Brief Report

LAMOTRIGINE ADJUNCTIVE TREATMENT IN RESISTANT UNIPOLAR DEPRESSION: AN OPEN, DESCRIPTIVE STUDY

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Adjunctive treatment of lamotrigine compared to other antidepressants in the treatment of partially responsive, poorly functioning patients with unipolar depression was assessed. Fourteen consenting patients with confirmed DSM-IV-R diagnosis of unipolar depression were identified as treatment resistant. All patients failed at least two 8-week treatment trials with antidepressants. All were treated with lamotrigine as an adjunct to other antidepressants for at least 6 months. The primary effectiveness measure was the Clinical Global Impression Severity subscale (CGI-S). Other scales included the Montgomery–Åsberg Depression Scale (MADRS) and the Global Assessment of Functioning Scale (GAF). Monitoring for skin rashes, headache, dizziness, somnolence, and gastrointestinal disturbances was carried out to assess for adverse events. Baseline measures prior to adding lamotrigine were compared to those at 8 weeks and 6 months with adjunctive treatment. Twelve patients of the total (n = 14) completed the trial, and two discontinued treatment. There was significant, rapid, and robust resolution in symptoms in all effectiveness measures, including the core symptoms of depression, as shown by the changes from baseline in CGI-S, and MADRS at 8 weeks. Social and occupational functioning was significantly improved at 6 months. Eight patients returned to gainful employment or started schooling. Patients tolerated the adjunctive lamotrigine treatment well. Lamotrigine may have antidepressant properties in patients with unipolar depression and may have an earlier onset of action when given in combination with antidepressants. Depression and Anxiety 23:485–488, 2006.

INTRODUCTION

Interest in lamotrigine's possible efficacy in the treatment of mood disorders arose from epilepsy studies that described improved mood and quality of life unrelated to seizure control [Barbosa et al., 2003]. The first placebo-controlled, randomized study of lamotrigine as maintenance treatment demonstrated statistical differences in relapse rates between lamotrigine and placebo at 6 month in patients with rapid-cycling bipolar disorder [Calabrese et al., 2000].

In a pooled analysis of two large maintenance studies, lamotrigine was found to be effective against depression and mania, with more robust activity against depression than lithium in patients with bipolar disorders, and lithium was found to be more effective against mania [Bowden et al., 2003; Calabrese et al., 2003; Goodwin et al., 2004].

A small number of reports suggest some efficacy of lamotrigine in unipolar depression. For example, in a retrospective chart review ($n = 37$), Barbee and Jamhour [2002] found that 48.4% of patients with recurrent, resistant major depression were rated much

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or very much improved upon completing a 6-week lamotrigine augmentation trial. Two small, placebo-controlled trials also provide evidence for the antidepressant efficacy of lamotrigine. In the first controlled trial ($n = 23$), lamotrigine was superior to placebo in patients receiving fluoxetine for resistant depression. Patients were treated with fluoxetine, 20 mg/day, and concomitantly randomly assigned to receive either lamotrigine or placebo for 6 weeks. Both patients with major depressive disorder and bipolar II disorder were enrolled in the study. Clinical Global Impression Severity scale (CGI-S) scores improved in patients with major depressive disorder and those with bipolar II disorder in the lamotrigine-treated group [Barbosa et al., 2003]. In the second randomized, placebo-controlled study, lamotrigine was studied in patients ($n = 40$) with nonresistant unipolar depression. All patients were treated with paroxetine. However the paroxetine–lamotrigine adjunctive group demonstrated more significant improvement on core depressive symptoms as reflected by Hamilton Depression Scale (HAM-D) items for depressed mood, guilt feelings, work, and interest [Normann et al., 2002]. Also in a more recent retrospective chart review of the efficacy and tolerability of lamotrigine as an augmentation drug in treatment-resistant unipolar depression, 76% of patients ($n = 25$) were rated as improved [Rocha and Hara, 2003]. Lamotrigine was, however, evaluated for its antidepressant efficacy and safety in unipolar depression in a number of GlaxoSmithKline-sponsored, multicenter, placebo-controlled, randomized trials. Although some of these trials reported that patients on lamotrigine experienced more improvement, the differences between lamotrigine and placebo were not statistically significant on any of the efficacy measures used [DeVeaugh-Geiss et al., 2000; Laurenza et al., 1999; Londborg et al., 1999].

