Monotherapy Versus Combined Treatment With Second-Generation Antipsychotics in Bipolar Disorder

Terence A. Ketter, M.D.

The American Psychiatric Association guidelines for treating bipolar disorder recommend combination therapies to treat patients experiencing severe acute manic or mixed episodes and breakthrough manic or mixed episodes during maintenance therapy. Combination therapies approved by the U.S. Food and Drug Administration for the treatment of acute manic states include the use of second-generation antipsychotics, such as olanzapine, risperidone, quetiapine, and aripiprazole in combination with lithium or divalproex; for the treatment of acute bipolar depression, the olanzapine plus fluoxetine combination; and for maintenance treatment, quetiapine combined with lithium or valproate. When combining medications for the management of patients with bipolar disorders, physicians face a potentially complex treatment strategy. Available agents have different mechanisms of action, routes of metabolism and excretion, therapeutic effects, and side effects. Combining treatments can be advantageous owing to therapeutic synergy; however, the liability is an increased possibility of adverse effects. The decision to use a combination therapy should be made on the basis of the efficacy, tolerability, and safety of each medication and their specific combination for individual patients.
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In recent years, an ever-expanding range of treatment options has become available to clinicians for the management of bipolar disorder. From 1970 until 1999, lithium, chlorpromazine, and divalproex were the only drugs approved by the U.S. Food and Drug Administration (FDA) for the treatment of acute mania. But from 2000 to 2004, 5 second-generation antipsychotics (olanzapine, risperidone, quetiapine, ziprasidone, and aripiprazole) received indications for monotherapy treatment of acute mania, 3 received indications for adjunctive (added to lithium or valproate) treatment of acute mania (olanzapine, risperidone, and quetiapine), and an anticonvulsant, carbamazepine, received a monotherapy indication for acute mania. In 2003, another anticonvulsant, lamotrigine, was approved for maintenance treatment, almost 30 years after lithium received that indication, followed by olanzapine and aripiprazole in 2004 and 2005. The combination of olanzapine and fluoxetine was approved for treating acute depressive episodes of bipolar disorder in 2003. In 2006, quetiapine was approved as a monotherapy for acute depressive episodes in bipolar disorder, and in 2008, aripiprazole was approved as an adjunctive therapy to lithium or valproate for manic and mixed episodes and quetiapine combined with lithium or valproate was approved for maintenance treatment.

Since 2002, the American Psychiatric Association (APA) bipolar disorder practice guidelines[1] have recommended combinations of second-generation antipsychotics with mood stabilizers to treat patients during severe acute manic or mixed episodes and during breakthrough manic or mixed episodes in the maintenance phase. The increasing use of combination therapies by clinicians is well documented—one retrospective review[2] found that the percentage of patients discharged with 3 or more medications grew from less than 4% in the 1970s to more than 43% by the mid-1990s—and the APA guidelines reflect this trend.

Combination therapies approved by the FDA for the treatment of acute manic states include the use of the second-generation antipsychotics olanzapine, risperidone, quetiapine, and aripiprazole in combination with the mood stabilizers lithium or divalproex; for the treatment of acute bipolar depression, the olanzapine-fluoxetine combination; and for bipolar maintenance, quetiapine combined with lithium or valproate. As of mid-2008, maintenance treatment combinations lacked FDA approvals, but were common practice in clinical settings.

SELECTION OF MONOTHERAPY VERSUS COMBINATION THERAPY

When combining medications for the management of patients with bipolar disorders, physicians face complex

From the Department of Psychiatry and Behavior Sciences and the Bipolar Disorders Clinic, Stanford University School of Medicine, Stanford, Calif.

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Corresponding author and reprints: Terence A. Ketter, M.D., Stanford University School of Medicine, 401 Quarry Rd., Rm 2124, Stanford, CA 94305-5723 (e-mail: tketter@stanford.edu).

treatment choices. Available agents have different mechanisms of action, routes of metabolism and excretion, therapeutic effects, and side effects. Combining treatments can be advantageous owing to therapeutic synergy, but the liability is an increased possibility of adverse effects and potential drug interactions.

Treatment combinations should be prescribed on the basis of efficacy, safety, and tolerability, and how these match individual patient characteristics. FDA-approved combination therapies have been proven in randomized, double-blind, placebo-controlled trials to have efficacy in specific situations and also have extensive safety data. Adverse effects can compromise the effectiveness of a combination, but, by paying careful attention to dosing, scheduling, and formulation of both of the agents in the combination, the clinician may obtain additive therapeutic effects while keeping each agent below its side effect threshold.

Combination therapies may be referred to by terms such as *multimodal therapy* or *polypharmacy*. *Multimodal therapy* has a good connotation, in that the combination is rational, increases efficacy, and has a neutral effect on toxicity. *Polypharmacy* can have a negative connotation as being irrational or not based on evidence, having a neutral or even deleterious effect on efficacy, and increasing toxicity.

