Newer Anticonvulsants in the Treatment of Bipolar Disorder

Lakshmi N. Yatham, M.D.

The anticonvulsants valproate and carbamazepine have efficacy in treating acute mania, but their efficacy in treating acute bipolar depression and preventing mood episodes remains uncertain. Despite this, and given their utility and widespread use, both are widely accepted as standard treatments for bipolar disorder. All the newer anticonvulsants that have become available during the last decade have been or are being assessed to determine their efficacy in the treatment of various phases of bipolar disorder. Among the newer anticonvulsants, some appear to have efficacy in treating core bipolar symptoms, while others have efficacy in treating psychiatric comorbidity such as substance abuse or an anxiety disorder. Lamotrigine is the most widely studied and is effective in treating and preventing bipolar depression, and it is the only anticonvulsant approved by the U.S. Food and Drug Administration as a maintenance treatment for bipolar disorder. Other newer anticonvulsants, levetiracetam, oxcarbazepine, phenytoin, and zonisamide offer promise, but further studies are required before they can be recommended for routine use to treat bipolar disorder. Gabapentin and topiramate do not appear to have efficacy in treating acute mania, but their utility in bipolar depression and prevention of mood episodes has not been studied in double-blind trials. Pregabalin has utility in treating generalized anxiety disorder, but it has not been studied in bipolar disorder. Given the success of lamotrigine in treating bipolar disorder, further double-blind controlled trials of the newer anticonvulsants in treating bipolar disorder are warranted. This article summarizes current evidence from trials of anticonvulsants in bipolar disorder and makes recommendations for their clinical use.

(J Clin Psychiatry 2004;65[suppl 10]:28–35)

John Cade first reported on the efficacy of lithium for treatment of mania in a seminal paper published in the Medical Journal of Australia in 1949.[1] Since then, several double-blind placebo-controlled trials confirmed the efficacy of lithium for the treatment of acute mania and the prevention of mood episodes in bipolar disorder.[2] Despite its discovery more than 50 years ago, lithium is still considered the gold standard for treatment of bipolar disorder. Its efficacy is impressive in double-blind trials, but naturalistic studies[3] show that only one fourth to one third of patients remain episode free over a 10-year period with lithium monotherapy. This suggests that the majority of patients with bipolar disorder may require augmentation or alternative strategies to remain symptom or episode free.

From the Division of Mood Disorders, University of British Columbia, Vancouver, British Columbia, Canada.

This article is derived from the teleconference "Managing Bipolar Depression," which was held June 18, 2003, and supported by an unrestricted educational grant from GlaxoSmithKline.

Corresponding author and reprints: Lakshmi N. Yatham, M.D., Division of Mood Disorders, University of British Columbia, 2255 Westbrook Mall, Vancouver, British Columbia, Canada V6T 2A1 (e-mail: yatham@interchange.ubc.ca).

Although carbamazepine and valproate have become standard alternatives to lithium for the treatment of bipolar disorder only in the past 2 decades, the first use of anticonvulsants for the treatment of bipolar disorder was in fact reported in 1966 in France.[4] Since then, several double-blind placebo-controlled as well as active comparator trials (see Yatham et al.[5] for review) have reported on the efficacy of carbamazepine and valproate for bipolar disorder. These studies indicate that both carbamazepine and valproate have proven efficacy for acute mania but their efficacy for acute bipolar depression and prevention of mood episodes requires further confirmation. For instance, carbamazepine was examined in 3 small placebo-controlled crossover trials (total N = 45), whereas valproate was examined in a small double-blind placebo-controlled trial (N = 21 in each group), for efficacy in treating acute bipolar depression (see Yatham et al.[6] for review). Carbamazepine studies were in general supportive of its efficacy, whereas the valproate trial showed numerical but not statistical superiority for valproate over placebo.[7] Similarly, although comparator studies suggest similar efficacy of valproate[8] or carbamazepine (see Yatham et al.[5] for review) to lithium, valproate failed to show superiority over placebo in preventing mood episodes in maintenance.[9] Despite the above limitations of confirmatory data from double-blind trials,

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valproate in North America and carbamazepine in other parts of the world have been widely used by clinicians for treating bipolar disorder.

Given the utility of carbamazepine and valproate for bipolar disorder, almost all newer anticonvulsants that have become available over the past decade have been assessed in open-label and controlled trials for their efficacy in the treatment of the various phases of bipolar disorder. These studies indicate that some anticonvulsants have efficacy in treating bipolar disorder (e.g., lamotrigine[10–15]) while others appear to have no role in treating core bipolar symptoms (e.g., tiagabine[16]). Interestingly, although some anticonvulsants do not have efficacy in treating the core bipolar symptoms of mania or depression, they seem to have efficacy in treating conditions that commonly co-occur with bipolar disorder such as anxiety (e.g., pregabalin[17]), panic disorder and social phobia (e.g., gabapentin[18,19]), and binge-eating disorder and alcohol dependence (e.g., topiramate[20,21]).

This article will review current data and make recommendations for the clinical use of anticonvulsants in bipolar disorder. Owing to the lack of controlled studies, many of the anticonvulsants discussed in this article will need further study before their routine use in bipolar disorder can be recommended.

