

TREATMENT OF MOOD DISORDERS: A SURPRISING OMISSION, AND THE ROLE OF LAMOTRIGINE AS A PROTOTYPICAL BIPOLAR ANTIDEPRESSANT

To the Editor:

Anna Lembke, MD,¹ provides a very helpful overview of optimal dosing and clinical treatment strategies for the mood stabilizers lithium, divalproex/valproate, and lamotrigine. Extremely surprising, however, is the omission by the article of a “standard therapy” traditional mood stabilizer with over 25 years of clinical use, which (in contrast to lamotrigine) is Food and Drug Administration approved² for treatment of acute mood episodes (manic and mixed) and is FDA approved as monotherapy: carbamazepine XR. Carbamazepine XR also has the advantage over lithium and divalproex/valproate of being relatively weight-neutral at a time when we are eager to reduce adverse metabolic events in our patients, and it is effective in numerous patients who fail on lithium and/or divalproex.³ As with the other three agents, there are, of course, concerns about the (roughly equivalent overall) risk of serious adverse events, in this case blood dyscrasias, serious rashes, and drug interactions; however, the approach to monitoring for, and managing these risks could be developed in similar fashion to the astute discussions of the risks of the other three mood stabilizers.

With regard to lamotrigine, the article points out that it is “FDA approved for maintenance of bipolar disorder.” Dr. Lembke’s article unfortunately omits the additional limitation included in the lamotrigine product information/FDA approval: “in patients treated for acute mood episodes with standard therapy.”⁴ Traditional standard therapy consists of lithium, divalproex, or carbamazepine, all of which are effective anti-manic agents, as are adequately dosed antipsychotics. As Dr. Lembke points out, “lamotrigine is more effective in preventing relapse to depression,”¹ ie, “protecting from below”⁵ or providing a “floor” against mood cycles into depression. Lamotrigine’s efficacy in providing a “ceiling” (ie, preventing manic or mixed episodes), is less robust^{1,6} and may prove inadequate, as in the case of a depressed patient with bipolar I or II disorder, where the clinician might be tempted or feel pressure to add an antidepressant^{7,8} to the mood stabilizer.

In this case, a 22-year-old woman sought help for mood episodes at a public mental health center. The intake team psychiatrist diagnosed bipolar disorder and ordered ini-

tiation and upward titration of lamotrigine monotherapy over 4 weeks to 100 mg/day. The outpatient team psychiatrist then saw her ~7 weeks later, and added paroxetine 10 mg/day, to increase after 1 week to 20 mg/day. Nine weeks after the initial evaluation, the patient sought a second opinion with a private psychiatrist, and reported prominent insomnia (3–5 hours sleep/night), irritability, distractibility, increased libido, impulsivity, high-risk behaviors, energy fluctuations, anxiety, and depression with disinterest and anhedonia—in short, a moderate-to-severe mixed episode. The private psychiatrist continued the lamotrigine, but immediately added an antimanic agent, while simultaneously tapering and discontinuing the paroxetine.

Dr. Lembke then goes on to state that lamotrigine “is also a first-line agent in bipolar depression, although it is not FDA-approved for this use.” This description is somewhat unclear, and the clarification lies in part in the distinction between treatment of acute bipolar depression and treatment for bipolar depression over the medium-to-long term, the latter being an area in which lamotrigine provides fairly robust prophylaxis. That is, lamotrigine can provide an extremely helpful medium-to-long term maintenance “floor,” ie, prevent cycling into depression (“stabilize from below”⁵). Lamotrigine offers a very favorable alternative to adjunctive conventional “antidepressants,” which appear to be helpful as maintenance beyond 10 weeks in only ~15% to 20% of patients (without triggering *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition,⁹ hypomania, mania, or worse cycling, as shown in the Stanley Foundation Bipolar Network studies^{10,11}), and appear to be even less helpful as maintenance in the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD) studies.¹²⁻¹⁵

In contrast, the lamotrigine product information states “The effectiveness of LAMICTAL in the acute treatment of mood episodes has not been established,”⁴ in part because two of the three early clinical trials of lamotrigine in acute bipolar depression failed to separate from placebo on the primary outcome measures, perhaps due at least in part to a high rate of placebo response in at least one of the two trials (Booth DV, GlaxoSmithKline Medical Information/Medical Affairs, personal communication, Jan. 31, 2004). Calabrese and colleagues¹⁶ recently concluded that “Lamotrigine monotherapy did not demonstrate efficacy in the acute treatment of bipolar depression in four out of five placebo-controlled clinical studies.” According to the recent meta-analysis conducted by principal/senior investigators in the original trials, “The five pivotal trials in acute phase therapy” showed

“no statistically significant benefit from lamotrigine.”¹⁷ Subsequently, a meta-analysis and meta-regression of individual patient data (N=1,072) finally demonstrated superiority over placebo, but “the overall pool effect was modest,”¹⁷ ie, lamotrigine demonstrated a “consistent,” but “overall modest benefit.”¹⁷ Interestingly, subjects in the trials with high baseline depression severity (Hamilton Rating Scale for Depression [HAM-D] >24) showed superiority of lamotrigine over placebo, whereas those with less severe baseline depression (HAM-D ≤24) did not; that is, lamotrigine seemed to work better in more severely depressed patients.