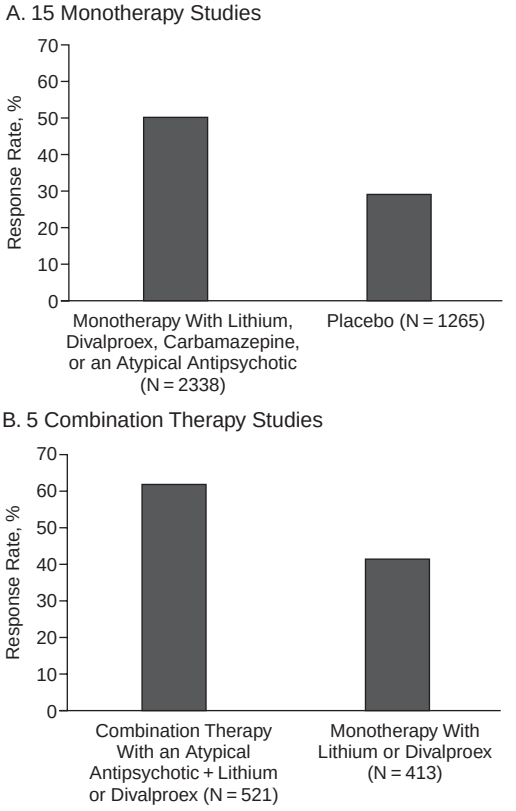
MONOTHERAPY VERSUS COMBINATION THERAPY

Acute Manic or Mixed Episodes

The severe mood disturbance in a manic episode is capable of causing serious disruption in a person's occupational and social life. Hospitalization may be necessary to safeguard the patient or those around him or her.[3] Bipolar patients may also experience mixed episodes, in which the criteria are met for both a manic and a major depressive episode nearly every day for at least 1 week. Quickly controlling affective symptoms—thereby attenuating the disruption to the patient's life and helping to ensure the safety of the patient and the patient's significant others—is an important goal during the treatment of a manic or mixed episode. Studies have sought to answer whether specific combinations of agents that have shown efficacy alone could provide more rapid and robust improvement.

A review[4] of 20 randomized, double-blind, controlled studies of monotherapy or combination therapy for the treatment of acute mania illustrated the benefits that can be obtained through combination treatments. In 15 monotherapy studies, in which patients were treated with lithium, divalproex, carbamazepine, or a second-generation antipsychotic, a 21% greater pooled response rate was found with the active agents compared with placebo (Figure 1A). In the remaining 5 studies, the results of combination therapy with a second-generation antipsychotic added to either lithium or divalproex were compared with the results of monotherapy with either lithium or divalproex. In these studies, combination therapy had a pooled response rate that was 20% greater than that of monotherapy (Figure 1B). Thus, the incremental benefit of adding a second agent compared to monotherapy (20%) was similar to that seen with monotherapy compared to placebo (21%).

Figure 1. Pooled Response Rates From 20 Acute Mania Studies[a,b]



[a]Reprinted with permission from Ketter et al.[4]; $p < .0001$.
[b]Response rates defined as ≥ 50% decrease in mania rating.

One of the studies in the meta-analysis[4] was by Sachs and colleagues,[5] who compared the efficacy and safety of adding risperidone or the first-generation antipsychotic haloperidol versus placebo to a mood stabilizer (either lithium or divalproex). The study included 156 patients with bipolar disorder having a current manic or mixed episode. Using the Young Mania Rating Scale (YMRS), the researchers found that either risperidone or haloperidol administered in combination with a mood stabilizer was more efficacious than a mood stabilizer plus placebo. More than twice as many patients taking haloperidol had to take medication to treat extrapyramidal symptoms compared to those taking risperidone. The mean daily doses were 3.8 mg of risperidone and 6.2 mg of haloperidol. Of note, the serum levels of the mood stabilizers in this study were relatively low, indicating that the synergistic benefit of combinations may allow for lower doses of both drugs, thereby diminishing dose-related side effects.

Another study reviewed in the meta-analysis[4] compared risperidone or placebo plus mood stabilizers (lithium,

divalproex, and carbamazapine)[6] in the treatment of acute mania, and this study also found risperidone superior to placebo using YMRS scores as the primary efficacy measure. An important aspect of this study is that patients treated with carbamazepine needed to be excluded from the results to optimize the reduction in YMRS scores for the risperidone group. This appeared to be due to carbamazepine having a clinically significant drug interaction with risperidone, lowering plasma concentrations of risperidone by 40%.

