Levetiracetam in the Management of Bipolar Depression: A Randomized, Double-Blind, Placebo-Controlled Trial

Aybala Saricicek, MD; Kathleen Maloney, BA; Anjana Muralidharan, BA; Barbara Ruf, BA; Hilary P. Blumberg, MD; Gerard Sanacora, MD, PhD; Boris Lorberg, MD; Brian Pittman, MS; and Zubin Bhagwagar, MD, PhD, MRCPsych

Objective: To study the efficacy of adjunctive levetiracetam therapy compared with placebo in the treatment of subjects with depression with bipolar disorder.

Method: This double-blind, placebo-controlled clinical trial randomly assigned outpatients with bipolar disorder type I and type II who were experiencing a major depressive episode (Structured Clinical Interview for *DSM-IV* Axis I Disorders–Clinician Version criteria) to treatment with either placebo or adjunctive levetiracetam (up to 2,500 mg/d flexibly dosed) for 6 weeks. The subjects were recruited from October 2005 to June 2008. The primary efficacy measure was mean change from baseline to week 6 in the Hamilton Depression Rating Scale (21-item). Secondary efficacy assessments included the Montgomery-Åsberg Depression Rating Scale, the Beck Depression Inventory, the Clinical Global Impressions–Bipolar Version scale, the Hamilton Anxiety Rating Scale, and the Young Mania Rating Scale.

Results: Of 42 subjects randomly assigned to placebo or drug, 32 received at least 1 post-baseline assessment and thus were included in the analysis. The mean (SD) levetiracetam daily dose at endpoint evaluation was 1,132 (425) mg/d. There was no significant difference in the mean change from baseline to week 6 in the Hamilton Depression Rating Scale scores for levetiracetam compared with placebo. There were no significant differences in any of the secondary outcome measures.

Conclusions: Levetiracetam adjunctive therapy was not superior to placebo in the short-term treatment of subjects with depression with bipolar disorder in the population studied.

Trial Registration: clinicaltrials.gov Identifier: NCT00566150

J Clin Psychiatry 2011;72(6):744–750

Submitted: *September 1, 2009; accepted November 10, 2009.*
Online ahead of print: *October 19, 2010 (doi:10.4088/JCP.09m05659gre).*
Corresponding author: *Zubin Bhagwagar, MD, PhD, MRCPsych, Bristol-Myers Squibb, 5 Research Parkway, Wallingford, CT 06492 (zubin.bhagwagar@bms.com).*

Bipolar disorder is a severe, chronic illness that exerts a crippling personal and financial toll on the individual, family, and wider society. Current estimates of bipolar disorder suggest that the lifetime prevalence estimates are 1.0% for bipolar disorder type I, 1.1% for bipolar disorder type II, and 2.4% for subthreshold bipolar disorder.[1] While it has been traditional to consider the manic episode as the more disruptive and devastating, elegant studies in the last decade have established that the main burden of illness in bipolar disorder is in the depressive pole.[2,3] In addition, patients with bipolar disorder with untreated residual symptoms following recovery from major depressive episodes show a poor prognosis,[4] underlining the need for vigorous and effective treatment of depressive episodes in the context of bipolar disorder. However, there are only a few currently validated treatments for patients experiencing a depressive episode in the context of bipolar disorder,[5] and contradictory to widespread assumption in the field, antidepressants added to mood stabilizers do not show superior efficacy compared to placebo in the largest study on antidepressants and bipolar depression.[6] Therefore, there is an urgent and critical need for the development of novel treatments.

Levetiracetam has been postulated as a potential novel agent that may have efficacy in the treatment of bipolar disorder. It is a relatively novel antiepileptic drug that shows evidence of possibly unique activity in regions implicated in the pathophysiology of bipolar disorder,[7,8] like the hippocampus[9,10] and the amygdala.[9,11] Although the mechanism of action of levetiracetam is not clear, it has been shown to act selectively on high-voltage–activated N-type calcium currents[12,13] and appears to indirectly facilitate GABAergic function.[14–16] Levetiracetam has been shown to have an antidepressant profile in an animal model,[17] and there are preliminary data suggesting that it is useful in patients with bipolar depression.[18,19] A recent open-label add-on trial with levetiracetam included 34 patients with treatment-resistant bipolar disorder, 16 of whom had depressive symptoms at the study baseline (13 acutely depressed, 3 rapid cycling). Of 16 subjects with depressive symptoms, 5 (31%) met the criterion for remission (Inventory for Depressive Symptomatology–Clinician-Rated score ≤ 13).[18] Based on recent preliminary data, we proposed to study the efficacy of levetiracetam add-on therapy compared with placebo in subjects with a depressive episode in the context of bipolar disorder who had failed to respond to conventional treatments. The primary hypothesis was that patients treated with levetiracetam would have a greater change in Hamilton Depression Rating Scale (HDRS)[20] score from baseline to endpoint than patients treated with placebo. Secondary outcome parameters selected were the change in scores from baseline for the Montgomery-Åsberg Depression Rating Scale (MADRS),[21] the Beck Depression Inventory (BDI),[22] the Clinical Global Impressions–Bipolar Version scale (CGI-BP),[23] and the Hamilton Anxiety Rating Scale (HARS).[24]

