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Lamotrigine as add-on treatment to lithium and divalproex: lessons learned from a double-blind, placebo-controlled trial in rapid-cycling bipolar disorder

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Abstract

Objectives—A substantial portion of the morbidity associated with rapid-cycling bipolar disorder (RCBD) stems from refractory depression. This study assessed the antidepressant effects of lamotrigine as compared with placebo when used as add-on therapy for rapid-cycling bipolar depression non-responsive to the combination of lithium plus divalproex.

Methods—During Phase 1 of this trial, hypomanic, manic, mixed, and/or depressed outpatients (n = 133) aged 18–65 with DSM-IV RCBD type I or II were initially treated with the open combination of lithium and divalproex for up to 16 weeks. During Phase 2, subjects who did not meet the criteria for stabilization (n = 49) (i.e., remained or cycled into the depressed phase) were randomly assigned to double-blind, adjunctive lamotrigine (n = 23) or adjunctive placebo (n = 26). The primary endpoint was the mean change in depression symptom severity from the beginning of Phase 2 to the end of Phase 2 (week 12) on the Montgomery-Åsberg Depression Rating Scale (MADRS) total score. Data were analyzed by analysis of covariance with last observation carried forward and a mixed-models analysis.

Results—During Phase 1, a high rate of study discontinuations occurred due to intolerable side effects (13/133; 10%) and study non-adherence (22/133; 17%). Only 14% (19/133) stabilized on the open combination of lithium and divalproex. Among the 49 (37%) patients randomized to the double-blind adjunctive treatment phase, mean $\pm$ standard error change from baseline on the MADRS total score was -8.5 ± 1.7 points for lamotrigine and -9.1 ± 1.5 points for placebo (p = NS; mixed-models analysis). No significant differences were observed in the rates of response, remission, or bimodal response between lamotrigine and placebo.

Conclusions—The poor tolerability, lack of efficacy, and high rate of early discontinuation with the combination of lithium and divalproex suggests this regimen was ineffective for the majority of patients with RCBD. Among patients who did not stabilize on lithium and divalproex, the addition of lamotrigine was no more effective than placebo in reducing depression severity. The

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Disclosures

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findings suggest an opportunity for several design modifications to enhance signal detection in future trials of RCBD. The main limitation is the small number of subjects randomized to double-blind treatment.

Keywords

rapid-cycling; bipolar depression; failed clinical trial; combination treatment; lamotrigine; lithium; divalproex

The rapid-cycling variant has been estimated to affect between 12–24% of patients with bipolar I or II disorder (1). Patients with rapid-cycling bipolar disorder (RCBD) exhibit shorter symptom-free intervals and more frequent depressive episodes than those without rapid cycling (2, 3), such that many consider the presence of highly recurrent treatment-refractory depression to be its hallmark (3–8).

A recent meta-analysis supports the long-term use of lithium as a prophylactic treatment for manic episodes; however, lithium monotherapy was associated with only a modest antidepressant effect (9). In the Bipolar Affective Disorder: Lithium/Anticonvulsant Evaluation (BALANCE) study, a large effectiveness study evaluating the combined use of lithium and valproate, the benefit of combination therapy compared to valproate monotherapy was apparent for preventing manic relapses (10). Yet, most participants who received the combination of lithium and valproate needed additional treatment during study follow-up, with interventions for depression occurring more often than interventions for mania (10). Complicating the treatment of this population, conventional antidepressant medications must be used with caution, as antidepressants have been associated with an increased likelihood of cycling during naturalistic treatment and may trigger and prolong mood destabilization (11).

The efficacy of lamotrigine as a maintenance treatment for bipolar disorder is well established, having particular benefit in delaying depressive episodes and for treating the rapid-cycling variant (12–14). A modicum of evidence also suggests that lamotrigine is efficacious for acute bipolar depression (15), including as an add-on treatment for patients non-responsive to lithium (16). However, it remains unknown whether lamotrigine can complement the spectrum of efficacy of other agents, including combination drug regimens.

Patients with more severe forms of bipolar disorder are frequently taking three to five different medications (17, 18) and may be less willing to enroll in clinical trials that require complete drug wash-outs or in which they may be randomized to drug monotherapy or placebo. Given these considerations, as well as the scarcity of combination treatment studies in bipolar depression, we chose to study lamotrigine as an add-on therapy in patients with RCBD whose major depressive episodes were inadequately responsive to the combination of lithium and divalproex. We hypothesized that add-on lamotrigine would be superior to placebo in reducing depression severity.

