

Update on bipolar disorder: How to better predict

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What does current evidence show regarding maintenance treatment with lithium, divalproex, carbamazepine, lamotrigine, or other agents? How well can you predict response? Which therapy will stop subsyndromal symptoms? The answers are here.



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response to maintenance therapy

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hat are we trying to accomplish in the maintenance treatment of patients with bipolar disorder? Given that the disorder recurs in more than 90% of patients who experience a manic episode,¹ there are 5 important goals:

1. Prevention of recurrent episodes;
2. Amelioration of subsyndromal symptoms;
3. Reduction of suicide risk;
4. Compliance enhancement;
5. Optimization of interpersonal, social, and vocational functioning.

There is a great premium on preventing mood episode recurrence in patients with bipolar disorder. Mood episodes themselves produce substantial morbidity, but morbidity is not confined to these episodes alone.

Full recovery of functioning often lags many months behind remission of symptoms.² Recurrent mood episodes also may lead to progressive loss of function between episodes. Mood episodes also carry risks of mortality from suicide, violence, and impulsive risk taking.

Clearly, mood-stabilizing medications form the cornerstone of maintenance treatment,^{3,4} along with a strong therapeutic alliance between patient and clinician and targeted psychosocial therapies. In the Expert Consensus Guidelines for medication treatment of bipolar I disorder, maintenance treatment was recommended for ≥ 1 year following an initial manic or mixed episode; longer (indefinite) treatment was recommended for patients with a family history of bipolar disorder or if ≥ 2 episodes occurred.³

Compared with clinical trials of agents for acute bipolar mania (and mixed episodes), there are relatively few randomized controlled trials of medications for the maintenance phase of bipolar disorder. Some naturalistic studies have provided data on relapse rates associated with treatment with a variety of different agents. Even fewer studies have examined psychosocial interventions designed specifically to reduce relapse rates.

But new data are beginning to emerge regarding the efficacy of divalproex, lamotrigine, and olanzapine as maintenance therapies. A number of clinical predictors of response to these agents have begun to be identified, as well as to lithium and carbamazepine. Eliciting these characteristics is important when making recommendations to patients about available drug therapies.

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In addition, effective maintenance treatment often requires combinations of mood-stabilizing, antidepressant, and antipsychotic agents to control or eliminate subsyndromal and breakthrough symptoms.

In this review, we will cover the available new data on pharmacologic maintenance treatments of bipolar disorder and their clinical implications.

What the studies show

Lithium has been the mainstay of therapy for bipolar disorder for more than 35 years. Most randomized, controlled trials of lithium maintenance therapy were conducted in the 1960s and 1970s⁵ (Table 1). Unfortunately, these studies had several



design limitations that inflated the expectations of lithium's efficacy as a maintenance treatment.⁶ These included discontinuation designs in which patients stabilized on lithium were abruptly switched to placebo; exaggerated early placebo relapse rates; enrollment of both unipolar and bipolar patients; lack of specific diagnostic criteria; and reported results only for patients completing studies. Pooled data from these trials indicated that lithium reduced the risk of relapse fourfold compared with placebo at 6 months and 1 year.⁵

Two contemporary randomized, placebo-controlled maintenance studies utilizing more rigorous designs provided further evidence of lithium's superiority over placebo in

extending time to manic relapse.^{7,8} Both studies enrolled patients who were currently or had recently been manic and had been stabilized in open-label treatment that included study medications.

In the first study, comparing 1-year relapse rates among patients randomized to lithium, divalproex, or placebo, lithi-

Previous studies had design limitations that inflated the expectations of lithium's efficacy as maintenance therapy

um extended time to recurrence of mania by 55% compared with placebo.⁷ In the second, an 18-month trial comparing lithium, lamotrigine, and placebo, lithium significantly increased the time to intervention for recurrence of mania

Table 1

What works in maintenance treatment of bipolar disorder (ranked by number of randomized, controlled trials)

