A Double-Blind Placebo-Controlled Trial of Lamotrigine as an Antidepressant Augmentation Agent in Treatment-Refractory Unipolar Depression

James G. Barbee, MD; Thomas R. Thompson, MD; Nowal J. Jamhour, MA; Jonathan W. Stewart, MD; Erich J. Conrad, MD; Frederick W. Reimherr, MD; Peter M. Thompson, MD, MS; and Richard C. Shelton, MD

ABSTRACT

Background: Previous reports have suggested that lamotrigine is effective as an antidepressant augmentation agent in patients with treatment-resistant unipolar depression. This study is the largest double-blind placebo-controlled study conducted to date of lamotrigine in this role.

Method: In this multicenter trial, conducted at 19 sites, patients aged 18–65 years with a *DSM-IV/ICD-10* diagnosis of unipolar, nonpsychotic major depressive disorder (confirmed by the Mini-International Neuropsychiatric Interview) who had failed at least 1 adequate trial of an antidepressant (N = 183) were first treated for 8 weeks with open-label paroxetine or paroxetine controlled-release in dosages up to 50 mg/d or 62.5 mg/d, respectively. Individuals with a 17-item Hamilton Depression Rating Scale (HDRS-17) score ≥ 15 (n = 96) were then randomized on a double-blind basis to receive either placebo or lamotrigine in dosages titrated upward to a maximum of 400 mg/d for 10 weeks. Sixty-five patients completed the study. The primary outcome measure was the Montgomery-Asberg Depression Rating Scale (MADRS), and the main secondary outcome measures were the HDRS-17 and Clinical Global Impressions-Severity of Illness (CGI-S) and Clinical Global Impressions-Improvement (CGI-I) ratings. Data were collected from 2003 to 2006.

Results: Results of the primary efficacy analysis of the randomized patients using the MADRS, HDRS-17, CGI-S, and CGI-I did not demonstrate a statistically significant difference between lamotrigine and placebo groups, although some secondary analyses were suggestive of efficacy, particularly in those patients who completed the study (completer analysis) and in more severely ill patients (HDRS-17 ≥ 25).

Conclusions: This add-on study of patients with treatment-resistant depression failed to detect a statistically significant difference between lamotrigine and placebo given for 10 weeks. However, post hoc analyses suggest that future studies of lamotrigine's efficacy might focus on specific subgroups with depression.

Trial Registration: clinicaltrials.gov Identifier: NCT00901407

J Clin Psychiatry 2011;72(10):1405–1412

Submitted: *May 8, 2009; accepted April 6, 2010.*
Online ahead of print: *February 22, 2011 (doi:10.4088/JCP.09m05355gre).*
Corresponding author: *James G. Barbee, MD, 3439 Magazine Street, New Orleans, LA 70115 (jgbmd@att.net).*

Treatment-resistant depression remains a major clinical management problem. Lamotrigine is among the agents that have been studied in depression—when used alone, initiated simultaneously with an antidepressant, or added to a preexisting antidepressant regimen. The drug has been extensively studied in bipolar disorder, for which studies[1,2] have shown lamotrigine's efficacy in the maintenance phase of bipolar disorder, particularly in preventing depressive episodes, and possibly in acute bipolar depression as well, although a number of large placebo-controlled trials[3,4] failed to show a significant effect.

Studies of lamotrigine have been less convincing for unipolar depression, both in refractory and nonrefractory depression. For example, in GlaxoSmithKline studies of patients with nonrefractory depression, none of 3 multicenter, double-blind, placebo-controlled trials of lamotrigine as monotherapy detected a significant drug-placebo difference.[5–7] Normann et al[8] conducted a double-blind, fixed-dose study of paroxetine started concomitantly with lamotrigine or placebo in a group of 40 acutely depressed patients. The primary outcome was negative, although some individual symptoms were more likely to improve in the lamotrigine-treated group.

In studies of patients with refractory depression,[9–15] only one study examined lamotrigine monotherapy. Obrocea et al[9] reported a double-blind study of 45 patients with "highly refractory" affective disorder and found higher response rates with lamotrigine (51%) than with gabapentin (28%) or placebo (21%). There was a significant relationship between lamotrigine response and bipolar illness. Barbosa et al[10] conducted the only study in which lamotrigine was started concomitantly with an antidepressant (fluoxetine) in a sample that included some bipolar II patients (8 of 23). There were significant drug-placebo differences on the Clinical Global Impressions-Severity of Illness (CGI-S) and Clinical Global Impressions-Improvement (CGI-I) scales at endpoint but not for the 17-item Hamilton Depression Rating Scale (HDRS-17) or Montgomery-Asberg Depression Rating Scale (MADRS) scores.

In all of the remaining published studies,[11–15] lamotrigine was added as an augmentation agent to a preexisting drug regimen in patients with treatment-resistant depression. Three of these reports[11–13] were retrospective chart reviews reporting positive outcomes; of these, Barbee and Jamhour[11] reported the most severely refractory group of patients. The average patient in this report had failed an average of 13.27 antidepressant trials. Forty-one percent of the 37 patients were retrospectively rated on the CGI-I as much or very much improved after the addition of lamotrigine to an antidepressant regimen. Two small prospective studies[14,15] of lamotrigine augmentation have been published, only one of which[15] was double-blind and placebo-controlled. Of these 2, the open-label study[14] yielded positive results that were statistically significant for the CGI-I and MADRS; the other

study[15] found no significant drug-placebo differences at its conclusion.

Although many of these reports suggest that lamotrigine may be effective as an antidepressant augmentation agent in unipolar depression, the results of the only prospective, randomized, placebo-controlled study[15] failed to show any evidence of efficacy. However, the sample size was relatively small. Thus, we report the results of the first large, multicenter, double-blind, placebo-controlled trial to evaluate the safety and efficacy of lamotrigine when added to an antidepressant (paroxetine) in a group of patients with treatment-resistant unipolar nonpsychotic major depressive disorder.

