A Double-Blind, Randomized, Placebo-Controlled Trial of Augmentation With Lamotrigine or Placebo in Patients Concomitantly Treated With Fluoxetine for Resistant Major Depressive Episodes

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Background: Evidence of the antidepressant efficacy of lamotrigine is increasing, although there are no placebo-controlled trials of lamotrigine augmentation in depression. The aim of this study was to assess if augmentation with lamotrigine was superior to placebo in patients who were receiving fluoxetine for resistant major depressive episodes.

Method: Twenty-three patients who had experienced at least 1 major depressive episode that was resistant to at least 1 prior trial of antidepressant therapy were selected. These patients were treated with fluoxetine, 20 mg/day, and concomitantly randomly assigned to receive either lamotrigine (N = 13) or placebo (N = 10) for 6 weeks. The dose of lamotrigine was titrated upward from 25 mg/day to 100 mg/day. Patients suffering from bipolar II disorder (N = 8) or from major depressive disorder (N = 15) (DSM-IV criteria) were enrolled, resulting in heterogeneity of the sample. The primary outcome measure was Hamilton Rating Scale for Depression score. Data were collected from 2000–2001.

Results: Lamotrigine was statistically superior to placebo on the Clinical Global Impressions scale at endpoint, both in absolute terms (mean ± SD Clinical Global Impressions-Severity of Illness scores: lamotrigine, 2.15 ± 1.28; placebo, 3.40 ± 1.17; p = .0308) and using a responder analysis, with response defined as a Clinical Global Impressions-Improvement score of 2 or less (lamotrigine, 84.62% [N = 11]; placebo, 30.00% [N = 3]; p = .013). The effect of lamotrigine on Clinical Global Impressions scale scores was seen in both major depressive disorder and bipolar II disorder. Lamotrigine, however, failed to separate statistically from placebo on the Hamilton Rating Scale for Depression and Montgomery-Asberg Depression Rating Scale. This failure to differentiate on a primary outcome measure is essentially a negative study result. This result is most likely an artifact of the small sample size used and the resultant limited power of the study.

Conclusion: The results of this trial add to the literature suggesting potential efficacy of the antidepressant profile of lamotrigine. In addition, this study points to a possible role of lamotrigine as an augmentation agent in depression.

(J Clin Psychiatry 2003;64:403–407)

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Supported jointly by the Department of Psychiatry of the University of the Witwatersrand Research Fund and GlaxoSmithKline, Research Triangle Park, N.C.

The authors thank the nursing staff and administration of Sterkfontein Hospital, Krugersdorp, South Africa.

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There is an increasing evidence base for lamotrigine in mood disorders. It is a novel anticonvulsant with several mechanisms of action, including inhibition of voltage-dependent sodium channels, inhibition of excitatory amino acids such as glutamate and aspartate, and calcium antagonism. There is some evidence that lamotrigine may also block 5-HT_3 receptors and act to potentiate dopaminergic transmission.[1,2]

Open-label studies provided the first suggestions of the efficacy of lamotrigine. Efficacy of lamotrigine in treatment-resistant bipolar disorder was suggested in an open chart review report.[3] A further open 48-week study of 75 patients with treatment-resistant bipolar disorder again suggested efficacy.[4] Lamotrigine has shown promise for rapid-cycling bipolar disorder, a pattern of the illness that is frequently refractory to lithium.[5–7] In a placebo-controlled study of 324 rapid-cycling patients, although the primary outcome measure, time to intervention, did not show statistically significant differences between treatment groups, there were statistically significant differences in favor of lamotrigine on a number of key secondary measures, including survival in study.[8] This result was more robust for the bipolar II disorder subgroup. In that study, 41% of patients in the lamotrigine group compared with 26% of patients in the placebo group did not relapse for 6 months. These data are interesting in that they demonstrate a potential mood-stabilizing effect of lamotrigine. Another small (N = 14) open-label study of rapid-cycling patients utilizing a 1-year follow-up period suggested efficacy of lamotrigine that was at least equivalent to that of lithium.[9]

