# Bipolar Disorders and the Effectiveness of Novel Anticonvulsants

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The discovery that valproic acid is helpful in the management of patients with rapid-cycling bipolar disorder led to an explosion of research culminating in the third-generation anticonvulsants. Refractory depressive phases are frequent in bipolar disorders. No studies to date have shown that gabapentin is effective in bipolar mania or hypomania. Lamotrigine may have a role in treating bipolar depressive episodes, but it is not a particularly effective antimanic agent. Topiramate has shown encouraging results in both depressed and manic bipolar patients, and it may also promote weight loss. The new anticonvulsants are promising agents for the treatment of bipolar disorders, but they are heterogeneous with regard to their efficacy, target symptoms, and adverse event profiles.

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Historically, the only drugs available for the management of bipolar disorders were the conventional antipsychotics, lithium, and carbamazepine.[1] The discovery that the anticonvulsant drug valproic acid was helpful for the management of rapid-cycling bipolar patients[2] was the start of an unprecedented explosion of research; we are currently in the new era of the third-generation anticonvulsants. The subject of this article is treatment of bipolar disorders using these new agents, including gabapentin, lamotrigine, and topiramate.

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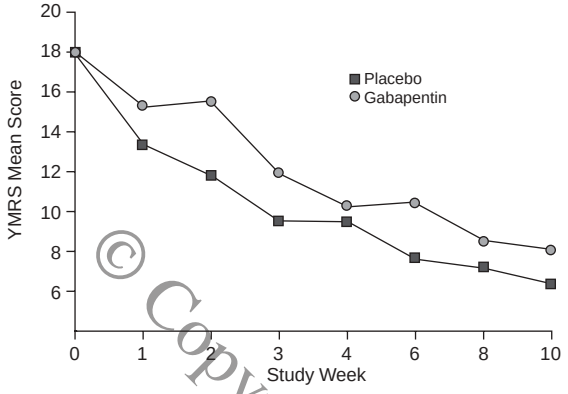
Probably the greatest unmet need in the treatment of bipolar disorders, and for patients with rapid-cycling bipolar disorder in particular, is the failure to achieve adequate control of refractory depressive phases.[5] In contrast, the management of acute mania has historically[5] tended to be more successful. In an ongoing prospective study of maintenance treatment in 215 patients with rapid-cycling bipolar disorder, both lithium and valproic acid have been found to be more effective during the hypomanic or manic phases than in the depressed phase of the illness. Among the nonresponders in this study, refractory mania or hypomania was found in only 24%, but refractory depression was seen in 76%. These results are consistent with those of Kukopulos et al.,[6] who stated 2 decades ago that the primary problem in rapid-cycling bipolar disorder was depression—depressive episodes in these patients tend to be longer, more severe, and more refractory to treatment than are typical depressive episodes.

## GABAPENTIN

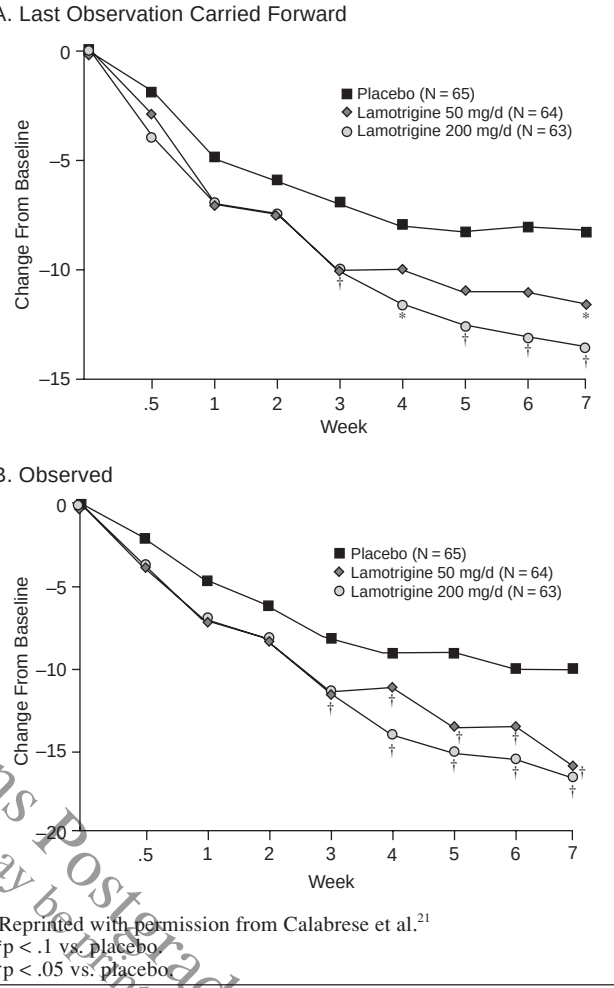
An 8-week multicenter study[7] comparing gabapentin and placebo add-on therapy in bipolar I manic or hypomanic patients yielded negative results (Figure 1). However, this study suffered from methodological limitations. For example, during the study's single-blinded lead-in phase, the doses of lithium and/or valproate could be adjusted to the clinician's satisfaction or to minimum therapeutic concentrations of 0.5 mEq/L or 50 μg/mL, respectively, and this appeared to selectively inflate placebo response. In another small, double-blind, randomized crossover trial,[8] 31 patients received gabapentin, lamotrigine, and placebo monotherapy for 6 weeks each. Of the