METHOD

Study Setting and Design

We conducted a randomized, placebo-controlled, double-blind clinical trial of adjunctive levetiracetam in patients with bipolar disorder who were currently depressed and not responding to current medication regimens (clinicaltrials.gov Identifier: NCT00566150). Subjects were recruited from New Haven, Connecticut, and surrounding areas by advertisement, word of mouth, and referrals over a period of approximately 2.5 years (October 2005 to June 2008). The study was reviewed and approved by the Yale Human Investigations Committee, and all subjects provided written informed consent for the study. Eligible subjects were randomly assigned to either levetiracetam (up to 2,500 mg/d flexibly dosed) or placebo treatment under double-blind conditions for 6 weeks. The study was designed to have a maximum of 50 subjects (n = 25 in each group). Based on an a priori power calculation, this would allow for 80% power to detect a difference in change in depression rating scores with minimum effect sizes of 0.40, 0.20, and 0.20 for the group, time, and group-by-time interaction effects, respectively.

Inclusion and Exclusion Criteria

Subjects aged 18–65 years were recruited to the study. All subjects had a diagnosis of bipolar disorder type I or type II currently depressed as assessed using the Structured Clinical Interview for *DSM-IV* Axis I Disorders–Clinician Version[25] and a clinician interview. All subjects included in the study had failed to respond to or were poorly tolerant of other treatments as judged by clinical interview, self-report, confirmation with outpatient treaters, availability, and an HDRS[20] score of 17 or greater. Subjects who met study entry criteria but who had discontinued their treatments following poor response or nonresponse were also included in the study. Subjects were considered as nonresponsive to their current medication regimen if they were stabilized on their current medication regimen for at least 2 weeks and had an HDRS score of 17 or greater or if they discontinued their medications due to lack of efficacy or tolerability. No medication changes were allowed for at least 2 weeks prior to starting study medication. If patients were receiving concomitant psychotherapy at the time of the study, they continued their psychotherapeutic treatment for the duration of the clinical trial.

To decrease diagnostic heterogeneity and sources of error, patients with comorbid diagnoses in which bipolar disorder was not the primary diagnosis were excluded from the study. Other exclusion criteria included current or past significant medical or surgical conditions, current active suicidal ideation, substance abuse or dependence within the preceding 3 months, and any women who were pregnant or currently lactating.

Interventions

In order to confirm diagnosis and suitability to participate in the study, all subjects had a comprehensive screening assessment. This included a complete psychiatric history and standardized psychiatric assessments, medical history and physical examination, and laboratory testing for hematologic and biochemical indices. Prior treatment history and failed medication trials were assessed using a semistructured clinical interview, self-report, and information from collateral sources (medical charts, previous treaters, family members, etc) when available. Failed medication trials were defined as inadequate response to minimum of 4 weeks of treatment using an adequate dose of standard treatments. The term "failed treatment trials" was used for lifetime episodes. A 21-item version of the clinician-administered HDRS[20] was used to assess severity of depression. Patients were also administered the BDI[22] to assess the severity of depression as well as the MADRS[21] and the CGI-BP.[23] The HARS[24] was used to assess anxiety, and the Young Mania Rating Scale[26] was used to assess treatment-emergent manic symptomatology, if any. All scales were administered at the initial screening and on a weekly basis throughout the 6-week trial.

Following the successful completion of the screening and baseline assessment, subjects were randomly allocated to placebo or levetiracetam. Study medications were packaged as identical capsules, with each capsule having either levetiracetam 250 mg or placebo. Subjects randomly assigned to either treatment were started on 1 capsule twice daily. The dose of levetiracetam was increased by 250–500 mg every week based on the patients' clinical response and tolerability of the drug in a flexible schedule. Based on previous work with levetiracetam and with the intention of striking a balance between efficacy and tolerability, we aimed to achieve a dose of between 500–3,000 mg. This dose range has been shown to be tolerable and efficacious with patients with epilepsy in clinical trials,[27] while anecdotal evidence from relevant investigators suggested that patients with bipolar disorder were less tolerant of higher doses of the medication. Patients did not receive any specific form of individual psychotherapy, and all current medications remained stable during the trial.

Study Outcomes

The primary outcome was change in HDRS score from baseline to endpoint. Additional efficacy measures included the MADRS, BDI, CGI-BP, and HARS. Secondary safety measures included the number of breakthrough manic and mixed episodes. The Side Effect Checklist and Young Mania Rating Scale were used to monitor treatment-emergent side effects and manic symptomatology. In addition, we also studied the number of remitters and responders. Response to treatment was defined a priori as a 50% reduction in HDRS score, whereas remission was defined as an HDRS score < 7. Diagnostic and outcome assessments were performed by clinicians blind to study treatment. Interrater reliability was established between raters by requiring that all raters receive training on the administration and scoring of the rating scales and complete a minimum number of observation and coscoring, followed by a minimum number of supervised interviews with coscoring. Interclass coefficients between

Table 1. Baseline Demographic and Clinical Characteristics of Subjects With Bipolar Depression