METHOD

The multicenter trial (clinicaltrials.gov Identifier: NCT00901407) was conducted at 19 sites, and data were collected from 2003 to 2006. Study subjects who met the entry criteria (see below) were initially given treatment with paroxetine or paroxetine controlled-release (CR) (paroxetine was used due to a temporary disruption in the supply of paroxetine CR from the manufacturer) in flexible dosages up to 50 mg/d or 62.5 mg/d (respectively) on an open-label basis. After 8 weeks, those individuals with an HDRS-17[16] score ≥ 15 were then randomized to either placebo or lamotrigine on a flexible-dose basis to a maximum of 400 mg/d for a period of 10 weeks. Subjects remained on the same dosage of paroxetine or paroxetine CR that they were taking at the time of the last study visit in the open-label phase of the study.

Subjects

Each site received approval from an institutional review board for the conduct of the study as well as for the informed consent form that was signed by each patient prior to enrollment in the study. Patients were between the ages of 18 and 65 years and had a primary *DSM-IV/ICD-10* diagnosis of unipolar major depressive disorder, confirmed by the Mini-International Neuropsychiatric Interview (MINI).[17] In addition, subjects were required to have an HDRS-17 score ≥ 18, confirmed by a central dial-in interactive voice response[18] questionnaire at the time they began study medication, and a history of failure of at least 1 adequate trial of a US Food and Drug Administration–approved antidepressant within the current episode of major depressive disorder. The definition of an adequate trial required a minimum of 6 weeks on the antidepressant (8 weeks with fluoxetine), titrated upward to the minimum dosages for each agent specified by the protocol (modified from Sackeim[19]). Patients were staged according to the Thase-Rush criteria.[20] Any antidepressant trial in which the individual initially had a satisfactory response and then lost this response was not classified as a failed trial.

Individuals with a primary diagnosis other than unipolar major depressive disorder were excluded, as well as anyone with a lifetime history of hypomania, mania, schizophrenia, schizoaffective disorder, or severe personality disorders. Individuals with a history of psychosis, dementia, organic affective disorders, or alcohol and/or substance abuse in the previous 6 months were also excluded. Individuals must not have had a history of prior failure to respond to an adequate trial of paroxetine or paroxetine CR or a history of failure to respond to a trial of electroconvulsive therapy during the current or prior episodes. Individuals with significant medical abnormalities or who were receiving medication that might interfere with the conduct of the study were also excluded, as were individuals with a positive screen for drugs of abuse or with abnormal thyroid function tests at screening. Concomitant medications that were known to affect the metabolism of lamotrigine were not allowed, and the only psychotropic agent permitted was zolpidem for a maximum of 2 nights weekly (except on the night prior to the study visit). Washout periods for preexisting medications were specified by the protocol (a minimum of 1 week for antidepressants other than fluoxetine, which required 4 weeks). Subjects were allowed to continue psychotherapy but could not have started or stopped the psychotherapy within 12 weeks of the screening visit.

Design

Open-label phase. After screening, individuals were started on treatment with paroxetine or paroxetine CR in once-daily dosages of 10 or 12.5 mg, respectively. The dosage was increased by these amounts on a weekly basis to maximum dosages of 50 mg/d or 62.5 mg/d (respectively) or until subjects reached an HDRS-17 score of ≤ 7—or until the emergence of side effects was prohibitive. Subjects were required to tolerate at least 20 mg/d of paroxetine or 25 mg/d of paroxetine CR to remain in the study. Study visits then occurred every 2 weeks through the remainder of this phase of the study.

Double-blind phase. At the end of the 8 weeks in the open-label phase of the study, those subjects with an HDRS-17 score of ≥ 15 (confirmed by interactive voice response) were then randomized to placebo or lamotrigine for the 10-week double-blind phase of the study. Subjects continued the paroxetine dose they were receiving at this visit for the remainder of the study.

The dosage of blinded medication was adjusted upward to a maximum of 400 mg/d in patients assigned to lamotrigine until the HDRS-17 score was ≤ 7 or until side effects were prohibitive. Lamotrigine was given once daily; it was started at a dosage of one 25-mg tablet daily for 2 weeks and then increased to two 25-mg tablets daily for 2 weeks. The dosage was then increased to 100 mg daily for 1 week and was subsequently increased in 100-mg increments weekly thereafter. Subjects had to be able to tolerate a minimum dosage of 100 mg to remain in the study. The first 2 visits of this phase of the study occurred weekly, and then visits occurred every 2 weeks thereafter.

At the last study visit (week 18), patients were tapered from the blinded medication by reducing the dosage by one-half for 1 week and then discontinuing it. Paroxetine and paroxetine CR were also tapered over a maximum of 4 weeks (depending on the dosage), although the drug could

© Copyright 2011 Physicians Postgraduate Press, Inc.

be continued if, in the judgment of the investigator, the patient had benefited significantly from it.

Measures

All raters were required to obtain satisfactory rating scores on the HDRS-17 and MADRS from a videotaped interview. The MADRS,[21] the primary efficacy outcome variable, was given at the screening visit, at the conclusion of the open-label phase of the study (week 8), at each of the visits in the double-blind phase of the study (weeks 9, 10, 12, 14, 16, and 18), and in the second week of discontinuation. The HDRS-17, which was utilized to determine eligibility in both the open-label and double-blind phases of the study, was given at all study visits. The 2 scales were utilized in this manner in an attempt to minimize any rating bias on the primary outcome measure (the MADRS). The CGI-S and CGI-I[22] were administered at the same visits as the MADRS. The self-rated Center for Epidemiologic Studies Depression scale (CES-D),[23] Medical Outcomes Study 36-Item Short-Form Health Survey (SF-36),[24] and Sheehan Disability Scale[25] were completed at weeks 8, 12, and 18; the Sheehan Disability Scale was completed at the screening visit as well. To be analyzed for a separate study, the Brief Pain Inventory (Short Form)[26] and the Wisconsin Personality Disorders Inventory-IV[27] were completed at screening and week 18, or at the last study visit, and the Wender Utah Rating Scale[28] was completed at the screening visit. Vital signs were measured at the first and last open-label visits and at all of the double-blind study visits.

