# New Approaches in Managing Bipolar Depression

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Historically, the pharmacologic treatment of bipolar depression has not been well studied. New data are beginning to emerge regarding the efficacy of new medications and the use of combinations of mood stabilizers and antidepressants in acute and long-term treatment of bipolar depression. We reviewed data from recent randomized, controlled trials of mood stabilizers and antidepressants in the treatment of bipolar depression and naturalistic studies examining the risk of switching and depressive relapse with ongoing antidepressant treatment.

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There is a resurgence of interest in the treatment of bipolar depression.[1] This is a welcome and overdue development driven by recent research findings indicating that depressive symptoms and episodes are often the most common long-term problems in managing bipolar illness for patients and clinicians.[2,3] The depressive phase of bipolar disorder is associated with substantial morbidity, impaired functioning, suicide, and other causes of excess mortality.[4–6] Until recently, there were very few randomized, controlled trials of mood stabilizers or antidepressants in the acute and long-term treatment of bipolar depression.[7,8] A number of new clinical trials and naturalistic studies have provided fresh data regarding the acute and long-term treatment of bipolar depression. These studies examined the efficacy of mood-stabilizer monotherapy and combination therapy with antidepressants. In addition, naturalistic studies have added new data regarding the risk of switching associated with continuation antidepressant therapy in combination with mood stabilizers and the risk of relapse with discontinuation of antidepressants following acute recovery. We review these new studies and their clinical implications.

## METHOD

Using Paper*Chase*[9] to cover the period from 1990 through early 2002, we conducted a computerized literature search for recent reports of studies using the terms *bipolar disorder*, *depression*, *mood stabilizers*, *lithium*, *divalproex*, *carbamazepine*, *antidepressants*, *olanzapine*, *risperidone*, *quetiapine*, *ziprasidone*, *anticonvulsants*, and *atypical antipsychotics*. We augmented the search by manually reviewing bibliographies from identified reports and recent reviews and by searching published abstracts from recent scientific meetings (e.g., annual meetings [2000–2002] of the American Psychiatric Association, American College of Neuropsychopharmacology, New Clinical Drug Evaluation Unit, etc.). The identified reports were divided into studies of acute and long-term treatment of bipolar depression and are presented below.

## TREATMENT OF ACUTE BIPOLAR DEPRESSION

### Mood Stabilizers

Most contemporary guidelines for the treatment of bipolar depression recommend the "mood stabilizer first" approach for patients receiving no medication at the time of presentation.[10,11] This approach is based on the rationale that mood stabilizers have at least some inherent antidepressant activity, a lower switch risk than mood stabilizer–antidepressant combinations, and protection against switching if antidepressants are subsequently needed in the event of inadequate response to the mood stabilizer.[12] Data regarding the efficacy of mood stabilizer monotherapy in the acute treatment of bipolar depression are summarized as follows.

***Lithium.*** Not surprisingly, most randomized, controlled studies of lithium in the treatment bipolar depression were conducted in the 1960s and 1970s. Lithium was superior to placebo in 8 of 9 trials (reviewed in Zornberg and Pope[13]). Zornberg and Pope analyzed 5 of these studies in which it was possible to distinguish the degree of lithium response.[13] They found that 79% of patients had at least par-

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tial improvement in depressive symptoms, but that only 36% displayed an unequivocal antidepressant response. These early studies have been augmented by 2 recent randomized, controlled trials.[14,15] In a study comparing the addition of paroxetine, imipramine, and placebo to lithium in patients with bipolar depression, Nemeroff et al.[14] found that patients receiving lithium at plasma concentrations of > 0.8 mEq/L experienced no significant benefit from the addition of an antidepressant compared with placebo. On the other hand, the addition of paroxetine conferred significantly greater antidepressant efficacy than placebo in patients receiving lithium at concentrations of < 0.8 mEq/L. These findings suggest that lithium alone exerted substantial antidepressant activity at higher therapeutic concentrations, but that paroxetine provided significant antidepressant efficacy when lithium concentrations were in low- to mid-therapeutic range. In the second recent lithium trial, Young et al.[15] compared the addition of a second alternative mood stabilizer (lithium or divalproex) or paroxetine to an ongoing mood stabilizer (lithium or divalproex) in 27 patients experiencing breakthrough depression. There was no significant difference in antidepressant response between the combination mood stabilizer and paroxetine–mood stabilizer groups, although the latter group had fewer dropouts due to side effects. Collectively, these studies suggest that lithium exerts significant acute antidepressant activity, especially at higher therapeutic levels. However, some patients experience only partial improvement, and some are unable to tolerate titration to levels above 0.8 mEq/L.