Methods

The study was conducted by the Mood Disorders Program at Case Western Reserve University/University Hospitals Case Medical Center (Cleveland, OH, USA) from August 2002 to June 2007. The affiliated Institutional Review Board approved all study procedures. Written informed consent was obtained from each subject before any study-related procedures were performed. Patients could discontinue from any phase of the study for poor tolerance, lack of efficacy, investigator or patient unwillingness to continue the study for any reason, or non-adherence with study procedures. Participation could last up to 34 weeks,

including a two to six week screening period, an open-label treatment phase lasting up to 16 weeks (Phase 1), and a 12-week double-blind treatment phase (Phase 2).

Study subjects

Patients eligible for participation were males and females, between 16 and 65 years of age, who met DSM-IV criteria for the following: (i) bipolar I or II disorder; (ii) rapid cycling during the 12 months preceding study entry, confirmed by retrospective mood charting (19); and (iii) experiencing a recent major depressive episode at the time of the screening evaluation or at baseline.

Patients were excluded from participation if they had previous intolerance to lithium, divalproex, or lamotrigine; had been completely non-responsive to adequate treatment with lamotrigine; had been treated with lithium, divalproex, and lamotrigine concurrently; had a medical illness precluding the use of lithium, divalproex or, lamotrigine; had been treated with any dose or duration of a tricyclic antidepressant within the last three months; were pregnant or planning to become pregnant; were taking exogenous steroids or required anticoagulant treatment; had a history of alcohol or drug abuse within the last three months or dependence within the last six months; were currently suicidal in the opinion of the investigator; or had a score ≥ 4 on the suicide item of the Montgomery-Åsberg Depression Rating Scale (MADRS) (20).

Screening

Screening occurred in the two weeks preceding patients' entry into the open-label treatment phase. Subjects who met DSM-IV criteria for RCBP type I or II with a recent major depressive episode were confirmed by Extensive Clinical Interview and the Mini International Neuropsychiatric Interview (MINI) (21), performed by a psychiatrist and a research assistant, respectively. Recent history of a substance use disorder was assessed by the Structured Clinical Interview for DSM-IV Axis I Disorders, Patient Version (SCID-P) (22).

Pretreatment psychiatric assessments included the following measures: MADRS (20), Young Mania Rating Scale (YMRS) (23), Clinical Global Impressions Scale of Bipolar Disorder–Severity (CGI-BP-S) (24), and Global Assessment of Functioning (GAF) (25). Patients currently in a manic/hypomanic episode could enter into a screening period lasting up to six weeks, during which they received treatment with the combination of lithium and divalproex and were evaluated every two weeks. Eligible patients were then enrolled into the open-label treatment phase.

Phase 1: Open-label treatment with lithium and divalproex

During the open-label treatment phase, lithium and divalproex were administered in an unblinded fashion. Participants were evaluated by the physician and the research assistant every two weeks; during this time the doses of lithium and divalproex were titrated and blood levels were obtained. Lithium monotherapy was initiated at 450 mg once daily and titrated slowly over three weeks to a minimum blood level of 0.5 mEq/L. Divalproex was then initiated at 250 mg twice daily and increased slowly over five weeks to a minimum blood level of 50 µg/mL. If patients were already taking lithium, but not divalproex, divalproex was initiated and titrated as described. If patients were already taking divalproex, but not lithium, lithium was initiated and titrated as described. Apart from lithium or divalproex, any other psychotropic medications that patients were taking at study entry were discontinued gradually at least four weeks prior to random assignment to double-blind lamotrigine or placebo (Phase 2).

Patients meeting criteria for non-response to treatment with lithium plus divalproex, as evidenced by the presence of at least moderately severe symptoms of depression and absent or minimal (hypo)manic symptoms, were eligible for random assignment to double-blind treatment. The specific criteria to enter this phase included the following: MADRS ≥ 20 , YMRS ≥ 12 , CGI-D ≥ 4 , CGI-M ≥ 2 , lithium level ≥ 0.5 mEq/L, valproate level ≥ 50 μ g/mL, and a stable dose of both lithium and divalproex for at least four weeks prior to randomization. During the four weeks prior to randomization, a one-time dose decrease of one tablet of either lithium or divalproex was permissible due to an adverse event, but the corresponding blood level must have remained within the therapeutic range as previously described.