Patient Characteristic	Levetiracetam Group (n = 17), Mean (SD)	Placebo Group (n = 15), Mean (SD)	Statistic[a] t_{30}	P
Age, y	46.2 (11.1)	41.2 (8.5)	1.41	.17
Age at onset for bipolar disorder, y	18.6 (9.3)	13.8 (8.4)	1.54	.13
Duration of bipolar disorder, y	27.5 (11.7)	27.5 (11.0)	0.01	.99
Duration of current depressive episode, wk	22.6 (19.2)	17.8 (15.1)	0.79	.44
Age at onset for first depressive episode, y	18.6 (9.3)	15.3 (7.7)	1.09	.29
Age at onset for first manic episode, y	25.1 (10.7)	22.6 (13.0)	0.58	.57
No. of failed medication trials	4.8 (3.1)	6.2 (3.0)	−1.28	.21
No. of psychiatric hospitalizations	3.5 (7.1)	2.8 (2.6)	0.38	.71
	n (%)	n (%)	χ^2_1	P
Sex, male	8 (47)	6 (40)	0.16	.69
Race				
Caucasian	17 (100)	11 (73)	5.18	**.02**
Noncaucasian	0 (0)	4 (27)		
Bipolar disorder type				
I	12 (71)	11 (73)	0.03	.86
II	5 (29)	4 (27)		
Rapid cycling	3 (18)	4 (27)	0.38	.54
History of suicide attempt(s)	5 (29)	7 (46)	1.37	.24
No. of depressive episodes ≥ 20	13 (77)	13 (87)	0.54	.46
No. of manic episodes ≥ 20	11 (65)	11 (73)	0.28	.60
Substance abuse/dependence (past)				
Alcohol	11 (65)	7 (46)	1.05	.30
Cannabis	8 (47)	5 (33)	0.62	.43
Cocaine	8 (47)	6 (40)	0.16	.68
Opioid	5 (29)	2 (13)	1.20	.27
Other	2 (12)	3 (20)	0.41	.52
Anxiety disorder (current/past)				
Panic disorder	5 (29)	6 (40)	0.40	.53
Generalized anxiety disorder	2 (12)	3 (20)	0.41	.52
Social phobia	2 (12)	2 (13)	0.02	.89
Posttraumatic stress disorder	1 (6)	4 (27)	2.61	.10
Obsessive-compulsive disorder	1 (6)	2 (13)	0.52	.47
Specific phobia	0 (0)	4 (27)	5.18	**.02**
Eating disorder (current/past)	2 (12)	4 (27)	1.16	.28
Medication				
Mood stabilizers	6 (35)	9 (60)	1.95	.16
Antidepressants	5 (29)	7 (46)	0.73	.39
Antipsychotics	6 (35)	6 (40)	0.07	.78
Anxiolytics	5 (29)	6 (40)	0.40	.53
None	6 (35)	2 (13)	2.05	.15
Baseline psychometric assessment score	Mean (SD)	Mean (SD)	t_{30}	P
Hamilton Depression Rating Scale	23.2 (5.6)	18.2 (6.7)	0.45	.66
Montgomery-Åsberg Depression Rating Scale	28.5 (6.6)	22.1 (8.3)	0.68	.50
Hamilton Anxiety Rating Scale	18.4 (5.1)	14.5 (5.1)	0.66	.51
Young Mania Rating Scale	4 (2.3)	4.3 (2.0)	1.01	.32
Beck Depression Inventory	28 (11.5)	22.1 (8.5)	1.58	.12
Clinical Global Impressions–Bipolar Version scale depression severity	4.1 (0.8)	3.4 (0.9)	−0.57	.57

[a]Bold denotes significance.

raters for each mood rating scale were calculated and ranged from 0.89 to 1.00, with most scales greater than 0.94, suggesting a high degree of uniformity in mood rating scales.

Statistical Analyses

Demographic and baseline clinical parameters were analyzed using χ^2 tests or independent samples 2-tailed t tests as appropriate. The primary efficacy measure was change in total HDRS score from baseline to endpoint. All efficacy outcome parameters were normally distributed, and no transformations were required or performed for data analysis. Each outcome (subtracting out baseline measures) was compared between the groups across time using linear mixed models. In these models, group (patients vs controls) was included as a between-subjects explanatory factor, and time (baseline to week 6) was included as a within-subjects factor. The interaction between group and time was also modeled. All analyses were conducted based on an intent-to-treat basis, and an a priori decision was made to only include patients with at least 1 postbaseline assessment visit. The mixed-effects approach allowed us to use all data available on each subject. All analyses were performed using SAS, version 9.1 (SAS Institute Inc, Cary, North Carolina) in conjunction with the biostatistics core.

RESULTS

Patient Characteristics

The characteristics of patients taking levetiracetam or placebo are shown in Table 1. There were no statistically significant differences between the groups for demographic factors, including age; sex; type of bipolar disorder; age at onset for bipolar disorder; duration of the illness or duration of the current depressive episode; age at onset for the first depressive and manic episodes; number of manic episodes, depressive episodes, failed medication trials to lifetime episodes, and psychiatric hospitalizations; history of suicide attempt(s); past or current Axis I diagnosis; and medication status. As the patients were on a diverse set of medications, we have attempted to class the concomitant medications into classes of medications with a similar mode of action. Therefore, concomitant medications were categorized into 4 groups: mood stabilizers, antidepressants, antipsychotics, and anxiolytics. There were no statistically significant differences between the groups for any of these treatments (Table 1).