Tolerability and safety of lamotrigine has been established in at least eight placebo-controlled clinical trials, with an adverse-event profile generally comparable with that of placebo, when it is used as monotherapy or as an adjunctive therapy. Serious rash occurred rarely (0.1% incidence), and headaches was the commonest side effect [Goodwin et al., 2004]. Lamotrigine can be safely combined with most psychotropic drugs [Reimers et al., 2005].

METHODS

Fourteen patients, both males and females between ages 18 and 65, with DSM-IV-R diagnosis of unipolar depression were included in the study. Diagnosis was confirmed by the Mini-International Neuropsychiatric Interview [MINI; Sheehan and Lecrubier, 2001–2005].

Only patients who had failed to respond to at least two 8-week trials of antidepressant treatment, defined as failure to respond with >50% reduction in symptoms of depression, as measured by Montgomery–Åsberg Depression Rating Scale [MADRS; Montgomery and Asberg, 1979] score >30 were included. Modified criteria from Thase and Rush [1997] were used to classify treatment-resistant depression (TRD): Grade 1, absence of response to one antidepressant; Grade 2, absence of response to two or more antidepressants, one of them from a different group; Grade 3, absence of response to combination and/or augmentation strategy; Grade 4, Grade 3+ absence of response to an irreversible monoamine oxidase inhibitor; Grade 5, Grade 3+ absence of response to electroconvulsive therapy (ECT; Table 1). All patients were rated as moderately to severely ill prior to the adjunctive treatment and functioning poorly, and three patients had also failed ECT and/or transcranial magnetic stimulation trials, as well as the antidepressants trials (Table 1). Patients with psychotic disorders, alcohol or drug abuse, and eating disorders were excluded, and all patients remained compliant with the adjuctive treatment of lamotrigine for at least 6 months. Patients provided informed consent, approved by the University of Calgary Conjoint Scientific and Ethics Board.

Lamotrigine was added to existing antidepressants, and the dose was titrated, according to clinical response and tolerance, with 25- to 50-mg increments every 2 weeks, to a maximum dose of 200 mg/day. We recorded patients' demographic data and scores of effectiveness measures completed prospectively in patients' charts in follow-up visits for at least 6 months of adjuvant treatment. Efficacy measures included changes of the following scales at baseline (before adding lamotrigine), at 8 weeks, and at 6 months: the CGI-S [National Institute of Mental Health, 1970], as the primary efficacy measure, the MADRS, and the Global Assessment of Functioning Scale [GAF; Luborsky, 1962]. We paired baseline measures, prior to adding lamotrigine, with those at 8 weeks and at 6 months after adding lamotrigine, utilizing a paired *t*-test. A qualified psychiatrist carried out ratings, and no interrater reliability measures were taken.

TABLE 1. Patients' demographics

Demographic data $N = 14$	*M* (*SD*)
Age	45 (11.9)
Sex (M/F)	5/9
Illness duration (years)	11.5 (10)
Duration of current episode (months)	20 (8)
Number of failed antidepressant trials	4 (2)
Number of previous hospitalizations for depression	1 (0.9)
Average lamotrigine dosage (mg)	125 (55)
Number of relapses during the trial	0
Classification of treatment resistance[a]	**Patients**
Substitution with a different antidepressant	3
Two or more antidepressants of different class	4
Combination/augmentation (e.g. mood stabilizers or novel antipsychotics)	5
ECT and transcranial magnetic stimulation	2

[a]Modified from Thase and Rush [1997].

