# Lamotrigine as an Augmentation Agent in Treatment-Resistant Depression

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***Background:*** The anticonvulsant lamotrigine has been reported to be efficacious and well tolerated as monotherapy in the treatment of bipolar patients as well as in treatment-refractory bipolar disorder. However, there is a paucity of research on the use of lamotrigine as an augmentation agent in treatment-refractory unipolar major depressive disorder.

***Method:*** This study was a retrospective chart review on the efficacy of lamotrigine augmentation in 37 individuals diagnosed with chronic or recurrent major depressive disorder (DSM-IV) who had failed to respond adequately to at least 2 previous trials of antidepressants. Thirty-one patients who were on lamotrigine treatment for at least 6 weeks (6 discontinued prematurely due to adverse events) took a mean dose of 112.90 mg/day for a mean of 41.80 weeks. The primary efficacy parameter for this study was the Clinical Global Impressions scale, which was retrospectively applied. In addition, these data were supplemented by an analysis of prospectively rated Global Assessment of Functioning scores.

***Results:*** On the basis of intent-to-treat analysis, response rates were as follows: 40.5% (15/37) much improved or very much improved, 21.6% (8/37) mildly improved, and 37.8% (14/37) unchanged. The percentage of patients who were rated much or very much improved and completed 6 weeks on the drug was 48.4% (15/31). No differences were found in the doses of lamotrigine given to responders and nonresponders.

***Conclusion:*** Analyses revealed that lamotrigine treatment was most effective for patients who had been depressed for shorter periods of time and had failed fewer previous trials of antidepressants. Data also suggested a trend toward increased response for patients with comorbid anxiety disorders and/or chronic pain syndromes.

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According to a recent review,[1] 34% of patients entered in double-blind placebo-controlled trials of major depression showed either partial or no response to antidepressant medications (using data from completer analyses). Such patients are more likely to have chronic courses of depressive illness with larger numbers of prior episodes and higher rates of attempted suicide.[2,3] A number of articles have been written reviewing the pharmacologic management of these patients, and a wide variety of medications have been reported to be effective either when used as alternative single agents or when combined with other medications in so-called augmentation strategies.[4,5]

Interestingly, a recent review[6] of anticonvulsants as antidepressant augmentation agents made no mention of lamotrigine. It has been hypothesized that the anticonvulsant effects of the drug are due to its blockade of voltage-dependent sodium channels in presynaptic membranes, thereby inhibiting the release of the excitatory neurotransmitter glutamate.[7,8] Case reports and open-label studies have reported on the efficacy of the drug in depressed bipolar patients,[9–11] and 1 double-blind study has compared lamotrigine and lithium in mania.[12] One large, double-blind, placebo-controlled study[13] of lamotrigine in depressed bipolar I patients reported that the drug was efficacious and well tolerated in daily dosages of 50 and 200 mg. A recently published double-blind, placebo-controlled study[14] in a sample of both unipolar and bipolar treatment-refractory patients found that lamotrigine produced a significantly higher response rate (52%) than either gabapentin (26%) or placebo (23%) based on ratings utilizing the Clinical Global Impressions scale (CGI). More recently presented data[15] from a larger number of similar patients reported by the same research group showed similar response rates. Response to lamotrigine

was associated with fewer prior medication trials and hospitalizations, a bipolar diagnosis, and male gender. We are reporting what we believe to be the first study on the use of lamotrigine as an augmentation agent in a sample of treatment-refractory patients with pure unipolar major depression. Patients with any history suggestive of bipolarity were carefully excluded.

## METHOD

We conducted a retrospective chart review of patients who were evaluated and treated by the lead author, who has had extensive experience in clinical trials and practice. Approximately 1100 patients in the author's clinical practice were reviewed for the study. Any patients who were started on lamotrigine therapy and met the study criteria (see below) were included in this report. All of the individuals included were initially evaluated utilizing a semistructured interview in which all of the major Axis I diagnostic categories were assessed. Any positive diagnoses were recorded at baseline, along with information about prior treatment. All prior psychotropic medications utilized by the patients were also recorded, including information regarding dosage and duration of treatment, as well as response.

All of the patients included in the study qualified for a diagnosis of major depressive disorder by DSM-IV criteria, and most had been severely ill for long periods with a mean duration of 8.79 years for the current episode. To be started on lamotrigine therapy, each individual must have failed at least 2 adequate trials of antidepressants (defined as a period of exposure for a minimum of 6 weeks during which the patient reached the maximum tolerated dosage). Patients with any current psychotic symptoms, hypomania or mania, or active alcohol or drug abuse were excluded. Patients were also excluded if they had started any antidepressant or psychotropic medication (other than as-needed benzodiazepine treatment for anxiety or insomnia) in the 6 weeks prior to beginning treatment with lamotrigine. Global Assessment of Functioning (GAF)[16] scores were routinely recorded at the time of each visit. CGI scale[17] responder ratings were evaluated by retrospective review of the chart based on extensive, detailed progress notes recorded by the lead author at each visit. The period of time on treatment with lamotrigine required to obtain a rating of much improved or very much improved was also determined. Patients were seen within 1 to 2 weeks after starting the drug and every 1 to 4 weeks thereafter, as judged to be clinically appropriate.

