

Efficacy of Newer Anticonvulsant Medications in Bipolar Spectrum Mood Disorders

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Background: More treatment options for all phases of bipolar disorder are needed. While lithium, valproate, and carbamazepine remain the standard of care for treatment of bipolar disorder, many patients do not respond adequately to these treatments. Some new antiepileptic medications such as lamotrigine, gabapentin, topiramate, oxcarbazepine, tiagabine, and zonisamide are beginning to be used to treat bipolar disorder. **Data Sources:** Evidence for effectiveness of these novel antiepileptic drugs in treating acute mania and depression as well as in preventing the recurrence of mania and depression is reviewed. A MEDLINE search (1966–2001) was performed for clinical trials that were published in English using the keywords *lamotrigine, gabapentin, topiramate, oxcarbazepine, tiagabine, and zonisamide*, plus the terms *bipolar disorder* and *mania*. Evidence for effectiveness of monotherapy is presented first when it is available. Data from augmentation treatment studies and open case series in which standard ratings of symptoms were employed are presented when these are the only available data. **Data Synthesis:** Twenty-eight reports of the efficacy of novel antiepileptic medications in bipolar disorder are reviewed. Evidence is strongest for lamotrigine monotherapy in patients with bipolar depression, in some patients with rapid-cycling bipolar disorder, and as prophylaxis. Evidence for the efficacy of topiramate in acute and refractory mania is promising but comes predominantly from open trials. Although some very small studies have found that oxcarbazepine and zonisamide may have some effectiveness for treating mania, these data are very preliminary. Results are mixed from the 2 small open trials of tiagabine. Although gabapentin is widely used in bipolar disorder, controlled data do not support the use of gabapentin as an antimanic medication or mood stabilizer. **Conclusion:** More controlled trials are needed to assess the effectiveness of novel antiepileptic medications in bipolar disorder.

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The first line of treatment for bipolar disorder remains unchanged: lithium, valproate, carbamazepine, and, if symptoms are severe, electroconvulsive therapy. Unfortunately, many patients are refractory or only partially responsive to these treatments. Newer anticonvulsants such as lamotrigine, gabapentin, topiramate, oxcarbazepine, tiagabine, and zonisamide are beginning to be used for monotherapy and treatment augmentation in bipolar disorder. In this article, I examine available evidence for effectiveness of the newer anticonvulsants in treating and preventing major mood disturbances associated with bipolar

affective disorder. Twenty-eight reports of the efficacy of novel antiepileptic medications in bipolar disorder are reviewed. A MEDLINE search (1966–2001) was performed for clinical trials that were published in English using the keywords *lamotrigine, gabapentin, topiramate, oxcarbazepine, tiagabine, and zonisamide*, plus the terms *bipolar disorder* and *mania*. Evidence for the effectiveness of monotherapy is presented when it is available. Data from augmentation treatment studies and open case series in which standard ratings of symptoms were employed and open case series of treatment augmentation in patients with treatment-refractory symptoms are presented when these are the only available data. Table 1 provides a brief outline of the quality of data supporting standard treatments and newer antiepileptic drugs, and Table 2 outlines the major efficacy studies.

LAMOTRIGINE

Preliminary evidence suggests that lamotrigine, an established antiepileptic drug that blocks voltage-sensitive sodium channels, may be effective for both the depressed and manic phases of bipolar affective disorder. Evidence is strongest for effectiveness in bipolar depression.

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Table 1. Anticonvulsants as Mood Stabilizers: Reasonable Choices

Strongest evidence for efficacy
Divalproex
Carbamazepine
At least 1 double-blind study with positive results
Lamotrigine
Positive open trials or case series
Topiramate
Oxcarbazepine
Zonisamide
Tiagabine
Double-blind trials with negative results
Gabapentin

Mania

Frye and colleagues⁴ conducted a series of 3-week, double-blind, random-assignment, crossover trials of lamotrigine, gabapentin, and placebo in 31 patients with bipolar I and bipolar II disorder and reported a 44% response rate to lamotrigine, a 20% response rate to gabapentin, and a 32% response rate to placebo. This Clinical Global Impressions scale (CGI) response rate was not significantly different between the 3 treatment groups. This trial is limited by the small number of subjects, crossover design, and low Young Mania Rating Scale (YMRS) scores at baseline.

