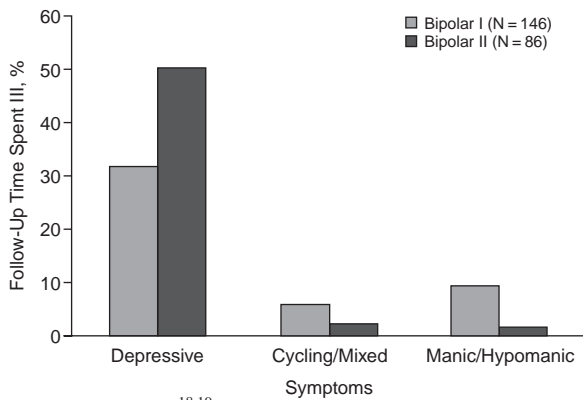


Figure 1. Symptomatology of Patients With Bipolar I and II Disorder During Long-Term Follow-Up^a



^aData from Judd et al.^{18,19}

antidepressants, although the usefulness of antidepressants in bipolar treatment is a subject of continued debate in the field. Agents approved by the U.S. Food and Drug Administration (FDA) to treat bipolar depression or bipolar mood episodes are the olanzapine-fluoxetine combination and quetiapine monotherapy for acute treatment and lamotrigine for maintenance and preventive treatment.

Antidepressant Treatment in Acute Bipolar Depression

A fundamental question is whether or not antidepressants are effective and safe in bipolar depression. Because of concerns about efficacy and the possibility of antidepressant-induced mood switching, it is generally not recommended that antidepressants be used without a concurrent mood stabilizer when treating patients with bipolar disorder. More research is needed on this question, especially concerning long-term treatment.

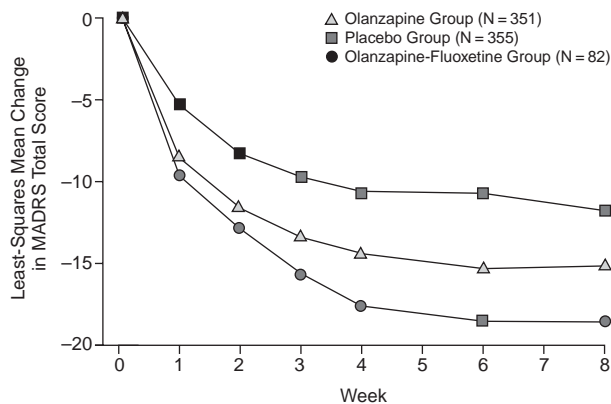
A large 8-week study²⁰ showed favorable results for an antidepressant versus placebo in bipolar depression, but the antidepressant was used in conjunction with an atypical antipsychotic; specifically, the olanzapine-fluoxetine combination was used. In a meta-analysis, Gijsman and colleagues²¹ examined the results of that study²⁰ and 4 others^{22–25} that compared response and/or remission rates of an antidepressant against those of placebo for up to 10 weeks. The antidepressants used by the other studies were fluoxetine, paroxetine, imipramine, tranylcypromine, and deprenyl, but only the patients taking tranylcypromine and deprenyl were not taking concurrent medications. These studies favored antidepressants over placebo for treating bipolar depression. However, most of these trials had small sample sizes, and some had methodological problems including insufficiently defined response measurements and failure to distinguish subjects who were or were not receiving concurrent medication when reporting response rates. Thus, not enough evidence exists to support antidepressant efficacy for patients with bipolar depression.

Clinicians should keep in mind that antidepressant monotherapy treatment of bipolar disorder may increase the risk for some patients of switching to mania, hypomania, or mixed states.²⁶ The meta-analysis²¹ found that the rate of switching was higher with tricyclic antidepressants (10.0%) than with the other antidepressants combined (3.2%).²⁷ One study²³ compared lithium plus paroxetine, lithium plus imipramine, and lithium plus placebo. Overall, paroxetine and imipramine were no different than placebo in alleviating the depressive symptoms of bipolar disorder in patients taking lithium. However, the study was underpowered, with only 117 patients. Interestingly, superiority was noted between the 2 active drugs and placebo among patients who had low serum lithium levels, but this does not indicate any efficacy for the antidepressants so much as it demonstrates that the placebo does not work if the lithium level is too low. And again, if the lithium level is too low, patients may switch to mania or hypomania due to the presence of an antidepressant.

The Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD),²⁸ a more recent, large, semi-naturalistic series of studies, was reasonably powered and contained an embedded randomized trial that added an antidepressant (bupropion or paroxetine) or placebo to ongoing treatment with a mood stabilizer among patients with bipolar disorder who were experiencing a major depressive episode. Outcome measurements were rigorously defined and consistent with *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV)* criteria. The primary outcome, called *durable recovery*, was defined as at least 8 consecutive weeks of euthymia with no more than 2 depressive symptoms or 2 manic symptoms. A second outcome measurement, *transient remission*, which was defined as 1 to 7 consecutive weeks of euthymia, was added because the trial was only 16 weeks long, and if a subject recovered at week 12, he or she might sustain the remission for the remaining 4 weeks but could not be called *recovered*. The third important outcome measurement was *treatment-affective switch*, which applied to subjects who switched into mania or hypomania from depression.

Of the patients who had an antidepressant added to mood stabilizer treatment, 23.5% achieved durable recovery, and 27.3% of those who had placebo added achieved durable recovery.²⁹ So, no statistically significant difference in durable recovery was found between the antidepressant and placebo groups, and in fact, the group that received placebo had slightly more improvement. In addition, no difference was noted between the groups in regard to treatment-emergent switching into mania.²⁹ Of the patients taking an antidepressant and a mood stabilizer, 10.1% experienced a treatment-emergent affective switch, compared with 10.7% of patients being treated with placebo plus a mood stabilizer. Thus, no harm or benefit occurred in this study by adding an antidepressant.

Figure 2. Improvement in Acute Bipolar Depression Using Olanzapine With or Without Fluoxetine^a



^aReprinted with permission from Tohen et al.²⁰ Improvement in MADRS scores with use of olanzapine and the olanzapine-fluoxetine combination was significantly greater than with use of placebo throughout the study ($p < .001$). Improvement in MADRS scores with use of olanzapine-fluoxetine combination was significantly greater than with use of olanzapine at weeks 4 to 8 ($p < .02$).
Abbreviation: MADRS = Montgomery-Asberg Depression Rating Scale.

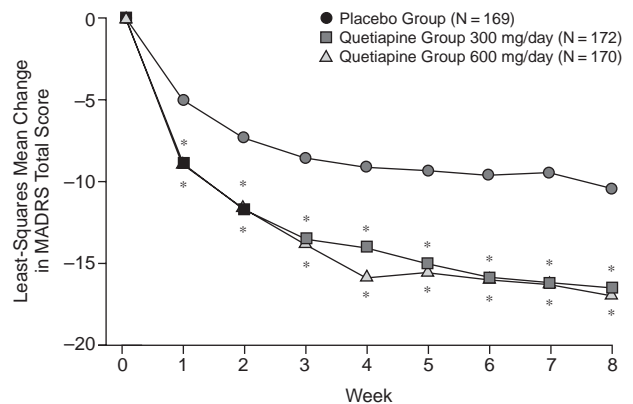
Other Pharmacologic Treatments for Acute Bipolar Depression

A controlled, multicenter study³⁰ of lamotrigine, an anti-convulsant that also acts as a mood stabilizer, evaluated the agent's efficacy compared with that of placebo in 195 subjects with bipolar I disorder who were experiencing a major depressive episode. For 7 weeks, subjects received lamotrigine monotherapy dosed at 50 mg/day or 200 mg/day or placebo. Subjects taking the higher dose of lamotrigine had significantly improved scores on the 17-item Hamilton Rating Scale for Depression (HAM-D-17), the Hamilton Rating Scale for Depression (HAM-D) Item 1 (depressed mood), the Montgomery-Asberg Depression Rating Scale (MADRS), the Clinical Global Impressions-Severity of Illness scale (CGI-S), and the Clinical Global Impressions-Improvement scale (CGI-I) compared with the placebo group, and some of these improvements were significant by the third week of treatment. Efficacy superior to that of placebo was also demonstrated on some measures in the group receiving the lower dose of lamotrigine. The results of this trial have not been replicated in 4 additional studies.³¹ While lamotrigine is not approved by the FDA for the acute treatment of bipolar depression, lamotrigine is approved for the prevention of mood episodes in bipolar disorder.

Tohen et al.²⁰ compared the combination of the atypical antipsychotic olanzapine and the antidepressant fluoxetine with olanzapine monotherapy and placebo in patients with bipolar I depression. Improvement in MADRS scores with olanzapine and the olanzapine-fluoxetine combination was significantly greater ($p < .001$) than with placebo for all 8 weeks of the study (Figure 2).