Olanzapine is another second-generation antipsychotic that has been shown to have acute antimanic efficacy.[7] Tohen and colleagues[8] conducted a 6-week, double-blind, randomized, placebo-controlled trial to determine the efficacy and safety of combined therapy with olanzapine and either valproate or lithium versus monotherapy with valproate or lithium for patients with acute manic or mixed episodes at enrollment. The olanzapine cotherapy group showed a mean decrease in YMRS total score of 13.1 points, corresponding to a 58.5% improvement from baseline, compared with a decrease of 9.1 points for the monotherapy group, or 40.1%. The response rate to treatment for the cotherapy group was 67.7%, compared with a response rate of 44.7% for the patients in the monotherapy group ($p < .001$). Another benefit was that the time to response was significantly shorter for the cotherapy population, with a median response of 18 days versus 28 days for monotherapy ($p = .002$). Again, lower blood levels of lithium and valproate were reported in this trial; the sample was limited to partial responders, and because patients received monotherapy for only 2 weeks before beginning cotherapy, the mood stabilizer doses may not yet have been optimized.

In a recent combination therapy study,[9] carbamazepine yielded lower than expected blood olanzapine concentrations, and even though this was addressed in part by more aggressive olanzapine dosage, the efficacy of the olanzapine plus carbamazepine combination was still not significantly better than that of carbamazepine monotherapy in the treatment of acute mania. However, olanzapine plus carbamazepine therapy compared to carbamazepine monotherapy yielded higher triglyceride levels and more frequent clinically significant (≥ 7%) weight gain (24.6% versus 3.4%). Thus, in controlled studies, combination of carbamazepine with both risperidone and olanzapine appeared to fail to yield additional benefit in acute mania compared to treatment with carbamazepine alone.

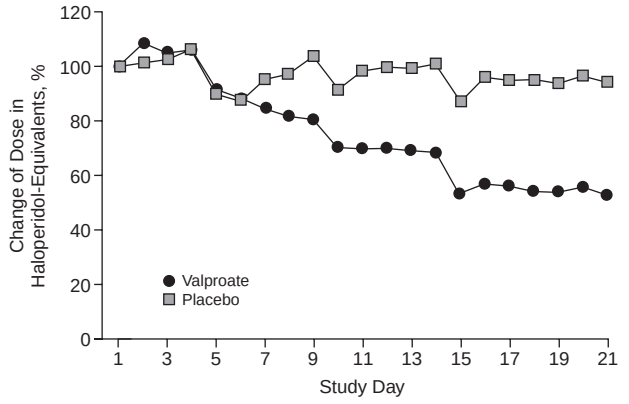
The efficacy of the antipsychotic quetiapine as a monotherapy in the treatment of mania has been well established.[10] Yatham et al.[11] studied the effectiveness of 3 to 6 weeks of the addition of quetiapine or placebo to lithium or divalproex. In this double-blind study, significantly more patients in the quetiapine plus lithium or divalproex group (N = 185) than in the placebo plus lithium or divalproex group (N = 185) met the criteria for response on the YMRS; 55.7% versus 41.6% of patients responded, respectively ($p < .01$). In addition, the combination therapy of quetiapine and lithium or divalproex resulted in an earlier onset of action, higher rates of remission, and greater effectiveness in treating aggression. Although quetiapine requires some titration to an optimal dose, many patients can tolerate a regimen of 100 mg on the first day, 200 mg on the second, and so on up to a daily dosage range of 500 mg to 800 mg.

A recent trial[12] assessed adjunctive aripiprazole (added to lithium or valproate) in acute mania. In this 6-week, multicenter, randomized, double-blind, placebo-controlled acute mania study, aripiprazole or placebo was added in patients with inadequate responses to lithium (mean serum concentration 0.77 mEq/L) or valproate (mean serum concentration 77 μg/mL) monotherapy. Aripiprazole was started at 15 mg/day with a mean final dose of 19.0 mg/day. The YMRS response rate was greater in 247 patients taking combination therapy (62.8%) than in 130 patients taking mood stabilizer monotherapy (48.5%), and the mean time to response was shorter with aripiprazole plus mood stabilizer than with mood stabilizer monotherapy. Combination treatment compared to monotherapy yielded more extrapyramidal symptoms (28.1% versus 13.8%, primarily akathisia—18.6% versus 5.4%) and discontinuations due to adverse events (9% versus 5%), but similar weight gain (0.55 kg versus 0.23 kg) and percentage of patients with ≥ 7% weight gain (3.0% versus 3.9%).