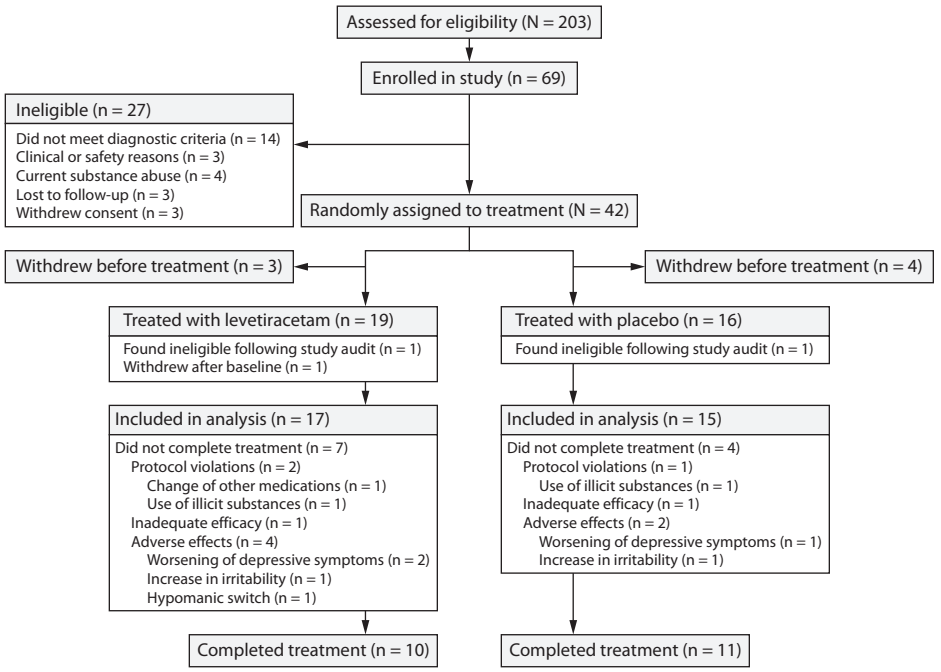
The baseline scores for HDRS, MADRS, HARS, Young Mania Rating Scale, BDI, and CGI-BP depression severity were also comparable between the 2 groups (all P values > .12; for baseline mean and SD values, see Table 2). The mean endpoint dose for patients treated with levetiracetam was 1,132 (425) mg/d. Six-week study completion rates (Figure 1) were somewhat lower in the levetiracetam group (10 [59%] of 17) than in the placebo group (11 [73%] of 15), but the difference

Table 2. Baseline and Endpoint Mean and SD Values for Psychometric Assessment Scores

	Levetiracetam Group (n = 17), Mean (SD)		Placebo Group (n = 15), Mean (SD)		Statistic (group × time interaction)[a]	
Assessment Score	Baseline	Endpoint	Baseline	Endpoint	*F*	*P*
Hamilton Depression Rating Scale	23.2 (5.6)	18.2 (6.7)	22.3 (5.7)	13.1 (9.2)	$F_{5,115} = 1.25$	.29
Montgomery-Åsberg Depression Rating Scale	28.5 (6.6)	22.1 (8.3)	26.8 (7.1)	19.2 (12.4)	$F_{5,114} = 2.09$	.07
Hamilton Anxiety Rating Scale	18.4 (5.1)	14.5 (5.1)	17.2 (4.5)	12.9 (8.4)	$F_{5,115} = 0.36$	.87
Young Mania Rating Scale	4 (2.3)	4.3 (2.0)	3.2 (3.2)	2.1 (1.4)	$F_{5,113} = 0.41$	.84
Beck Depression Inventory	28 (11.5)	21.2 (12.9)	22.1 (8.5)	10.5 (9.3)	$F_{5,103} = 2.0$	.08
Clinical Global Impressions–Bipolar Version scale depression severity	4.1 (0.8)	3.4 (0.9)	4.3 (0.7)	3.3 (1.6)	$F_{5,112} = 0.47$	.79

[a]All the statistics are based on change from baseline.

Figure 1. CONSORT Diagram



between groups was not significantly different ($\chi^2_1 = 0.94$, $P = .33$) (Figure 2A). Figure 1 shows the CONSORT diagram detailing subject participation in each phase of the study protocol and reasons for withdrawal.