PROVEN TREATMENT FOR BIPOLAR DISORDER: LAMOTRIGINE

Lamotrigine is the most widely investigated anticonvulsant for the treatment of bipolar disorder. Lamotrigine was examined for its efficacy in treating acute mania, acute bipolar depression, and maintenance in bipolar disorder as well as rapid cycling. On the basis of 2 positive double-blind maintenance trials,[10,11] lamotrigine was recently approved by the U.S. Food and Drug Administration (FDA) for maintenance treatment of bipolar disorder. Although the data support its use in maintenance treatment, particularly in preventing depressive episodes, data for treating patients in other phases of bipolar disorder have been mixed, inadequate, or negative.

Mania

In the only double-blind study that supports the efficacy of lamotrigine in patients with acute mania,[12] 45 patients were randomly assigned to treatment with lamotrigine, olanzapine, or lithium for 4 weeks. Reductions in scores on the Mania Rating Scale indicated that lamotrigine was as effective as olanzapine or lithium in treating acute manic symptoms. Although these results were positive, this study was not properly powered to show equivalence. Conversely, the results of 3 double-blind studies[22,23] did not support the use of lamotrigine in mania. Anand et al.[22] conducted an 8-week double-blind study in lithium-refractory manic or hypomanic patients (N = 16) to examine the efficacy of lamotrigine and found that lamotrigine was not more effective than placebo. Similarly, Bowden et al.[23] reported no significant differences between lamotrigine and placebo in acute mania in 2 double-blind trials. Of these, one study compared lamotrigine 50 mg/day (N = 84) with lithium (serum levels = 0.8 to 1.3 mEq/L) (N = 36) or placebo (N = 95) monotherapy over a 3-week period, and the other study compared add-on lamotrigine 200 mg/day (N = 74) versus add-on lithium (N = 78) or placebo (N = 77) to antipsychotics for a 6-week period. Both studies failed to show efficacy of lamotrigine in treating acute mania, but in the latter study, lithium was superior to placebo. In summary, 3 of the 4 double-blind studies of the use of lamotrigine in acute mania did not support its efficacy.

Depression

Evidence for the efficacy of lamotrigine in bipolar disorder is stronger for treating and preventing bipolar depression than mania. Calabrese et al.[13] randomly assigned 195 patients with bipolar depression to lamotrigine monotherapy (50 or 200 mg/day) or placebo in a 7-week, double-blind study. Patients taking lamotrigine at 200 mg/day experienced significantly greater improvement in depressive symptoms as measured by the Clinical Global Impressions-Improvement scale (CGI-I) and the Montgomery-Asberg Depression Rating Scale (MADRS) than patients assigned to placebo. The proportions of patients exhibiting a response on the CGI-I were 51% (N = 63) for lamotrigine at 200 mg/day, 41% (N = 66) for lamotrigine at 50 mg/day, and 26% (N = 66) for placebo. More than 50% of patients receiving the higher dose also met response criteria on the 17-item Hamilton Rating Scale for Depression (HAM-D) and MADRS, and clinical improvements were evident as early as the third week of treatment.

Similar findings were reported in a smaller randomized study[14] of lamotrigine or gabapentin monotherapy compared with placebo in refractory mood disorders. Lamotrigine demonstrated slightly greater efficacy against depression than mania. All 31 patients in this double-blind, crossover study received the 3 agents sequentially in three 6-week phases. Ratings of "much improved" or "very much improved" for depressive symptoms on the CGI modified for bipolar illness (CGI-BP) were reported by 45% (14/31) of patients in the lamotrigine period, 26% (8/31) of patients in the gabapentin period, and 19% (6/31) in the placebo period. These improvement ratings for symptoms of mania were reported by 44% (11/25) of patients in the lamotrigine period, 20% (5/25) of patients in the gabapentin period, and 32% (8/25) in the placebo period.

A third double-blind trial[23] of 10 weeks' duration compared lamotrigine with placebo in treating patients with acute bipolar I and bipolar II depression. This study failed

to find superiority of lamotrigine over placebo on the 17-item HAM-D or MADRS. The placebo response rate was almost 50% in this study, which may have accounted for negative results. Overall, these studies suggest that lamotrigine has antidepressant efficacy in bipolar depression. A further study is currently underway to confirm this.

Prophylaxis

Two recent long-term studies[10,11] using modern survival analytical methods reported on the efficacy of lamotrigine in the maintenance treatment of bipolar disorder. One study enrolled patients who were currently or recently depressed (N = 463),[10] while the other enrolled patients who were recently manic or hypomanic (N = 175).[11] In both studies, patients were randomly assigned to lamotrigine, lithium, or placebo as double-blind maintenance treatment for up to 18 months. Treatment began after their mood had been stabilized in an 8- to 16-week open-label treatment phase with lamotrigine during which other psychotropic drug regimens were discontinued. The results of both studies were strikingly similar, with both studies showing superiority of lamotrigine and lithium to placebo in time to intervention for any mood episode.

A further analysis in both studies revealed that lamotrigine prolonged time to intervention for a depressive episode but not a manic episode, while lithium prolonged time to intervention for a manic episode but not a depressive episode. Although each of these studies failed to show superiority of lamotrigine in preventing manic episodes, an analysis of the pooled data[24] found that lamotrigine was statistically superior to placebo in delaying manic episodes. These results suggest that lamotrigine is clearly effective in delaying depressive episodes in both recently depressed and recently manic patients, but its efficacy in preventing manic episodes, at best, is modest.