Randomization and Blinding

The subjects' assignment to lamotrigine or placebo was performed using a random number table and was provided to an unblinded pharmacist who packaged the study medication kits in a blinded manner. The randomized treatment kits were shipped to sites as needed. Each site was assigned the lowest available treatment kit.

Data Analysis

The current study was estimated to require 45 participants per treatment group in the double-blind portion of the study (total N = 90) for a power level of approximately 0.90 (ie, a 90% probability of finding a treatment effect when one exists) at an α level of .05. The estimate was based on the authors' prior retrospective chart review of lamotrigine augmentation[11] and a double-blind study of olanzapine and fluoxetine alone and in combination.[29] The effect size for both studies ($f = 0.36$) was used to guide the sample size estimate for the current study, which followed a parallel-group, randomized, complete block design. Given that 30%–50% of patients were likely to respond to paroxetine monotherapy, the study allowed for 180 participants to be entered into the open-label phase.

Data were analyzed using the SAS statistical software package, version 9.1 (SAS Institute Inc, Cary, North Carolina). Descriptive statistics, including means, frequencies, and correlations, were analyzed prior to analysis of inferential statistics, which followed a previously established data analysis plan. For the primary outcome analysis, data for the 96 randomized patients were subjected to a 2 × 7 (2 types of treatment [placebo or augmentation] × 7 time periods [weeks of treatment: 8, 9, 10, 12, 14, 16, and 18]) repeated-measures analysis of covariance, using the MIXED procedure in SAS. The primary outcome measure was the MADRS, and secondary outcome measures were the HDRS-17 and CGI scores. Planned covariates for this analysis included gender, Thase-Rush category, atypical/melancholic specification, presence of comorbid Axis I anxiety disorder diagnosis, and open-label response as measured by differences in MADRS scores from baseline to randomization. The statistical model included fixed effects for treatment, week, and treatment by week interaction, with patient as a random effect. The baseline outcome score and any covariates that showed significant treatment group difference were included as covariates. This analysis was conducted separately for the 2 outcome measures of MADRS and HDRS-17 ratings, both on the observed and difference-score data. For the difference-score analyses, HDRS-17 and MADRS difference scores, calculated by subtracting scores at randomization from scores at termination, were used, such that negative difference scores were indicative of improvement. Difference-score data were analyzed using general linear model methods.

Analysis of the CGI (severity and improvement), response (MADRS and CGI), and remission variables was done using a Cochran-Mantel-Haenszel χ^2 statistic, controlling for the same covariates used in the repeated-measures analysis.

The CES-D, SF-36, Sheehan Disability Scale, and Brief Pain Inventory were used as additional outcome measures, with difference scores calculated by subtracting randomization visit scores from termination visit scores. Statistical analyses involving difference scores were performed using the general linear model procedure, with open-label MADRS response, anxiety, gender, Thase-Rush category, and diagnostic specifier, as well as all 2-way and 3-way interactions with treatment group, added to the model. A post hoc last-observation-carried-forward analysis compared MADRS difference scores for patients who were severely and nonseverely depressed, as defined by randomization visit HDRS-17 scores ≥ 25, a cutoff for severe depression recommended by other researchers.[30]

Additional outcome measures also included response status (as determined by percentage change in MADRS scores from randomization to termination: < 25% = nonresponse; 25%–50% = partial response; > 50% = response) and remission status (based on an HDRS-17 score of ≤ 7 at termination).

RESULTS

Open-Label Phase

The number of patients who were screened for the study and their disposition appear in Figure 1. For participants entered into the open-label portion of the study (descriptive statistics for this population appear in Table 1), the

mean MADRS score (N = 180) at the initial visit was 30.3 (SD = 5.26), and the mean HDRS-17 score (N = 183) was 23.6 (SD = 3.92). At the end of open-label treatment, the mean MADRS score (N = 134) was 23.2 (SD = 9.85), and the mean HDRS-17 score (N = 132) was 18.4 (SD = 7.23) for the patients who completed the open-label phase of the study. The CGI-S ratings also decreased from an initial open-label visit mean of 4.5 (SD = 0.62) to a mean of 3.9 (SD = 1.07). The mean CGI-I rating at the end of the open-label phase was 3.2 (SD = 1.12). Open-label differences between screening and the end of open-label treatment for the MADRS (mean = −7.6, SD = 10.44), HDRS-17 (mean = −5.7, SD = 7.50), and CGI-S (mean = −1.1, SD = 1.14) scores were all statistically significant at the .0001 level ($t_{133} = 8.43$, $t_{131} = 8.76$, and $t_{131} = 6.87$, respectively). While these changes represent significant improvement from baseline, they occurred similarly across treatment groups for patients who were subsequently randomized to lamotrigine augmentation or placebo.