One clinical limitation of lamotrigine as treatment of acute bipolar depression involves the slow titration schedule required to reduce the risk of severe cutaneous reactions. This schedule results in the patient not even receiving the likely lowest effective doses (in the range of 50–100 mg/day) until 2–4 weeks into treatment. Some of the clinical trials had more rapid forced titration schedules which would be ethically and medico-legally untenable at the current state of knowledge in the field, and thus may have shown more rapid efficacy than that reproducible in current clinical practice.

Lembke’s point that lamotrigine is “a first-line agent in the treatment of bipolar depression” is reflected in various expert consensus guidelines, including those in *Postgraduate Medicine*.¹⁸ These guidelines reported only one published clinical trial of lamotrigine, which failed to separate from placebo on the primary outcome measure but did separate on a number of other measures. They nonetheless listed lamotrigine seven times among the “preferred initial medications” for bipolar depression, as compared to only three times for the antidepressants.¹⁸ In my view, the striking and somewhat surprising popularity of lamotrigine with bipolar specialists has to do with the extremely limited treatment options for bipolar depression, ie, options that would work both short-term (up to 10 weeks) and medium-to-long term (beyond 10 weeks). The conventional or “unimodal antidepressants”¹⁰ are reported to be relatively effective in the short-term treatment of bipolar depression^{11,19} by reports of studies up to 10 weeks. Beyond 10 weeks, however, they appear to have been shown to be helpful only as adjuncts to standard mood stabilizers, and in “only 15-20% of those initially treated.”¹⁰

A subsequent study by the same (Stanley Foundation Bipolar Network) group¹¹ reports “sustained antidepressant response in the continuation phase in the absence of a threshold switch” “in only 16.2% of the original 228 acute [antidepressant] trials,” “or in only 22.3% of the patients.” This study, however, used a cutoff of 7 days

duration for “threshold switch” into hypomania instead of the *DSM-IV*’s cutoff of 4 days for hypomania. A conservative correction for this would seem to bring things back to the 15% to 20% range described in 2003 by Post and colleagues.¹⁰ Efficacy of antidepressants for bipolar depression in the STEP-BD trials has been even less,^{12,13} along with the risk of worsening manic symptoms if any are present,¹⁴ as they were in two-thirds of a sample of 1,380 STEP-BD patients.¹⁵ Therefore, if conventional “antidepressants” work long term in “only 15-20%”¹⁰ or less^{12,13} of bipolar depressed patients over the medium to long term, what are we supposed to do for the remaining 80% to 85% of bipolar depressed patients coming to our offices?

It is into this relative therapeutic vacuum that lamotrigine stepped as a prototype of a new group of antidepressants, the bipolar antidepressants, which are much more effective overall in bipolar depression than in unipolar depression. Other possible single-compound members of this group might include quetiapine, olanzapine, and lithium (with lithium mentioned six times among the “preferred initial medications” to three times for the traditional antidepressants in the above guidelines.¹⁸ The unipolar antidepressants, by contrast, have been demonstrated to be overall significantly more effective in unipolar depression than bipolar depression, especially after 10 weeks.)

Lamotrigine, a bipolar antidepressant, is one of the most helpful agents we have for bipolar disorder, with certain strengths and weaknesses. Lamotrigine would appear to be somewhat helpful in acute bipolar depression, more robust in prevention of recurrent depressive episodes, and of relatively limited benefit in prevention of manic, hypomanic, or mixed episodes.

Sincerely,

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RESPONSE

Although my article was not meant to be a comprehensive review of all mood stabilizers in the treatment of bipolar disorder, I appreciate Dr. Sparhawk's pointing out that carbamazepine is an effective and relatively safe mood stabilizer, and unlike lamotrigine, is Food and Drug Administration approved for the treatment of acute mood episodes. I also appreciate Dr. Sparhawk's comprehensive summary of the benefits and limitations of lamotrigine in treating bipolar disorder.

Sincerely,

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Disclosure: Dr. Lembke reports no affiliation with or financial interest in any organization that may pose a conflict of interest.

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