Rapid Cycling

In a large, placebo-controlled, prospective study,[15] 324 patients with rapid-cycling bipolar I or bipolar II disorder in manic, hypomanic, mixed, or depressed states were enrolled in a preliminary open-label phase and treated with add-on lamotrigine (100 to 300 mg/day). Concomitant medications were tapered, and 182 patients who met response criteria (130 with bipolar I and 52 with bipolar II disorder) were randomly assigned to double-blind treatment with placebo (N = 89) or lamotrigine monotherapy (N = 93) for 26 weeks. The primary efficacy measure was time to additional pharmacotherapy for emerging mood symptoms or a mood episode. About half of the lamotrigine-treated patients (N = 45) and placebo-treated patients (N = 49) required intervention. Although the time to intervention was not statistically significantly different between the lamotrigine and placebo groups, the percentage of patients who remained clinically stable for 6 months was significantly greater with lamotrigine than placebo ($p = .03$). Furthermore, analysis of survival time showed that lamotrigine conferred significant benefit over placebo, in particular for bipolar II patients but not for bipolar I patients. These results suggest that lamotrigine may offer some benefit in stabilizing mood in rapid-cycling bipolar II patients.

As already discussed, Frye et al.[14] found that lamotrigine monotherapy was more effective than gabapentin monotherapy for treating patients with depression and mania. An analysis of the effects of lamotrigine in patients with rapid-cycling bipolar disorder was also positive. Of the 31 patients in that study, (11 with bipolar I disorder, 14 with bipolar II disorder, and 6 with unipolar depression), 23 had rapid-cycling bipolar disorder. Overall ratings of "much improved" or "very much improved" on the CGI-BP were reported by 52% (16/31) of patients in the lamotrigine period, 26% (8/31) in the gabapentin period, and 23% (7/31) in the placebo period. This study further suggests that lamotrigine may be more effective than gabapentin or placebo in patients with treatment-resistant, rapid-cycling bipolar disorder.

However, a third double-blind trial[25] failed to show superiority of lamotrigine over placebo on the primary outcome measure of time to intervention for mood episode. Further analysis revealed that lamotrigine was more effective in prolonging time to intervention for a depressive episode than placebo while placebo was more effective in prolonging time to intervention for mania or hypomania. Overall, these results suggest that lamotrigine may have some efficacy in stabilizing mood in rapid-cycling bipolar II patients, but further studies are needed to confirm this.

NEWER ANTICONVULSANTS WITH MIXED, NEGATIVE, OR NO EVIDENCE IN BIPOLAR DISORDER

Three newer anticonvulsants are under consideration for possible use in bipolar disorder: gabapentin, pregabalin, and tiagabine. Of these, gabapentin and tiagabine have had mixed or negative results (Table 1), and pregabalin has not yet been studied in bipolar disorder.

Gabapentin

Although gabapentin was reported to be effective as an add-on agent in several open-label studies,[28–37] double-blind trials in various phases of bipolar disorder failed to confirm these observations. For example, Pande et al.[26] added gabapentin (N = 58) or placebo (N = 59) to lithium or valproate in treatment-refractory manic, hypomanic, and mixed episode patients. Patients in both groups showed significant reductions in Young Mania Rating Scale (YMRS) scores relative to baseline but the reductions were significantly greater in the placebo group compared with the gabapentin group, thus suggesting that gabapentin add-on does not confer any additional benefit

Table 1. Newer Anticonvulsants With Mixed, Negative, or No Evidence in Bipolar Disorder

Study	Disorder/Methodology	Therapy Condition	Findings
Gabapentin			
Pande et al, 2000[26]	Acute mania or mixed episode, placebo controlled, N = 117	Adjunctive to lithium, valproate, or the combination	Decrease in mania greater in placebo group than gabapentin group
Frye et al, 2000[14]	Refractory mood disorder, placebo controlled, N = 31	Monotherapy	No significant difference between gabapentin and placebo response rates
Tiagabine			
Grunze et al, 1999[27]	Acute mania, open label, N = 8	Monotherapy in 2 patients, adjunctive to current medication in 6 patients	None responded; 2 had serious side effects
Suppes et al, 2002[16]	Refractory bipolar disorder, open add-on treatment, N = 17	Adjunctive to current medication	3 patients improved, 10 had no change or worsened, 4 discontinued; 3 serious adverse events were reported
Pregabalin			
No published studies are available on pregabalin as a treatment for bipolar disorder[a]			

[a]A MEDLINE search using the search phrase "pregabalin and bipolar disorder" yielded no clinical trials.

over placebo in treating acute mania and hypomania. As has already been stated,[14] gabapentin monotherapy was not superior to placebo in the treatment of mania or depression in patients with treatment-refractory bipolar or unipolar mood disorders.

Gabapentin, however, has demonstrated anxiolytic properties in double-blind trials that may be useful in treating patients with panic disorder[18] and social phobia.[19] In addition, gabapentin is currently being studied for its utility in delaying drinking episodes among patients with alcohol dependence.

Pregabalin

Pregabalin is an anticonvulsant not yet approved by the FDA for use in the United States. No data are available for the use of pregabalin in bipolar disorder, but Pande et al.[17] reported positive results for the use of pregabalin in the treatment of generalized anxiety disorder. It is also being investigated for the potential treatment of central nervous system disorders, including epilepsy, neuropathic pain, and fibromyalgia,[38] as well as other anxiety disorders.