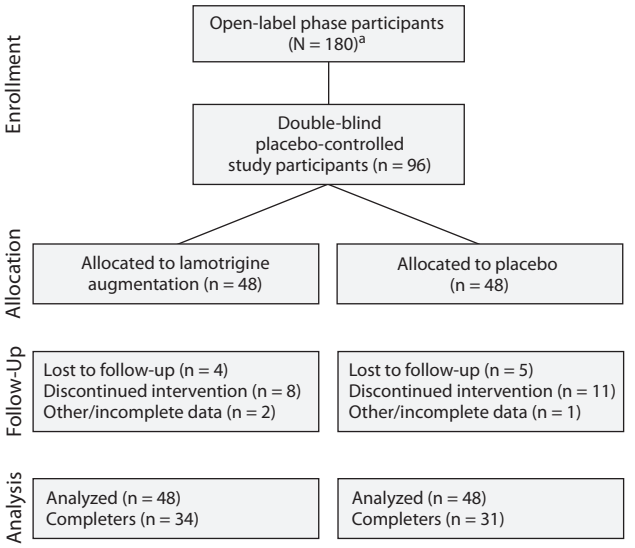
Double-Blind Phase

The mean dosage of paroxetine immediate-release at randomization was 44.84 mg/d, and the mean dosage of paroxetine CR at randomization was 49.53 mg/d. At the end of the study, the mean dosage of lamotrigine for patients in the drug treatment group was 271.88 mg/d (SD = 105.45 mg/d). The median and modal dosages of lamotrigine were 200 mg/d. There were no significant associations between lamotrigine dosage and treatment group.

Descriptive statistics and frequencies for variables used in the primary and secondary outcome analyses for the 96 patients who were randomized into the double-blind phase of the study appear in Tables 1 and 2. At the time of the randomization visit (week 8), neither the MADRS nor HDRS-17 mean scores differed between treatment groups. Examination of the demographic variables of age, gender, and race did not show any significant treatment group differences at the beginning of the open-label or double-blind phases of the study (see Table 1); however, *DSM-IV* depression severity ratings showed significant ($P = .021$) treatment group differences for the psychiatric history variables in the randomized phase of the study (see Table 1): 50% of the patients in the lamotrigine group were classified as having severe depression, compared to 26% of the patients in the placebo group.

Total MADRS scores for the observed-case analyses in the drug and placebo groups at each visit during the double-blind phase of the study appear in Figure 2A. The primary efficacy analysis did not find statistically significant differences between the lamotrigine and placebo treatment groups, and similar secondary analyses of HDRS-17, CGI-I, and CGI-S scores also did not demonstrate significant between-group differences for the observed-case analyses. Examination of the treatment differences at each visit showed a trend toward significance for the observed-case total MADRS score at the final study visit (visit 10/week 16; $P = .097$). Inclusion of the preplanned covariates did produce a significant between-group difference for the HDRS-17 scores

Figure 1. CONSORT Diagram of Enrollment and Randomization



[a]Although 183 patients were initially entered into the study, 3 patients terminated participation prior to the second study visit.
Abbreviation: CONSORT = Consolidated Standards of Reporting Trials.

($F_{1,87} = 4.24$, $P = .04$) but not for the MADRS ($F_{1,87} = 2.45$, $P = .12$). The CES-D, Sheehan Disability Scale, and SF-36 revealed no significant drug-placebo differences (Table 2).

MADRS scores obtained at each visit utilizing an observed-case analysis appear in Figure 2A. For the similar completer analysis that appears in Figure 2B, in the absence of covariates, differences in actual MADRS and HDRS-17 mean scores between groups at each individual study visit were statistically nonsignificant. Correlational analyses between all outcome difference scores and independent variables were conducted both for all patients and separately for each treatment group. In these analyses, in the absence of any covariates, there was a trend toward significance of the association between lamotrigine treatment and improvement, as defined by a decrease in scores from baseline to final visit for both the MADRS and the HDRS-17, but only for those patients who completed participation in the study (MADRS: $r_{64} = -0.21$, $P = .09$; HDRS-17: $r_{65} = -0.22$, $P = .07$).

Overall, the responder analyses based on changes in MADRS scores (described in the Method) showed no significant drug-placebo differences. Both the lamotrigine and placebo groups had 16 patients (33%) classified as responders. There was no significant difference in the response distribution between treatment groups ($P = .956$). However, when MADRS response category was used as a dependent variable in a general linear model analysis that included covariates and interaction terms, a significant interaction was revealed between group, anxiety, and Thase-Rush category ($F_{1,57} = 4.48$, $P = .04$). Cell means for this analysis, shown in Table 3, indicate that the greatest response in both the placebo and lamotrigine groups was found among patients with comorbid anxiety. The 2 patients who were rated

© Copyright 2011 Physicians Postgraduate Press, Inc.

Table 1. Descriptive Statistics for Demographic and Disease-Related Variables for All Patients Entered Into the Study (open-label phase), All Randomized Patients, the Placebo Group, and the Lamotrigine Group[a]

Variable	Total Sample (N = 183), Mean (SD)	Randomized Patients (n = 96), Mean (SD)	Placebo Group (n = 48), Mean (SD)	Lamotrigine Group (n = 48), Mean (SD)
Age, y	44.23 (11.97)	45.21 (11.56)	45.83 (10.95)	44.59 (12.22)
Thase-Rush category	1.39 (0.39)	1.35 (0.48)	1.30 (0.46)	1.39 (0.49)
Duration of current depressive episode, wk	106.52 (143.60)	116.78 (159.80)	127.11 (174.82)	106.67 (144.73)
Number of prior episodes	12.01 (57.46)	9.24 (20.35)	3.93 (4.55)	14.33 (17.30)
Age at first depressive episode, y	26.23 (13.41)	27.22 (13.64)	28.61 (14.15)	25.90 (13.14)
	N (%)	N (%)	N (%)	N (%)
Sex				
Male	59 (32.78)	30 (31.25)	15 (31.25)	15 (31.25)
Female	121 (67.22)	66 (68.75)	33 (68.75)	33 (68.75)
DSM-IV diagnosis				
Single episode	31 (16.94)	13 (13.54)	9 (18.75)	4 (8.33)
Recurrent	152 (83.06)	83 (86.46)	39 (81.25)	44 (91.67)
DSM-IV severity code				
Mild	2 (1.09)	0 (0.00)	0 (0.00)	0 (0.00)
Moderate	125 (68.31)	59 (61.46)	35 (72.92)[b]	24 (50.00)
Severe	56 (30.60)	37 (38.54)	13 (27.08)[b]	24 (50.00)
Diagnostic specification				
Atypical	13 (7.26)	8 (8.33)	5 (10.42)	3 (6.25)
Melancholic	75 (41.90)	42 (43.75)	21 (43.75)	21 (43.75)
None	91 (50.84)	46 (47.92)	22 (45.83)	24 (50.00)
Comorbid anxiety				
No	145 (81.01)	77 (80.21)	42 (87.50)	35 (72.92)
Yes	34 (18.99)	19 (19.79)	6 (12.50)	13 (27.08)

[a]Table represents patients for whom data were available/provided.
[b]Significant between-group difference, $P < .05$.