***Divalproex.*** The efficacy of divalproex and other formulations of valproic acid in the acute treatment of bipolar depression has not been well studied. In the only randomized, controlled trial reported to date, Sachs and Collins[16] did not find a significant difference between divalproex and placebo. Further evidence of the efficacy of divalproex in acute bipolar depression is clearly needed.

***Carbamazepine.*** Carbamazepine has been studied in 3 small placebo-controlled trials in patients with acute bipolar depression.[17-19] In the first study, Post et al.[17] observed marked improvement in 12 (34%) of 35 patients (24 bipolar, 11 unipolar) with treatment-refractory depression who received carbamazepine in a crossover trial. Switch to placebo was associated with recurrence of depressive symptoms in carbamazepine responders. Small[18] compared lithium, carbamazepine, or the combination in a 4-week trial of 28 patients (4 bipolar, 24 unipolar) with treatment-refractory depression. Of patients receiving carbamazepine, alone or in combination with lithium, 32% displayed at least moderate improvement in depressive symptoms compared with 13% receiving lithium. Kramlinger and Post[19] assessed efficacy of lithium augmentation compared with placebo in patients partially responsive to carbamazepine and found that 46% responded to the combination.

***Olanzapine.*** Olanzapine and the combination of olanzapine and fluoxetine had significantly greater efficacy compared with placebo in an 8-week trial of 833 patients with bipolar I depression.[20] The olanzapine group (mean dose = 9 mg/day) displayed significantly greater improvement in depressive symptoms compared with the placebo group by the end of the first week of treatment. There was no significant difference in switch rates into mania between the olanzapine and placebo groups. This was the first placebo-controlled trial of olanzapine, or any atypical antipsychotic, in the treatment of acute bipolar depression and suggests that, like lithium, olanzapine may have efficacy as a mood stabilizer in acute bipolar depression.

**Antidepressants**

***Lamotrigine.*** Two placebo-controlled trials demonstrated the efficacy of lamotrigine in acute bipolar depression.[21,22] Calabrese et al.[21] found lamotrigine, 50 mg/day and 200 mg/day, significantly more efficacious than placebo in reduction of depressive symptoms in 195 patients with bipolar I depression in a 7-week trial. There was also a trend for greater efficacy of 200 mg/day over 50 mg/day, a trend that might have become significant in a longer trial since patients in the 200-mg/day group did not reach this dose until the fourth week of the study because of the slow titration required of lamotrigine. There were no significant differences in switch rates (3%–8%) between the treatment groups.

Frye et al.[22] compared lamotrigine, gabapentin, and placebo in a crossover study in patients with treatment-refractory rapid-cycling bipolar I and II disorders. Among the 3 treatment groups, only lamotrigine was associated with significant reductions in depressive symptoms.

In contrast to these positive results, a second placebo-controlled, parallel-group flexible-dose trial of 206 patients with bipolar I and II depression did not find significantly greater efficacy for lamotrigine over placebo.[23]

***Other antidepressants.*** There are a limited number of randomized, controlled trials of antidepressants in the treatment of acute bipolar depression. Tranylcypromine, among all antidepressants studied, has the most substantial evidence for efficacy in acute bipolar I depression.[10] One recent review of the available studies concluded that "not a single antidepressant medication, nor even a particular class of antidepressant, has been demonstrated to be effective in at least 2 adequately powered, placebo-controlled clinical trials."[10(p558)] Nevertheless, several recent studies have begun to expand this limited literature. Two studies, reviewed above, suggested that paroxetine, when added to mood stabilizers, exerted significant antidepressant activity, especially when lithium levels were in the low- to mid-therapeutic range.[14,15] Notably, the switch rate in the paroxetine-treatment groups in these 2 trials was very low. These results, when added to other studies of selective serotonin reuptake inhibitors,[24,25] venlafaxine,[26] and bupro-

pion,[27] suggest that second-generation antidepressants have comparable efficacy to but lower switch rates than tricyclic antidepressants when administered in combination with mood stabilizers.