Tiagabine

Tiagabine is an anticonvulsant with selective γ-aminobutyric acid (GABA) reuptake inhibitor properties that has been studied in bipolar mania with mixed results. Low-dose, open-label adjunctive tiagabine treatment was effective for manic and rapid-cycling symptoms in 2 cases reported by Schaffer and Schaffer,[39] but Suppes et al.[16] found adjunctive tiagabine to have limited efficacy for 17 treatment-refractory patients with DSM-IV bipolar disorder. In fact, 10 patients showed no change or some worsening of symptoms. Similar negative results were reported in an earlier study[27] of 8 acutely manic inpatients with DSM-IV bipolar I disorder. Two patients received tiagabine monotherapy and 6 received tiagabine adjunctive to previously insufficient mood-stabilizing medication for 14 days. None of the patients showed improvement in manic symptoms, and 2 patients experienced pronounced adverse events (possibly associated with the rapid upward titration of the tiagabine dose in these subjects).

These results suggest that tiagabine is unlikely to have any beneficial effects in treating patients with bipolar disorder. Further, tiagabine appears to be poorly tolerated when the dose is rapidly escalated.

POSSIBLE AND EMERGING TREATMENTS FOR BIPOLAR DISORDER

Several newer anticonvulsants are being studied for their efficacy in bipolar disorder, and in particular for acute mania (Table 2). Although the sample sizes in these studies were very small, the results are promising.

Levetiracetam

Levetiracetam is an anticonvulsant drug that was recently approved by the FDA for use in epilepsy and is currently under investigation for use in bipolar disorder. Antimanic effects have been reported in one case report[40] and in one small controlled open-label trial,[41] but its use in other phases of bipolar disorder have not yet been studied. Levetiracetam is generally well tolerated, but given very limited data, further studies are needed before it can be recommended for treating bipolar disorder.

Oxcarbazepine

Oxcarbazepine is a keto-derivative of carbamazepine. During the 1980s, it was used as an alternative to carbamazepine for its mild-to-moderate mood-stabilizing effects, but it has recently been investigated on its own as a possible therapy in bipolar disorder.

Oxcarbazepine was shown to have efficacy for acute mania in 2 crossover and 3 active comparator trials (see Table 2). Emrich et al.[42] reported improvement in 6 of 7 patients with oxcarbazepine monotherapy while Hummel et al.[43] noted significant improvements in 4 of 12 acutely manic inpatients with DSM-IV bipolar I or II disorder. Oxcarbazepine was well tolerated, and patients with mild-

Table 2. Possible and Emerging Treatments for Bipolar Disorder

Study	Disorder/Methodology	Therapy Condition	Findings
Levetiracetam			
Goldberg and Burdick, 2002[40]	Acute mania, case report, N = 1	Monotherapy	Patient had improvement in both mania and depression with no side effects
Grunze et al, 2003[41]	Acute mania, open label, on-off-on design, N = 10	Adjunctive to haloperidol	At day 28, 7 patients were responders; manic symptoms worsened during "off" period and improved during both "on" periods
Oxcarbazepine			
Emrich et al, 1983[42]	Acute mania, placebo-controlled crossover, N = 7	Monotherapy	6 of 7 patients improved
Hummel et al, 2002[43]	Acute mania, open label, on-off-on design, N = 12	Monotherapy	Most improvement was seen in patients with mild-to-moderate manic symptoms
Muller and Stoll, 1984[44]	Acute mania, haloperidol-controlled, N = 20	Monotherapy	The 2 groups had comparable reduction in manic symptoms; a faster onset was noticed in the oxcarbazepine group
Emrich et al, 1985[45]	Acute mania, randomized, double-blind vs valproate, N = 12	Monotherapy	No difference in efficacy between groups
Emrich, 1990[46]	Acute mania, randomized, double-blind vs lithium, N = 52	Monotherapy	Significant reduction in mania scores over 2 weeks
Phenytoin			
Mishory et al, 2000[47]	Mania (bipolar or schizoaffective), double-blind vs placebo, N = 39	Adjunctive to haloperidol	More improvement was noted in patients receiving haloperidol and phenytoin vs haloperidol and placebo
Topiramate			
Grunze et al, 2001[48]	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
McIntyre et al, 2002[49]	Bipolar depression, randomized, single-blind vs bupropion, N = 36	Adjunctive to current medication	The 2 groups had comparable reduction in depression
Zonisamide			
Kanba et al, 1994[50]	Acute mania, open label, N = 24	Adjunctive to current medication	71% patients had at least moderate improvement in manic symptoms

to-moderate manic symptoms benefited the most from its antimanic effects. Oxcarbazepine was reported to have similar efficacy to haloperidol[44] and valproate[45] as well as lithium[46] in the treatment of mania.

Similar reports of the efficacy of oxcarbazepine add-on were reported in a 12-week, open-label study.[51] Twenty-eight patients with bipolar disorder (21 manic and 7 depressed) were included. The mean dose of oxcarbazepine was higher for patients with mania than for patients with depression (1063 mg/day vs. 959 mg/day). Fifteen (71%) of the 21 patients with mania responded within 3 weeks as did all 7 patients with depression. Most patients (24 of 28; 86%) remained euthymic to endpoint.

Chart reviews[52,53] of patients with treatment-refractory DSM-IV bipolar disorder who were given oxcarbazepine as add-on therapy and as monotherapy have supported its use in this population as well. In a review of 13 charts,[52] adjunctive oxcarbazepine was mildly effective in about half of the treatment-refractory population. The investigators concluded that response rates may be higher in a nonrefractory population and that oxcarbazepine may possess more antimanic than antidepressant properties. In a review of 42 charts[53] of outpatients with DSM-IV bipolar I and II disorder who received naturalistic treatment with oxcarbazepine, researchers again found oxcarbazepine to be effective in about half of the treatment-refractory subjects.