Phase 2: Double-blind treatment with lamotrigine or placebo

Patients were assigned in a one to one ratio to adjunctive lamotrigine versus placebo after stratification for illness type (bipolar I versus bipolar II), historical response to lithium (response versus non-response), and length of current exposure to combination treatment with lithium and divalproex (< 2 months versus ≥ 2 months). During Phase 2, patients were continued on the same doses of lithium and divalproex as during the open-label treatment phase and equal capsules of double-blind lamotrigine or matching placebo were gradually added per a structured dosing schedule up to a minimum dose of 150 mg and a maximum dose of 200 mg per day.

Participants were evaluated by the physician and the research assistant every two weeks until the beginning of a bimodal response was observed, after which they were evaluated weekly for four consecutive bimodal response weeks. Bimodal response was defined as meeting the following three conditions over four consecutive weeks after random assignment: (i) MADRS score ≥ 19 (the upper limits of mild severity); (ii) YMRS score ≥ 12 ; (iii) GAF score ≤ 51 . This definition of bimodal response was similar to criteria used to define stabilization in a previous trial of lithium and divalproex in RCBD (6).

Concomitant medications

During Phase 2, patients could receive lorazepam in doses up to 4 mg/day throughout the first eight weeks of the double-blind treatment phase and 2 mg thereafter for anxiety, agitation, or insomnia. Zolpidem up to 10 mg/day could be prescribed for severe insomnia.

Safety monitoring

For each study phase, the safety population comprised all patients who received at least one dose of study medication. Safety was assessed by summarizing treatment-emergent adverse events and evaluating clinical laboratory test results, including lithium and valproate levels, white blood cell count, platelet count, electrolytes, free thyroxine index, thyroid-stimulating hormone level, liver function tests (alanine aminotransferase and aspartate aminotransferase), serum creatinine, and urine pregnancy test (if applicable). A urine drug test was obtained to screen for illicit substance use.

Data analysis

Analysis of the primary outcome measure, the change from baseline to endpoint (Week 12) in MADRS total score, was performed using analysis of covariance (ANCOVA) in which the baseline MADRS score and the treatment group were considered as the covariate and the main fixed effect, respectively. The last observation carried forward (LOCF) methodology was used to impute missing values for those subjects who did not complete the study. A mixed-models analysis was also undertaken to complement the results from the ANCOVA.

For the secondary outcome measures of response, bimodal response, and remission rates, Fisher's exact test was used to compare the two treatment arms. Response and remission were defined as 50% decrease from baseline to endpoint on the MADRS total score and a MADRS total score 10 at endpoint, respectively. A bimodal response was defined by the following three conditions maintained over four consecutive weeks after random assignment: (i) MADRS score 19; (ii) YMRS score 12; (iii) GAF score 51. All statistical analyses were performed with the SAS 9.2 software program. Criterion for statistical significance was set at $\alpha = 0.05$.

Results

Patient disposition and characteristics

A total of 162 patients were screened for study participation, of whom 137 were eligible for enrollment and 133 were assigned to the open-label acute treatment phase (Fig. 1). During this phase, 19 (14%) met criteria for bimodal response and thus were not eligible for participation in the blinded, randomized phase. Other reasons for lack of progression to the randomized phase included study non-adherence (22/133; 17%) and intolerable side effects (13/133; 10%). Among the 49 patients who entered the blinded treatment phase, 23 were randomly assigned to receive lamotrigine, lithium, and divalproex and 26 were assigned to placebo, lithium, and divalproex.

Patients randomized to lamotrigine were younger on average than patients randomized to placebo ($p = 0.02$). There were no other statistically significant differences between the two treatment arms in patient characteristics or illness severity at baseline (Table 1). However, a numerically higher percentage of subjects with bipolar I disorder were randomized to placebo (62%) as compared with lamotrigine (48%) ($p = 0.40$).