Open-label data support the efficacy of lamotrigine in depression.[10,11] A subsequent large double-blind multicenter study of 437 patients compared lamotrigine, 200 mg/day; placebo; and desipramine, 200 mg/day, in patients with unipolar depression.[12] Both active treatments differentiated from placebo on the Clinical Global Impressions-Severity of Illness (CGI-S) and -Improvement (CGI-I) and the 17-item Hamilton Rating Scale for Depression (HAM-D) at 1 or more timepoints. At week 8, both agents differentiated from placebo on the CGI-S and the CGI-I, but not on the 17-item HAM-D. Given the ambivalent results of that unpublished study, further data in unipolar depression are necessary to establish efficacy. A pivotal double-blind, placebo-controlled study of lamotrigine at doses of 50 and 200 mg/day in 195 bipolar I patients suffering from a depressive episode showed significant efficacy for lamotrigine, particularly at the 200-mg dose. Significant efficacy was demonstrated on the 17-item HAM-D, HAM-D item 1, Montgomery-Asberg Depression Rating Scale (MADRS), CGI-S, and CGI-I compared with placebo. On the CGI-I, 51%, 41%, and 26% of patients receiving lamotrigine, 200 mg/day; lamotrigine, 50 mg/day; and placebo, respectively, demonstrated response.[13]

A smaller double-blind crossover study also showed superiority of lamotrigine to both placebo and gabapentin in patients with treatment-refractory depression.[14] A recent study compared lamotrigine, 200 mg/day, with placebo as adjunctive therapy to paroxetine in 40 patients. In this trial, there was no difference on the HAM-D at endpoint, although scores on individual items of the HAM-D (depressed mood, guilt, and work and interest) improved. Accelerated onset of antidepressant action was described in the lamotrigine group, as were lower rates of benzodiazepine utilization.[15]

Given the accumulating body of evidence of the efficacy of lamotrigine in a spectrum of mood disorders, the study reported here was conceived to examine the utility of lamotrigine augmentation in treatment-refractory depression. In this study, the efficacy and tolerability of lamotrigine were compared with those of placebo as "add-on" therapy in a cohort of patients receiving fluoxetine in a group of patients who had failed at least 1 trial of treatment for a major depressive episode. The hypothesis of the study was that lamotrigine would show efficacy compared with placebo in a placebo-controlled design.

METHOD

Patients

Twenty-three inpatients aged 18 to 65 years who were admitted with a major depressive episode diagnosed according to DSM-IV criteria on structured interview (Mini-International Neuropsychiatric Interview [MINI][16]), met inclusion and exclusion criteria, and gave informed written consent were selected for the study. Data were collected in 2000 and 2001. The study was conducted at a single site, Sterkfontein Hospital (Krugersdorp, South Africa). While all patients began the study as inpatients, some completed the study as outpatients. All patients had failed at least 1 previous trial of adequate antidepressant therapy (excluding fluoxetine). Failed treatment was defined as at least 6 weeks of therapy at an adequate dose (150 mg/day of tricyclic or equivalent), such that the patient continued to meet diagnostic criteria for a major depressive episode despite prior treatment. With regard to prior treatment of the index episode, 74% (N = 17) had previously had a trial of a tricyclic antidepressant at a dose over 150 mg/day, 22% (N = 5) had had a trial of citalopram, and 13% (N = 3) had had a trial of venlafaxine. Prior augmentation strategies included anticonvulsants (carbamazepine, 9% [N = 2]; valproate, 4% [N = 1]) and atypical neuroleptics (4% [N = 1]). The MINI was administered at admission. All patients needed a 17-item HAM-D[17] score of at least 18 to be included.

The patients were assigned randomly and consecutively to treatment with lamotrigine or placebo in a double-blind fashion according to a randomization log. All patients were commenced on a fixed dose of fluoxetine, 20 mg/day, for the index episode at the beginning of the study. No patients had previously failed a trial of treatment with fluoxetine. All patients began the trial as inpatients, and some were discharged and followed up as outpatients according to clinical response.

Exclusion Criteria

Exclusion criteria included patients with abnormal hepatic, thyroid, renal, or hematologic findings and those with positive screening assays for drugs of abuse. Patients who were pregnant or breastfeeding were excluded from the study, and women were required to use contraception (oral contraception, intrauterine device, implant, or double barrier) and have negative serum chorionic gonadotropin test results. Patients who had received a neuroleptic depot preparation in the last month, patients with current psychotic features, and patients who were actively suicidal, as defined as a HAM-D item 3 score greater than 3, were excluded. In addition, patients with an acute systemic medical disorder or a medical disorder requiring frequent changes in medication and patients who displayed DSM-IV–defined psychoactive substance abuse or dependence, including those who regularly consumed more than 3 alcoholic drinks per day, were excluded from the study. Patients who had previously had a manic episode and were thus diagnosed as suffering from bipolar I disorder were excluded from the study, although patients meeting criteria for bipolar II disorder were not excluded from the study. A full physical and neurologic examination and urinalysis were performed at baseline. An electrocardiogram was performed prior to the commencement of the study if clinically indicated.