A 7-week study³² comparing the olanzapine-fluoxetine combination with lamotrigine found that subjects receiv-

Figure 3. Improvement in Acute Bipolar Depression With Quetiapine^a



^aReprinted with permission from Calabrese et al.³³
^{*}Intent-to-treat, last-observation-carried-forward analysis.
Improvement in MADRS total score with both doses of quetiapine (600 mg/day and 300 mg/day) was significantly greater than with placebo at every assessment ($p < .001$).
Abbreviation: MADRS = Montgomery-Asberg Depression Rating Scale.

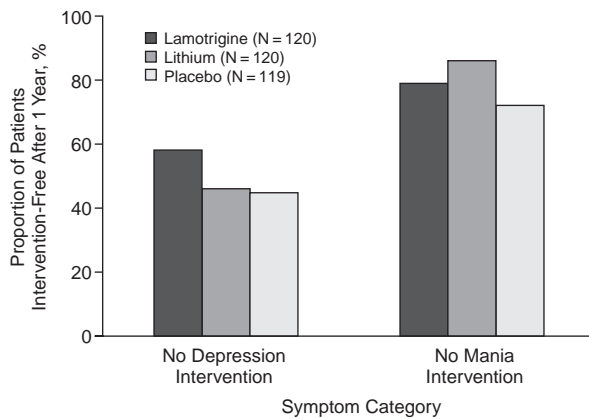
ing the combination treatment had significantly greater changes from baseline on the CGI-S, MADRS, and the Young Mania Rating Scale (YMRS), and patients receiving the combination treatment responded sooner than those taking lamotrigine. However, differences between treatment groups were insignificant when response was defined as a MADRS score reduced by 50% or more or as a CGI-S score of 3 or less. Patients receiving lamotrigine experienced a significantly higher incidence of suicidality and self-injurious behavior ($p = .037$), whereas increases in weight, triglycerides, and total cholesterol were greater with olanzapine-fluoxetine than with lamotrigine ($p \leq .001$).

Like olanzapine-fluoxetine, quetiapine monotherapy is approved by the FDA for the treatment of acute bipolar depression. In 1 study³³ of quetiapine monotherapy in patients with bipolar I or II depression, significant improvement was found in MADRS scores for quetiapine at a dose of either 600 mg/day or 300 mg/day compared with placebo (Figure 3). A second study confirmed these results.³⁴ The higher dose was slightly more effective but was associated with more treatment discontinuation owing to adverse events than the lower dose. Another study³⁵ found that quetiapine-treated patients with bipolar depression were more likely to experience antipsychotic-induced movement disorders than patients with schizophrenia.

PHARMACOTHERAPY FOR MAINTENANCE TREATMENT OF BIPOLAR DEPRESSION

Once a successful acute treatment medication has been found and the depressive episode is in remission, treatment must then be geared toward relapse prevention. When

Figure 4. Survival Comparison for Recently Depressed Patients With Bipolar Disorder Treated With Lamotrigine or Lithium^a



^aData from Calabrese et al.³⁸

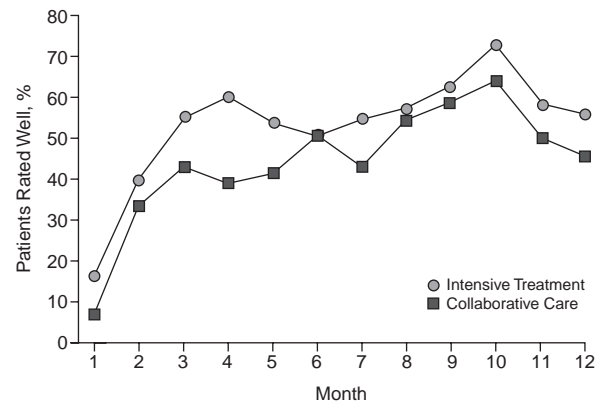
interpreting maintenance study results, the polarity of patients' index episode should be considered. For example, if the sample included patients who were recently manic, then the results may not necessarily be indicative of the agent's success in treating patients with bipolar disorder who had depressive symptoms in their index episode.

A meta-analysis³⁶ examined randomized, double-blind, placebo-controlled maintenance trials of lithium, lamotrigine, divalproex, olanzapine, and carbamazepine. While the authors called lithium the gold standard for relapse prevention, they stated that lithium may be more effective in mania prevention than depression prevention. They concluded that, for many patients, no monotherapy is sufficient for long-term maintenance therapy of bipolar disorder.

