Current PSYCHIATRY

# Antiepileptic drugs for

**Paul E. Keck, Jr, MD** | **Susan L. McElroy, MD**

Biological Psychiatry Program, Department of Psychiatry
University of Cincinnati College of Medicine, Cincinnati, Ohio

Carbamazepine and valproate are effective in treating various aspects of bipolar disorder. Now seven more antiepileptics present possible additional options. The following literature review can help you decide a course of therapy.

# bipolar disorder

## Are there any clear winners?

The newer antiepileptic drugs pose a sometimes bewildering range of options for bipolar disorder treatment. Which work best for acute bipolar I mania? Which are best suited for maintenance in patients with mixed episodes, or for those with a history of rapid cycling? What about prevention of depressive episodes? And how do the antiepileptics compare with lithium?

For many patients with bipolar disorder, lithium is still the drug of choice. For others, however, an increasing body of evidence supports the efficacy of some antiepileptics and atypical antipsychotics.

The mood-stabilizing properties of two antiepileptic agents, carbamazepine and valproate, were demonstrated some years ago in randomized controlled trials in patients with bipolar disorder. Since then, there has been considerable interest in the potential thymoleptic properties of the new antiepileptic drugs.[1] In recent years gabapentin, lamotrigine, topiramate, oxcarbazepine, zonisamide, tiagabine, and levetiracetam have been approved in the United States for the treatment of various types of epilepsy. These medications have diverse pharmacological properties that distinguish them from earlier agents and from one another.

Do these new agents have anything to offer patients? For the most part, the evidence is not yet in hand, but we will examine what's available, starting with the most recent trial data regarding the efficacy of valproate and carbamazepine.

### Carbamazepine for bipolar mania

Five randomized, controlled trials[2] have shown the efficacy of carbamazepine in patients with acute bipolar I mania. Carbamazepine was superior to placebo and comparable to chlorpromazine and lithium. Pooled data reveal an overall response rate (defined as the proportion of patients experiencing > 50% reduction in manic symptoms) of 50% for carbamazepine, 56% for lithium, and 61% for chlorpromazine (differences in overall response rates are not significant).

Until recently, the efficacy of carbamazepine as a maintenance therapy for bipolar disorder was controversial.[3] However, two recent large randomized, controlled maintenance studies that compared carbamazepine with lithium validated use of the agent for that purpose.[4,5]

In the first study, 144 patients received either drug and were followed for up to 2 1/2 years.[4] The study showed no significant differences between the two groups in time-to-mood episode recurrence or hospitalization. However, significantly more patients receiving carbamazepine required treatment discontinuation for side effects and additional medications for breakthrough symptoms than did the patients receiving lithium.

Patients without both comorbid disorders and mood-incongruent delusions responded better to lithium, whereas those with mixed episodes and bipolar II disorder or NOS appeared to respond better to carbamazepine.

In the second trial, 52 patients with bipolar I or II disorders received either lithium or carbamazepine for one year, crossed over to the alternate drug the second year, and received both drugs during the third year.[5] No significant differences were reported in relapse rates during the first year between lithium (31%) and carbamazepine (37%), or in the

percentage of patients who experienced a moderate or better response: 33% on lithium, 31% on carbamazepine, and 55% on the combination. On a variety of other measures, lithium was superior to carbamazepine. But patients with a history of rapid cycling responded significantly better to the combination (56%) than to lithium (28%) or carbamazepine (19%) alone.

As in the previous study, a higher proportion of patients receiving carbamazepine withdrew after experiencing side effects. Both studies found that while carbamazepine is efficacious, lithium is superior overall. But since neither study included a placebo group, carbamazepine's efficacy in maintenance treatment cannot be determined.

Carbamazepine also was evaluated in three randomized, controlled trials in patients with bipolar depression.[2] These small trials suggest that carbamazepine's antidepressant activity may be less robust than its antimanic effects. Response rates (>50% improvement in depressive symptoms) ranged from 32% to 34%, although many patients who participated had treatment-resistant bipolar depression.