Figure 1. Young Mania Rating Scale (YMRS) Scores (observed cases) in Patients Taking Gabapentin or Placebo[a]




[a]Reprinted with permission from Pande et al.[7]

Figure 2. Montgomery-Asberg Depression Rating Scale Scores for Patients With Bipolar I Disorder With Depression Taking Lamotrigine or Placebo[a]




[a]Reprinted with permission from Calabrese et al.[21]
*p < .1 vs. placebo.
†p < .05 vs. placebo.

31 patients, 8 had a moderate or marked response to gabapentin, 7 to placebo, and 16 to lamotrigine, suggesting that lamotrigine—but not gabapentin—may be a useful agent for some patients with bipolar disorder.

## LAMOTRIGINE

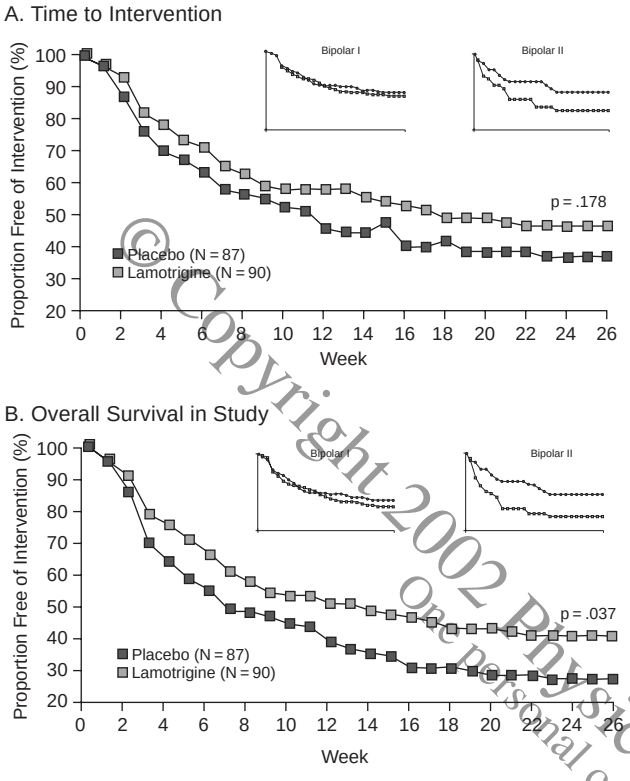
Ten published trials[9–18] have reported results of lamotrigine admistration in over 270 patients. One of the earlier studies to provide evidence of a therapeutic effect was an open trial[19] of lamotrigine as adjunctive therapy in 75 patients with refractory bipolar disorder; this agent also appeared to be effective for patients with refractory rapid-cycling bipolar disorder.[20] The first controlled trial[21] enrolled 195 patients with bipolar I disorder and depression. The intent-to-treat analysis showed that over the 7-week course of the study, both low-dose (50 mg/day) and high-dose (200 mg/day) lamotrigine improved Montgomery-Asberg Depression Rating Scale (MADRS) scores (Figure 2). In this study, patients experienced all adverse events except headache with similar frequencies in the lamotrigine and placebo groups, and the incidence of switching to mania or hypomania was also similar. Thus, lamotrigine appears to have antidepressant properties.