In another small controlled trial of lamotrigine in mania,¹⁷ 30 inpatients with a DSM-IV diagnosis of bipolar I disorder, currently manic, were randomly allocated to receive either lamotrigine or lithium in a 4-week, randomized, double-blind clinical trial. Both treatments improved symptoms of mania, as assessed by the Mania Rating Scale (MRS), Brief Psychiatric Rating Scale, CGI-Severity of Illness (CGI-S) and CGI-Improvement (CGI-I) scales, and Global Assessment of Functioning. There were no significant differences between groups at any timepoint, suggesting that the dose escalation required for lamotrigine did not adversely affect its onset of action. Secondary outcome measures, including the use of rescue medication, also did not differ between the groups. In this pilot study, lamotrigine was as effective as lithium in the treatment of patients with bipolar disorder hospitalized for acute mania.¹⁷

In a 48-week open-label prospective trial conducted in 75 patients with bipolar I or bipolar II disorder,¹⁸ 31 subjects with manic, hypomanic, or mixed states taking lamotrigine as monotherapy or adjunctive therapy were evaluated. Eighty-one percent of subjects displayed marked improvement after lamotrigine was added to their treatment regimen. From baseline to endpoint, these patients exhibited a 74% decrease in MRS scores.

Bipolar Depression

A number of open trials have indicated that lamotrigine may have some activity in bipolar depression.¹⁸⁻²² Controlled trials are presented below.

In a large double-blind, placebo-controlled, multicenter trial¹ evaluating lamotrigine monotherapy in 195 outpatients

with bipolar depression, lamotrigine, 50 mg/day and 200 mg/day, and placebo were administered for 7 weeks. Lamotrigine, 200 mg/day, was superior to placebo on the 17-item Hamilton Rating Scale for Depression (HAM-D), Montgomery-Asberg Depression Rating Scale (MADRS), MRS, CGI-S, and CGI-I. Lamotrigine was superior to placebo after 3 weeks as assessed by changes in the MADRS. A response, defined as $\geq 50\%$ improvement in MADRS score, occurred in 56% and 48% of patients in the lamotrigine, 200 mg/day and 50 mg/day groups, respectively, compared with 29% for placebo. There was no evidence that lamotrigine destabilized mood or precipitated mania.

Prophylaxis

There is 1 reported double-blind, placebo-controlled trial² of lamotrigine for prophylaxis in rapid-cycling bipolar disorder. In this trial, lamotrigine was initially added to the psychotropic regimen in 324 patients with rapid-cycling bipolar disorder and titrated to clinical effect during an open-label treatment phase. Stabilized patients were tapered off treatment with other psychotropics and randomly assigned to lamotrigine or placebo monotherapy for 6 months. One hundred eighty-two patients were randomly assigned to the double-blind maintenance phase. The difference between the treatment groups in time to additional pharmacotherapy, the primary outcome measure, was not significant. Secondary efficacy measures included survival in study (time to any premature discontinuation), percentage of patients stable without relapse for 6 months, and changes in the Global Assessment Scale and CGI-S. Survival in the study was statistically different between the treatment groups ($p = .036$). Analyses also indicated a 6-week difference in median survival time favoring lamotrigine. Forty-one percent of lamotrigine patients versus 26% of placebo patients ($p = .03$) were stable without relapse for 6 months of monotherapy. A limitation to this study is that enrollment in the double-blind phase was limited to patients who initially responded to lamotrigine augmentation.

GABAPENTIN

Gabapentin is an antiepileptic drug whose mechanism of action is unknown. It does not affect γ -aminobutyric acid (GABA) receptors, but alters synthesis and release of GABA, blocks voltage-sensitive sodium channels, and alters monoamine neurotransmitter release.

Mania

Although a number of open trials have supported the efficacy of gabapentin for acute mania,²³⁻²⁷ an open trial did not find gabapentin effective for severe mania,²⁸ and 2 placebo-controlled trials^{3,4} have failed to support the effectiveness of gabapentin for acute mania.