Medication RCTs (n)	Trial results	Strong evidence	Some evidence
Lithium (15)	Equal to divalproex and lamotrigine; equal to or better than carbamazepine; better than placebo	4-fold reduction of relapse risk vs. placebo at 6, 12 months; more efficacious in mania than in depression; higher lithium level correlated with lower relapse rates, but more side effects	
Carbamazepine (7)	No significant benefit vs. lithium; better than placebo		May be more efficacious in mania than in depression; may be less tolerable than lithium; no data on serum levels
Divalproex (4)	Equal to lithium and olanzapine; better than placebo		May be more efficacious in mania than in depression; may be more tolerable than lithium; data on serum levels pending
Lamotrigine (2)	Better than placebo	More efficacious in depression than in mania	Dosage 200-400 mg/d
Olanzapine (1)	Equal to divalproex		Data on dosage and differential efficacy related to dosage pending
Clozapine (1)	Better than treatment as usual	Efficacy in treatment-resistant mania (bipolar schizoaffective disorder, bipolar type)	

compared with placebo.⁸ The overall manic relapse rates were 17% for lithium-treated patients and 41% for those on placebo. However, lithium did not significantly extend time to depressive relapse or intervention for depressive relapse, respectively, in either study. Moreover, in the first study, patients who received lithium tended to have greater sub-threshold depressive symptoms.⁸

These findings were consistent with earlier placebo-controlled studies of lithium maintenance treatment and a recent crossover comparison trial with carbamazepine.⁹ Lithium was also recently compared with carbamazepine in a 2.5-year maintenance multisite study in Europe.¹⁰ There was no significant difference in efficacy between the two in time to hospitalization, the primary outcome measure. On other outcome measures, including time to relapse or need for additional medication, lithium was superior to carbamazepine.

Pooled results from a number of naturalistic studies, which mirror clinical practice, indicated that approximately one-third of patients maintained on lithium had good functional outcomes without relapses and only minimal symptoms.¹¹ In general, these studies found higher rates of relapse with longer durations of follow-up.

Valproate maintenance treatment has been studied in two randomized, controlled trials (one vs. placebo,⁷ and one vs. olanzapine¹²) and two open-label comparison studies against lithium.^{13,14} In the placebo-controlled trial, which also included a lithium comparison group described earlier, there was no significant difference in the time to development of any mood episode among the three treatment groups.⁷ However, divalproex was superior to placebo on a number of other outcome measures, including rate of study termination for any mood episode, termination for depression, and termination for noncompliance.

Divalproex was superior to placebo in patients who received divalproex in the open-label treatment phase before randomization. This is clinically relevant, as this group reflects expected relapse rates in patients treated initially with divalproex for acute mania who then remain on the drug for maintenance therapy. Patients receiving divalproex had significantly lower rates of intolerance and noncompliance compared to those treated with lithium.

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In the second comparison study, 167 patients initially randomized and responding to divalproex or olanzapine in a 3-week acute bipolar mania trial continued in a double-blind 44-week extension study.¹² There were no significant differences in relapse into mania between the two groups (olanzapine 41%, divalproex 50%, $p = 0.4$) or time to manic relapse (olanzapine 270 days, divalproex 74 days, $p = 0.4$). There was no significant difference in tolerability between the two.

Two open-label studies compared valproate with lithium. In an 18-month study conducted in France, patients randomized to the valpromide formulation of valproate displayed a 20% lower relapse rate than those receiving lithium.¹³ The second open-label comparison trial found comparable efficacy between lithium and divalproex in a 1-year naturalistic pharmacoeconomic study that allowed additional medications as needed for recurrent symptoms.¹⁴

Carbamazepine has been evaluated in a limited number of studies for maintenance treatment of bipolar disorder. The results of many early randomized, controlled maintenance trials were criticized on methodologic grounds.¹⁵ But two recent comparison trials with lithium, as noted earlier, provided clinically important data regarding carbamazepine's prophylactic efficacy.^{9,10} Several additional clinically relevant observations emerged from analyses of secondary outcome measures in these two trials.