Table 2. Descriptive Statistics for Outcome Measures of Randomized Patients (N = 96) in the Double-Blind Phase of the Study, Last-Observation-Carried-Forward Analysis

		Placebo (n = 48)			Lamotrigine (n = 48)	
Variable	Randomization/ Visit 5, Mean (SD)	Final Visit, Mean (SD)	Difference, Mean (SD)	Randomization/ Visit 5, Mean (SD)	Final Visit, Mean (SD)	Difference, Mean (SD)
MADRS score	26.63 (4.88)	17.37 (8.62)	−9.37 (8.33)	27.40 (6.59)	18.08 (9.84)	−9.31 (11.21)
HDRS score	20.73 (3.85)	13.72 (6.53)	−7.04 (5.96)	22.19 (4.23)	14.67 (7.79)	−7.52 (8.12)
CGI-S score	4.29 (0.50)	3.15 (1.11)	−1.17 (1.12)	4.40 (0.54)	3.35 (1.12)	−1.04 (1.17)
CGI-I score	3.67 (0.75)	2.48 (1.11)	NA	3.63 (0.61)	2.90 (1.40)	NA

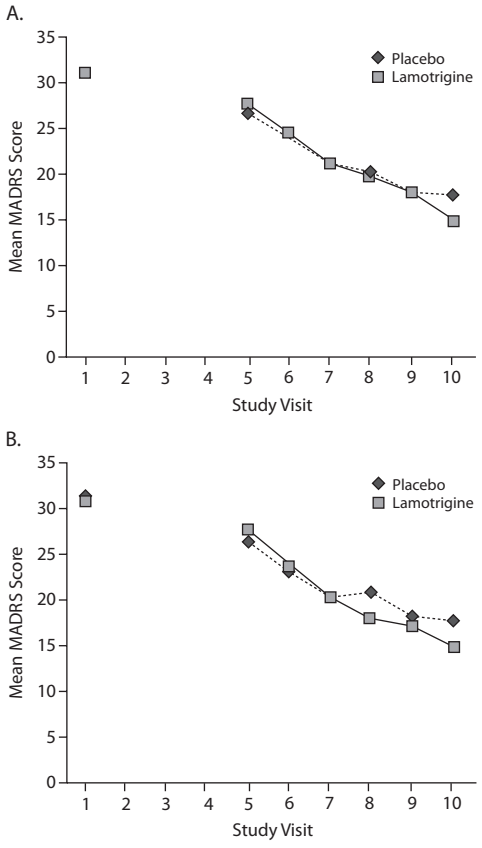
Abbreviations: CGI-I = Clinical Global Impressions-Improvement scale, CGI-S = Clinical Global Impressions-Severity of Illness scale, HDRS = Hamilton Depression Rating Scale, MADRS = Montgomery-Asberg Depression Rating Scale, NA = not applicable.

as a category 2 in terms of treatment resistance, and who had comorbid anxiety as well, showed a relatively greater response to lamotrigine. However, the small number of patients in this group and the absence of any placebo patients in this cell raise a question about the significance of this finding.

An additional post hoc analysis of covariance, using the general linear model procedure in SAS, was also conducted to further explore the effects of severity of depression on outcome. The MADRS difference scores were used as dependent variables, with treatment group as the categorical independent variable and HDRS-17 total scores at randomization as covariates. This analysis revealed a significant interaction between treatment group and depression severity (as measured by randomization HDRS-17) ($F_{1,90} = 5.83$, $P = .02$). Simple Pearson correlations used to describe the pattern of this interaction suggested that for the lamotrigine group, baseline severity of depression was significantly correlated with drug response ($r_{46} = -0.38$, $P < .01$). This correlation, which was not present in the placebo group ($r_{46} = 0.08$, $P = .61$), suggests that higher HDRS-17 scores (ie, more severe depression) at randomization were associated with a greater decrease in MADRS scores (ie, greater improvement) during the double-blind portion of the study. To explore this association further, visit 5/randomization HDRS-17 scores were dichotomized into severe and nonsevere classifications, such that individuals scoring over 24 were classified as severely depressed, while all other cases were classified as nonsevere. A factorial analysis of variance was conducted using last-observation-carried-forward MADRS difference scores as the dependent variable and treatment group and severity classification as independent variables. This analysis revealed, despite unbalanced data (78 nonsevere and 18 severe cases overall), a near-significant 2-way interaction between treatment group and severity category ($F_{1,90} = 3.63$, $P = .06$), such that, while placebo and nonsevere lamotrigine patients had similar decreases in MADRS scores, severely depressed patients in the lamotrigine group showed the greatest decreases in MADRS scores (Figure 3).