Efficacy

Results are presented in Table 2. On the primary outcome measure of change in MADRS total score from baseline to endpoint, no significant differences were observed between the lamotrigine and placebo groups (-2.5 versus -5.7 , respectively, $p = 0.24$). Furthermore, an ANCOVA analysis of change from baseline in MADRS score, with baseline score as a covariate, did not yield significant differences between treatment groups [$F(2,46) = 1.10$, $p = 0.34$]. The rate of bimodal response—defined as a MADRS total score 19, YMRS total score 12, and GAF score 51—was nonsignificantly different in the lamotrigine group as compared with the placebo group (30% versus 31%, $p = 1.0$). Remission rates (MADRS 10) were 13% (3/23) and 31% (8/26) for the lamotrigine and placebo groups, respectively ($p = 0.18$). The mean change from baseline in CGI-severity scores for the lamotrigine (-0.22) and placebo (-0.92) arms showed a trend favoring the placebo group ($p = 0.06$).

In order to minimize any bias in estimates of the treatment effect due to attrition, a mixed-models analysis was also undertaken. No significant between-group differences were observed for visit wise MADRS, YMRS, or CGI mean change scores. After adjustment for age and bipolar subtype, endpoint mean $\pm$ standard error change scores were -8.5 ± 1.7 and -9.1 ± 1.5 on the MADRS, -2.1 ± 0.8 and -0.8 ± 0.7 on the YMRS, and -1.2 ± 0.2 and -1.4 ± 0.2 on the CGI for the lamotrigine and placebo groups, respectively. The Cohen's d effect size for MADRS, YMRS, and CGI were 0.08, 0.40 and 0.23, respectively. A significant effect of diagnosis was present for change in YMRS after adjusting for treatment, time, and age. Patients with bipolar I disorder had greater mean $\pm$ standard error reductions in YMRS scores as compared to those with bipolar II disorder [-2.6 ± 0.8 versus -0.27 ± 0.7 ; $F(1,45) = 6.69$, $p = 0.01$]. Effect size in this instance was 0.79.

Safety

During the open stabilization phase (Phase 1), 95% (127/133) of patients reported an adverse event. Study discontinuation due to an adverse event occurred in 10% (13/133) of subjects. Two serious adverse events of imminent suicidality ($n = 1$) and hospitalization for a depressive episode ($n = 1$) occurred in the lamotrigine group. One patient in each treatment group experienced pruritis and one patient receiving lamotrigine experienced a benign rash. Most of the adverse events were mild or moderate. A treatment-emergent switch into hypomania or mania occurred in two patients (8%) receiving adjunctive placebo.

Serum blood levels

During the randomized phase, lithium and divalproex levels were within the predefined therapeutic range (0.5 mEq/L for lithium and $50 \text{ }\mu\text{g/ml}$ for divalproex) for participants in the blinded lamotrigine ($0.76 \pm 0.2 \text{ mEq/L}$ and $67 \pm 18.1 \text{ }\mu\text{g/ml}$, respectively) and placebo ($0.78 \pm 0.2 \text{ mEq/L}$ and $58 \pm 17.9 \text{ }\mu\text{g/ml}$, respectively) groups. During this phase, lithium levels $< 0.8 \text{ mEq/L}$ were observed in 45.8% ($n = 11$) and 50.0% ($n = 13$) of participants in the lamotrigine and placebo groups, respectively. One participant in each of the lamotrigine (4.2%) and placebo groups (3.8%) had a valproate level $< 50 \text{ }\mu\text{g/ml}$.

Discussion

To our knowledge, this is one of only two randomized, parallel-group, placebo-controlled trials to evaluate the efficacy of a triple medication combination in RCBD (26). It is also the first controlled study to evaluate the role of lamotrigine in combination with lithium and divalproex in presentations of RCBD not accompanied by a co-occurring substance use disorder.

The study provides several insights into the treatment of RCBD, perhaps most notably the limited effectiveness, acceptability, and tolerability of the combination of lithium plus divalproex when used in this population. Of 133 participants treated with the combination of lithium plus divalproex during the open stabilization phase, approximately 90% presented in the depressed phase of the illness and only 14% achieved stabilization. Almost half (49%) of participants either did not respond or were unable to tolerate the combination of lithium plus divalproex. Moreover, the addition of lamotrigine during the randomized, double-blind study phase showed no greater efficacy than the addition of placebo in achieving bimodal stabilization.

The natural history of this population of patients suggests they were very ill. The majority had their onset of illness in early adolescence, 74% had a co-occurring anxiety disorder, 40% made past attempts at suicide, and one-half to one-third had been psychotic, previously hospitalized, physically abused, or sexually abused. These illness features characterize the magnitude of the unmet need in this population and the accompanying human suffering. Of those participants randomized to double-blind treatment, approximately 85% completed the study, but the randomized sample was too small to formulate definitive conclusions.