In the first study, 52 patients with bipolar I or II disorder received lithium or carbamazepine for 1 year, crossed over to the alternate drug the second year, and received both drugs the third year.⁹ There was little difference in relapse rates during the first year between the lithium (31%) and carbamazepine (37%) groups. Similarly, in the overall trial, there was little difference in the percentage of patients who were rated as having a moderate or better response—33% on lithium, 31% on carbamazepine, and 55% on the combination. A higher proportion of patients receiving carbamazepine withdrew due to side effects. In the second trial, significantly more patients receiving carbamazepine required additional medications for breakthrough symptoms and experienced side effects requiring treatment discontinuation.¹⁰



Lamotrigine has been studied in two placebo-controlled, randomized maintenance studies in patients with bipolar disorder.^{8,16} The first evaluated bipolar I patients who had experienced a manic or hypomanic episode within 60 days of entry into an open-label treatment phase with lamotrigine.⁸ Patients who, in turn, improved or remained stable during the open-label treatment phase were then randomized to treatment with lamotrigine 200-400 mg/d, lithium, or placebo for up to 18 months. Both lamotrigine and lithium were

superior to placebo on the primary outcome measure, which was time to need for additional medication for a mood episode. The median time until 25% of patients relapsed was 72 weeks for lamotrigine, 58 weeks for lithium, and 35 weeks for placebo.

On secondary outcome measures, lamotrigine, but not lithium, was superior to placebo in delaying time to depressive relapse. In contrast, lithium, but not lamotrigine, was superior to placebo in delaying time to manic relapse. Finally, lamotrigine, but not lithium, was superior to placebo in time to discontinuation for any reason.

From this study, it appears that lamotrigine is most effective in preventing depressive relapse, whereas lithium is most effective in preventing manic relapse. Thus, lithium and lamotrigine may complement each other in maintenance treatment by preventing manic and depressive episodes in combination.

The findings of the first trial were consistent with those of the second placebo-controlled lamotrigine (100-500 mg/d) maintenance study conducted specifically in patients with rapid cycling bipolar I and II disorders.¹⁶ In this 6-month trial, there was no significant difference in time to need for additional medications, the primary outcome measure, between the lamotrigine and placebo groups.

Median survival time was significantly greater for the lamotrigine group (18 weeks) than for the placebo group (12 weeks). The lamotrigine group had significantly longer time to need for additional medications in bipolar II, but not bipolar I, patients. Patients with bipolar II disorder also displayed significantly greater improvement with lamotrigine on global scales compared with bipolar I patients. Because bipolar II disorder is characterized predominantly by depressive episodes, these findings suggest that lamotrigine was again more beneficial in preventing recurrent depression, in this case, specifically, in rapid cycling bipolar II patients.

Taken together, the results of these studies are also consistent with the results of two placebo-controlled trials of lamotrigine in the treat-

Table 2

POTENTIAL PREDICTORS OF RESPONSE TO MAINTENANCE MEDICATIONS

Medication	Predictor of response	Strength of evidence
Lithium	Nonrapid cycling	◆◆◆
	Few episodes	◆
	Few depressive symptoms	◆
	Family history bipolar disorder	◆
	Episode sequence M-D-I	◆
	No substance/alcohol use disorder	◆
Divalproex	Equal efficacy in rapid & non-rapid cycling, manic & mixed,	◆
	No personality disorder	◆
Carbamazepine	Equal efficacy in rapid & non-rapid cycling, manic & mixed	◆◆
	Mood-incongruent symptoms	◆
Lamotrigine	Bipolar II > bipolar I	◆
	Depression > mania	◆◆
Olanzapine	Equal efficacy in rapid & non-rapid cycling, manic & mixed, psychotic & nonpsychotic mania in acute studies; data pending in maintenance	◆
Clozapine	Efficacy in treatment-resistant mania rapid & nonrapid cycling, manic & mixed, psychotic & nonpsychotic in naturalistic studies	◆◆◆

Key ◆ = reported in 1 study; ◆◆ = reported in 2 studies; ◆◆◆ = reported in > 3 studies.

ment of acute bipolar depression.^{17,18} Its efficacy in acute bipolar I depression was first demonstrated in a 6-week, double-blind, randomized, parallel-group trial in which patients received lamotrigine 50 mg/d, 200 mg/d (after gradual titration over the first 4 weeks), and placebo.¹⁷

Both dosage groups of lamotrigine displayed significantly greater improvement in depressive symptoms as measured by the Montgomery-Asberg Depression Rating Scale (but not the Hamilton Depression Rating Scale) and by the Clinical Global Improvement Scale compared with the placebo group. There was a trend for the 200 mg/d group to have greater improvement than the 50 mg/d group, a trend that might have become significant had the study been longer, as the 200 mg/d group did not receive this dose for the full trial. There was no significant difference in the incidence of hypomanic or manic switches among the three study groups.