Phenytoin

Like levetiracetam, phenytoin is an anticonvulsant drug that has exhibited antimanic effects in case series or smaller, controlled trials. Although phenytoin was first used in the 1940s for the treatment of epilepsy, it was largely forgotten for the treatment of bipolar disorder until recently. Mishory et al.[47] enrolled 39 patients with mania (bipolar or schizoaffective) into a 5-week, double-blind study of haloperidol plus phenytoin versus haloperidol plus placebo. Of these, 30 completed 3 weeks of treatment and 25 completed 5 weeks. Results showed that phenytoin add-on was more effective than placebo add-on in treating manic symptoms.

The efficacy of phenytoin in prophylaxis of bipolar disorder was examined in a recent double-blind add-on study.[54] Bipolar patients who had at least 1 episode per year in the previous 2 years with current maintenance therapy and had been stable for about 4 months were randomly assigned to phenytoin or placebo add-on in a double-blind crossover study with each treatment phase lasting for 6 months. There were a total of 30 observation periods for 23 patients. Relapse rates were significantly greater with placebo (N = 9) compared with phenytoin (N = 3).

These pilot data suggest that phenytoin add-on may have utility in the treatment of acute mania and in mainte-

nance treatment, but further studies are clearly needed to confirm these observations.

Topiramate

Topiramate has demonstrated efficacy as an add-on agent in several open-label trials[48,55–57] for various phases of bipolar disorder. A small, double-blind, pilot trial[58] showed efficacy on post-hoc analysis in the treatment of acute mania. However, 4 placebo-controlled monotherapy trials (2 of which had lithium as the active comparator) failed to confirm the efficacy of topiramate for treatment of acute mania. As treatment for bipolar depression, topiramate showed efficacy equal to the antidepressant bupropion in a single-blind trial,[49] but this finding requires confirmation in double-blind, placebo-controlled trials.

Topiramate has not been studied in double-blind trials for efficacy in prophylaxis or rapid cycling in bipolar disorder. However, trials of topiramate for other health concerns (e.g., binge-eating disorder associated with obesity,[20,59] alcohol dependence,[21] and migraines[60]) have had positive results.

Zonisamide

Although no studies of the effects of zonisamide in bipolar depression or prophylaxis have been conducted, results of a case series[50] have shown some promise of efficacy in mania in bipolar patients. Fifteen of 21 patients with DSM-III-R bipolar and schizoaffective mania showed moderate-to-marked improvement on the CGI with adjunctive zonisamide (100–600 mg/day). These favorable results indicate a need for controlled studies of zonisamide for the treatment of mania.

SUMMARY AND RECOMMENDATIONS

The data reviewed in this article suggest that anticonvulsants do not have efficacy as a "class effect" in the treatment of bipolar disorder. In other words, only some anticonvulsants have efficacy in treating core bipolar disorder or symptoms while others do not. Gabapentin and tiagabine do not appear to have efficacy in treating acute mania while pregabalin has not been tested for its efficacy to date. Among those that have efficacy in treating bipolar disorder, the spectrum of efficacy seems to be different as well. For example, valproate and carbamazepine clearly have efficacy in treating acute mania while their efficacy in treating acute bipolar depression remains uncertain. Levetiracetam, oxcarbazepine, phenytoin, and zonisamide show promise in treating mania, but further studies are needed to confirm these observations. In contrast, lamotrigine clearly has efficacy in preventing bipolar depressive episodes and in treating acute bipolar depression, but it does not appear to have efficacy in treating acute mania.

Gabapentin has been reported to have efficacy in treating anxiety symptoms in panic disorder and social phobia, while pregabalin has been reported to have utility in treating generalized anxiety disorder. Gabapentin and topiramate have been reported to be useful in alcohol dependence while topiramate is also effective in migraines and binge eating associated with obesity.

Among the newer anticonvulsants, lamotrigine is the only one that has been approved by the FDA as maintenance therapy for bipolar disorder. Lamotrigine monotherapy can be used as a first-line treatment for acute bipolar depression and for prevention of depressive episodes. Lamotrigine add on can also be used to prevent depressive episodes in recently manic patients. Lamotrigine should not be used as monotherapy in patients with bipolar I disorder with a history of moderate-to-severe manic episodes because its utility in preventing manic episodes is not impressive. Lamotrigine monotherapy may be appropriate to stabilize mood in rapid-cycling bipolar II disorder with predominant depression. Lamotrigine dosing should begin low (25 mg/day) and be gradually titrated in 25-mg increments at 2-week intervals over the first 6 weeks to approximately 150 to 200 mg/day. Lower doses and slower titration should be used when combining lamotrigine with valproate, and higher doses should be used when combining lamotrigine with carbamazepine.