Monitoring for skin rashes, headache, dizziness, somnolence, and gastrointestinal (GI) disturbances was carried out to assess tolerance to adjunctive treatments [Bowden et al., 2004]. Patients were instructed to stop the drug, and to report rashes immediately should they develop. All patients in follow-up visits were asked about headache, dizziness, somnolence, and insomnia, in addition to skin rashes.

RESULTS

Table 1 displays demographic variables, details of the current illness, and data on past failed biological treatment trials. Twelve patients (85.7%) completed the 6-month trial of the adjuvant treatment. Lamotrigine dosage ranged from 50 mg/day to 200 mg/day.

At the time of adding lamotrigine, nine patients were on one antidepressant (citalopram or venlafaxine), and five patients were on two or more antidepressants. In addition to the significant improvement of the core symptoms of depressive symptomatology at 8 weeks and at 6 months, some patients had recognizable clinical improvement within the first 2 weeks (Table 2). On the primary efficacy measure at 6 months, there was at least a 1 point change, from *moderately ill* to *mildly ill* at week 8, and further improvement by 2 points, from *mildly ill* to *borderline*. At 6 months, four patients were *very much improved*, seven were *much improved*, one was *minimally improved*, and two displayed no change on the CGI Improvement (CGI-I) subscale. Two female patients discontinued lamotrigine at week 8: one due to the development of a scalp rash, which was not verified, and the other due to travel. These two patients did not report significant changes or improvements.

Table 2 summarizes the efficacy measures findings.

Occupational and Social Functioning: Eight patients returned to gainful employment and resumed regular leisure activities. For example, a 62-year-old male resumed playing hockey. A 55-year-old female who had suffered from nonremitting symptoms for 6 years, and who had failed an ECT trial and a recent trial of transcranial magnetic stimulation, reported robust mood improvement and relief of associated anxiety. A lawyer who had been nonfunctional for 4 years started part-time work.

Tolerance: Reported side effects were generally mild and transient. Two patients reported mild drowsiness, somnolence, and decrease in sexual desire; one patient reported mild transient headaches and dizziness, and another complained of dry mouth and nervousness. One patient discontinued the treatments after 8 weeks due to the development of a scalp rash, which was not verified.

TABLE 2. Changes in efficacy measures

			Paired *t*-test	
			At 8 weeks	At 6 months
	Measures	*M* (*SD*) *df*: 11	*t* (*P*≤)	(*P*≤)
CGI	* Baseline	3.8 (0.7)		
	8 weeks	2.4 (0.5)		
	6 months	1.6 (0.7)	9.5 (.001)	12.5 (.0001)
MADRS	Baseline	35 (6)		
	8 weeks	22 (7)	6.0 (.001)	14.0 (.001)
	6 months	15 (6)		
GAF	Baseline	49 (7)		
	8 weeks	59 (6)	−4.0 (.002)	−5.0 (.001)
	6 months	65 (8)		

*Baseline: prior to adding lamotrigine.

DISCUSSION

Lamotrigine may have antidepressant properties in patients with unipolar depression and may accelerate the onset of action when given in combination with atypical antidepressants. Large-scale, double-blind studies are critically needed to explore further the efficacy and tolerability of lamotrigine treatment in unipolar depression.

Clinical Implications: Clinicians will (1) consider lamotrigine as an adjunct to antidepressants in TRD; (2) initiate large-scale, controlled trials to test lamotrigine's efficacy and tolerability in unipolar depression; and (3) recognize that lamotrigine is generally a safe drug if patients are monitored carefully.

Limitations: Limitations include small sample size, open design, and heterogeneous antidepressant that patients were taking at the time lamotrigine was added.

REFERENCES

Barbee JG, Jamhour NJ. 2002. Lamotrigine as an augmentation agent in treatment-resistant depression. J Clin Psychiatry 63: 737–741.