Maintenance treatment for bipolar disorder with olanzapine or lithium was studied in 431 patients who had achieved symptomatic remission with the combination of these agents.³⁷ Patients had manic or mixed bipolar disorder before remission and had a history of 2 or more manic or mixed episodes within 6 years. Significantly fewer patients taking olanzapine experienced any symptomatic (30.0%) or syndromal (26.2%) recurrence (according to HAM-D or YMRS scores and DSM-IV criteria) than those taking lithium (38.8% and 35.8%, respectively). No significant difference was found between groups for the development of a depressive episode ($p = .15$), but significantly fewer patients taking olanzapine experienced a manic ($p = .02$) or mixed ($p = .005$) episode than those taking lithium in the 12-month trial.

Lamotrigine has also been found to be efficacious in preventing mood episodes in patients with bipolar I disorder. In an 18-month placebo-controlled study³⁸ of 463 stabilized patients who were recently depressed, lamotrigine outperformed lithium in preventing bipolar depression, whereas lithium was more effective in the prevention of mania (Figure 4). However, the incidence of depressive re-

Figure 5. Adjunctive Intensive Psychosocial Intervention Versus Collaborative Care in Patients With Bipolar Disorder^a



^aReprinted with permission from Miklowitz et al.⁴¹

lapse was almost 3 times greater than that of manic relapse. Both agents had a significantly longer time to intervention for any mood episode than placebo ($p = .029$). Research on the combination of lamotrigine and lithium is needed.

In an 18-month study³⁹ of 175 patients with bipolar I disorder who were recently manic or hypomanic, both lamotrigine and lithium prolonged the time to intervention for any mood episode significantly more than placebo ($p = .006$). In preventing bipolar depression, lamotrigine was superior to placebo ($p = .02$), whereas lithium was more effective than placebo ($p = .006$) in the prevention of mania, hypomania, or a mixed episode.

Although lithium appears to be insufficient for preventing bipolar depression, a meta-analysis⁴⁰ suggested that lithium is effective in preventing suicide, self-harm, and death from other causes. Thus, combining lithium with other effective medications may be clinically useful.

ADJUNCTIVE NONPHARMACOLOGIC TREATMENTS FOR BIPOLAR DISORDER

In addition to pharmaceutical treatment options, adjunctive psychosocial interventions for patients with bipolar disorder include cognitive-behavioral therapy, family-focused therapy, interpersonal and social rhythm therapy, and group psychoeducation. In the STEP-BD study, Miklowitz et al.⁴¹ found that patients receiving intensive psychosocial interventions in addition to pharmacotherapy over 1 year not only had better recovery rates than those who received collaborative care (brief psychoeducation) but also recovered up to 110 days sooner (Figure 5).

CONCLUSION

In summary, the olanzapine-fluoxetine combination and quetiapine monotherapy have FDA approval for the treatment of acute bipolar major depressive episodes, and

lamotrigine is approved for the prevention of mood episodes, although it has more of an effect on bipolar depression than on mania or hypomania. Other agents have also been found to be efficacious for acute or maintenance treatment of bipolar depression. Many patients will require polypharmacy for acute and long-term treatment, and, while many clinicians use judicious polypharmacy strategies, most combinations have not been studied. Future research should focus on evaluating real-world combinations in naturalistic settings. Also, structured psychosocial interventions are an important component of the effective management of bipolar disorder and should be used in conjunction with pharmacotherapy as a part of everyday practice.

Drug names: bupropion (Wellbutrin, Aplenzin, and others), carbamazepine (Carbatrol, Equetrol, and others), divalproex (Depakote), fluoxetine (Prozac and others), imipramine (Tofranil and others), lamotrigine (Lamictal and others), lithium (Eskalith, Lithobid, and others), olanzapine (Zyprexa), olanzapine-fluoxetine combination (Symbyax), paroxetine (Paxil, Pexeva, and others), quetiapine (Seroquel), tranylcypromine (Parnate).

Disclosure of off-label usage: The author has determined that, to the best of his knowledge, bupropion, carbamazepine, divalproex, fluoxetine, imipramine, lithium, olanzapine, paroxetine, tranylcypromine, and deprenyl are not approved by the U.S. Food and Drug Administration for the treatment of bipolar depression.

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