Four recent randomized, controlled trials have investigated other innovative agents for the treatment of acute bipolar depression.[28–30] McIntyre et al.[28] observed comparable efficacy between topiramate (mean dose = 176 mg/day) and bupropion sustained release (SR) (mean dose = 250 mg/day) in an 8-week, single-blind comparison study of each agent added to a mood stabilizer. There were no switches into mania or hypomania with either treatment, and patients lost weight in each group, but significantly more with topiramate (mean = 5.8 kg [12.9 lb]) compared with bupropion SR (mean = 1.2 kg [2.7 lb]). Goldberg et al.[29] recently reported significantly greater efficacy for pramipexole (mean dose = 1.7 mg/day), a dopamine agonist, compared with placebo added to mood stabilizers in 24 patients with bipolar depression. Omega-3 fatty acids, alone or added to mood stabilizers, yielded significantly greater reductions in global ratings of depressive symptoms compared with placebo in 1 pilot trial.[30] Lastly, the olanzapine-fluoxetine combination (olanzapine, mean dose = 7 mg/day; fluoxetine, mean dose = 38 mg/day) was superior in efficacy not only to placebo, from the end of the first week of treatment, but also to olanzapine monotherapy from weeks 4 to 8.[20] Again, there were no significant differences in switch rates among the olanzapine-fluoxetine combination, olanzapine, and placebo groups. These results suggest that the antidepressant activity of olanzapine was substantially augmented by the addition of fluoxetine without an attendant increase in switch risk.

## LONG-TERM TREATMENT OF BIPOLAR DEPRESSION

### Recent Clinical Trials of Mood-Stabilizer Monotherapy

***Lamotrigine versus lithium.*** Two recently reported randomized, controlled trials examined the efficacy of lithium, lamotrigine, and placebo in the prevention of bipolar mood episodes.[31,32] Both studies were of similar design (18-month, monotherapy, parallel-group randomized treatment following an initial 8- to 16-week period of stabilization during which lamotrigine treatment was introduced and other agents gradually tapered), but differed primarily in that the first study enrolled patients who had recently experienced a manic or hypomanic episode,[31] whereas the second study enrolled patients with a recent depressive episode.[32] Both studies had convergent findings: lamotrigine but not lithium was superior to placebo in prolonging time to intervention for a depressive relapse; lithium but not lamotrigine was superior to placebo in prolonging time to intervention for a manic, hypomanic, or mixed episode relapse. The obvious implication of these 2 studies is that the combination of lithium and lamotrigine may be well suited to prevent both manic and depressive episodes.

One other placebo-controlled maintenance study of lamotrigine has been reported.[33] Calabrese et al.[33] conducted a 6-month comparison between lamotrigine (mean dose = 288 mg/day) and placebo in 182 patients with rapid-cycling bipolar I and II disorders following an initial 4- to 8-week stabilization period on lamotrigine monotherapy. The lamotrigine group experienced relapse rates comparable to the placebo group. However, in a post hoc analysis, patients with bipolar II disorder exhibited a strong trend in favor of lamotrigine in time to need for additional pharmacotherapy for affective symptom recurrence.

***Olanzapine versus divalproex.*** Tohen et al. compared the efficacy of olanzapine with divalproex in the prevention of relapse over 44 weeks[34] in 109 patients who had responded acutely to each respective agent in a 3-week trial.[35] For patients maintained on olanzapine, the median time to relapse was 270 days compared with 74 days for patients maintained on divalproex ($p = .3$).[34] Relapse rates did not differ significantly between the olanzapine (45%) and divalproex (52%) groups. When depressive symptoms were specifically examined using a mixed-model repeated measures analysis, mean improvement on the Hamilton Rating Scale for Depression favored olanzapine over divalproex ($p = .06$). Overall, however, only 15% of patients in each treatment group completed the 47-week trial, underscoring the limitations of mood-stabilizer monotherapy in the long-term treatment of bipolar disorder.

### Recent Clinical Trials of Mood-Stabilizer Combination Treatment

Solomon et al.[36] conducted the first prospective, randomized, controlled trial of combination mood-stabilizer treatment compared with monotherapy. In this pilot study, patients randomly assigned to the combination of lithium and divalproex experienced significantly lower relapse rates compared with patients receiving lithium and placebo after 1 year. However, patients receiving the combination also experienced more side effects.