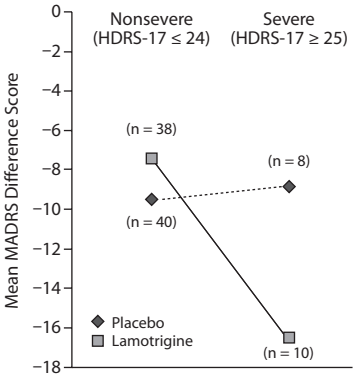
Lamotrigine was generally well tolerated. The percentage of participants reporting any treatment-emergent adverse event in the double-blind phase of the study was identical for both treatment groups at 87.5%. The most commonly reported adverse events (incidence ≥ 5%) in the lamotrigine group were headache, diarrhea, nausea, fatigue, urinary tract infection, rash, and excoriation. Rash occurred in 6 of the 48 lamotrigine patients and in 3 of the 48 placebo patients. Patients experiencing rashes during the double-blind phase were permanently discontinued from the study, except for 2 patients whose rashes were deemed not to be related to study participation. There were no significant differences in the rates of adverse events between treatment groups. Only 5 serious adverse events were reported in the study. One

Figure 2. Mean MADRS Scores by Study Visit for (A) All Randomized Participants (observed-case analysis) and (B) Completer Analysis



Abbreviation: MADRS = Montgomery-Asberg Depression Rating Scale.

Figure 3. Mean MADRS Difference Scores (final MADRS – randomization MADRS) by Treatment Group and Depression Severity, Last-Observation-Carried-Forward Analysis



Abbreviations: HDRS-17 = 17-item Hamilton Depression Rating Scale, MADRS = Montgomery-Asberg Depression Rating Scale.

Table 3. Cell Means and Standard Deviations of Outcome Scores for MADRS Response Category Means (1 = no response, 2 = partial response, 3 = full response) for Group × Anxiety × Thase-Rush Category Interaction

Thase-Rush Category	Group	No Anxiety, Mean (SD)	Anxiety, Mean (SD)
1	Placebo	1.65 (0.88) [n = 23]	2.40 (0.55) [n = 5]
	Lamotrigine	2.00 (0.87) [n = 17]	2.20 (0.92) [n = 10]
2	Placebo	1.83 (1.03) [n = 12]	NA [n = 0]
	Lamotrigine	1.60 (0.83) [n = 15]	2.50 (0.71) [n = 2]

Abbreviations: MADRS = Montgomery-Asberg Depression Rating Scale, NA = not applicable.

patient in the lamotrigine group contracted pneumonia during the study and was only temporarily taken off study medications. Two patients were permanently terminated from the study only 2 days after beginning open-label paroxetine monotherapy; these adverse events were deemed not to be related to study medication. One patient in the placebo group experienced suicidality during the double-blind phase. A patient in the placebo group was hospitalized during the double-blind phase for increased irritability and anger, but no action was taken with regard to study medication because the adverse effect was deemed not drug-related.

Of the 48 patients in the lamotrigine group, 14 were terminated from the study prematurely (including 2 individuals with incomplete data), with 7 terminations due to adverse events, 1 because of withdrawn consent, and 4 because the patients were lost to follow-up. Among the 48 placebo patients, 17 discontinued prematurely (including 1 with incomplete data), with 10 terminations due to adverse events, 1 because of withdrawn consent, and 5 because the patients were lost to follow-up.

DISCUSSION

This study was designed to demonstrate the efficacy of lamotrigine as an augmentation treatment for refractory unipolar depression. Since the primary a priori analysis did not differentiate lamotrigine from placebo, it must be considered a negative study. The most conservative interpretation of the outcome is that lamotrigine is not efficacious in this role. Such a conclusion is similar to that of Geddes et al[4] in a meta-analysis of the 5 clinical trials completed to date in which lamotrigine was used as monotherapy in the acute treatment of bipolar depression. Although pooled data from the 5 studies showed a significant drug effect, only 1 of the studies[3] independently separated from placebo. Although the previously cited studies of lamotrigine as an augmentation agent in resistant unipolar depression[11–15] suggest its effectiveness, the only other prior double-blind, placebo-controlled study[15] of lamotrigine with a similar design to this study also failed to find evidence of an effect.

The outcome was not completely negative, however, as some of the secondary and post hoc analyses suggested possible drug-placebo differences and guidance for design of any future studies. Thus, the drug-placebo differences were significant for the HDRS-17 when several covariates were controlled for, and the differences in mean change scores

© Copyright 2011 Physicians Postgraduate Press, Inc.

for both the MADRS and the HDRS-17 neared significance in those individuals who completed the study. Inspection of the data in Figure 2B, depicting MADRS scores in the 2 study groups among the patients who completed the study, suggests a trend toward separation between drug and placebo in the final study visits. Indeed, among those patients who completed the study, even excluding covariates, the association between lamotrigine treatment and decreases in scores on the MADRS ($r_{64} = -0.21$, $P = .09$) and HDRS-17 ($r_{65} = -0.22$, $P = .07$) approached significance. It may be that the 10-week trial period was too short, perhaps related to the lengthy titration for lamotrigine in the first 4 weeks, as suggested by the manufacturer due to the risk of drug-induced rash and Stevens-Johnson syndrome.

Also, although the mean MADRS and HDRS-17 scores were not significantly different across treatment groups at baseline, it is curious that there was a significantly greater number of lamotrigine patients who were rated as severely ill at the time of randomization—and they had numerically a greater number of prior episodes of major depressive disorder (see Table 1). These differences may have interfered with the ability to demonstrate a drug-placebo difference, although, paradoxically, post hoc analyses suggested a greater response to lamotrigine in the more severely depressed and more treatment-resistant patients than that seen with placebo. As seen in Figure 3, those patients who were severely ill (based on HDRS-17 ratings ≥ 25) seemed to show a much greater response to lamotrigine than those who were less severely ill. Because only a small percentage of patients in this study could be classified as severely depressed, data for this analysis were unbalanced, and the test did not achieve statistical significance at the $P < .05$ level; however, the fact that this result approached significance ($P = .06$) attests to the magnitude of the effect it represents. This finding is similar to that of Geddes et al[4] in the meta-analysis of clinical trial results of lamotrigine in bipolar depression. The patients recruited for our study were neither severely depressed, based on rating scale results (the mean MADRS score at randomization was 27.1), nor particularly treatment-resistant. The average Thase-Rush staging score upon entry into the randomized portion of the study was only 1.35 (the lowest possible score on this scale is 1), indicating that most of the patients in this trial had never failed an adequate trial of more than 1 class of antidepressant. None of the subjects scored higher than a 2, meaning that none of them had experienced an adequate trial of a tricyclic or monoamine oxidase inhibitor. These factors may explain why the placebo response rate was higher than expected. It has been suggested that patients with true treatment resistance may constitute a clinically and neurobiologically unique subgroup of individuals with depression.[31]