Consistent with previously reported findings from our center, the 14% rate of bimodal stabilization during the open-label phase suggests that combination treatment with lithium and divalproex will likely be ineffective for the large majority of patients with RCBD (6). Previous studies of RCBD have shown the rate of bimodal stabilization over six months to be 24% in patients without substance use disorders (6) and to range from 7% to 21% in those with recent substance use disorders (7, 26). These results are consistent with the only other clinical trial evaluating add-on lamotrigine to ongoing treatment with lithium and divalproex (26), albeit both trials suffered from a small sample size and diminished statistical power.

Role of lamotrigine in bipolar depression

Greater clarity is needed as to the effectiveness of lamotrigine in treating refractory bipolar depression, as previously conducted studies have provided inconsistent results. On the primary outcome measure, lamotrigine monotherapy was not found to more effectively reduce depressive symptoms than placebo in five studies of bipolar I or II disorder (27). However, the effect of lamotrigine compared with placebo became statistically significant when pooled in a meta-analysis (28). When studied as an add-on therapy to lithium over eight weeks, lamotrigine resulted in higher rates of response and greater improvement in depression severity than placebo (16). However, only 13% of patients in that study exhibited rapid cycling, perhaps reflective of a less severely ill cohort of patients than enrolled in the present study.

Lessons learned to inform clinical trial design

Although the current investigation does not allow definitive conclusions to be drawn regarding the adjunctive antidepressant efficacy of lamotrigine, several lessons were learned that can inform the design of future RCT studies. First, although the use of a prospective, open-label treatment phase unequivocally established inadequate response, the requirement to fail a combination of two mood stabilizers may have unnecessarily led to excess attrition. Approximately 49% of patients prematurely discontinued from the open stabilization phase due to poor adherence, poor tolerability, lack of efficacy, or other reasons, leading to too few patients entering the double-blind, randomized phase. In an effort to minimize attrition, we propose that future studies require prospective evidence of inadequate response to only one agent.

Second, as the present trial did not include an active comparator, it is not possible to determine whether the lack of statistical separation between lamotrigine and placebo reflects a negative or failed trial. The results can be interpreted either as a negative study (lamotrigine does not work in patients non-responsive to the combination of lithium and divalproex) or a failed study (we do not know if lamotrigine works in patients non-responsive to the combination of lithium and divalproex). In the absence of a positive control treatment, the answer remains unsettled. Future studies may consider randomizing patients to a third arm of a medication known to be effective in bipolar depression (i.e., quetiapine).

Third, the maximum duration of prospective stabilization might be shortened to less than 16 weeks. Although it could be inferred that individuals with rapid cycling may need an extended period of time to demonstrate cessation of cycling, frequent mood shifts appeared to dissipate after the introduction of combination mood stabilizer therapy. What emerged was a group of patients with predominantly depressive symptoms, exemplary of the limitations of existing treatments in sufficiently reducing the severity of bipolar depression. Other studies have likewise suggested that rapid cycling is a transitory phenomenon (11, 29), prospectively observed in only a small percentage of patients after naturalistic treatment (11). A shorter open stabilization phase may still identify inadequately response patients but lead to decreased rates of attrition.

Fourth, consideration may be given to a data analytic strategy that involves mixed-effects models, a class of models that can examine illness severity over the course of the randomized controlled trial and can accommodate participants who have missing data (30). Although effects on the primary outcome did not change when separately analyzed using ANCOVA with LOCF or mixed models in the present analysis, mixed models should minimize any bias in estimation of the treatment effect that is due to premature drop-out during the double-blind phase (30).

Finally, consideration must be given to optimally balancing efficacy and effectiveness in clinical trial design. The use of limited exclusion criteria, combination drug treatment, inclusion of bipolar I and II subtypes, and inclusion of participants with comorbid Axis I and III disorders all biased the study toward the effectiveness continuum. Similar to other effectiveness studies that utilized broad entry criteria, the resulting sample heterogeneity detracted from an ability to detect any relevant between-group differences [(31); submitted manuscript: Nierenberg AA, Friedman ES, Bowden CL et al. *Lithium use for bipolar disorder (LiTMUS): a randomized comparative effectiveness trial*]. An ideal balance between assay sensitivity and generalizability has proven difficult to establish, as the majority of patients in real-world settings do not qualify for traditional efficacy trials (32, 33). Moreover, the effect sizes of existing treatments are so small that detection of drug-placebo differences in studies of enhanced generalizability is extremely challenging.