The efficacy of lamotrigine in mania, on the other hand, remains unclear. In 2 studies of acute or mixed mania (a monotherapy study in North America and a 21-day augmentation study in Europe), results were both negative.[22] Although lamotrigine may have a role in treating bipolar depressive episodes, it does not appear to be a particularly effective antimanic compound.

Can lamotrigine prevent depressive episodes among rapid cyclers? In a monotherapy placebo-controlled trial[23] designed to address this question, other medications were discontinued and lamotrigine was added and titrated to clinical effect. Final doses ranged from 100 to 500 mg/day. The primary outcome variable was the time to addition of treatment for emerging symptoms. Overall efficacy for this variable was not statistically different from placebo (p = .178), but overall survival in the study was significant (p = .037). Intriguingly, the curves were virtually superimposable in bipolar I patients, but in bipolar II patients, there was a trend in favor of lamotrigine for time to addition of treatment (p = .07) and a significant difference in favor of lamotrigine for survival in the study (p = .015) (Figure 3). Overall, 41% of patients receiving lamotrigine but only 26% of patients receiving placebo were stable without relapse for 6 months on monotherapy (p = .03); again, the between-group difference was largely confined to patients with bipolar II disorder (18% vs. 46%). At a minimum, this curious finding validates the typological distinction between bipolar I and II disorder; its significance beyond this remains a matter of speculation.

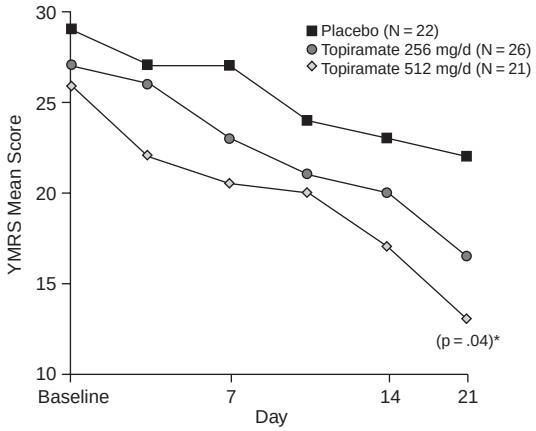
Although somewhat unclear, the therapeutic range of lamotrigine in bipolar disorder appears to be 50 to 200 mg/day. However, additional benefit is occasionally ob-

**Figure 3. Lamotrigine Versus Placebo in Rapid-Cycling Bipolar Disorder[a]**



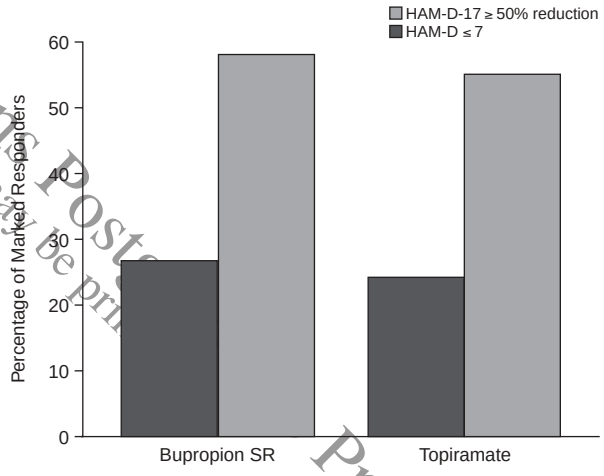

[a]Reprinted with permission from Calabrese et al.[23]

**Figure 4. Topiramate Versus Placebo in Bipolar Mania[a]**




[a]Reprinted with permission from Calabrese et al.[24] Young Mania Rating Scale (YMRS; N = 69) post hoc analysis of patients whose mania began while taking antidepressant medication.
*p value based on post hoc data review and not corrected for multiple analyses.