In future studies with lamotrigine or other prospective augmentation agents, alternative clinical trial design strategies should be considered. In the recently published study[32] of aripiprazole augmentation of antidepressants in a similar clinical population, the aripiprazole response rate was only 33.7% at endpoint, but the drug was statistically superior to placebo, with which the response rate was only 23.8%. In the study, the placebo was started from the beginning of antidepressant treatment, and patients were not informed of the time of randomization. Other strategies might include requiring higher degrees of refractoriness, or more severely ill patients, and excluding patients with comorbid anxiety disorders, who demonstrated a greater response to placebo in this study. Alternative staging strategies such as the Massachusetts General Hospital Staging Method[33] may be more useful than the Thase-Rush criteria in an era when the use of tricyclics and monoamine oxidase inhibitors seems to be steadily dwindling. Given the very real unmet needs of the patient population, one can only hope that further investigation with lamotrigine and other potential augmentation agents will continue.

Drug names: aripiprazole (Abilify), fluoxetine (Prozac and others), gabapentin (Neurontin and others), lamotrigine (Lamictal and others), olanzapine (Zyprexa), olanzapine-fluoxetine (Symbyax), paroxetine (Paxil, Pexeva, and others), zolpidem (Ambien, Edluar, and others).

Author affiliations: Department of Psychiatry, Louisiana State University Health Sciences Center, New Orleans (Drs Barbee and Conrad and Ms Jamhour); GlaxoSmithKline, Research Triangle Park, North Carolina (Dr T. R. Thompson); New York State Psychiatric Institute and Department of Psychiatry, Columbia University, New York (Dr Stewart); Mood Disorders Clinic, Department of Psychiatry, University of Utah School of Medicine, Salt Lake City (Dr Reimherr); Department of Psychiatry, University of Texas Health Sciences Center, San Antonio (Dr P. M. Thompson); and Department of Psychiatry, Vanderbilt University Medical Center, Nashville, Tennessee (Dr Shelton).

Potential conflicts of interest: **Dr Barbee** has received grant/research support from Pfizer, Pamlab, and Forest and has been a member of the speakers bureaus for AstraZeneca, Bristol-Myers Squibb, Eli Lilly, Merck, Pfizer, and Novartis. **Dr T. R. Thompson** is an employee and stock shareholder of GlaxoSmith Kline. **Ms Jamhour** has been a consultant for GlaxoSmithKline. **Dr Conrad** has received grant/research support from Forest, Pfizer, Pamlab, and Otsuka. **Dr Reimherr** has received research support from Eli Lilly, Bristol-Myers Squibb, GlaxoSmithKline, Cyberonics, Shire, Pfizer, Novartis, and Sepracor and has received research support paid by GlaxoSmithKline to the University of Utah; has been a member of the advisory boards of Eli Lilly and Shire; and is a stock shareholder of Celgene. **Dr Shelton** has received grant/research support from Eli Lilly, GlaxoSmithKline, Janssen, Pfizer, Sanofi, Wyeth-Ayerst, AstraZeneca, Abbott, and Pamlab; has been a paid consultant for Pfizer, Janssen, and Sierra Neuropharmaceuticals; and has been a member of the speakers bureaus for Bristol-Myers Squibb, Eli Lilly, Janssen, Pfizer, GlaxoSmithKline, Wyeth-Ayerst, and Abbott. **Drs Stewart** and **P. M. Thompson** have no personal affiliations or financial relationships with any commercial interest to disclose relative to the article.

Funding/support: This project received research funding and support from GlaxoSmithKline (protocol number LMC-R93).

Previous presentation: Presented as a poster at the 160th Annual Meeting of the American Psychiatric Association; May 19–24, 2007; San Diego, California; and at the 47th Annual Meeting of the New Clinical Drug Evaluation Unit; June 11–14, 2007; Boca Raton, Florida.

REFERENCES

1. Calabrese JR, Bowden CL, Sachs G, et al; for the Lamictal 605 Study Group. A placebo-controlled 18-month trial of lamotrigine and lithium maintenance treatment in recently depressed patients with bipolar I disorder. *J Clin Psychiatry*. 2003;64(9):1013–1024.
2. Bowden CL, Calabrese JR, Sachs G, et al; for the Lamictal 606 Study Group. A placebo-controlled 18-month trial of lamotrigine and lithium maintenance treatment in recently manic or hypomanic patients with bipolar I disorder. *Arch Gen Psychiatry*. 2003;60(4):392–400.
3. Calabrese JR, Bowden CL, Sachs GS, et al; Lamictal 602 Study Group. A double-blind placebo-controlled study of lamotrigine monotherapy in outpatients with bipolar I depression. *J Clin Psychiatry*. 1999;60(2):79–88.
4. Geddes JR, Calabrese JR, Goodwin GM. Lamotrigine for treatment of bipolar depression: independent meta-analysis and meta-regression of