All of the patients were started on a regimen of lamotrigine 25 mg at bedtime for 2 weeks. The dosage was then increased to 50 mg for 2 weeks as tolerated. Further dosage increases were made after week 4 until the patient was either much improved or no longer able to tolerate further increases in dosage. Individuals taking concomitant valproate received half of the above dosages of lamotrigine as per the recommendations of the manufacturer (due to the potential for drug interactions). Patients were continued on treatment with primary antidepressant or concomitant augmentation medications with lamotrigine only if they had shown a partial response to those agents, which were given in the maximum dosages that could be comfortably tolerated by the patients. One patient had discontinued all antidepressant medications prior to treatment with lamotrigine. All of the individuals included in this study were moderately to severely depressed.

Patients were systematically queried about side effects at each visit. Any of those that were reported were recorded in the chart.

In order to explore potential individual predictors of response to lamotrigine, descriptive and 2-tailed correlational analyses were performed on the following variables: age, sex, age at onset of first depressive episode, duration of current episode, recurrence/chronicity, atypical symptomatology, presence of comorbid pain disorder and comorbid anxiety disorders, number of prior antidepressant trials, maintenance dose of lamotrigine, concomitant psychotherapy, and CGI response scores (0 = no change, 1 = mildly improved, 2 = much improved, 3 = very much improved). For patients taking the drug for at least 6 weeks, the efficacy of lamotrigine augmentation was assessed by comparing initial and final GAF scores using a dependent-means t test. To determine whether response was related to dosage, the mean maintenance dose for responders (i.e., CGI = much improved or better) was compared with that of nonresponders using an independent-means t test. In addition, to examine the influence of degree of treatment resistance (as measured by Thase-Rush classification criteria[18]) on response, correlational analyses were performed on Thase-Rush category, CGI score, and completion status (i.e., dropouts vs. completers).

## RESULTS

Of the 37 individuals who met all of the criteria for inclusion in the analysis, 17 (46%) were men and 20 (54%) were women. The mean ± SD age of the patients was 50.22 ± 11.24 years; range, 18–75 years). Thirty-six patients were white (97%), and 1 was African American (3%). All of the patients had current diagnoses of primary major depressive disorder by DSM-IV criteria. Secondary comorbid anxiety disorders included generalized anxiety disorder (N = 16), panic disorder (N = 5), social phobia (N = 5), posttraumatic stress disorder (N = 3), obsessive-compulsive disorder (N = 3), specific phobia (N = 2), and anxiety not otherwise specified (N = 1). No patient had any other Axis I diagnoses, except 1 patient diagnosed with dysthymia and 1 diagnosed with bereavement. Six patients had comorbid chronic pain syndromes due to various medical conditions. No patient had any psychotic symptoms at baseline.

Table 1. Staging and Response Rates Utilizing the Thase-Rush Classification System[a] for Treatment-Resistant Depression

| | Intent-to-Treat | | Completer Analysis | |
|---|---|---|---|---|
| Stage[b] | N | Response Rate (%) | N | Response Rate (%) |
| I | 0 | ... | 0 | ... |
| II | 16 | 63 | 16 | 63 |
| III | 5 | 40 | 3 | 66 |
| IV | 9 | 22 | 6 | 33 |
| V | 7 | 14 | 6 | 17 |

[a]Based on Thase and Rush.[18]
[b]Stage I: failure of one adequate trial of an antidepressant. Stage II: failure of both Stage I and one adequate trial of an alternative antidepressant from a different class. Stage III: failure of both Stage II and an adequate trial of a tricyclic antidepressant. Stage IV: failure of both Stage III and an adequate trial of a monoamine oxidase inhibitor. Stage V: failure of both Stage IV and a trial of electroconvulsive therapy.

The patients included in this report had participated in a mean of 13.27 (range, 2–29) antidepressant trials prior to the initiation of lamotrigine (this figure includes trials of antidepressants conducted by other clinicians as reported by the patient at the initial interview). Classification of these patients according to the Thase-Rush criteria[18] for treatment resistance appears in Table 1. In those patients with recurrent depression (N = 18), this classification is based on history of prior or current drug treatment for the current episode only.

