Lamotrigine for bipolar I disorder improved depressive symptoms on some depression scales

Calabrese JR, Bowden CL, Sachs GS, et al, for the Lamictal 602 Study Group. ***A double-blind placebo-controlled study of lamotrigine monotherapy in outpatients with bipolar I depression.*** *J Clin Psychiatry 1999 Feb;**60**:79–88.*

Question
In patients with bipolar I disorder, is lamotrigine effective for treating a major depressive episode?

Design
7 week randomised, double blind, placebo controlled trial.

Setting
15 centres in the US and 6 in the UK, France, and Australia.

Patients
195 patients who were ⩾18 years of age (mean age 42 y, 61% women) with bipolar 1 disorder according to *DSM-IV* criteria and a current major depressive episode (score ⩾18 on the 17 item Hamilton Rating Scale for Depression [HAM-D]) lasting 2–52 weeks. Patients had had ⩾2 mood episodes with ⩾1 manic or mixed episode in the previous 10 years. Exclusion criteria were rapid cycling bipolar disorder; abnormal thyroid function tests; panic disorder, obsessive compulsive disorder, social phobia, or bulimia nervosa in the previous 12 months; substance abuse or dependence; pregnancy; lactation; suicidal tendency; or serious or unstable medical conditions. 69% of patients completed the study, and 98% were analysed.

Intervention
Patients were allocated to lamotrigine, 50 mg/day (n = 66) or 200 mg/day (n = 63), or placebo (n = 66) in tablets given twice daily.

Main outcome measures
Treatment response (defined as ⩾50% reduction in score on the HAM-D or Montgomery-Asberg Depression Rating Scale [MADRS] or a rating of very much improved or much improved on the Clinical Global Impressions scale for Improvement [CGI-I]).

Main results
Analysis was by intention to treat. Differences in mean HAM-D scores for lamotrigine and placebo were not statistically significant. Lamotrigine, 200 mg/day, led to more improved scores than did placebo on the MADRS (mean score difference 13.3 *v* 7.8, $p < 0.05$) and CGI-I (mean score difference 2.6 *v* 3.3, $p < 0.05$). Both lamotrigine groups had greater responder rates on the MADRS than did the placebo group ($p < 0.05$ for both comparisons) (table). Lamotrigine, 200 mg/day, led to greater responder rates on the CGI-I than did placebo ($p < 0.05$) (table).

Conclusion
In patients with bipolar I disorder and a major depressive episode, lamotrigine was effective for improving depressive symptoms on some depression scales.

*Responder rates for lamotrigine (Lam) v placebo in bipolar I disorder**

Lam dose	*Scale*	*Lam*	*Placebo*	*RBI (95% CI)*	*NNT (CI)*
50 mg/day	HAM-D	45%	37%	23% (−19 to 87)	Not significant
	MADRS	48%	29%	66% (6 to 163)	6 (3 to 43)
	CGI-I	41%	26%	55% (−5 to 159)	Not significant
200 mg/day	HAM-D	51%	37%	38% (−7 to 107)	Not significant
	MADRS	56%	29%	90% (24 to 198)	4 (3 to 11)
	CGI-I	51%	26%	94% (23 to 215)	5 (3 to 13)

*HAM-D = 17 item Hamilton Rating Scale for Depression; MADRS = Montgomery-Asberg Depression Rating Scale; CGI-I = Clinical Global Impressions scale for Improvement. Other abbreviations defined in glossary; RBI, NNT, and CI calculated from data supplied by author.

Source of funding: Glaxo Wellcome Research and Development.

For correspondence: Dr J R Calabrese, Case Western Reserve University, 11400 Euclid Avenue, Suite 200, Cleveland, Ohio 44106, USA. Fax +1 216 795 0300.

Commentary

The question posed is clinically important given the poor response of patients with bipolar depression to lithium and the switching to mood elevation or rapid cycling associated with many antidepressant medications. As the first randomised, parallel group, placebo controlled trial of lamotrigine for bipolar depression, it provides the most robust answer to date.

In this study, the clinical significance of the CGI-I score as a measure of treatment response is easier to appreciate than the MADRS and HAM-D. The CGI-I number needed to treat of 5 (95% CI 3 to 13) for lamotrigine, 200 mg/day for 7 weeks, is similar to that seen in pharmacotherapy for unipolar depressive disorders.[1,2]

Lamotrigine does not induce P450 isoenzymes, has no substantial pharmacokinetic effects on concentrations of commonly used psychotropic medications, and was well tolerated in this trial.

Several cases of delirium have been reported.[3] Rare events possibly associated with lamotrigine include Stevens-Johnson syndrome, neutropenia, thrombocytopenia, and agranulocytosis.[4]

The patient characteristics in this study help to inform the application of its results to clinical practice. At baseline, most patients had a "moderately ill" CGI-S score and all were non-suicidal outpatients. Exclusion of patients with substance abuse or dependence and other relatively common conditions will limit further the generalisation of these data to clinical practice. Ultimately, appropriate application of this trial in clinical practice may best be guided by deciding whether the clinical and physiological features of a patient with bipolar I disorder and a current major depressive episode are so unlike those in this study that the results should not apply.

Clinicians await a similarly robust trial comparing lamotrigine with a mood stabiliser or antidepressant for patients with bipolar depression. This would more closely approximate standard practice. Until then, lamotrigine's place in the treatment of these patients remains unclear.

David Haslam, MD, MSc
Dalhousie University
Halifax, Nova Scotia, Canada

1 *Evidence-Based Mental Health* 1998;**1**:49. Abstract of: Emslie GJ, Rush AJ, Weinberg WA, *et al. Arch Gen Psychiatry* 1997;**54**:1031–7.
2 *Evidence-Based Mental Health* 1998;**1**:111. Abstract of: Lima MS, Moncrieff J. (Cochrane Review, latest version 5 Jan 98). In: *Cochrane Library*. Oxford: Update Software.
3 Hennessey MJ, Wiles CM. [letter]. *Lancet* 1996; **347**:974–5.
4 Mackay FJ, Wilton LV, Pearce GL, *et al. Epilepsia* 1997;**38**:881–6.