In contrast to when this study was initiated in 2002, it is now well established that atypical antipsychotics can effectively treat symptoms of bipolar depression (34) and may be particularly useful in rapid-cycling presentations (35, 36). The consistently replicated efficacy of some atypical antipsychotics in treating bipolar depression when prescribed as monotherapy (37–40) or combination therapy (41) leads us to believe that selecting an agent from this class would have been a more appropriate add-on therapy.

As discussed previously, the inability to detect significant differences may reflect either a failed or negative study. In one of the few trials evaluating triple therapy in bipolar disorder, van der Loos and colleagues (42) found that among individuals with bipolar depression not responding to lithium, the addition of paroxetine effectively reduced depression severity. However, if patients had been non-responsive to the combination of lithium and lamotrigine, the addition of paroxetine provided no additional antidepressant benefit. Thus, failure to respond after two drugs treatments may have impeded any ability to detect additional mood improvement with a third agent. Alternatively, the 30% bimodal response rate may be secondary to inherent changes in the illness over time. In a separate study evaluating combination therapy with lithium and divalproex over 24 weeks, the rate of bimodal response was 24%, similar to the 30% rate of bimodal response observed in the present study (6). The inability to titrate patients to sufficient lithium levels may have also contributed to lack of statistical separation in the present trial, although the number of subjects with a level < 0.8 mEq/L was equivalent in the lamotrigine and placebo groups.

The logistical challenges associated with the design and conduct of this triple therapy study in RCBBD diminish the feasibility of undertaking such trials in the future. This is despite several reports suggesting a high proportion of patients with bipolar disorder receive multiple medications simultaneously, with nearly half receiving three or more psychotropic medications (17, 18). Given the limited response to single drug therapies for many patients with bipolar depression, the unmet need in this population remains substantial and deserves our persistent attention through the conduct of well-designed clinical trials.

Conclusions

There is a paucity of controlled investigations examining combination treatment with mood stabilizers in RCBBD. The present analysis evaluated the adjunctive use of lamotrigine as compared with placebo in patients with RCBBD type I or II who were non-responsive to the combination of lithium and divalproex, but found no significant benefit over placebo in achieving bimodal stabilization. However, the results can only be considered as exploratory given the limited sample size. Future trials should give consideration to the use of atypical antipsychotics during the open or blinded phases of studies assessing combination treatments for rapid-cycling bipolar depression. Future studies may achieve a lower attrition

rate by employing a single drug treatment to establish inadequate response and shortening the duration of the prospective open-label treatment phase. Use of an active comparator can assist in interpreting the trial outcomes when drug-placebo differences are small. The diminished ability to recruit and retain an adequate number of subjects within this trial suggests that increased methodological rigor may sacrifice study feasibility when studying RCBD. The trial underscores an unmet need for agents more effective at decreasing symptoms of bipolar depression, as well as for clinical trial designs more adept at balancing assay sensitivity with generalizability.

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Fig. 1. Disposition of patients with rapid-cycling bipolar disorder treated with a combination of lithium and divalproex followed by double-blind acute continuation with adjunctive lamotrigine or placebo.

Table 1

Baseline demographic and clinical characteristics of rapid-cycling bipolar disorder patients treated with a combination of lithium and divalproex followed by double-blind acute continuation with adjunctive lamotrigine or placebo