Paul Keck, MD


Susan McElroy, MD

Based on the studies reviewed above, carbamazepine is considered a second-line agent for bipolar mania and maintenance treatment with very limited data regarding its antidepressant effects.[6]

## Valproate: For patients with mixed and mood episodes

The evidence seems to point to valproate as a suitable agent for patients with mixed and mood episodes.

Two earlier randomized, controlled studies[7,8] showed that the divalproex sodium formulation of valproate was superior to a placebo, leading to the indication of divalproex for treatment of acute mania in patients with bipolar disorder. Additional analyses of data from the second controlled trial[8] indicated that

## Comparing the known efficacy of antiepileptic agents in bipolar disorder

| Drug | Mania | Depression | Maintenance | Comments |
|---|---|---|---|---|
| Valproate | ◆◆◆◆ | ◆ | ◆◆◆ | New Depakote ER formulation |
| Carbamazepine | ◆◆◆ | ◆◆ | ◆◆◆ | 2 new maintenance studies v. lithium |
| Gabapentin | — | ◆ | ◆ | 2 negative placebo-controlled studies in mania |
| Lamotrigine | ✖ | ◆◆◆ | ◆◆◆ | Antidepressant activity in several controlled trials |
| Topiramate | ◆ | ◆ | ◆ | Dose-related weight loss |
| Oxcarbazepine | ◆◆ | ◆ | ◆ | Improved tolerability & pharmacokinetics |
| Zonisamide | ◆ | ND | ND | May produce weight loss in some patients |
| Tiagabine | ✖ | ND | ND | More data needed regarding tolerability and efficacy |
| Levetiracetam | ND | ND | ND | Data needed regarding efficacy and tolerability |

**Key**

- ◆◆◆◆ efficacy demonstrated in ≥ 2 placebo-controlled trials
- ◆◆◆ efficacy demonstrated in one placebo-controlled or two large, active comparator trials
- ◆◆ efficacy in two small or one large active comparator trial
- ◆ efficacy only in open trials and case series
- ✖ conflicting evidence of efficacy in available studies
- — lack of efficacy demonstrated in randomized, controlled trials
- ND no data presently available

patients with prominent depressive symptoms during mania (mixed episodes) responded better to divalproex than lithium. Further, multiple prior mood episodes were associated with poor lithium response but not with divalproex response.

Two recent randomized, controlled trials compared the antimanic efficacy and tolerability of divalproex and olanzapine.[9,10] The design of these two studies differed in two important ways: sample size and starting doses. This may explain the different results of the two trials.

In the first study, 248 patients received starting doses of either divalproex 750 mg/d with upward titration to therapeutic concentrations, or olanzapine 15 mg/d with titration if clinically indicated.[9] Olanzapine was found to be superior in the mean reduction of manic symptoms and in the proportion of patients who either responded to treatment or were in remission.

Findings suggest that divalproex helps prevent mood episodes in patients with bipolar disorder, but the data are not conclusive

In the second study, the number of patients (N=120) randomized was not sufficient to detect a statistically significant difference between treatment groups.[10] Initial dosing consisted of rapid divalproex loading (20 mg/kg/d) versus olanzapine (10 mg/d) with upward titration as clinically indicated. This trial revealed no significant differences in efficacy on any outcome measure and the mean valproic acid plasma concentration was higher than in the first trial.

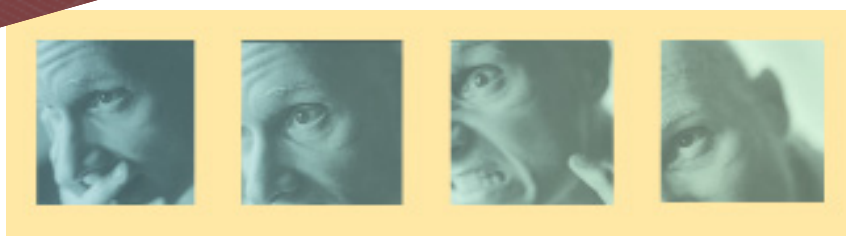
Differences in side effects between the two agents were similar in both studies. Olanzapine was associated with greater sedation, appetite stimulation, and weight gain, and divalproex with greater gastrointestinal symptoms. Taken together, these two studies indicate that olanzapine is at least as efficacious as divalproex in treating acute mania and that divalproex should be titrated to plasma concentrations well within the therapeutic range consistent with response and tolerability.