**Figure 5. Response Rates Following 8 Weeks of Treatment With Topiramate or Bupropion SR[a]**




[a]Reprinted with permission from McIntyre et al.[40]
Abbreviations: HAM-D = Hamilton Rating Scale for Depression, SR = sustained release. The number of patients meeting a priori response criteria was significant for both bupropion SR (59%) and topiramate groups (56%).

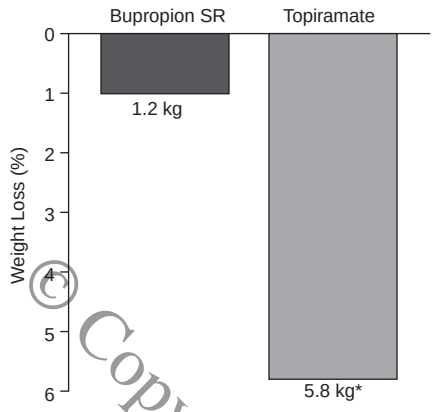
tained by increasing the dose to as high as 500 mg/day. The dose of lamotrigine should be halved if given concurrently with valproate, which inhibits the metabolism of lamotrigine; on the other hand, the dose should be doubled if given concurrently with carbamazepine, which induces the metabolism of lamotrigine.

## TOPIRAMATE

In the 4 years that the anticonvulsant topiramate has been in use for bipolar disorders, 12 trials[24–35] have reported on a total of 225 patients, obtaining an overall response rate of about 50%. Topiramate has been explored chiefly in the setting of hypomania and mania, but also in mixed states.[36–38]

In the first open-label monotherapy study of topiramate in hospitalized patients with severe bipolar mania,[24] 10 patients with severe treatment-refractory mania were administered topiramate. Of these, 5 showed moderate or marked improvement in Young Mania Rating Scale (YMRS) scores. These encouraging results led to a placebo-controlled, double-blind, phase II monotherapy maintenance trial, carried out in 20 U.S. cities.[39] In this latter study, 97 acutely ill patients with manic bipolar I disorder were assigned to receive placebo (N = 31); topiramate, 256 mg/day (N = 33); or topiramate, 512 mg/day (N = 33). An interim analysis of data for 36 patients showed significant differences in YMRS scores, but by the end of the study the differences appeared to have dissipated. However, a significant difference between Global Assessment Scale scores for high-dose topiramate and placebo was maintained (p = .019). The results may have been influenced by concurrent antidepressant therapy; 28 patients had been treated with antidepressants during the index episode. When these patients were excluded from the analysis, the YMRS scores at the end of the study remained significantly different between

Figure 6. Change in Weight After 8 Weeks of Treatment (%)[a]




[a]Repinted with permission from McIntyre et al.[40]
Abbreviation: SR = sustained release. The absolute weight loss was 1.2 kg (2.6 lb) for bupropion SR and 5.8 kg (12.8 lb) for topiramate.
*p = .019.

the high-dose group and the placebo group (Figure 4). The washout intervals allowed by the study design might, therefore, have been too brief.

Finally, a 16-week, single-blind, randomized study[40] compared topiramate (mean dose = 176 mg/day) with sustained-release bupropion (mean dose = 250 mg/day) as add-on therapy to mood stabilizer (lithium or divalproex sodium) for 36 patients with depressed bipolar I and II disorder. Both agents produced significant improvements in the 17-item Hamilton Rating Scale for Depression, MADRS, and Clinical Global Impressions-Improvement scale scores, and response rates for each of the medications were similar (Figure 5). In addition, topiramate was associated with significantly more weight loss than was bupropion (5.8 kg vs. 1.2 kg; p = .019) (Figure 6). Other studies have also hinted that topiramate, in contrast to most drugs used in the treatment of bipolar disorders, may promote weight loss.[37,38]

## SUMMARY

In summary, preliminary indications are that the new anticonvulsants are a promising group of compounds that warrant further investigation in the setting of bipolar disorders. However, this is a heterogeneous group with regard to efficacy, target symptoms, and adverse event profiles.

*Drug names:* bupropion (Wellbutrin and others), carbamazepine (Tegretol and others), divalproex sodium (Depakote), gabapentin (Neurontin), lamotrigine (Lamictal), topiramate (Topamax), valproic acid (Depakene and others).

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