Characteristic	Baseline at study entry (n = 133)		Baseline at entry into double-blind, randomized phase		p-value ^a
	n (%)	n (%)	Lithium + divalproex + lamotrigine (n = 23)	Lithium + divalproex + placebo (n = 26)	
Gender					0.78
Male	59 (44.4)	11 (47.8)		11 (42.3)	
Female	74 (55.6)	12 (52.2)		15 (57.7)	
Race					1.00
White	113 (85.0)	21 (91.3)		24 (92.3)	
Black	19 (14.3)	2 (8.7)		2 (7.7)	
Other	1 (0.7)	0 (0)		0 (0)	
Bipolar subtype					0.40
Bipolar I disorder	82 (61.7)	11 (47.8)		16 (61.5)	
Bipolar II disorder	51 (38.3)	12 (52.2)		10 (38.5)	
Mood state at study entry					
Depressed	117 (88.0)	23 (100)		26 (100)	NA
Hypomanic/manic	11 (8.2)	0 (0)		0 (0)	NA
Mixed	4 (3.0)	0 (0)		0 (0)	NA
Euthymic	1 (0.7)	0 (0)		0 (0)	NA
Lifetime anxiety disorder	99 (74.4)	19 (82.6)		17 (65.4)	0.21
Lifetime psychosis	49 (36.8)	12 (51.7)		9 (34.6)	0.26
Lifetime physical abuse	37 (28.0)	6 (26.1)		8 (30.8)	0.76
Lifetime sexual abuse	28 (21.2)	3 (13.0)		4 (15.4)	1.00
Past suicide attempts	53 (40.0)	11 (47.8)		8 (30.8)	1.00
Past hospitalizations	67 (24.8)	7 (30.4)		9 (34.2)	1.00
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	p-value ^b
Age, years	37.9 (11.1)	35.7 (11.0)		43.0 (9.6)	0.02
Age of first depressive episode, years	13.4 (3.5)	13.7 (6.7)		15.4 (8.6)	0.45

Characteristic	Baseline at study entry		Baseline at entry into double-blind, randomized phase		p-value ^a
	(n = 133)	n (%)	Lithium + divalproex + lamotrigine (n = 23)	Lithium + divalproex + placebo (n = 26)	
Age of first manic/hypomanic/mixed episode, years	17.0 (8.0)	18.0 (5.2)	18.1 (8.4)	18.1 (8.4)	0.96
Episode duration	80.6 (186.9)	56.8 (42.8)	57.4 (57.1)	57.4 (57.1)	0.97
Mean no. of episodes in last 12 months					
Mania/hypomania/mixed	9.6 (18.1)	6.0 (3.7)	13.3 (25.5)	13.3 (25.5)	0.16
Depression	11.0 (20.4)	6.3 (3.9)	16.2 (28.1)	16.2 (28.1)	0.12
Baseline illness severity					
MADRS	25.1 (9.0)	28.5 (6.1)	27.3 (6.1)	27.3 (6.1)	0.50
YMRS	11.6 (6.4)	7.3 (3.6)	6.5 (4.8)	6.5 (4.8)	0.52
CGI-S	4.2 (1.0)	4.4 (0.8)	4.4 (0.8)	4.4 (0.8)	NA

SD = standard deviation; MADRS = Montgomery-Asberg Depression Rating Scale; YMRS = Young Mania Rating Scale; CGI-S = Clinical Global Impressions Scale Severity.

^aFisher's Exact Test.

^bTwo-sample *t*-test.

Table 2

Efficacy endpoints (LOCF) in the double-blind randomized phase

Outcome variable	Lithium + divalproex + lamotrigine (n = 23)	Lithium + divalproex + placebo (n = 26)	Chi-square	p-value
	n (%)	n (%)		
Response ^a	2 (9)	10 (38)	5.85	0.02
Remission ^b	3 (13)	8 (31)	2.20	0.18
Bimodal criteria ^c	7 (30)	8 (31)	0	1.00
MADRS	Mean (SD)	Mean (SD)	t-value	p-value
Baseline	28.52 (6.09)	27.27 (5.71)	0.74	0.46
End ^d	26.00 (9.01)	21.58 (11.44)	1.49	0.14
Change	-2.52 (7.91)	-5.69 (10.45)	1.19	0.24
YMRS				
Baseline	7.26 (3.65)	6.50 (4.79)	0.62	0.54
End ^d	6.65 (5.31)	6.15 (5.23)	0.33	0.74
Change	-0.61 (5.08)	-0.35 (5.51)	-0.17	0.86
CGI-S				
Baseline	4.43 (0.79)	4.44 (0.77)	-0.02	0.98
End ^d	4.22 (1.28)	3.52 (1.58)	1.67	0.10
Change	-0.22 (1.04)	-0.92 (1.41)	1.95	0.06

MADRS = Montgomery-Asberg Depression Rating Scale; YMRS = Young Mania Rating Scale; CGI-S = Clinical Global Impressions Scale-Severity; SD = standard deviation.

^aResponse defined as 50% decrease from baseline to endpoint in total MADRS score.

^bRemission defined as 10 on MADRS total score at endpoint.

^cBimodal response criteria defined as MADRS total score 10, YMRS total score 12, Global Assessment of Functioning score 51.

^dLOCF.