Efficacy

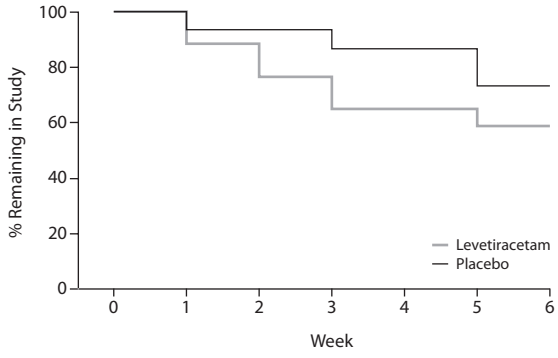
All the statistics performed were based on the change from baseline. Raw data for primary and secondary efficacy measures are shown in Figure 2. There was no statistically significant group-by-time interaction for HDRS scores ($F_{5,115} = 1.25$, $P = .29$). Change from baseline for MADRS scores was greater in the placebo group than in the levetiracetam group, but the group-by-time interaction for MADRS scores was not statistically significant ($F_{5,114} = 2.09$, $P = .07$). An exploratory post hoc comparison of weekly MADRS scores showed that there was no significant group-by-time interaction for any of the weeks studied. Group-by-time interactions for CGI-BP depression severity scores and for HARS scores were also not statistically significant ($F_{5,112} = 0.47$, $P = .79$, and $F_{5,115} = 0.36$, $P = .87$, respectively). There was no statistically significant difference in response rates between the groups (levetiracetam: n = 4 [22%], placebo: n = 4 [23%]; $\chi^2_1 = 0.04$, $P = .83$), whereas there were a statistically significantly greater number of remitters (n = 4, 23%) in the placebo group compared with the levetiracetam group (n = 0, 0%) ($\chi^2_1 = 5.18$, $P = .02$).

Safety and Tolerability

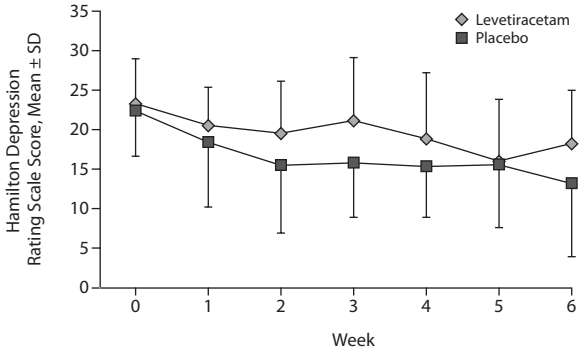
The overall clinical adverse event profile in the study is summarized in Table 3. Lack of efficacy led to premature termination of the study for 1 patient in each group. Four patients in the levetiracetam group and 2 patients in the placebo group discontinued the study due to adverse events (Figure 1). One patient taking levetiracetam experienced a mixed episode in the second week of the study; however, this mixed episode did not result in premature termination of the study. The most common adverse events in the levetiracetam group included lethargy (53%), gastrointestinal symptoms (31%), increased irritability (26%), and coordination problems (21%). Coordination problems were

Figure 2. Time Course of Treatment Discontinuation and Primary and Secondary Outcome Measures

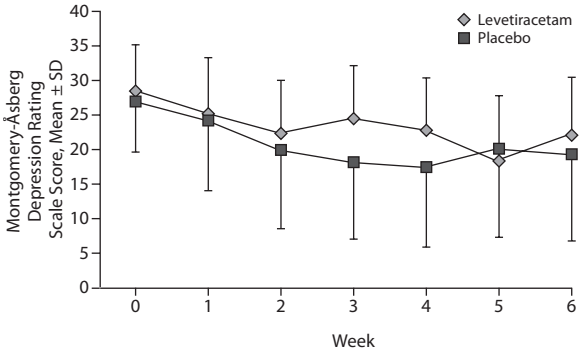
A. Kaplan-Meier survival curves for each treatment arm (log rank test, $\chi^2_1 = 0.94$, $P = .33$).



B. Hamilton Depression Rating Scale scores in patients with depression with bipolar disorder taking levetiracetam or placebo (group-by-time interaction: $F_{5,115} = 1.25$, $P = .29$).



C. Montgomery-Åsberg Depression Rating Scale scores in patients with depression with bipolar disorder taking levetiracetam or placebo (group-by-time interaction: $F_{5,114} = 2.09$, $P = .07$).



D. Clinical Global Impressions–Bipolar Version scale scores for severity of depression in patients with depression with bipolar disorder taking levetiracetam or placebo (group-by-time interaction: $F_{5,112} = 0.47$, $P = .79$).

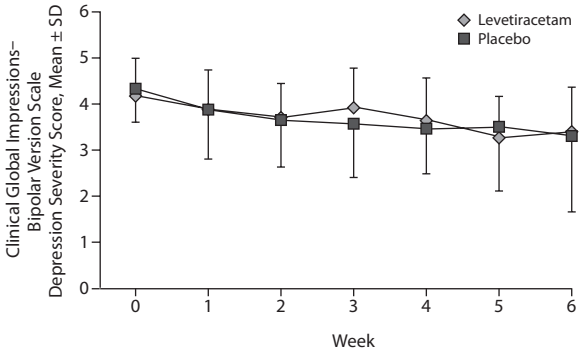


Table 3. Adverse Events Reported in Subjects With Depression With Bipolar Disorder Taking Levetiracetam or Placebo