The efficacy of divalproex as a maintenance therapy for patients with bipolar disorder has been studied in four trials to date:

1. A randomized, open comparison of lithium and divalproex found generally good efficacy for both drugs across 18 months.
2. A second naturalistic, pharmacoeconomic, one-year open comparison also found both lithium and divalproex fairly equal in efficacy.
3. A large, prospective, randomized one-year maintenance trial showed little difference in relapse rates among patients receiving divalproex (24%), lithium (31%), and a placebo (38%).[11]
4. A recently completed one-year comparison of relapse rates between divalproex and olanzapine showed little difference between the two drugs.[12]

The overall results suggest that divalproex helps prevent mood episodes in patients with bipolar disorder, but the data are less substantial and conclusive than from placebo-controlled trials of lithium.

The antidepressant effects of divalproex in treating acute bipolar depression have not been studied in randomized controlled trials. Impressions from case reports and case series suggest that divalproex may exert some antidepressant activity, but that this action may be less robust than its antimanic effects.

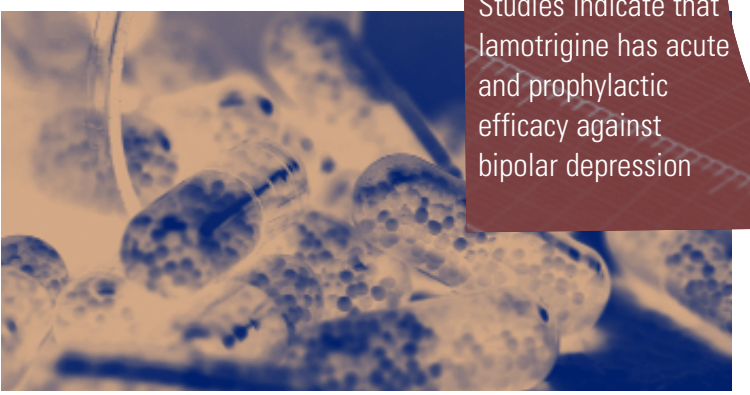


Divalproex is now available in a once-daily extended release (ER) formulation. This appears to have improved tolerability, especially regarding gastrointestinal side effects. (Clinical experience suggests that the immediate release formulation of divalproex can also be given once daily.) The ER formulation is not bioequivalent to its immediate-release counterpart; it produces plasma concentrations of approximately 80% of those achieved with immediate release. Thus, switching a patient to the ER formulation might require a dose increase.

## Lamotrigine for bipolar depression

Several recent randomized controlled trials indicate that lamotrigine has important thymoleptic properties.[14-17]

Three studies addressed the efficacy of lamotrigine in treating patients with acute bipolar mania. In two small trials, lamotrigine did not display superior efficacy over placebo in



Studies indicate that lamotrigine has acute and prophylactic efficacy against bipolar depression

reducing manic symptoms.[14] A third trial revealed differences between lithium and lamotrigine in reducing manic symptoms, but this study lacked sufficient power to detect potential differences in efficacy.

Two placebo-controlled maintenance studies of lamotrigine were recently reported.[15, 16] The first found no significant differences in relapse rates in patients with rapid cycling bipolar I and II disorders randomized to lamotrigine or placebo after initial stabilization on lamotrigine.[15] However, in a post hoc analysis among bipolar II (but not bipolar I) patients, lamotrigine was significantly more efficacious than placebo in time-to-study dropout and considerably better ($P$=0.07) in time to need for additional medication.

In the second randomized, placebo-controlled trial, patients with bipolar I disorder who had recently experienced a manic episode were treated with lamotrigine 100-200 mg/d during an open-label phase (8-16 weeks) while other psychotropic agents were tapered and discontinued.[16] Patients (N=171) who remained stable were then randomized to lamotrigine 200-400 mg/d, lithium, or placebo for up to 18 months.