Skin rashes with lamotrigine are more common in children and females than in males and tend to appear with rapid dose titration and concomitant valproate administration.[61–64] The majority of lamotrigine-induced rashes occur within 2 to 8 weeks of therapy, although they may occur later. Most rashes are benign but in a small minority of cases, the rash may herald or progress to more serious life-threatening conditions such as Stevens-Johnson syndrome or toxic epidermal necrolysis. Although a 1 in 10 risk of any rash and 1 in 1000 risk of serious rash is sometimes quoted, these values come primarily from earlier experience with lamotrigine in the treatment of epilepsy prior to recommended decreases in starting dose by the drug manufacture. More recent epilepsy data[65] suggest that risk of serious rash with gradual initial titration may be as low as 1 in 5000, although risk may be significantly higher if risk factors discussed above are present. All patients treated with lamotrigine should receive clear instructions about rash and the need to contact their physician immediately should a rash occur. Rash should be carefully evaluated and lamotrigine should be immediately discontinued if a serious rash is suspected.

Gabapentin and tiagabine monotherapy appears to be ineffective for treating the various phases of bipolar disorder. Gabapentin may be useful and safe as an adjunctive treatment to other standard treatments in bipolar disorder and for treating comorbid social phobia, panic disorder, anxiety symptoms, or substance abuse. An appropriate starting dose of gabapentin is 200 to 300 mg b.i.d., which may be increased by 200- to 300-mg increments every 2 to 3 days as tolerated. Doses ranging from 1200 to 3000

mg/day may be needed to achieve therapeutic efficacy. Gabapentin has no known clinically significant pharmacokinetic interactions and is safe to use in combination with other agents. The most common adverse events are sedation and dizziness. Tiagabine, on the other hand, as either monotherapy or as adjunctive therapy, has shown limited efficacy and some worsening of symptoms.

Topiramate may be useful as an adjunct to other mood stabilizers (i.e., lithium, valproate, or carbamazepine) or atypical antipsychotics in the treatment of bipolar disorder, particularly in patients with a history of weight gain (if weight gain is undesirable) as well as those with comorbid alcohol abuse, migraine, or binge-eating disorder. An appropriate starting dose is 25 to 50 mg/day. Doses may then be increased by 25 to 50 mg/day every 4 to 7 days to between 100 and 400 mg/day as clinically indicated and tolerated. Adverse events include potential weight loss when used as an add-on treatment, some cognitive changes related to dose and dose escalation, renal stones, and acute angle closure glaucoma with sudden loss of bilateral vision. These effects resolve rapidly following topiramate discontinuation.

Levetiracetam, oxcarbazepine, phenytoin, and zonisamide have shown promise as possible treatments for bipolar disorder, particularly in mania, but further research and controlled studies are needed before they can be recommended as standard treatment. Of these, oxcarbazepine appears to be effective in acute mania and possibly in depression and prophylaxis. Patients with acute mania who do not respond to or do not tolerate lithium, valproate, or atypical antipsychotics may benefit from oxcarbazepine monotherapy or add-on therapy. Doses may range from 600 to 3000 mg/day in 2 divided doses. Common side effects include dizziness, sedation, blurred vision, and hyponatremia. Other anticonvulsants have shown little promise (tiagabine) or have not yet been studied (pregabalin) for efficacy in bipolar disorder.

Until such time as reliable, controlled data are available, very few anticonvulsants may be recommended for use in bipolar disorder. Given the success of lamotrigine in treating bipolar disorder, however, further double-blind, controlled trials of other newer anticonvulsants are urgently warranted.

Drug names: bupropion (Wellbutrin and others), carbamazepine (Carbatrol, Tegretol, and others), gabapentin (Neurontin and others), haloperidol (Haldol and others), lamotrigine (Lamictal), levetiracetam (Keppra), lithium (Eskalith, Lithobid, and others), olanzapine (Zyprexa), oxcarbazepine (Trileptal), phenytoin (Dilantin and others), tiagabine (Gabitril), topiramate (Topamax), zonisamide (Zonegran).

Disclosure of off-label usage: The author has determined that, to the best of his knowledge, gabapentin is not approved by the U.S. Food and Drug Administration for the treatment of anxiety disorder; lamotrigine is not approved for the treatment of acute bipolar depression; and gabapentin, levetiracetam, oxcarbazepine, phenytoin, tiagabine, topiramate, zonisamide, pregabalin, and valproate are not approved for the treatment of bipolar disorder.