In the second study, Tohen et al.[37] compared the combination of olanzapine and lithium or divalproex with lithium or divalproex monotherapy over 18 months. Patients ($N = 94$) participated who had initially responded to the combination in a 6-week acute treatment trial[38] and who agreed to be randomly assigned again for the maintenance study participated in the trial. The combination therapy group had a significantly longer time to recurrence of mania than patients in the monotherapy group. Similarly, the combination group did significantly better in rates of manic recurrence (15%) compared with the monotherapy group (35%). The time to recurrence of a depressive episode was not significantly different between the 2 groups,

although there was a trend favoring the combination group (155 days) compared with the monotherapy group (27 days, p = .07). Regarding tolerability, significantly more patients in the combination group experienced weight gain while insomnia occurred significantly more commonly in the monotherapy group.

Taken together, the results of these 2 studies indicate that for many patients combination therapy with lithium and divalproex or olanzapine and lithium or divalproex, respectively, may be superior in preventing manic and depressive relapse compared with lithium or divalproex monotherapy.

### Antidepressants, Mood Stabilizers, and Switching into Mania

To what extent mood stabilizers diminish the risk of switching into hypomanic, manic, or mixed episodes when antidepressants are needed to treat bipolar depression is an important clinical issue. This issue has been addressed in a number of recent naturalistic studies.[39–43] In a review of the medical records of 158 inpatients with bipolar I depression treated with mood stabilizers, antidepressants, or the combination, Bottlender et al.[39] found an overall switch rate of 25%. Patients who switched were more likely to have received a tricyclic antidepressant and to have received a tricyclic without a mood stabilizer. Among all patients who experienced a switch, the proportion of patients switching who were not receiving a mood stabilizer (82%) was significantly higher than the proportion who were receiving a mood stabilizer (59%). The results of this study were similar to earlier naturalistic reports that found that coadministration of a mood stabilizer with an antidepressant decreased the risk of switching by up to 50%.[40,41]

Henry et al.[42] conducted a similar comparison of switch rates in 44 patients treated for bipolar depression with antidepressants in 6-week naturalistic trials. The overall switch rate of 27% (16% mania; 11% hypomania) was very similar to that of Bottlender et al.[39] Patients receiving lithium were significantly less likely to experience a switch into mania or hypomania (15%) compared with patients not receiving lithium (44%). Interestingly, there was no correlation between the number of prior manic episodes and switch risk, although a history of hyperthymia was associated with a greater switch risk.

Post et al.[43] analyzed the switch rates among acute 10-week treatment and 1-year maintenance trials in patients randomly assigned to receive bupropion, sertraline, or venlafaxine added to therapeutic doses of mood stabilizers. In 95 acute treatment trials, there were 13 (14%) switches, 6 (6%) into mania and 7 (7%) into hypomania. For the subsequent 48 maintenance treatment trials in patients responding during the acute treatment phase, there were 16 (33%) switches, 6 (13%) into mania and 10 (21%) into hypomania. No antidepressant was associated with a significantly higher switch risk. The overall switch risk into mania in this study was relatively low, but, because of the lack of a placebo group, could not be compared with the risk of spontaneous switching from the illness itself.

These studies indicate that mood stabilizers reduce but do not eliminate the risk of switching in patients with bipolar depression treated with antidepressants. One encouraging finding from the studies of Henry et al.[42] and Post et al.[43] was the relatively low rate of switches into mania compared with hypomania.