In the first, Pande and colleagues³ reported in a 10-week, double-blind, placebo-controlled treatment augmentation

Table 2. Efficacy of Newer Anticonvulsants in Bipolar Disorder

Drug Study	Type of Study	Adjunct Therapy or Monotherapy	Findings
Lamotrigine			
Calabrese et al, 1999 ¹	Acute depression; placebo controlled; N = 195	Monotherapy	Both doses used were more effective in treating bipolar depression than was placebo
Calabrese et al, 2000 ²	Rapid cycling prophylaxis; placebo controlled; N = 182	Monotherapy	41% of lamotrigine group was stable at 6 months vs 26% of placebo group
Gabapentin			
Pande et al, 2000 ³	Acute mania, depression, or mixed; placebo controlled; N = 116	Adjunctive to lithium, valproate, or the combination	Decrease in mania greater in placebo group than gabapentin group; no difference in depression
Frye et al, 2000 ⁴	Refractory mood disorder; placebo controlled; N = 31	Monotherapy	No significant difference between gabapentin and placebo
Topiramate			
Chengappa et al, 2001 ⁵	Acute mania; placebo controlled; N = 69	Monotherapy	512 mg/d was more effective in treating mania than was placebo in post hoc analyses excluding patients with antidepressant-induced mania
Calabrese et al, 2001 ⁶	Acute mania; open label; N = 10	Monotherapy	All patients saw some improvement; 5 of 10 saw moderate-to-marked improvement
Marcotte, 1998 ⁷	Refractory rapid cycling; open label; N = 58	Adjunctive to current medication	Half of the patients experienced moderate-to-marked improvement
Chengappa et al, 1999 ⁸	Refractory bipolar I disorder or schizoaffective disorder; open label; N = 20	Adjunctive to current medication	60% of subjects were much or very much improved
Grunze et al, 2001 ⁹	Acute mania; open label, on-off-on design; N = 11	Adjunctive to current medication	Topiramate was associated with improvement; its withdrawal was associated with worsening
McElroy et al, 2000 ¹⁰	Bipolar disorder; open label; N = 56	Adjunctive to current medication	Manic symptoms decreased; status of depressed and euthymic patients did not change
McIntyre et al, 2001 ¹¹	Bipolar depression; randomized single-blind vs bupropion; N = 36	Adjunctive to current medication	The 2 groups saw comparable reduction in depression
Oxcarbazepine			
Emrich et al, 1985 ¹²	Acute mania; placebo-controlled crossover; N = 6	Monotherapy	4 of 6 patients displayed a $\geq 50\%$ decrease in Inpatient Multidimensional Psychiatric Scale score
Muller and Stoll, 1984 ¹³	Acute mania; haloperidol controlled; N = 20	Monotherapy	The 2 groups saw comparable reduction in manic symptoms
Zonisamide			
Kanba et al, 1994 ¹⁴	Acute mania; open label; N = 24	Monotherapy	80% of bipolar manic patients had at least moderate improvement in manic symptoms
Tiagabine			
Grunze et al, 1999 ¹⁵	Acute mania; open label; N = 8	Monotherapy in 2 patients, adjunctive to current medication in 6 patients	None of the patients responded; 2 had serious side effects
Schaffer and Schaffer, 1999 ¹⁶	Refractory bipolar disorder; N = 2	Adjunctive to current medication	Positive response in both patients

study that placebo augmentation was significantly more effective than gabapentin augmentation (900–3600 mg/day) of mood-stabilizer treatment in 116 patients with mania, mixed state, or hypomania. Patients with a lifetime diagnosis of bipolar I disorder who were currently suffering from symptoms of either mania, hypomania, or a mixed state with a YMRS score ≥ 12 despite ongoing therapy with lithium, valproate, or lithium and valproate in combination were eligible for inclusion. Both treatment groups had a decrease in total YMRS from baseline to endpoint, but this decrease was significantly ($p < .05$) greater in the placebo group (–9) than in the gabapentin group (–6).

No difference between treatments was found for the total score on the HAM-D. Results on the secondary efficacy measures, the CGI-S, HAM-D, Hamilton Rating Scale for Anxiety, and Internal States Scale, were not different between treatment groups. There was a question of compliance with study medication in the gabapentin group. The authors of the study concluded that the findings did not support the hypothesis that gabapentin is an effective adjunctive treatment when administered to outpatients with bipolar disorder.

In the second trial, Frye and colleagues⁴ reported a series of double-blind monotherapy trials of gabapentin

(900–4800 mg/day), lamotrigine, and placebo in 31 patients with refractory symptoms of bipolar disorder. Clinical Global Impressions-Bipolar Version (CGI-BP) response for mania was no different among the 3 trials: gabapentin, 20%; lamotrigine, 44%; and placebo, 32%; however, the very low baseline YMRS scores for subjects (4.4, 5.5, and 6.1, respectively) severely limit the ability to find a change in the subjects in this trial.

Depression

Open trials^{27,29} have indicated that gabapentin may have a role in treating bipolar depression. Anxiolytic properties of gabapentin have been reported in human and animal models.