REFERENCES

1. Cade JFJ. Lithium salts in the treatment of psychotic excitement. Med J Aust 1949;36:349–352
2. Goodwin FK, Jamison KR. Manic-Depressive Illness. New York, NY: Oxford University Press; 1990
3. Rybakowski JK, Cholpocka-Wozhiak M, Suwalska A. The prophylactic effect of long-term lithium administration in bipolar patients entering treatment in the 1970s and 1980s. Bipolar Disord 2001;3:63–67
4. Lambert P, Cavaz G, Borselli S, et al. Action neuropsychotrope d'un nouvel anti-epileptique: le de pamide. Ann Med Psychol 1966;1:707–710
5. Yatham LN, Kusumakar V. Anticonvulsants in treatment of bipolar disorder: a review of efficacy. In: Yatham LN, Kusumakar V, Kutcher SP, eds. Bipolar Disorder: A Clinician's Guide to Biological Treatments. New York, NY: Brunner-Routledge; 2002:201–240
6. Yatham LN, Kusumakar V, Kutcher SP. Treatment of bipolar depression. In: Yatham LN, Kusumakar V, Kutcher SP, eds. Bipolar Disorder: A Clinician's Guide to Biological Treatments. New York, NY: Brunner-Routledge; 2002:17–32
7. Sachs G, Altshuler L, Ketter T, et al. Divalproex versus placebo for the treatment of bipolar depression [poster]. Presented at the 40th annual meeting of the American College of Neuropsychopharmacology; Dec 9–13, 2001; Waikoloa, Hawaii
8. Lambert PA, Venaud G. Comparative study of valpromide versus Li in treatment of affective disorders. Nervure 1992;5:57–65
9. Bowden CL, Calabrese JR, McElroy SL, et al. A randomized, placebo-controlled 12-month trial of divalproex and lithium in treatment of outpatients with bipolar I disorder. Arch Gen Psychiatry 2000;57:481–489
10. Calabrese JR, Bowden CL, Sachs G, et al., for the 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 2003;64:1013–1024
11. Bowden CL, Calabrese JR, Sachs G, et al., for the Lamictal 606 Study Group. 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 2003;60:392–400
12. Berk M. Lamotrigine and the treatment of mania in bipolar disorder. Eur Neuropsychopharmacol 1999;9(suppl 4):S119–S123
13. 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;60: 79–88
14. Frye MA, Ketter TA, Kimbrell TA, et al. A placebo-controlled study of lamotrigine and gabapentin monotherapy in refractory mood disorders. J Clin Psychopharmacol 2000;20:607–614
15. Calabrese JR, Suppes T, Bowden CL, et al., for the Lamictal 614 Study Group. A double-blind, placebo-controlled, prophylaxis study of lamotrigine in rapid-cycling bipolar disorder. J Clin Psychiatry 2000;61:841–850
16. Suppes T, Chisholm KA, Dhavale D, et al. Tiagabine in treatment refractory bipolar disorder: a clinical case series. Bipolar Disord 2002;4: 283–289
17. Pande AC, Crockatt JG, Feltner DE, et al. Pregabalin in generalized anxiety disorder: a placebo-controlled trial. Am J Psychiatry 2003;160: 533–540
18. Pande AC, Pollack MH, Crockatt J, et al. Placebo-controlled study of gabapentin treatment of panic disorder. J Clin Psychopharmacol 2000;20:467–471
19. Pande AC, Davidson JRT, Jefferson JW, et al. Treatment of social phobia with gabapentin: a placebo-controlled study. J Clin Psychopharmacol 1999;19:341–348
20. Bray GA, Holander P, Klein S, et al. A 6-month randomized, placebo-controlled, dose-ranging trial of topiramate for weight loss in obesity. Obes Res 2003;11:722–733
21. Johnson BA, Aid-Daoud N, Bowden CL, et al. Oral topiramate for treatment of alcohol dependence: a randomised controlled trial. Lancet 2003;361:1677–1685
22. Anand A, Oren DA, Berman A, et al. Lamotrigine treatment of lithium failure in outpatient mania [abstract]. Bipolar Disord 1999;1:23
23. Bowden C, Calabrese JR, Asher J, et al. Spectrum of efficacy of lamotrigine in bipolar disorder: overview of double-blind placebo controlled studies. Presented at the 39th annual meeting of the American College of Neuropsychopharmacology; Dec 10–14, 2000; San Juan, Puerto Rico
24. Goodwin GM, Bowden CL, Calabrese JR, et al. A pooled analysis of