### Long-Term Antidepressant Treatment: Balancing the Risk of Relapse and Switching

Most treatment guidelines have recommended that antidepressants (administered in conjunction with mood stabilizers) be discontinued relatively soon after remission of an episode of bipolar depression.[44,45] This recommendation is based on the assumption that protracted antidepressant exposure increases the risk of switching beyond that associated with mood stabilizer–treated bipolar disorder. On the other hand, antidepressant discontinuation carries with it the possibility of recurrence of depressive symptoms or episodes. Two naturalistic studies have recently examined these dual risks by comparing switch rates in patients maintained on antidepressants and relapse rates in patients discontinued from antidepressant therapy after initially responding.[46,47] In the first study, Altshuler et al.[46] compared the relapse rates of 25 patients who discontinued antidepressants (administered with mood stabilizers) with 19 patients who continued antidepressants (with mood stabilizers). The group discontinuing antidepressants had a significantly higher risk of depressive relapse (odds ratio = 3.13; p = .007), but the group continuing to receive antidepressants did not have a significantly increased risk of switching into hypomania or mania (odds ratio = 1.92; p = .35). Altshuler et al.[47] followed up these observations in a larger cohort of 84 patients successfully treated acutely with bupropion, sertraline, or venlafaxine (with a mood stabilizer). At 1-year follow-up, patients who discontinued antidepressants within 6 months of achieving remission from depression were significantly more likely to experience a depressive relapse (71%) compared with patients maintained on antidepressants (41%). Of the 15 (18%) patients who experienced a manic relapse during the year, only 6 (7%) were receiving antidepressants at the time of relapse. The 2 studies found that antidepressant discontinuation was significantly associated with depressive relapse, but that antidepressant continuation was not associated with a significantly greater risk of switching. There are several caveats to consider in interpreting these results. First, they may not be generalizable to patients with rapid cycling. Second, the lower switch rates may have been due to treatment with second-generation antidepressants rather than tricyclics or to use of mood stabilizers well within the therapeutic range for these agents.

Nevertheless, these studies suggest that the prevention of bipolar depressive symptoms and episodes may require use of mood stabilizer–antidepressant combinations for many patients.

## CONCLUSIONS

A number of important advances have transpired in the treatment of bipolar depression. Lamotrigine appears to have efficacy in both the acute treatment and prevention of bipolar depressive episodes. Lithium but not lamotrigine had significantly greater efficacy in preventing manic episodes. Olanzapine is the first atypical antipsychotic to have demonstrated efficacy compared with placebo in acute bipolar depression. Furthermore, the combination of olanzapine and fluoxetine produced significantly greater improvement than both olanzapine and placebo. Preliminary data from maintenance studies suggest that, for many patients with bipolar disorder, combination therapy with mood stabilizers (e.g., lithium and divalproex; olanzapine and lithium or divalproex) or mood stabilizers and antidepressants (e.g., lithium and lamotrigine; lithium or divalproex and second-generation antidepressants) may provide better efficacy in preventing depressive relapses. Many questions remain unanswered. For example, reliable predictors of depressive relapse and switching are needed to inform decisions about the relative risks of continuation treatment with antidepressants in conjunction with mood stabilizers. The efficacy of divalproex, carbamazepine (and its congener, oxcarbazepine), new antiepileptic agents (e.g., zonisamide, levetiracetam), and other atypical antipsychotics in treating bipolar depression needs to be addressed in randomized, controlled trials.

*Drug names:* bupropion (Wellbutrin and others), carbamazepine (Tegretol and others), divalproex (Depakote), fluoxetine (Prozac and others), gabapentin (Neurontin), imipramine (Tofranil and others), lamotrigine (Lamictal), levetiracetam (Keppra), olanzapine ((Zyprexa), oxcarbazepine (Trileptal), paroxetine (Paxil), pramipexole (Mirapex), quetiapine (Seroquel), risperidone (Risperdal), sertraline (Zoloft), topiramate (Topamax), tranylcypromine (Parnate), venlafaxine (Effexor), ziprasidone (Geodon), zonisamide (Zonegran).

*Disclosure of off-label usage:* The authors of this article have determined that, to the best of their knowledge, bupropion, carbamazepine, divalproex, fluoxetine, gabapentin, imipramine, lamotrigine, levetiracetam, olanzapine, oxcarbazepine, paroxetine, pramipexole, quetiapine, risperidone, sertraline, topiramate, tranylcypromine, venlafaxine, ziprasidone, zonisamide, and lithium mentioned in this article are not approved by the U.S. Food and Drug Administration for the treatment of bipolar depression.