The lamotrigine-treated group showed significantly lower relapse rates than placebo-treated patients in time-to-study dropout, time to intervention for a mood episode, and time to intervention for depressive relapse. Differences between the lamotrigine and placebo groups in time to intervention for manic relapse were insignificant. Lithium was superior to a placebo in time to relapse for any mood episode and time to intervention for a manic episode. Lithium also outperformed lamotrigine in that manic symptoms did not worsen as quickly from baseline to endpoint.

The results here are consistent with those of the rapid cycling study: Lamotrigine helps prevent recurrence of depressive symptoms and episodes. Evidence of prophylaxis against manic recurrences was not compelling, however.

The findings of these two maintenance trials are consistent with the results of a placebo-controlled, randomized, 6-week acute treatment trial of lamotrigine (50 mg/d and 200 mg/d) in patients with bipolar depression.[17] Seventeen lamotrigine-treated patients in both dosage groups saw more-significantly reduced depressive symptoms than did placebo-treated patients on the MADRS (but not the HAMD) total score and on the CGI. The 200 mg/d group tended to have greater improvement than the 50 mg/d group. There was little difference among the three treatment groups in the incidence of switching into hypomania or mania.

These studies indicate that lamotrigine has acute and prophylactic efficacy against bipolar depression. In contrast, evidence of the agent's acute or prophylactic efficacy in mania is lacking.

## Other new antiepileptics: More testing needed

Use of the six other newer antiepileptics in patients with bipolar disorder is still being explored. (See "Comparing the known efficacy of antiepileptic agents in bipolar disorder," page 20.) Let's look at what we know about these agents to this point.

**Gabapentin** A number of case reports and case series published in recent years suggest that gabapentin may have mood-stabilizing properties. In two randomized, controlled trials, however, gabapentin did not display significantly greater efficacy than a placebo in treating acute mania.[13, 14] Gabapentin has not been studied in controlled trials as a maintenance treatment or for bipolar depression.

In contrast to these negative studies, gabapentin was superior to placebo in studies of patients with panic disorder, social anxiety disorder, and neuropathic pain. Overall, these studies suggest that gabapentin is not a bona fide mood stabilizer for most patients.

**Topiramate** More than 10 case reports and case series suggest that topiramate may have mood-stabilizing properties. A number of open trials also have found significant dose-related weight loss in patients with weight gain associated with other psychotropic agents.[18] These observations have sparked interest in topiramate's potential role as an obesity treatment.

Only one randomized, controlled trial of topiramate for bipolar disorder has appeared to date.[19] An interim analysis of

## CHARACTERISTICS OF THE NEWER ANTIEPILEPTICS

**Lamotrigine** is a novel drug that blocks voltage-sensitive sodium channels, thereby indirectly inhibiting the release of excitatory neurotransmitters, particularly glutamate and aspartate.

**Gabapentin** was developed to mimic the synaptic effects of gamma-aminobutyric acid (GABA); it does not appear to appreciably interact with GABA receptors, however, and its mechanism of action in epilepsy remains unknown. It has several attractive pharmacokinetic properties, including lack of protein binding, renal clearance rather than hepatic metabolism, and few known drug-drug interactions.

**Topiramate** is a sulfamate-substituted monosaccharide with a number of possible mechanisms of action, including blockade of voltage-gated sodium channels, antagonism of the kainate/AMPA glutamate receptor subtype, enhancement of GABA activity at the $GABA_A$ receptor via interaction with a nonbenzodiazepine receptor site, and carbonic anhydrase inhibition.

**Oxcarbazepine** is the 10-keto analogue of carbamazepine, a chemical difference that translates into a number of safety advantages over carbamazepine. Oxcarbazepine is converted to an active 10-hydroxy metabolite rather than to the 10,11-epoxide metabolite of carbamazepine. The 10,11-epoxide metabolite of carbamazepine is associated with neurological side effects. Oxcarbazepine is a weak inducer of the CYP450 system, appears to have fewer drug-drug interactions, and offers better overall tolerability.

**Zonisamide**, a sulfonamide derivative, blocks voltage-sensitive sodium channels and T-type calcium currents, modulates GABAergic and dopaminergic neurotransmission, and is a free-radical scavenger.