Outcome Measures

Rating scales used included the HAM-D, MADRS,[18] and CGI,[19] as well as the Global Assessment of Functioning (GAF).[20] The HAM-D was regarded as the primary outcome measure. These scales were administered at baseline and weekly for the next 6 weeks or on the day of study termination if the patient withdrew prior to day 42. Consistency of interrater reliability was enhanced by utilizing a single rater (L.B.) for all patients during both inpatient and outpatient phases of the trial. The study duration was 42 days. Adverse events were noted at each visit. Vital signs, including blood pressure and pulse, were checked weekly by the investigator, and weight was monitored at baseline and trial end. To ensure confidentiality, all study material was marked with the patient's initials and the study number only.

Study Design

Any existing psychotropic medication was discontinued before the first day of the study prior to commencement of trial medication (fluoxetine and either lamotrigine or placebo) after consent was obtained. All patients were commenced on treatment with a fixed dose of fluoxetine, 20 mg/day, and randomly assigned to receive either lamotrigine or placebo. The starting dose of lamotrigine was 25 mg/day for 2 weeks, and this dose was increased to 50 mg/day for 2 weeks and to a final maximum dose of 100 mg/day thereafter. All medication was administered as a single daily dose. Oxazepam was given when necessary for control of anxiety or insomnia. No other psychotropic medication was permitted during the course of the study. The use of oxazepam was a secondary outcome measure. Compliance was assessed by counting returned medication packs.

The protocol was passed by the Committee for Research of Human Subjects of the University of the Witwatersrand and the hospital Pharmaceutical and Therapeutics Committee (Ethics ref. 990201). Patients could be withdrawn from the study if they withdrew consent, failed to improve (this could be judged at the discretion of the clinician or patient), or had significant adverse events. In particular, the protocol stipulated withdrawal from the trial of all patients who developed skin rashes.

Statistical Analysis

Comparison between the 2 treatment groups at the baseline was performed using the Mann-Whitney U test. The Fisher exact test was used to assess differences in proportion between the 2 groups. Comparison between the scores at different times within groups was made using the Wilcoxon signed rank test. Both absolute scores and percent change from baseline on the rating scales were calculated for each patient. Data were analyzed on a last-observation-carried-forward basis. An analysis of covariance was performed, but as the data were not normally distributed, they are not quoted. All tests were 2-tailed at a 95% level of significance. The sample size (N = 23) was determined by the resources available in a single-site study, rather than on the basis of formal power calculations.

RESULTS

Twenty-three patients were randomly assigned to receive either lamotrigine (N = 13) or placebo (N = 10). The mean ± SD age of the lamotrigine group was 30.2 ± 8.4 years, and that of the placebo group was 34.1 ± 6.9 years. The mean total illness duration was 6.9 ± 8.2 years in the lamotrigine group and 11.4 ± 6.3 years in the placebo group. The mean number of episodes was 3.2 (2.4 ± 1.3 in the lamotrigine group and 3.5 ± 1.4 in the placebo group). The mean duration of the current episode was 5.3 months (4.6 ± 4.9 months in the lamotrigine group and 6.6 ± 1.5 months in the placebo group). There were 5 women and 8 men in the lamotrigine group and 6 women and 4 men in the placebo group. Only 5 of the 23 subjects were employed. The sample included both patients suffering from bipolar II disorder (N = 8) and patients suffering from major depressive disorder (N = 15). Comorbid diagnoses included generalized anxiety disorder (N = 1), body dysmorphic disorder (N = 1), dependent personality disorder (N = 1), borderline personality disorder (N = 2), and antisocial personality disorder (N = 3). There were 7 premature dropouts, 3 in the placebo group and 4 in the lamotrigine group. The chi-square test and the Mann-Whitney U test showed no statistically significant difference in any of these variables between the groups.

There was no statistically significant difference between the 2 groups in baseline scores on the HAM-D, MADRS, CGI, or GAF. Although the numerical values favored the lamotrigine-treated group, at the end of the trial, the mean HAM-D scores (placebo, 14.5 ± 10.04; lamotrigine, 9.69 ± 6.58; p = .2148) were not significantly different between the groups. Similarly, there was no statistically significant difference between the 2 groups with regard to the mean MADRS score (placebo, 18.0 ± 13.9; lamotrigine, 12.38 ± 10.24; p = .4568) or the mean GAF score (placebo, 57.0 ± 16.2; lamotrigine, 71.9 ± 15.5; p = .1353) at the end of the trial, although the numerical scores again favored the lamotrigine group.