## REFERENCES


1. Keck PE Jr, Nelson EB, McElroy SL. Advances in the pharmacological treatment of bipolar depression. Biol Psychiatry. In press
2. Angst J, Sellaro R. Historical perspectives and natural history of bipolar disorder. Biol Psychiatry 2000;48:445–457
3. Judd LL, Akiskal HS, Schettler PJ, et al. The long-term natural history of the weekly symptomatic status of bipolar I disorder. Arch Gen Psychiatry 2002;59:530–537
4. Gladstone GL, Mitchell PB, Parker G, et al. Indicators of suicide over 10 years in a specialist mood disorders unit sample. J Clin Psychiatry 2001;62: 945–951
5. Hiroeh U, Appleby L, Mortensen PB, et al. Death by homicide, suicide, and other unnatural causes in people with mental illness: a population-based study. Lancet 2001;358:2110–2112
6. López P, Mosquera F, de León J, et al. Suicide attempts in bipolar patients. J Clin Psychiatry 2001;62:963–966
7. Ghaemi SN, Lenox MS, Baldessarini RJ. Effectiveness and safety of long-term antidepressant treatment of bipolar disorder. J Clin Psychiatry 2001; 62:565–569
8. Sachs GS, Koslow CL, Ghaemi SN. The treatment of bipolar depression. Bipolar Disord 2000;2:256–260
9. Paper*Chase* [online search service]. Boston, Mass: Beth Israel Deaconess Medical Center. Available at: http://www.paperchase.com
10. Thase ME, Sachs GS. Bipolar depression: pharmacotherapy and related therapeutic strategies. Biol Psychiatry 2000;48:558–572
11. Moller H-J, Grunze H. Have some guidelines for the treatment of acute bipolar depression gone too far in the restriction of antidepressants? Eur Arch Psychiatry Clin Neurosci 2000;250;57–68
12. Keck PE Jr, McElroy SL. Treatment of bipolar disorder. In: Schatzberg AF, Nemeroff CB, eds. Textbook of Psychopharmacology. 3rd ed. Washington, DC: American Psychiatric Publishing. In press
13. Zornberg GL, Pope HG Jr. Treatment of depression in bipolar disorder: new directions for research. J Clin Psychopharmacol 1993;13:397–408
14. Nemeroff CB, Evans DL, Gyulai L, et al. Double-blind, placebo-controlled comparison of imipramine and paroxetine in the treatment of bipolar depression. Am J Psychiatry 2001;158:906–912
15. Young LT, Joffe RT, Robb JC, et al. Double-blind comparison of addition of a second mood stabilizer versus an antidepressant to an initial mood stabilizer for treatment of patients with bipolar depression. Am J Psychiatry 2000;157:124–127
16. Sachs GS, Collins MC. A placebo-controlled trial of divalproex sodium in acute bipolar depression [abstract]. Presented at the 40th annual meeting of the American College of Neuropsychopharmacology; Dec 9–13, 2001; Waikola, Hawaii
17. Post RM, Uhde TW, Roy-Byrne PP, et al. Antidepressant effects of carbamazepine. Am J Psychiatry 1986;43:29–34
18. Small JG. Anticonvulsants in affective disorders. Psychopharmacol Bull 1990;26:25–36
19. Kramlinger KG, Post RM. The addition of lithium to carbamazepine. Arch Gen Psychiatry 1989;46:794–800
20. Tohen M, Baker RW. Olanzapine and olanzapine plus fluoxetine vs. placebo for bipolar depression [abstract]. Presented at the 155th annual meeting of the American Psychiatric Association. May 18–23, 2002; Philadelphia, Pa
21. 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
22. 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
23. Bowden CL. Novel treatments for bipolar disorder. Expert Opin Investig Drugs 2001;10:661–671
24. Cohn J, Collins G, Ashbrook E, et al. A comparison of fluoxetine, imipramine and placebo in patients with bipolar depressive disorder. Int Clin Psychopharmacol 1980;3:313–322
25. Kupfer DJ, Chengappa KNR, Gelenberg AJ, et al. Citalopram as adjunctive therapy in bipolar depression. J Clin Psychiatry 2001;62:985–990
26. Vieta E, Martinez-Aran A, Goikolea JM. A randomized trial comparing paroxetine and venlafaxine in the treatment of bipolar depressed patients taking mood-stabilizers. J Clin Psychiatry 2002;63:508–512
27. Sachs GS, Lafer B, Stoll AL, et al. A double-blind trial of bupropion versus desipramine for bipolar depression. J Clin Psychiatry 1994;55:391–393
28. McIntyre RS, Mancini DA, McCann S, et al. Topiramate versus 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
29. Goldberg JF, Burdick KE, Endick CJ. A placebo-controlled trial of pramipexole for bipolar depression. In: New Research Abstracts of the 155th Annual Meeting of the American Psychiatric Association; May 22, 2002; Philadelphia, Pa. Abstract NR416:112