TOPIRAMATE

Topiramate is similar in mechanism of action to other known mood stabilizers such as valproate, carbamazepine, and lamotrigine. It modulates sodium conductance, inhibits calcium channels, potentiates GABAergic activity, and decreases glutamatergic transmission through α -amino-3-hydroxy-5-methylisoxazole-4-propionic acid (AMPA) and kainate receptors. It is also a weak carbonic anhydrase inhibitor and inhibitor of protein kinases A and C.

Mania

Naturalistic studies and case series of topiramate monotherapy have indicated that topiramate may have antimanic effects as well as beneficial weight-loss properties in some patients.^{7,9,10} Grunze and colleagues⁹ reported an open on-off-on–design trial of adjunctive topiramate, 25–200 mg/day, with a 64% response rate after 10 days of open-label treatment. Response was defined as a $\geq 50\%$ reduction in YMRS score. In another open trial¹⁰ of adjunctive topiramate in 54 patients, those with manic, mixed, or rapid-cycling symptoms ($N = 30$) showed significant improvement on the YMRS and other measures.

A pilot open-label trial of topiramate monotherapy in 10 patients with acute mania was reported.⁶ The mean YMRS score decreased from 32 (range, 26–40) at baseline to 22 (range, 2–40) at the end of the study. Four subjects completed the trial. Among 10 evaluable subjects, 3 had YMRS scores that improved by 50% or more at doses of 200, 250, and 300 mg/day. Two had 25% to 49% improvement in YMRS score at doses of 200 and 550 mg/day, and 5 had scores that improved by less than 20% at doses of 100, 250, 400, 500, and 750 mg/day. The authors concluded that these preliminary findings suggest that topiramate may be effective in acute mania.

Studies of adjunctive topiramate also indicate that topiramate may have antimanic properties. In another well-designed open trial, Chengappa and colleagues⁸ reported a 60% response rate in 20 patients with mania, hypomania, mixed state, and rapid-cycling bipolar disorder and

schizoaffective disorder, bipolar type, who had failed to respond to combination treatment with mood stabilizers and/or antipsychotic agents and continued to exhibit symptoms of mania or hypomania. This was a 5-week open trial of adjunctive topiramate treatment in 18 patients with DSM-IV bipolar I disorder (mania, $N = 12$; hypomania, $N = 1$; mixed episode, $N = 5$; and rapid cycling, $N = 6$) and 2 subjects with schizoaffective disorder, bipolar type. Weekly ratings with the YMRS, HAM-D, and CGI-BP were conducted. Response was defined as a $\geq 50\%$ reduction in YMRS score and a CGI-BP rating of “very much improved.” Additionally, impulsivity and self-injurious behavior were noted to be markedly reduced in those treated with adjunctive topiramate. The response rate in patients with psychosis was 55% (6 of 11 patients). In this trial, adjunctive topiramate was started at 25 mg/day and increased by 25 to 50 mg/day every 3 to 7 days, based on tolerability, to a dose of 50 to 300 mg/day (mean = 210.5 mg/day). All other psychotropic medications were unchanged throughout the trial. Estimated time to response was 2 to 4 weeks. Six subjects had paresthesia, 3 experienced fatigue, and 2 had “word-finding” difficulties; in all cases, side effects were transient. All patients lost weight, with a mean loss of 9.4 lb (4.2 kg) in 5 weeks. The authors of both of these open studies concluded that preliminary findings suggest that topiramate may have efficacy for the manic and mixed phases of bipolar illness and called for controlled trials to confirm initial results.

In a double-blind, placebo-controlled trial,⁵ 2 doses of topiramate (256 mg/day and 512 mg/day) were compared with placebo as monotherapy in patients with acute mania. After an initial analysis of the data with the first 36 subjects enrolled, both doses of topiramate monotherapy were superior to placebo on the YMRS at the day-21 endpoint. In the full analysis of the 97 subjects who completed the trial, both doses of topiramate were significantly superior to placebo on the CGI and the HAM-D. The topiramate group was not statistically significantly superior to placebo on the YMRS at 21 days. In the full analysis of 97 subjects, the placebo response rate was very high. When a third analysis was performed that excluded 28 subjects who were taking antidepressants during the trial, topiramate, 512 mg/day, was significantly superior to placebo on the YMRS. This study, although flawed, supports the open data demonstrating that topiramate may be effective in mania.