In terms of the CGI-S, there was a statistically significant difference between the groups at endpoint (placebo, 3.40 ± 1.17; lamotrigine, 2.15 ± 1.28; p = .0308), with the score for the lamotrigine group being significantly lower than that of the placebo group. The CGI-I reflected a similar pattern, with a significant advantage of lamotrigine over placebo (placebo, 2.22 ± 0.83; lamotrigine, 1.46 ± 0.66; p = .0341).

A responder analysis on the CGI-I (with response defined as a CGI-I score of 2 or less) showed a statistically significant difference between the groups, with 11 patients

(84.6%) in the lamotrigine group and 3 patients (30.0%) in the placebo group (p = .013) responding to treatment. On the CGI-S, there was again a statistically significant difference in response (with response defined as a score of 2 or less) between the groups (lamotrigine group, 5 responders [38.5%]; placebo group, 0 responders [0.0%]; p = .046). A responder analysis with response defined as a 50% reduction in symptoms on the HAM-D showed no statistically significant difference between the groups, with 10 patients (76.9%) responding in the lamotrigine group and 5 patients (50.0%) responding in the placebo group. The same nonsignificant result was also found in a responder analysis with response defined as a 50% reduction in symptoms on the MADRS (10 responders [76.9%] in the lamotrigine group and 4 responders [40.0%] in the placebo group). If remission is defined as a HAM-D score less than 7, the numerical difference between the groups did not reach significance (p = .379). Six patients (46.2%) in the lamotrigine group and 2 (20.0%) in the placebo group went into remission.

Comparison of the bipolar II disorder group and the major depressive disorder group showed no statistically significant difference between the groups. There was no overall difference between the 2 groups on any of the HAM-D, MADRS, or GAF scores. At the end of the trial, the HAM-D scores (bipolar disorder, 10.75 ± 9.94; major depressive disorder, 12.33 ± 7.8; p = .6985) were not significantly different between the groups. There was also no statistically significant difference between the 2 groups with regards to the MADRS score at the end of the trial (bipolar disorder, 15.75 ± 12.04; major depressive disorder, 14.33 ± 12.38; p = .5186) or the GAF score (bipolar disorder, 65 ± 20.7; major depressive disorder, 65.7 ± 15.8; p = .0861). In terms of the CGI-S, there was no statistically significant difference between the groups at endpoint (bipolar disorder, 2.75 ± 1.75; major depressive disorder, 2.67 ± 1.18; p = .8963). The CGI-I reflected a similar pattern (bipolar disorder, 1.88 ± 0.99; major depressive disorder, 1.71 ± 0.73; p = .7690).

A single patient in the lamotrigine group became hypomanic and was withdrawn from the trial. This patient had no previous history suggestive of a bipolar diagnosis. No patients developed treatment-emergent rashes.

DISCUSSION

In contrast to the abundance of trials that exist on the first-line management of depression, data pertaining to patients who are refractory to first-line therapy are marked by their paucity. The results of this study suggest that in patients suffering from depression that has been refractory to one or more attempts at therapy, augmentation of fluoxetine therapy with lamotrigine is associated with a superior outcome to treatment with fluoxetine alone. This study not only confirms previous trials demonstrating antidepressant efficacy of lamotrigine monotherapy,[13] but provides further randomized, placebo-controlled data suggesting that lamotrigine is a promising option as an augmentation strategy.[15]

There are a number of methodological issues pertaining to this study, the small sample size and statistical power being principal. For both the HAM-D and MADRS, the sample size did not permit the numerical advantage of the lamotrigine group over placebo to be reflected by statistical significance. While bipolar I patients were excluded from the study, patients with bipolar II patterns of illness were included. Although there were no differences between the unipolar and bipolar II groups on any outcome measures, the small sample size may have contributed to this finding. The sample was not powered to show a difference in terms of the presence of between-group personality differences. The use of the fairly restrictive DSM-IV criteria for hypomania may have missed patients with hypomania of shorter duration; this possibility is of interest, as lamotrigine appears to have a particular role in soft bipolar conditions. Data regarding the dose range of lamotrigine in depression are insufficient, although it is likely that 100 mg/day is in the range of antidepressant utility[13]; further dose-ranging data would add clarity to this issue.

In conclusion, this pilot study suggests that lamotrigine augmentation of selective serotonin reuptake inhibitor (SSRI) therapy is a tolerable and efficacious combination and is associated with superior efficacy to SSRI monotherapy in a group of patients who have failed a prior course of antidepressant therapy. Larger trials of lamotrigine augmentation are indicated.

Drug names: carbamazepine (Tegretol and others), citalopram (Celexa), fluoxetine (Prozac and others), gabapentin (Neurontin), lamotrigine (Lamictal), oxazepam (Serax and others), paroxetine (Paxil), venlafaxine (Effexor).

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