Barbosa L, Berk M, Vorster M. 2003. 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 64:403–407.

Bowden CL, Asnis GM, Ginsberg LD, Bentley B, Leadbetter R, White R. 2004. Safety and tolerability of lamotrigine for bipolar disorder. Drug Saf 27:173–184.

Bowden CL, Calabrese JR, Sachs G, Yatham N, Akthar AS. 2003. 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 60:392–400.

Calabrese JR, Bowden CL, Sachs GS, Swann AC, McElroy SL, Kusumakar V, Ascher JA, Earl NL, Greene PL, Monaghan ET. 2000. A double-blind, placebo-controlled, prophylaxis study of lamotrigine in rapid-cycling bipolar disorder: Lamictal 614 Study Group. J Clin Psychiatry 61:841–850.

Calabrese JR, Bowden CL, Sachs G, Yatham LN, Behnke K, Mehtonen OP, Montgomery P, Ascher J, Paska W, Earl N, DeVeaugh-Geiss J. 2003. 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 64:1013–1024.

DeVeaugh-Geiss J, Ascher J, Brook S, Cedrone J, Earl N, Emsley R, Frangou S, Huffman R. 2000. Safety and tolerability of lamotrigine in controlled monotherapy trials in mood disorders. Presented at the 39th Annual ACNP Meeting, December 10–14, San Juan, Puerto Rico.

Goodwin GM, Bowden CL, Calabrese JR, Grunze H, Kasper S, White R, Greene P, Leadbetter R. 2004. A pooled analysis of two placebo-controlled 18-month trials of lamotrigine and lithium maintenance in bipolar I disorder. J Clin Psychiatry 65: 432–441.

Laurenza A, Asnis G, Beaman M. 1999. A double-blind placebo controlled study supporting the efficacy of lamotrigine in unipolar depression. Bipolar Disorder 1:39–40.

Londborg PD, Cutler NR, Cunningham LA, Haines FX, Pahl JJ, West SA. 1999. A double-blind, placebo-controlled study supporting the efficacy of lamotrigine in unipolar depression. Poster presented at the American Psychiatric Association Annual Meeting, May 15–20, Washington, DC. (SCAA2011 [613]).

Luborsky L. 1962. Clinician's judgment of mental health. Arch Gen Psychiatry 7:407–417.

Montgomery SA, Åsberg M. 1979. A new depression scale designed to be sensitive to change. Br J Psychiatry 134:382–389.

National Institute of Mental Health. 1970. CGI: Clinica Global Impression. In: Guy W, Bonato RR, editors. Manual for the ECDEU assessment battery. 2nd rev. ed. Chevy Chase, MD: Author. p 12-1–12-6.

Normann C, Hummel B, Scharer LO, Horn M, Grunze H, Walden J. 2002. Lamotrigine as adjunct to paroxetine in acute depression: A placebo-controlled, double-blind study. J Clin Psychiatry 63: 337–344.

Reimers A, Skogvoll E, Sund JK, Spigset O. 2005. Drug interactions between lamotrigine and psychoactive drugs: Evidence from a therapeutic drug monitoring service. J Clin Psychopharmacol 25: 342–348.

Rocha FL, Hara C. 2003. Lamotrigine augmentation in unipolar depression. Int Clin Psychopharmacol 18:97–99.

Sheehan DV, Janavs J, Baker R (University of South Florida, Tampa), Lecrubier Y, Hergueta T, Weiller E (INSERM, Paris, France), Proeschel T. M.I.N.I. SCREEN 5.0.0/English version/DSM-IV 1/1/05. © 2001–2005 Sheehan DV and Lecrubier Y. All rights reserved.

Thase ME, Rush AJ. 1997. When at first you don't succeed: Sequential strategies for antidepressant nonresponders. J Clin Psychiatry 58(Suppl 13):23–29.