2 placebo-controlled 18-month trials of lamotrigine and lithium maintenance in bipolar I disorder. J Clin Psychiatry 2004;65:432–441
25. Fung J, Mok H, Yatham LN. Lamotrigine for bipolar disorder: translating research into clinical practice. Drug Profile. In press
26. Pande AC, Crockatt JG, Janney CA, et al. Gabapentin in bipolar disorder: a placebo-controlled trial of adjunctive therapy. Bipolar Disord 2000;2 (3 pt 2):249–255
27. Grunze H, Erfurth A, Marcuse A, et al. Tiagabine appears not to be efficacious in the treatment of acute mania. J Clin Psychiatry 1999;60: 759–762
28. Carta MG, Hardowy MC, Hardowy MJ, et al. The clinical use of gabapentin in bipolar spectrum disorders. J Affect Disord 2003;75:83–91
29. Wang PW, Santosa CM, Schumacher M, et al. Gabapentin augmentation therapy in bipolar depression. Bipolar Disord 2002;4:296–301
30. Ghaemi SN, Goodwin FK. Gabapentin treatment of the non-refractory bipolar spectrum: an open case series. J Affect Disord 2001;65:167–171
31. Altshuler LL, Keck PE Jr, McElroy SL, et al. Gabapentin in the acute treatment of refractory bipolar disorder. Bipolar Disord 1999;1:61–65
32. Vieta E, Martinez-Aran A, Nieto E, et al. Adjunctive gabapentin treatment of bipolar disorder. Eur Psychiatry 2000;15:433–437
33. Sokolski KN, Green C, Maris DE, et al. Gabapentin as an adjunct to standard mood stabilizers in outpatients with mixed bipolar symptomatology. Ann Clin Psychiatry 1999;11:217–222
34. Young LT, Robb JC, Hasey GM, et al. Gabapentin as an adjunctive treatment in bipolar disorder. J Affect Disord 1999;55:73–77
35. Perugi G, Toni C, Ruffolo G, et al. Clinical experience using adjunctive gabapentin in treatment-resistant bipolar mixed states. Pharmacopsychiatry 1999;32:136–141
36. Cabras PL, Hardoy MJ, Hardoy MC, et al. Clinical experience with gabapentin in patients with bipolar or schizoaffective disorder: results of an open-label study. J Clin Psychiatry 1999;60:245–248
37. McElroy SL, Soutullo CA, Keck PE Jr, et al. A pilot trial of adjunctive gabapentin in the treatment of bipolar disorder. Ann Clin Psychiatry 1997;9:99–103
38. Pregabalin (Pfizer). Curr Opin Investig Drugs 2004;5:82–89
39. Schaffer LC, Schaffer CB. Tiagabine and the treatment of refractory bipolar disorder [letter]. Am J Psychiatry 1999;156:2014–2015
40. Goldberg JF, Burdick KE. Levetiracetam for acute mania [letter]. Am J Psychiatry 2002;159:148
41. Grunze H, Langosch J, Born C, et al. Levetiracetam in the treatment of acute mania: an open add-on study with an on-off-on design. J Clin Psychiatry 2003;64:781–784
42. Emrich HM, Altmann H, Dose M, et al. Therapeutic effects of GABAergic drugs in affective disorder: a preliminary report. Pharmacol Biochem Behav 1983;19:369–372
43. Hummel B, Walden J, Stampfer R, et al. Acute antimanic efficacy and safety of oxcarbazepine in an open trial with an on-off-on design. Bipolar Disord 2002;4:412–417
44. Muller AA, Stoll KD. Carbamazepine and oxcarbazepine in the treatment of manic syndromes: studies in Germany. In: Emrich HM, Okuma T, Muller AA, eds. Anticonvulsants in Affective Disorders. Amsterdam, the Netherlands: Excerpta Medica; 1984:139–147
45. Emrich HM, Dose M, von Zerssen D. The use of sodium valproate, carbamazepine and oxcarbazepine in patients with affective disorders. J Affect Disord 1985;8:243–250
46. Emrich HM. Studies with oxcarbazepine (Trileptal) in acute mania. Int Clin Psychopharmacol 1990;5(suppl):83–88
47. Mishory A, Yaroslavsky Y, Bersudsky Y, et al. Phenytoin as an antimanic anticonvulsant: a controlled study. Am J Psychiatry 2000;157:463–465
48. Grunze HCR, Normann C, Langosch J, et al. Antimanic efficacy of topiramate in 11 patients in an open trial with an on-off-on design. J Clin Psychiatry 2001;62:464–468
49. McIntyre RS, Mancini D, McCann S, et al. Topiramate vs bupropion SR when added to mood stabilizer therapy for the depressive phase of bipolar disorder: a preliminary single-blind study. Bipolar Disord 2002;4: 207–213
50. Kanba S, Yagi G, Kamijima K, et al. The first open study of zonisamide, a novel anticonvulsant, shows efficacy in mania. Prog Neuropsychopharmacol Biol Psychiatry 1994;18:707–715
51. Munoz RA. Oxcarbazepine for the treatment of bipolar disorder. In: New Research Abstracts of the 155th Annual Meeting of the American Psychiatric Association; May 22, 2002; Philadelphia, Pa. Abstract NR479: 129–130
52. Ghaemi NS, Ko JY, Katzow JJ. Oxcarbazepine treatment of refractory bipolar disorder: a retrospective chart review. Bipolar Disord 2002;4: 70–74
53. Ghaemi SN, Berv DA, Klugman J, et al. Oxcarbazepine treatment of bipolar disorder. J Clin Psychiatry 2003;8:943–945
54. Mishory A, Winokur M, Bersudsky Y. Prophylactic effect of phenytoin in bipolar disorder: a controlled study. Bipolar Disord 2003;5:464–467
55. Marcotte D. Use of topiramate, a new anti-epileptic as a mood stabilizer. J Affect Disord 1998;50:245–251
56. Chengappa KNR, Rathore D, Levine J, et al. Topiramate as add-on treatment for patients with bipolar mania. Bipolar Disord 1999;1:42–53
57. McElroy SL, Suppes T, Keck PE Jr, et al. Open-label adjunctive topiramate in the treatment of bipolar disorders. Biol Psychiatry 2000;47:1025–1033
58. Calabrese JR. Topiramate versus placebo in mania [poster]. Presented at the 153rd Annual Meeting of the American Psychiatric Association; May 13–18, 2000; Chicago, Ill
59. McElroy SL, Arnold LM, Shapira NA, et al. Topiramate in the treatment of binge eating disorder associated with obesity: a randomized, placebo-controlled trial. Am J Psychiatry 2003;160:255–261. Correction 2003; 160:612
60. Storey JR, Calder CS, Hart DE, et al. Topiramate in migraine prevention: a double-blind, placebo-controlled study. Headache 2001;41:968–975
61. Wong IC, Mawer GE, Sander JW. Factors influencing the incidence of lamotrigine-related skin rash. Ann Pharmacother 1999;33:1037–1042
62. Anderson GD. Children versus adults: pharmacokinetic and adverse-effect differences. Epilepsia 2002;43(suppl 3):53–59
63. Guberman AH, Besag FM, Brodie MJ, et al. Lamotrigine-associated rash: risk/benefit considerations in adults and children. Epilepsia 1999;40: 985–991
64. Calabrese JR, Sullivan JR, Bowden CL, et al. Rash in multicenter trials of lamotrigine in mood disorders: clinical relevance and management. J Clin Psychiatry 2002;63:1012–1019
65. Messenheimer J, Mullens EL, Giorgi L, et al. Safety review of adult clinical trial experience with lamotrigine. Drug Saf 1998;18:281–296