20–120 mg/d flexibly dosed in the continuation study).

In a sensitivity analysis, recovery rates observed at month 6 using MADRS total score ≤8 and all SDS domain scores ≤3 for at least 3 months were 45.7% (64/140) and 30.4% (21/69) for LUR–LUR and PBO–LUR groups, respectively, at the month-6 continuation study endpoint (p < 0.05, NNT = 7) (Fig. 3B).

The proportion of patients attaining sustained symptomatic remission was 73.2% (112/153) for LUR–LUR patients and 66.6% (50/75) for PBO–LUR patients in the 6-month continuation study (Fig. 4A, p = NS). The proportion of lurasidone treated patients attaining sustained functional remission was 64.6% (95/147) for LUR–LUR patients and 56.7% (42/74) for PBO–LUR patients in the 6-month continuation study (Fig. 4B, p = NS).

A majority of patients (> 50%) achieved no more than mild disability for the work, social life and family life domains (SDS domain score ≤ 3) at both months 3 and 6 of the continuation study in the LUR–LUR and PBO–LUR groups, with comparable improvements in the SDS work/school, family life and social life domains.

Recovery (combined symptomatic and functional remission sustained for at least 3 months) was associated with lower baseline global bipolar illness severity (CGI-BP overall, p = 0.004) (assessed at acute phase baseline) and non-white race (p < 0.001, 45.4% in white vs. 76.5% in non-white population), as well as lurasidone (rather than placebo) treatment received in the acute randomized phase (p = 0.029). The proposed model had acceptable calibration performance based on predictive accuracy (AUC ROC c-statistics = 0.74). The week-6 remission status for symptoms (MADRS total score ≤12) or functioning (all SDS domain scores ≤3) or both predicted month-6 recovery (all p-values < 0.001). The bivariate analysis for recovery found that gender (recovery rate was 64% in men vs. 49% in women) and duration of illness (mean 11 years in the recovery group vs. 14 years in the non-recovery group, p < 0.05) were significant predictors, but were not independent of race and baseline global bipolar illness severity.

4. Discussion

We propose here that recovery in patients with bipolar disorder be defined based on the attainment of both symptomatic and functional remission, sustained over time. This is one of the first analyses in the bipolar disorder literature to apply a rigorous definition of recovery (combined symptomatic and functional remission sustained for at least 3 months) to a population of patients undergoing long-term treatment for bipolar depression. We also assessed rates of attainment of combined symptomatic and functional remission at specific time points in this analysis.

Rates of combined symptomatic and functional remission increased over time in lurasidone treated patients (LUR–LUR), from 33.3% at 6-weeks to 74.8% at the 6-month continuation study endpoint. Using our recovery criteria (combined symptomatic and functional remission sustained for at least 3 months), a total of 60.7% of patients treated continuously with lurasidone in the acute and continuation studies (LUR–LUR) and 44.9% of patients treated with placebo in the acute study followed by lurasidone in the continuation study (PBO–LUR) achieved recovery; the between-group difference was statistically significant (NNT = 7). These findings require confirmation in future studies, but suggest that initiation of lurasidone earlier rather than later in the course of an acute depressive episode associated with bipolar disorder may result in enhanced rates of recovery after longer-term treatment.

The ISBD task force recommended that recovery in patients with bipolar disorder be defined based on symptom severity and duration (e.g. 8 consecutive weeks) alone, rather than including functioning status (Tohen et al., 2009). The basis for this recommendation was that symptomatic and functional improvement might not be sychronic or symmetrical (Tohen et al., 2009). However, precisely because symptomatic remission and functional remission are correlated (Bijl and Ravelli, 2000; Simon et al., 2009), but do not necessarily coincide (Sheehan and Sheehan, 2008; Sheehan et al., 2008; Mancini et al., 2012; Tohen et al., 2009), assessing them as separate outcomes could potentially fail to recognize their interaction effects and the importance of attaining both of these recovery components (Sheehan et al., 1996, 2008; Sheehan and Sheehan, 2008). Indeed, if a perfect correlation existed between symptomatic remission and functional performance, there would be no need to consider them together. We thus assessed symptomatic remission combined with functional remission for at least 3 months as the key measure of recovery in this analysis.

Our operationalized definition of recovery contrasts with prior definitions that do not include a requirement for sustained symptomatic remission and are less structured with respect to functional recovery (e.g., regaining individual premorbid levels of...
psychosocial, residential and occupational status.”) (Tohen et al., 2000, 2009, 2012; Sachs et al., 2001). We believe that our proposed operational criteria for recovery are both practical and meaningful in that both symptomatic and functional status over a sustained period of time are captured by these criteria. Sustained symptomatic and functional improvements are key components of full recovery that may be applicable across psychiatric disorders (Sheehan and Sheehan, 2008; Sheehan et al., 2008; Mancini et al., 2012; Tohen et al., 2009).