Adverse Event	Levetiracetam (n = 19), n (%)	Placebo (n = 16), n (%)	Statistic χ^2_1	Statistic P
Overall	17 (89)	15 (94)	0.20	.65
Somnolence, low energy, lethargy	10 (53)	7 (44)	0.27	.60
Gastrointestinal symptoms (ie, nausea, vomiting, cramps, diarrhea, constipation)	6 (31)	5 (31)	0.0001	.98
Increase in irritability, agitation	5 (26)	1 (6)	2.46	.12
Coordination problems	4 (21)	0 (0)	3.80	.051
Shakiness, tremor	2 (11)	2 (13)	0.03	.85
Dizziness, vertigo	3 (16)	2 (13)	0.08	.78
Weakness	3 (16)	0 (0)	2.76	.10
Headache	3 (16)	6 (38)	2.14	.14
Dry mouth	2 (11)	2 (13)	0.03	.85
Increase in hypomanic symptoms	2 (11)	0 (0)	1.78	.18
Worsening of depressive symptoms	2 (11)	1 (6)	0.20	.65
Relapse in alcohol or substance abuse, requiring hospitalization	2 (11)[a]	1 (6)	0.20	.65
Insomnia	1 (5)	1 (6)	0.01	.90
Slurred speech	1 (5)	0 (0)	0.87	.35
Increase in suicidality	1 (5)	0 (0)	0.87	.35
Cognitive side effects: memory, concentration	1 (5)	1 (6)	0.01	.90
Drooling	1 (5)	0 (0)	0.87	.35
Genitourinary symptoms: increase in frequency of micturation	1 (5)	0 (0)	0.87	.35
Blurred vision	0 (0)	1 (6)	1.22	.27
Unusual dreams or nightmares	0 (0)	1 (6)	1.22	.27
Change in taste	0 (0)	1 (6)	1.22	.27
Nosebleed	0 (0)	1 (6)	1.22	.27
Cardiac symptoms: palpitation	0 (0)	1 (6)	1.22	.27
Skin rash	0 (0)	1 (6)	1.22	.27
Muscle or joint soreness	0 (0)	1 (6)	1.22	.27
Cold, fever, or sinus congestion	0 (0)	2 (13)	2.52	.11

[a]Hospitalization in 1 patient occurred 4 days after completing the study.

observed to a higher degree in the levetiracetam group than in the placebo group and showed a trend for significance ($\chi^2_1 = 3.80$, $P = .051$). Most patients reported at least 1 adverse effect during the clinical trial (Table 3; levetiracetam: n = 17, placebo: n = 15).

DISCUSSION

We believe that this is the first randomized, double-blind, placebo-controlled clinical trial to investigate the efficacy of adjunctive levetiracetam in the management of patients with bipolar disorder experiencing a depressive episode. Levetiracetam adjunctive therapy did not show any advantage over placebo in the acute treatment of bipolar depression in this population. We do not believe that the lack of separation from placebo was due to patient sampling bias or a high placebo response.

Patients included in this study were moderately ill with an early age at onset, long duration of illness, and a number of failed medication trials and psychiatric hospitalizations, and these characteristics did not differ statistically between groups. The depression scores for these patients at baseline are slightly higher than those reported in some previous studies of bipolar depressed cohorts. This is an indicator of the fact these patients were significantly unwell and that a simple placebo response could not account for the effects we observed. The response rate to placebo and drug of 22% and 23% are small, and the study is therefore not confounded by a large placebo response.

It is interesting to note, however, that, though the finding was not significant, subjects in the placebo group had an earlier age at onset for bipolar disorder and had a greater number of lifetime treatment failures in comparison to those in the levetiracetam group. This might suggest that patients in the placebo group may have had a slightly more severe form of the illness and might have therefore been less likely to separate from the treatment group. However, this is in contradistinction to the results showing subtle nonsignificant trends in favor of placebo, although the outcome measure on the MADRS shows a trend level of significance.

The use of patients with both forms of bipolar disorder (type I and II) was justified as there were no previous data to suggest which of these 2 types, if any, would be more likely to respond to levetiracetam. Continuing patients taking their current medication was also the only scientifically and ethically judicious way of designing this trial, given the relative lack of data in clinical populations with psychiatric disorders. This also meant that we had a group of patients who were poorly responsive to previous medications, and that may confound the interpretation of these results. However, as shown in the results section, there was no suggestion in the many analyses that patients taking levetiracetam were performing better than those taking placebo.

Limitations of the current study include the small number of subjects, inclusion of patients with both bipolar I and bipolar II, inclusion of patients poorly responsive to treatment, and continuation of varied prestudy medications. While it may be that addressing these measures may marginally alter the outcome, we believe that, given the data presented above, these issues do not significantly detract from the overall conclusions of the study.

One significant concern with the interpretation of these results, as mentioned above, is the relatively small number of patients in the trial. The trial was originally designed to recruit 25 patients in each arm. However, considering the early phase of development of this drug in the management of bipolar disorder, patients in the study were carefully monitored for efficacy measures. An interim analysis performed with the current number of patients gave us sufficient cause for concern to decide that we had an adequate sample size and power to show statistical separation between placebo and drug. This belief is based on the following facts: analysis showed that patients treated with placebo showed a numerically larger change from baseline in MADRS and BDI scores compared with levetiracetam, with a trend toward statistical significance. There was a significantly higher number of remitters and a greater change in depression from the preceding phase (CGI-BP change in depression) in the placebo-treated group compared with the patients taking levetiracetam. Finally, a power analysis suggested that more than 100 patients would be required in each arm of the study to show statistical significance of placebo over drug. The findings of subtle advantages of placebo over drug, the lack of any immediate tangible benefit from levetiracetam, and the power analysis led us to believe that it was not ethically or scientifically justified to continue with the study and expose patients to the drug, justifying the sample size for the study.