Depression

Open trials of topiramate in depression have yielded mixed results. In the open trial¹⁰ of adjunctive topiramate in 54 patients described above, those presenting with depressive symptoms ($N = 11$) showed no improvement. However, McIntyre and colleagues¹¹ reported differing results in a more rigorously designed 8-week single-blind, randomized comparison trial of bupropion (250 mg/day)

and topiramate (176 mg/day) augmentation in 36 outpatients with bipolar I or II depression. Patients in the topiramate and bupropion groups showed comparable significant improvement from baseline on both the HAM-D and the CGI-I. The topiramate group had significantly greater weight loss, 6.2 kg (13.8 lb) versus 1.4 kg (3.1 lb) in the bupropion group.

Controlled trials are needed to clarify the role of topiramate in bipolar depression. There are several newer anticonvulsants for which only open data are available in bipolar disorder. These include oxcarbazepine, zonisamide, tiagabine, and levetiracetam.

OXCARBAZEPINE

Recently approved for use in the United States, oxcarbazepine, the 10-keto analogue of carbamazepine, has been used extensively in Europe.

Acute Mania

In a 2-week haloperidol-controlled trial¹³ of oxcarbazepine, 20 subjects with acute mania were randomly assigned to receive oxcarbazepine, 900 to 1200 mg/day (N = 10), or haloperidol 15 to 20 mg/day (N = 10). Both groups showed a 55% reduction in Bech-Rafaelson Mania Rating Scale scores. In a very small double-blind, placebo-controlled, crossover (ABA) trial of oxcarbazepine, 4 of 6 patients displayed a 50% or greater decrease in Inpatient Multidimensional Psychiatric Scale scores with oxcarbazepine treatment.¹² There are no reports of oxcarbazepine for bipolar depression or prophylaxis.

ZONISAMIDE

Zonisamide is an antiepileptic medication whose mechanisms include blockade of voltage-sensitive sodium channels, blockade of certain calcium currents, and modulation of GABA and dopaminergic neurotransmission.

Acute Mania

Kanba and colleagues¹⁴ reported an open case series in which adjunctive zonisamide (100–600 mg/day) was evaluated in 15 bipolar manic patients in a case series that included a total of 24 psychiatric patients. Thirty-three percent of bipolar manic subjects exhibited marked improvement on the CGI, and 80% exhibited at least moderate improvement. There are no reports of zonisamide in bipolar depression or prophylaxis.

TIAGABINE

Tiagabine is a selective GABA reuptake inhibitor approved for use in partial seizures. There are no controlled trials of tiagabine in bipolar disorder. There are reports of successful tiagabine augmentation in single cases of

treatment-refractory rapid cycling. Schaffer and Schaffer¹⁶ reported a series of 2 cases in which low-dose open adjunctive tiagabine treatment was effective for manic and rapid-cycling symptoms. However, in an open trial¹⁵ in 8 acutely manic patients, a 2-week trial of tiagabine monotherapy (N = 2) and adjunctive therapy (N = 6) was ineffective according to ratings with the Bech-Rafaelson Mania Rating Scale. There are no published reports of tiagabine in bipolar depression or prophylaxis.

CONCLUSION

Review of the literature indicates that lamotrigine monotherapy is a useful treatment for bipolar depression, for some patients with rapid-cycling bipolar disorder, and as prophylaxis. Although gabapentin is widely used in bipolar disorder, controlled data do not support the use of gabapentin as an antimanic medication or mood stabilizer. It is well tolerated, and controlled trials are needed to assess its role in treating anxiety or depression in bipolar patients. Preliminary open trials have indicated that topiramate may have antimanic as well as beneficial weight-loss properties in some patients. Although some very small studies have found that oxcarbazepine and zonisamide may have some effectiveness for treating mania, these data are very preliminary. Results are mixed from the 2 small open trials of tiagabine.

Drug names: bupropion (Wellbutrin and others), carbamazepine (Tegretol and others), gabapentin (Neurontin), haloperidol (Haldol and others), lamotrigine (Lamictal), levetiracetam (Keppra), oxcarbazepine (Trileptal), tiagabine (Gabitril), topiramate (Topamax), zonisamide (Zonegran).

Disclosure of off-label usage: The author of this article has determined that, to the best of her knowledge, bupropion, carbamazepine, gabapentin, haloperidol, lamotrigine, levetiracetam, oxcarbazepine, tiagabine, topiramate, and zonisamide are not approved by the U.S. Food and Drug Administration for the treatment of bipolar disorder; haloperidol is not approved for the treatment of acute mania; and lamotrigine is not approved for the treatment of depression or rapid cycling.

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