As recommended by the ISRD task force (Tohen et al., 2009), both symptomatic and functional remission were also investigated as separate outcomes in our analysis. A majority of the LUR–LUR patients attained sustained functional and symptomatic remission for at least 3 months (65% and 73%, respectively). Among patients who met recovery criteria, improvements in the SDS work/school, family life and social life domains were similar, suggesting that lurasidone was effective across all domains of functional impairment. Our findings are consistent with previous reports suggesting that functional recovery is less common than symptomatic recovery in bipolar disorder patients (Tohen et al., 2000, 2003a, 2009; MacQueen et al., 2001), but in our study the absolute difference (8.6%) was relatively modest. Symptomatic and functional recovery rates (26% and 24%, respectively) were similar in a 12-month follow-up study of patients with bipolar disorder after hospitalization for the treatment of a manic or mixed episode (Keck et al., 1998). In contrast, there were marked differences between symptomatic recovery (72%, having low total Young Mania Rating Scale score ≤ 5 and Hamilton depression scale score ≤ 8 for at least 8 weeks) and functional recovery (43%, regaining both occupational level and residential status) 2 years after onset of a first manic/mixed bipolar episode in the McLean–Harvard First Episode project (Tohen et al., 2003a).

Recovery in the continuation study was more likely in patients with lower acute baseline global bipolar illness severity (CGI-BP overall), non-white race, and taking lurasidone (rather than placebo) during the randomized controlled acute phase. These findings are consistent with those observed in previous studies involving patients with bipolar disorder (Gitlin et al., 1995; Coryell et al., 1998; Tohen et al., 2000; Goldberg and Harrow, 2004, 2005, 2011).

Symptomatic remission and/or functional remission status at week 6 (end of the acute treatment phase) was strongly and significantly related to the attainment of recovery at the subsequent week 32 continuation study endpoint. The association between remission status at week 6 (end of acute treatment phase) and recovery at week 32 reaffirms the relationship of acute phase treatment response to long-term treatment efficacy and outcome in bipolar disorder (Goldberg and Harrow, 2004, 2005, 2011; Ketter et al. 2006; Berk et al., 2011). The lower recovery rate among whites compared to other races is somewhat inconsistent with existing findings (Tohen et al., 1990; Gonzalez et al., 2010), and warrants further investigation. Shorter illness duration was associated with symptomatic and functional remission and recovery. These results are consistent with prior findings showing that a shorter illness duration since an initial mood episode predicted better functioning in bipolar disorder patients (Keck et al., 1998; Tohen et al., 2000; Wingo et al., 2010). Gender differences in recovery rate and illness duration were not significant after adjusting for baseline severity and race.

4.1. Limitations

Several limitations of this analysis should be noted. The definitions of symptomatic and functional remission and recovery used in this analysis have not been previously validated and the analysis was post hoc. Although the SDS is a well-validated measure of disability and functional impairment in patients with bipolar and other psychiatric disorders (Leon et al., 1997; Arbuckle et al., 2009), it does not assess functional capacity in the same objective and comprehensive manner as more recently developed measures of functional impairment such as the Functioning Assessment Short Test (FAST) (Rosa et al., 2007) or the University of California at San Diego Performance-Based Skills Assessment (UPSA) (Mausbach et al., 2010). However, SDS total score was highly significantly correlated with FAST, total score (correlation r = 0.74), and SDS work domain score correlated significantly with FAST occupational functioning (r = 0.74) in patients with bipolar disorder (Suominen et al., 2015). Another limitation derives from the lack of inclusion of a measure of neurocognitive performance in the parent studies. Therefore, the relationship between change in neurocognition and recovery could not be assessed here (Wingo et al., 2009; Harvey et al., 2010). Importantly, the interpretation of our findings is limited by the absence of a control group in the continuation study. Since only patients with bipolar I depression were enrolled, the extent to which findings of the study can be generalized to patients with bipolar II depression warrants further investigation. Study entry criteria that excluded patients with serious psychiatric or medical comorbidity and active suicidal ideation or behavior, reduced the generalizability of the results.

5. Conclusions

In this post hoc analysis, recovery in patients with bipolar depression treated with lurasidone was assessed based on rates of sustained symptomatic and functional remission after a 6-week acute phase followed by a 6-month continuation study. A majority of lurasidone-treated patients 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. Our criteria for recovery and predictors of recovery in patients with bipolar disorder warrant further investigation and validation in future studies.

Role of funding source

This research was supported by Sunovion Pharmaceuticals Inc. The sponsor was involved in design, collection, and analysis of the data.

Conflict of interest

Dr. Ketter has received grant support from Agency of Healthcare Research and Quality and Sunovion Pharmaceuticals; lecture honoraria from Abbott Laboratories; Royalties from American Psychiatric Publishing, Inc. He has served as a consultant to Genentech, Janssen Pharmaceuticals, Merck Pharmaceuticals, and Sunovion Pharmaceuticals. Dr. Siu has been a consultant for Sunovion Pharmaceuticals Inc. and Pfizer Inc. Drs. Loebel, Rajagopal, Cucchiaro, and Pikalov are employees of Sunovion Pharmaceuticals, Inc.

Contributors

Dr. Loebel, Ketter, and Siu undertook the analysis and developed the first draft of the manuscript. All authors contributed to the critical review and approved the final manuscript for submission.

Acknowledgments

This study was supported by Sunovion Pharmaceuticals Inc., Marlborough, MA and Fort Lee, NJ, USA. Clinicaltrials.gov identifier: NCT00868699. Presented in part at the 18th annual meeting of the American Psychiatric Association, Toronto, Canada, May 16–20, 2015; the 53rd annual meeting of the American College of Neuropsychopharmacology, Phoenix, Arizona, December 7–11, 2014; and the 17th annual conference of the International Society of Bipolar Disorders, Toronto, Canada, June 3–6, 2015.