While levetiracetam has been shown to have an effect in the brain regions widely implicated in mood disorders (see Muralidharan and Bhagwagar[28] for details), such as the hippocampus[9,12] and the amygdala,[11,16] its mechanism of action is not fully understood and may not necessarily be relevant to the underlying pathophysiology of mood disorders.

Levetiracetam was generally well tolerated when combined with other mood-stabilizing agents, but coordination problems were reported more frequently in subjects taking levetiracetam. Sedation, gastrointestinal problems, and increased irritability were the other common side effects, but none of these were found to be statistically higher than the levels found in the placebo group in this study. However, this may be an area in which future studies using this drug may want to focus more attention.

In conclusion, we have shown that there is no advantage of adjunctive levetiracetam treatment over placebo in this small sample of moderately unwell patients with bipolar disorder experiencing a depressive episode. The results cannot be attributed to the power of the study, sample bias, or a significant placebo response. The interpretation of these results, therefore, has to be that there may not be a place for levetiracetam in the treatment of patients with bipolar disorder in a depressive episode. Although recent data may suggest a role for the drug in bipolar mania,[29,30] this will need further clarification.

Author affiliations: Department of Psychiatry (Drs Saricek, Blumberg, Sanacora, and Lorberg; Mss Maloney, Muralidharan, and Ruf; and Mr Pittman) and School of Medicine, Yale University, New Haven, and Bristol-Myers Squibb, Wallingford (Dr Bhagwagar), Connecticut.
Author contributions: Dr Saricicek and Ms Maloney contributed equally to the preparation of the paper.
Potential conflicts of interest: **Dr Bhagwagar** has previously served on the speaker's panels of Bristol-Myers Squibb, AstraZeneca, and Janssen; has received research funding from Bristol-Myers Squibb; has served as a consultant to Janssen; and is currently employed by Bristol-Myers Squibb. **Dr Sanacora** has received consulting fees from AstraZeneca, Bristol-Myers Squibb, Evotec, Eli Lilly, Johnson & Johnson, Roche, Ruxton, and Sepracor; has also received grant support from AstraZeneca, Bristol-Myers Squibb, Merck & Co, Pfizer, Roche, Ruxton, and Sepracor; has received fees for expert witness testimony from Shook, Hardy, and Bacon; is a member of the speakers/advisory boards for Ruxton and Johnson & Johnson; and is a coinventor on a filed patent application by Yale University (PCTWO06108055A1). **Drs Saricicek**, **Blumberg**, and **Lorberg**; **Mss Maloney**, **Muralidharan**, and **Ruf**; and **Mr Pittman** report no competing interests.
Funding/support: Supported by Stanley Medical Research Institute (grant no. 05T-681) and in part by a National Alliance for Research on Schizophrenia and Depression Young Investigator Award (Dr Bhagwagar), the National Institutes of Health (grant no. K23-MH077914; Dr Bhagwagar), and a Clinical and Translational Science Award (grant no. UL1 RR024139) from the National Center for Research Resources to Yale University (Dr Bhagwagar).
Disclaimer: The study was performed prior to Dr Bhagwagar's employment with Bristol-Myers Squibb, and the contents of the paper represent the author's personal views and do not in any way represent the view of Bristol-Myers Squibb.
Previous presentations: Study presented in poster form at the Society of Biological Psychiatry Annual Meeting, May 14–16, 2009, Vancouver, Canada; the 8th International Conference for Bipolar Disorder, June 25–27, 2009, Pittsburgh, Pennsylvania; and the New Clinical Drug Evaluation Unit Program Annual Meeting, June 29–July 2, 2009, Hollywood, Florida.
Acknowledgments: We acknowledge support from the Clinical Neuroscience Research Unit at the Connecticut Mental Health Center and the Department of Mental Health and Addictions Services (New Haven, Connecticut).