During treatment with lamotrigine, patients were taking a mean of 2.78 additional medications (range, 1–5). In terms of antidepressant use, 14 patients were taking selective serotonin reuptake inhibitors, 9 were taking monoamine oxidase inhibitors (MAOIs), and 4 were taking tricyclic antidepressants. Nineteen patients were also using other second-generation antidepressants, including mirtazapine (N = 8), trazodone (N = 5), bupropion (N = 3), venlafaxine (N = 2), and nefazodone (N = 2), and 9 patients had been using psychostimulants. Antidepressant augmentation strategies had been previously attempted for all patients. Many patients were taking concomitant anxiolytic medications, including 28 patients taking benzodiazepines, 3 taking propranolol, and 2 taking buspirone. Other concomitant psychotropic medications included anticonvulsants (N = 8), antipsychotics (N = 7), zolpidem (N = 7), and lithium carbonate (N = 1). Among patients who started lamotrigine treatment, the mean duration of treatment was 35.41 weeks (range, 1–214 weeks), and those taking the drug for at least 6 weeks were treated for a mean of 41.80 weeks.

Of the 37 patients who began lamotrigine, 6 discontinued the drug prematurely (i.e., before 6 weeks) due to side effects. The most commonly reported side effects during treatment were insomnia (N = 8), somnolence (N = 6), nausea (N = 5), tremor (N = 4), memory difficulties (N = 4), headache (N = 3), irritability (N = 3), nightmares (N = 3), fatigue (N = 3), and constipation (N = 3). Other side effects included orthostasis, weight gain, anxiety, dysgraphia, speech disorder, concentration disturbances, and erectile dysfunction (N = 2 for each adverse event). No instances of skin rash were observed during lamotrigine treatment. Two patients, after several weeks of treatment with lamotrigine, developed paranoid delusions, judged to be due to extremely high levels of environmental stress and unrelated to the drug.

On the basis of an intent-to-treat analysis, which included dropouts (i.e., those individuals who did not complete 6 weeks of lamotrigine therapy), 15 patients (40.5%) were rated as much or very much improved, 8 (21.6%) as mildly improved, and 14 (37.8%) as unchanged. In completer analysis, which excluded dropouts, the response rates were 48.4% (15/31), 22.6% (7/31), and 29.0% (9/31), respectively. Among those patients taking lamotrigine for at least 6 weeks, no significant difference in the doses of lamotrigine taken by responders (mean ± SD = 113.33 ± 93.48) or nonresponders (mean ± SD = 112.50 ± 58.45) was found, $t = 0.03$, $df = 29$, $p = .98$. Responders took lamotrigine for a mean of 7.20 ± 4.14 weeks (range, 2–16 weeks) before obtaining CGI ratings of much improved. Of the individuals who were rated as much or very much improved, 86.7% (N = 13) continued to take lamotrigine, while 85.7% (N = 6) of those completers who were mildly improved continued the drug as well.

Response rates for patients in each stage of the Thase-Rush classification system[18] for treatment resistance are reported in Table 1. For the intent-to-treat sample, stage of treatment resistance and CGI score were significantly negatively correlated, $r = –0.39$, $df = 35$, $p < .05$. For the completer sample, however, this relationship was nonsignificant, $r = –0.32$, $df = 29$, $p > .05$. Completion of 6 weeks on lamotrigine treatment correlated significantly with CGI score, $r = 0.43$, $df = 35$, $p < .01$, but not with stage of treatment resistance, $r = –0.24$, $df = 35$, $p > .05$.

The mean GAF score of the 37 patients who started drug therapy was 48.26 ± 8.27 at the beginning of the study. When the scores of those individuals who prematurely discontinued drug therapy due to adverse events are excluded, the mean ± SD GAF score at the time of the last visit while taking lamotrigine (including those who discontinued due to a lack of efficacy) was 53.16 ± 10.69. Results of the efficacy analysis revealed a statistically significant improvement in GAF scores following treatment with lamotrigine ($t = 3.38$, $df = 29$, $p = .002$), with a mean GAF difference score of 5.76. CGI rating scores were significantly negatively correlated with duration of the current depressive episode ($r = –0.43$, $df = 29$, $p < .05$) and number of prior antidepressant trials ($r = –0.52$, $df = 29$, $p < .01$). Near-significant positive correlations were found for chronic pain comorbidity and anxiety disorder comorbidity ($r = 0.33$, $df = 29$, $p < .10$) for both analyses. No other factors analyzed, including age, gender, age at onset of the first depressive episode, or

concomitant psychotherapy, were significantly correlated with CGI scores.

## DISCUSSION

As stated previously, this is the first report to our knowledge regarding the efficacy of lamotrigine as an augmentation agent in a fairly large series of patients with treatment-resistant unipolar depression. Given the severity of depressive illness and the either complete or partial lack of response to any prior treatment in these patients, a response rate of 40.5% seems significant. This figure is more impressive when one includes only those patients who completed 6 weeks or more of drug therapy and therefore had an adequate trial of lamotrigine. With this adjustment, the response rate becomes 48.4%, which is only slightly lower than the response rates of 50% to 72% previously reported in studies[10–15] of lamotrigine in bipolar patients.