**Tiagabine** is a selective GABA reuptake inhibitor.

**Levetiracetam** is the S-enantiomer of the ethyl analogue of the nootropic agent piracetam. Its mechanism of action in treating epilepsy is unknown. It does not appear to interact significantly with voltage-sensitive sodium channels or T-type calcium channels, nor does it significantly alter levels of GABA, glutamate, or glutamine in the central nervous system.

a placebo-controlled, randomized trial of two doses of topiramate (approximately 250 mg/d and 500 mg/d) in 97 hospitalized patients with acute bipolar I mania revealed strong trends toward reduced manic symptoms for both topiramate groups over placebo. These differences were not significant by the time the study was concluded, however.

When patients with mania associated with recent antidepressant use were excluded from post hoc analysis, topiramate's superiority over placebo was re-established. These tantalizing results require further study. Similarly, studies of topiramate's potential efficacy in acute bipolar depression and as a maintenance treatment are needed.

**Oxcarbazepine** Oxcarbazepine is a relative newcomer to the United States, but has been available abroad for some time.

While numerous studies have tested carbamazepine in treating various aspects of bipolar disorder, few controlled trials have tested oxcarbazepine for this use.[20]

Oxcarbazepine as a treatment for acute bipolar mania was comparable to haloperidol in two small randomized, controlled trials and to lithium in one small trial. None of these studies had adequate power to detect potential differences in efficacy. Similarly, two very small maintenance studies (total N=25) found no differences in efficacy between oxcarbazepine and lithium.[20]

Additionally, to our knowledge oxcarbazepine has not been formally tested as a treatment for acute bipolar depression. So while oxcarbazepine is an attractive alternative to carbamazepine for pharmacokinetic and pharmacodynamic reasons, data supporting oxcarbazepine's efficacy in bipolar disorder are far less substantial.

**Zonisamide** The only report of zonisamide as a bipolar disorder treatment so far is a case series of 15 patients who received the drug adjunctively for manic symptoms. Of these patients, 80% showed at least moderate improvement and 33% were rated as markedly improved. These preliminary observations require further study. Like topiramate, zonisamide may also be associated with weight loss in some patients.

**Tiagabine** A few case reports and case series describe tiagabine's effects in patients with bipolar disorder. Conflicting results have been reported to date and some reports of poor tolerability have emerged. Fundamental safety and efficacy data for this agent in bipolar disorder are needed.

**Levetiracetam** Studies of levetiracetam for treatment of

bipolar disorder are just under way. The Stanley Foundation Bipolar Treatment Network, a program of the National Alliance for the Mentally Ill Research Institute, is investigating its potential thymoleptic properties.

## Related resources

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### DRUG BRAND NAMES

Carbamazepine • Tegretol, Epitol, Atretol
Gabapentin • Neurontin
Lamotrigine • Lamictal
Levetiracetam • Keppra
Oxcarbazepine • Trileptal
Tiagabine • Gabatril
Topiramate • Topamax
Valproate-divalproex sodium • Depakote, Depakote ER
Zonisamide • Zonegran

### DISCLOSURE

Dr. Keck reports that he receives grant/research support from and serves as a consultant to Abbott Laboratories, AstraZeneca, Pfizer Inc., and Eli Lilly and Co. He also receives grant/research support from Merck and Co. and Otsuka America Pharmaceutical, and serves as a consultant to Bristol-Myers Squibb Co., GlaxoSmithKline, and Janssen Pharmaceutica.

Dr. McElroy reports that she receives grant/research support from and serves as a consultant to Abbott Laboratories, Elan Pharmaceuticals, Cephalon Inc. GlaxoSmithKline, and Eli Lilly and Co. She also receives grant/research support from Forest Pharmaceuticals and Solvay Pharmaceuticals, and serves as a consultant to Bristol-Myers Squibb Co., Ortho-McNeil Pharmaceutical, and Janssen Pharmaceutica.

**Bottom Line**

**W**hen considering antiepileptic agents vs. lithium for patients with bipolar disorder: Valproate and carbamazepine have antimanic efficacy and support for efficacy as maintenance treatments. Lamotrigine exhibits efficacy in acute bipolar depression and in the prevention of depressive episodes. Other agents need more investigation.

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