Frye and colleagues also found lamotrigine to be superior to placebo in global improvement in depressive (but not manic) symptoms in a crossover monotherapy trial in treatment-refractory bipolar I and II patients.¹⁸

Olanzapine, as described earlier, was comparable to divalproex in a head-to-head comparison 44-week extension trial in patients who responded to double-blind treatment in an acute mania study.¹² These results were consistent with the preliminary findings of an open-label extension study of olanzapine.¹⁹ There are no placebo-controlled trials of olanzapine or any other atypical antipsychotic in the maintenance phase of bipolar disorder published to date.

Clozapine was more effective than “treatment as usual” (combinations of mood-stabilizers and typical antipsychotics) in patients with treatment-refractory bipolar and schizoaffective (bipolar subtype) disorders.²⁰ Many patients with bipolar disorder now receive adjunctive maintenance treatment with typical antipsychotics, but the limited data from the few controlled trials of typical agents administered in combination with mood-stabilizers do not support the efficacy of this strategy.²¹ Moreover, some reports suggest that maintenance treatment incorporating typical antipsychotics may increase the frequency and severity of depressive episodes in patients with bipolar disorder.

Predicting response to pharmacologic treatment

Clinical experience and data from the randomized, controlled trials reviewed earlier have identified several tentative predictors of response—or nonresponse—to specific medications. Lithium, divalproex, and carbamazepine appear to have greater efficacy in the prevention of manic rather than depressive episodes.¹¹ In contrast, lamotrigine appears to have greater efficacy in preventing depressive rather than manic episodes.

It is unclear whether olanzapine and perhaps other atypical antipsychotics may have a more favorable effect in preventing one pole of the illness over another (*Table 2*). The

Maintenance treatment incorporating typical antipsychotics may increase the frequency and severity of depressive episodes



currently available atypicals (clozapine, risperidone, olanzapine, quetiapine, and ziprasidone) in general appear to differ from typical antipsychotics in having bidirectional (antimanic and antidepressant) effects on mood symptoms.

Atypicals may exert antidepressant effects via a number of different mechanisms, including 5HT₂ receptor antagonism (a property shared by all atypicals and the antidepressants trazodone, nefazodone, and mirtazapine); alpha₂-adrenergic antagonism (clozapine and risperidone); and 5HT_{1D} antagonism, 5HT_{1A} agonism, and 5HT and NE reuptake inhibition (ziprasidone).²²

Patients with rapid-cycling bipolar disorder have a relatively poor response to lithium (response rates of approximately 20%).¹¹ Patients with rapid-cycling bipolar I disorder may have a greater likelihood of response to combined treatment with lithium and carbamazepine,⁹ or divalproex.¹¹ Alternately, patients with rapid-cycling bipolar II disorder have lower relapse rates on lamotrigine compared with placebo.¹⁶ Anecdotal reports and the results of acute treatment studies suggest that clozapine and olanzapine may be beneficial maintenance agents for rapid-cycling bipolar I patients.



Other predictors of favorable response to lithium prophylaxis include a family history of bipolar disorder, illness course characterized by mania-depression-euthymia episode sequence, and few prior mood episodes.²¹ Conversely, co-occurring alcohol or substance use disorder, multiple prior mood episodes, and familial negative affective style have been associated with poor response to lithium maintenance treatment.

Tentative predictors of response to divalproex maintenance treatment include mixed episodes, rapid cycling, and absence of co-occurring personality disorder. In one lithium comparison trial, patients with mixed episodes, bipolar II, and NOS disorders and mood-incongruent symptoms appeared to have a better response to carbamazepine.¹⁰

The dosage and relevant plasma concentrations of maintenance agents may also affect long-term efficacy. Gelenberg et al observed that the risk of relapse in bipolar patients maintained on low (0.4-0.6 mmol/L) serum concentrations was 2.6 times higher than for patients maintained on high (0.8-1.0 mmol/L) serum concentrations.²³ However, there was a tradeoff in tolerability. Patients treated at the higher concentrations experienced significantly more and often treatment-limiting side effects.