30. Stoll AL, Severus WE, Freeman MP, et al. Omega 3 fatty acids in bipolar disorder: a preliminary double-blind, placebo-controlled trial. Arch Gen Psychiatry 1999;56:407–412
31. Bowden CL, Calabrese JR, Sachs GS, et al. A placebo-controlled 18-month trial of lamotrigine and lithium maintenance treatment in recently manic or hypomanic patients with bipolar I disorder [abstract]. Presented at the 4th International Conference on Bipolar Disorder; June 14–16, 2001; Pittsburgh, Pa
32. Bowden CL, Calabrese JR, Sachs GS, et al. A placebo-controlled trial of lamotrigine and lithium maintenance treatment in recently depressed patients with bipolar I disorder [abstract]. Presented at the 40th annual meeting of the American College of Neuropsychopharmacology; Dec 9–13, 2001; Waikola, Hawaii
33. 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
34. Tohen M, Baker RW, Altshuler LL, et al. Olanzapine versus divalproex sodium for bipolar mania: a 47-week study [abstract]. Presented at the 40th annual meeting of the American College of Neuropsychopharmacology; Dec 9–13, 2001; Waikola, Hawaii
35. Tohen M, Baker RW, Altshuler LL, et al. Olanzapine versus divalproex in the treatment of acute mania. Am J Psychiatry 2002;159:1011–1017
36. Solomon DA, Ryan CE, Keitner GI, et al. A pilot study of lithium carbonate plus divalproex sodium for the continuation and maintenance treatment of patients with bipolar I disorder. J Clin Psychiatry 1997;58:95–99
37. Tohen M, Chengappa KNR, Suppes T, et al. Efficacy of olanzapine in combination with lithium or valproate in prevention of recurrence in bipolar disorder: an 18-month study [abstract]. Presented at the US Psychiatric and Mental Health Congress; Nov 15–18, 2001; Boston, Mass
38. Tohen M, Chengappa KNR, Suppes T, et al. Efficacy of olanzapine in combination with valproate or lithium in the treatment of mania in patients partially nonresponsive to valproate or lithium monotherapy. Arch Gen Psychiatry 2002;59:62–69
39. Bottlender R, Rudolf D, Strauss A, et al. Mood-stabilizers reduce the risk for developing antidepressant-induced maniform states in acute treatment of bipolar I depressed patients. J Affect Disord 2001;63:79–83
40. Boerlin J, Gitlin MJ, Zoellner LA, et al. Bipolar depression and antidepressant-induced mania: a naturalistic study. J Clin Psychiatry 1998; 59:374–379
41. Rouillon F, Lejoyeaux M, Filteau MJ. Unwanted effects of long-term treatment. In: Montgomery SA, Rouillon FA, eds. Long-Term Treatment of Depression. New York, NY: Wiley; 1992:81–111
42. Henry C, Sorbara F, Lacoste J, et al. Antidepressant-induced mania in bipolar patients: identification of risk factors. J Clin Psychiatry 2001;62: 249–255
43. Post RM, Altshuler LL, Frye MA, et al. Rate of switch in bipolar patients prospectively treated with second-generation antidepressants as augmentation to mood stabilizers. Bipolar Disord 2001;3:259–265
44. Nolen WA, Bloemkolk D. Treatment of bipolar depression, a review of the literature and suggestion for an algorithm. Neuropsychobiol 2000;42 (suppl 1):11–17
45. Yatham LN, Kusumaker V, Parikh SV, et al. Bipolar depression: treatment options. Can J Psychiatry 1997;42:87S–91S
46. Altshuler L, Kiriakos L, Calcagno J, et al. The impact of antidepressant discontinuation versus antidepressant continuation on a 1-year risk for relapse of bipolar depression: a retrospective chart review. J Clin Psychiatry 2001; 62:612–616
47. Altshuler LL, Suppes T, Black D, et al. Impact of antidepressant discontinuation after acute remission from bipolar depression on rates of depressive relapse at one-year follow-up. Am J Psychiatry. In press