REFERENCES

1. Merikangas KR, Akiskal HS, Angst J, et al. Lifetime and 12-month prevalence of bipolar spectrum disorder in the National Comorbidity Survey Replication. *Arch Gen Psychiatry*. 2007;64(5):543–552.
2. Judd LL, Akiskal HS, Schettler PJ, et al. The long-term natural history of the weekly symptomatic status of bipolar I disorder. *Arch Gen Psychiatry*. 2002;59(6):530–537.
3. Judd LL, Akiskal HS, Schettler PJ, et al. A prospective investigation of the natural history of the long-term weekly symptomatic status of bipolar II disorder. *Arch Gen Psychiatry*. 2003;60(3):261–269.
4. Judd LL, Schettler PJ, Akiskal HS, et al. Residual symptom recovery from major affective episodes in bipolar disorders and rapid episode relapse/recurrence. *Arch Gen Psychiatry*. 2008;65(4):386–394.
5. Tohen M, Vieta E, Calabrese J, et al. Efficacy of olanzapine and olanzapine-fluoxetine combination in the treatment of bipolar I depression. *Arch Gen Psychiatry*. 2003;60(11):1079–1088.
6. Sachs GS, Nierenberg AA, Calabrese JR, et al. Effectiveness of adjunctive antidepressant treatment for bipolar depression. *N Engl J Med*. 2007; 356(17):1711–1722.
7. Blumberg HP, Kaufman J, Martin A, et al. Amygdala and hippocampal volumes in adolescents and adults with bipolar disorder. *Arch Gen Psychiatry*. 2003;60(12):1201–1208.
8. Blumberg HP, Leung HC, Skudlarski P, et al. A functional magnetic resonance imaging study of bipolar disorder: state- and trait-related dysfunction in ventral prefrontal cortices. *Arch Gen Psychiatry*. 2003;60(6): 601–609.
9. Husum H, Bolwig TG, Sánchez C, et al. Levetiracetam prevents changes in levels of brain-derived neurotrophic factor and neuropeptide Y mRNA and of Y1- and Y5-like receptors in the hippocampus of rats undergoing amygdala kindling: implications for antiepileptogenic and mood-stabilizing properties. *Epilepsy Behav*. 2004;5(2):204–215.
10. Niespodziany I, Klitgaard H, Margineanu DG. Desynchronizing effect of levetiracetam on epileptiform responses in rat hippocampal slices. *Neuroreport*. 2003;14(9):1273–1276.
11. Löscher W, Hönack D, Rundfeldt C. Antiepileptogenic effects of the novel anticonvulsant levetiracetam (ucb L059) in the kindling model of temporal lobe epilepsy. *J Pharmacol Exp Ther*. 1998;284(2):474–479.
12. Niespodziany I, Klitgaard H, Margineanu DG. Levetiracetam inhibits the high-voltage-activated Ca(2+) current in pyramidal neurones of rat hippocampal slices. *Neurosci Lett*. 2001;306(1–2):5–8.
13. Lukyanetz EA, Shkryl VM, Kostyuk PG. Selective blockade of N-type calcium channels by levetiracetam. *Epilepsia*. 2002;43(1):9–18.
14. Rigo JM, Hans G, Nguyen L, et al. The anti-epileptic drug levetiracetam reverses the inhibition by negative allosteric modulators of neuronal GABA- and glycine-gated currents. *Br J Pharmacol*. 2002;136(5):659–672.
15. Poulain P, Margineanu DG. Levetiracetam opposes the action of GABAA antagonists in hypothalamic neurones. *Neuropharmacology*. 2002;42(3): 346–352.
16. Klitgaard H, Matagne A, Gobert J, et al. Evidence for a unique profile of levetiracetam in rodent models of seizures and epilepsy. *Eur J Pharmacol*. 1998;353(2–3):191–206.
17. Lamberty Y, Margineanu DG, Klitgaard H. Effect of the new antiepileptic drug levetiracetam in an animal model of mania. *Epilepsy Behav*. 2001; 2(5):454–459.
18. Post RM, Altshuler LL, Frye MA, et al. Preliminary observations on the effectiveness of levetiracetam in the open adjunctive treatment of refractory bipolar disorder. *J Clin Psychiatry*. 2005;66(3):370–374.
19. Soria CA, Remedi C. Levetiracetam as mood stabilizer in the treatment of pharmacogenic hypomania in bipolar disorder II in elderly patients. *Int J Neuropsychopharmacol*. 2002;5(suppl 1):S57.
20. Hamilton M. A rating scale for depression. *J Neurol Neurosurg Psychiatry*. 1960;23(1):56–62.
21. Montgomery SA, Åsberg M. A new depression scale designed to be sensitive to change. *Br J Psychiatry*. 1979;134(4):382–389.
22. Beck AT, Ward CH, Mendelson M, et al. An inventory for measuring depression. *Arch Gen Psychiatry*. 1961;4:561–571.
23. Spearing MK, Post RM, Leverich GS, et al. Modification of the Clinical Global Impressions (CGI) scale for use in bipolar illness (BP): the CGI-BP. *Psychiatry Res*. 1997;73(3):159–171.
24. Hamilton M. The assessment of anxiety states by rating. *Br J Med Psychol*. 1959;32(1):50–55.
25. First MB, Spitzer RL, Gibbon M, et al. *Structured Clinical Interview for DSM-IV Axis I Disorders–Clinician Version (SCID-CV)*. Washington, DC: American Psychiatric Press; 1997.
26. Young RC, Biggs JT, Ziegler VE, et al. A rating scale for mania: reliability, validity and sensitivity. *Br J Psychiatry*. 1978;133(5):429–435.
27. Betts T, Waegemans T, Crawford P. A multicentre, double-blind, randomized, parallel group study to evaluate the tolerability and efficacy of two oral doses of levetiracetam, 2000 mg daily and 4000 mg daily, without titration in patients with refractory epilepsy. *Seizure*. 2000;9(2):80–87.
28. Muralidharan A, Bhagwagar Z. Potential of levetiracetam in mood disorders: a preliminary review. *CNS Drugs*. 2006;20(12):969–979.
29. Desarkar P, Das B, Sinha VK. Adjuvant levetiracetam in adolescent mania. *J Clin Psychopharmacol*. 2007;27(2):215–216.
30. Krüger S, Sarkar R, Pietsch R, et al. Levetiracetam as monotherapy or add-on to valproate in the treatment of acute mania: a randomized open-label study. *Psychopharmacology (Berl)*. 2008;198(2):297–299.