The results of this study are obviously tentative given the open-label, retrospective design. The limitations—as well as the clinical relevance—of research with treatment-resistant depressed patients in clinical practice settings have been eloquently addressed elsewhere.[19] However, data from both retrospective (CGI ratings) and prospective (GAF scores) measures in this study supported the hypothesized efficacy of lamotrigine. Furthermore, the patients included in this analysis also had comorbid anxiety disorders and/or chronic pain, unlike those patients included in most randomized trials in depression, but more like those seen in the "real world" of clinical practice. The information derived from studies such as this one seems likely to be of value, especially when one keeps in mind the realistic limitations of such study designs.

It also seems appropriate to note that the placebo response rate of the patients in this study was likely quite low, given the history of multiple prior treatment failures. In this regard it seems worth noting that the response rate to lamotrigine in this study (40.5%) was actually somewhat lower than that reported in the previously cited study (52%) by Frye et al.,[14] which was double-blind and placebo-controlled, though in a different patient population.

Several issues of clinical interest include the findings that the duration of the current episode, number of prior antidepressant trials, and Thase-Rush stage of treatment resistance appeared to be negatively correlated with improvement. This suggests that lamotrigine treatment was less successful in patients with very long courses of depressive illness, who had failed to respond to large numbers of antidepressant trials or were highly treatment resistant. However, it should be noted that even those severely ill patients classified as Stage IV in the Thase-Rush classification scheme showed a 33% response rate in the completer analysis. Unfortunately, only 1 of 6 patients in Stage V, the most severely ill group, was classified as a responder, even after adequate trials of lamotrigine. However, the presence of any responders at all in this group is encouraging. Our results are consistent with the notion that highly treatment-resistant individuals are generally more likely to fail to respond to any form of treatment. These findings are similar to those in the previously cited report by Obrocea et al.[15] in a group of patients on lamotrigine treatment that included patients with unipolar and bipolar diagnoses.

Depressed patients with comorbid anxiety and pain syndromes are often particularly difficult to treat and are common in clinical practice. The findings in these 2 subgroups of patients in this study are intriguing, in that the presence of either of these comorbid disorders showed a trend toward a positive response to the addition of lamotrigine. Despite statistical nonsignificance, most likely due to a small and unbalanced sample, correlations of 0.33 indicate relationships of moderate magnitude. In this study, 5 of the 6 patients with comorbid chronic pain symptoms were rated as much improved (1 was rated mildly improved). The efficacy of lamotrigine in patients with chronic pain has been previously reported,[20,21] and our results suggest that lamotrigine may be particularly beneficial in this subgroup of depressed patients.

One very positive feature of lamotrigine as an augmentation agent was its relatively good tolerability as demonstrated in this series of patients. None of the patients had a rash or more serious allergic reaction—a common concern with lamotrigine based on clinical trial data in epileptic patients. This may be due to the dosages that were utilized in the first 4 weeks of treatment, per the recommendations of the manufacturer. It is particularly interesting that 9 of the patients were on treatment with a concomitant MAOI. In only 1 patient, who had severe orthostasis when given lamotrigine with phenelzine (lamotrigine was discontinued) was there any evidence of significant drug-drug interactions.

Finally, it would seem to be appropriate to speculate briefly on the possible mechanism of action of lamotrigine in major depression. It has been reported[22,23] that major depression is associated with a reduction in the volume of multiple structures in the central nervous system. Such effects may be mediated through the toxic effects of the excitatory amino acid glutamate on neurons or glial cells in multiple structures in the brain.[24] It has been suggested that *N*-methyl-D-aspartate receptor desensitization (a subtype of glutamate receptors) may represent a final common pathway for antidepressant efficacy.[25,26] The inhibitory effects of lamotrigine on glutamate release would fit neatly with such a theory in explaining its efficacy as an antidepressant.

In summary, our findings suggest that lamotrigine is efficacious and well tolerated as an augmentation agent in the treatment of depression. Furthermore, the response rate achieved with our sample of treatment-refractory

depressed patients was similar to that previously reported in bipolar patients and is especially promising in terms of the potential effectiveness of lamotrigine for a larger treatment population. Clearly, further research on the efficacy of lamotrigine augmentation in the treatment of major depressive disorder is warranted.

*Drug names:* bupropion (Wellbutrin and others), gabapentin (Neurontin), lamotrigine (Lamictal), mirtazapine (Remeron), nefazodone (Serzone), phenelzine (Nardil), propranolol (Inderal and others), venlafaxine (Effexor), zolpidem (Ambien).



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