individual patient data from five randomised trials. *Br J Psychiatry*. 2009; 194(1):4–9.
5. GlaxoSmithKline. An eight-week, multicenter, double-blind, randomized, fixed-dose evaluation of the efficacy and safety of lamotrigine (200 mg/d), desipramine (200 mg/d), and placebo in outpatients with unipolar depression (result summary for study SCAA2011 [105-613]). http://download.gsk-clinicalstudyregister.com/files/1666.pdf. Verified October 7, 2010.
6. GlaxoSmithKline. A randomized, multicenter, double-blind, placebo-controlled, fixed-dose, 7-week evaluation of the efficacy and safety of lamotrigine in patients with major depression (result summary for study SCA20022). http://download.gsk-clinicalstudyregister.com/files/1661.pdf. Verified October 7, 2010.
7. GlaxoSmithKline. A randomized, multicenter, double-blind, placebo-controlled, fixed-dose, 7-week evaluation of the efficacy and safety of lamotrigine in treatment of a major depressive episode in unipolar depressed patients (result summary for study SCA20025). http://download.gsk-clinicalstudyregister.com/files/1663.pdf. Verified October 7, 2010.
8. Normann C, Hummel B, Schärer LO, et al. Lamotrigine as adjunct to paroxetine in acute depression: a placebo-controlled, double-blind study. *J Clin Psychiatry*. 2002;63(4):337–344.
9. Obrocea GV, Dunn RM, Frye MA, et al. Clinical predictors of response to lamotrigine and gabapentin monotherapy in refractory affective disorders. *Biol Psychiatry*. 2002;51(3):253–260.
10. Barbosa L, Berk M, Vorster M. A double-blind, randomized, placebo-controlled trial of augmentation with lamotrigine or placebo in patients concomitantly treated with fluoxetine for resistant major depressive episodes. *J Clin Psychiatry*. 2003;64(4):403–407.
11. Barbee JG, Jamhour NJ. Lamotrigine as an augmentation agent in treatment-resistant depression. *J Clin Psychiatry*. 2002;63(8):737–741.
12. Rocha FL, Hara C. Lamotrigine augmentation in unipolar depression. *Int Clin Psychopharmacol*. 2003;18(2):97–99.
13. Gutierrez RL, McKercher RM, Galea J, et al. Lamotrigine augmentation strategy for patients with treatment-resistant depression. *CNS Spectr*. 2005;10(10):800–805.
14. Gabriel A. Lamotrigine adjunctive treatment in resistant unipolar depression: an open, descriptive study. *Depress Anxiety*. 2006;23(8):485–488.
15. Santos MA, Rocha FL, Hara C. Efficacy and safety of antidepressant augmentation with lamotrigine in patients with treatment-resistant depression: a randomized, placebo-controlled, double-blind study. *Prim Care Companion J Clin Psychiatry*. 2008;10(3):187–190.
16. Hamilton M. A rating scale for depression. *J Neursurg Psychiatry*. 1960; 23(1):56–62.
17. Sheehan DV, Lecrubier Y, Sheehan KH, et al. The Mini-International Neuropsychiatric Interview (M.I.N.I.): the development and validation of a structured diagnostic psychiatric interview for *DSM-IV* and *ICD-10*. *J Clin Psychiatry*. 1998;59(suppl 20):22–33, quiz 34–57.
18. Mundt JC, Kobak KA, Taylor LV, et al. Administration of the Hamilton Depression Rating Scale using interactive voice response technology. *MD Comput*. 1998;15(1):31–39.
19. Sackeim HA. The definition and meaning of treatment-resistant depression. *J Clin Psychiatry*. 2001;62(suppl 16):10–17.
20. Thase ME, Rush AJ. When at first you don't succeed: sequential strategies for antidepressant nonresponders. *J Clin Psychiatry*. 1997;58(suppl 13): 23–29.
21. Montgomery SA, Asberg M. A new depression scale designed to be sensitive to change. *Br J Psychiatry*. 1979;134(4):382–389.
22. Guy W. *ECDEU Assessment Manual for Psychopharmacology*. US Dept Health, Education, and Welfare publication (ADM) 76-338. Rockville, MD: National Institute of Mental Health; 1976:218–222.
23. Radloff LS. The CES-D Scale: a self-report depression scale for research in the general population. *Appl Psychol Meas*. 1977;1(3):385–401.
24. Ware JE Jr, Sherbourne CD. The MOS 36-Item Short-Form Health Survey (SF-36), 1: Conceptual framework and item selection. *Med Care*. 1992;30(6):473–483.
25. Sheehan DV, Harnett-Sheehan K, Raj BA. The measurement of disability. *Int Clin Psychopharmacol*. 1996;11(suppl 3):89–95.
26. Cleeland CS. Measurement of pain by subjective report. In: Chapman CR, Loeser JD, eds. *Issues in Pain Measurement*. New York, NY: Raven Press; 1989:391–403.
27. Smith TL, Klein MH, Benjamin LS. Validation of the Wisconsin Personality Disorders Inventory-IV with the SCID-II. *J Pers Disord*. 2003;17(3):173–187.
28. Wender PH. Wender AQCC (Adult Questionnaire–Childhood Characteristics) Scale. *Psychopharmacol Bull*. 1995;21:927–928.
29. Shelton RC, Tollefson GD, Tohen M, et al. A novel augmentation strategy for treating resistant major depression. *Am J Psychiatry*. 2001;158(1): 131–134.
30. Nemeroff CB. The burden of severe depression: a review of diagnostic challenges and treatment alternatives. *J Psychiatr Res*. 2007;41(3-4): 189–206.
31. Fagiolini A, Kupfer DJ. Is treatment-resistant depression a unique subtype of depression? *Biol Psychiatry*. 2003;53(8):640–648.
32. Berman RM, Marcus RN, Swanink R, et al. The efficacy and safety of aripiprazole as adjunctive therapy in major depressive disorder: a multicenter, randomized, double-blind, placebo-controlled study. *J Clin Psychiatry*. 2007;68(6):843–853.
33. Petersen T, Papakostas GI, Posternak MA, et al. Empirical testing of two models for staging antidepressant treatment resistance. *J Clin Psychopharmacol*. 2005;25(4):336–341.

 © Copyright 2011 Physicians Postgraduate Press, Inc.