No data are available regarding a possible plasma concentration-response relationship between maintenance treatment with divalproex or carbamazepine, but based on data from acute treatment trials, concentrations well within the therapeutic range of each drug appear essential.

The problem of subsyndromal symptoms

Evidence from a number of long-term outcome studies in bipolar disorder indicates that many patients spend protracted periods of time neither well nor in syndromal manic or depressive episodes, but rather experiencing chronic subsyndromal symptoms.^{24,25} In these studies, depressive symptoms were twice as prevalent as hypomanic symptoms between acute episodes of illness. Furthermore, persistent subsyndromal depressive symptoms were strongly associated with an increased risk for relapse and poor occupational functioning.

Keller et al²⁶ found that patients maintained on low

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lithium serum concentrations (0.4-0.6 mmol/L) were more likely to experience subsyndromal symptoms and that their symptoms were more likely to worsen at any time than were symptoms of patients maintained at higher serum concentrations (0.8-10 mmol/L). The first occurrence of subsyndromal symptoms increased the risk of full-episode relapse fourfold. These findings indicate that the optimal pharmacological maintenance treatment of bipolar disorder requires titration of mood-stabilizer medications to eradicate subsyndromal symptoms. Eliminating these residual or recurrent symptoms, in turn, substantially decreases the risk of relapse and of enduring functional impairment.

Conventional wisdom, in part supported by limited data from a small number of studies, suggests that antidepressants be used sparingly and for limited periods of time in conjunction with mood-stabilizers for bipolar depression. However, new data indicate that this strategy may significantly increase the risk of recurrence of depressive symptoms and episodes.²⁷ Thus, combined treatment with mood-stabilizing agents and antidepressants for patients without rapid cycling and with recurrent depressive episodes may be indicated more often than previously thought.

In practice, perhaps the majority of patients with bipolar disorder require treatment with more than one mood-stabilizing medication to suppress subsyndromal symptoms as well as to prevent full episode recurrence. The use of combinations has been very poorly studied in randomized, controlled trials. In a pilot study of 12 patients with bipolar I disorder, Solomon et al compared the efficacy of lithium alone versus the combination of lithium and divalproex for 1 year.²⁸ Not surprisingly, the combination significantly reduced the risk of recurrence of mania and depression but was also associated with more bothersome side effects.

Clinical practice has greatly outstripped the limited data available from formal studies. Recently reported as useful maintenance treatment strategies are combinations of:

- lithium and divalproex
- lithium and carbamazepine
- divalproex and carbamazepine
- lithium, divalproex, and carbamazepine
- lithium and/or divalproex with atypical antipsychotics, antidepressants, and lamotrigine.

The dosage and relevant plasma concentrations of maintenance agents may also affect long-term efficacy

Related resources

- ▶ Nathan PE, Gorman JM, eds. *A Guide to Treatments that Work*. 2nd ed. New York: Oxford University Press, 2001.
- ▶ Buckley PF, Waddington JL, eds. *Schizophrenia and Mood Disorders: the New Drug Therapies in Clinical Practice*. Boston: Butterworth-Heiman, 2000.
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- ▶ Hirschfeld RMA, Bowden CL, Gitlin MJ, et al. Practice guideline for the treatment of bipolar disorder (revision). *Am J Psychiatry*, in press.

DRUG BRAND NAMES

Clozapine • Clozaril	Olanzapine • Zyprexa
Divalproex • Depakote, Depakote Sprinkle	Quetiapine • Seroquel
Lamotrigine • Lamictal	Risperidone • Risperdal
Mirtazapine • Remeron, Remeron Soltab	Trazodone • Desyrel
Nefazodone • Serzone	Valproate sodium • Depacon
	Ziprasidone • Geodon

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Long-term management of bipolar disorder is challenging. New data show that lithium, divalproex, and carbamazepine appear to have greater efficacy in treating mania, lamotrigine in treating depression. Consider clozapine for treatment-resistant disorder. Combinations, though not well studied, may be best to suppress subsyndromal symptoms.

BottomLine