In Europe, in the past, antipsychotics were viewed as the primary treatment for acute mania, with mood stabilizers added as maintenance agents or perhaps as adjuncts during acute treatment. Following this European model, Müller-Oerlinghausen and colleagues[13] conducted a 3-week, randomized, double-blind, parallel-group, placebo-controlled trial to evaluate the efficacy and safety of valproate given as an adjunctive medication to the antipsychotics haloperidol and/or perazine for a patient sample primarily with bipolar or schizoaffective episodes. Some patients were taking antipsychotics other than the recommended haloperidol or perazine. In the valproate group, patients (N = 69) were administered valproate and haloperidol (50.7%), valproate and perazine (20.3%), or valproate and a combination of haloperidol and perazine (13.0%); patients receiving placebo (N = 67) were administered haloperidol (40.3%), perazine (19.4%), or haloperidol plus perazine (25.4%). A higher percentage of responders (patients showing an improvement of at least 50% on the YMRS) was found for patients treated with the combination of valproate and an antipsychotic (70.2%) than with antipsychotics alone (46.5%; $p = .005$), a difference similar to the 20% greater benefit seen in the U.S. combination studies as compared with monotherapy.[4] Combination therapy not only produced faster response rates than monotherapy (4 to 7 days sooner) but also helped to lower the antipsychotic dosage needed (Figure 2; $p = .0007$).[13]

These trials have shown the efficacy of combining second-generation antipsychotics with mood stabilizers in the treatment of acute manic or mixed episodes. In many

Figure 2. Changes in Dose of Antipsychotics With and Without Valproate Augmentation[a]



[a]Reprinted with permission from Müller-Oerlinghausen et al.[13]

cases, lower dosages of each agent, when combined together, can not only deliver better treatment response rates and shorter response times but often avoid the adverse side effects associated with higher dosage levels.

Acute Bipolar Depression

Although patients spend more time depressed than manic or hypomanic in both bipolar I and bipolar II disorders,[14–16] only 1 combination treatment—olanzapine plus fluoxetine—has been approved for treating bipolar depression. As of mid-2008, the only other approved treatment was quetiapine monotherapy, and it was unclear whether adjunctive antidepressants (added to mood stabilizers or second-generation antipsychotics) yielded additional benefit in acute bipolar depression. Indeed, a review by Sachs[17] of trials of monotherapies and combination therapies in studies that included more than 100 patients with acute bipolar depression found that, unlike with adding fluoxetine to olanzapine, addition of antidepressants (paroxetine or imipramine) to lithium failed to yield additional benefit, and that monotherapy with quetiapine yielded benefits comparable to combination therapies in other trials (Figure 3).

The role of antidepressants in treating bipolar depression is controversial. Although no antidepressants have FDA approval for treating bipolar disorder (except for fluoxetine when combined with olanzapine), prescribing antidepressants adjunctively with mood stabilizers is a common practice.[18]

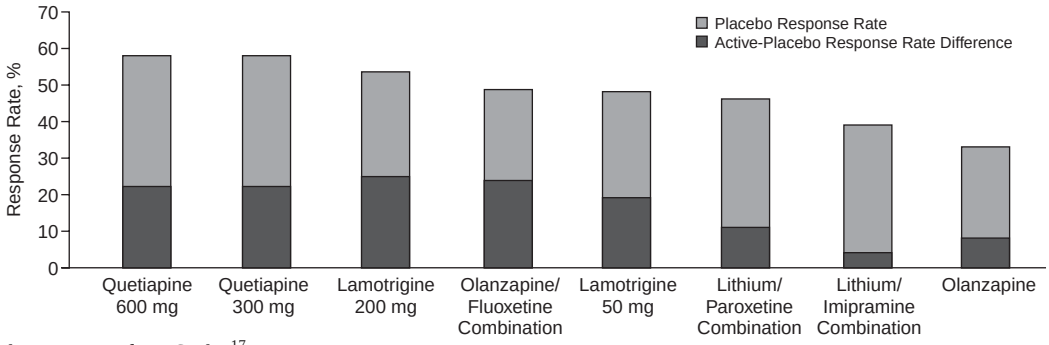
The Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD) is a multicenter National Institute of Mental Health initiative designed to collect and evaluate longitudinal data on patients with bipolar disorder.[19] Since the Sachs review[17] was published, Sachs et al.[20] have reported results of a large STEP-BD double-blind, randomized, placebo-controlled trial of adjunctive antidepressants (paroxetine or bupropion) combined with mood stabilizers. No increased efficacy was found by adding either antidepressant to mood stabilizers. Both recovery rates—defined as the percentage of patients achieving 8 consecutive weeks of euthymia—and treatment-emergent affective switch rates were comparable to those with placebo. Of the patients receiving a mood stabilizer plus adjunctive antidepressant therapy (N = 179), 23.5% had a durable recovery, and, of those receiving a mood stabilizer plus placebo (N = 187), 27.3% had a durable recovery ($p = .40$). Thus, these combinations caused no harm but also added no benefit.

These findings were consistent with earlier observations by Nemeroff et al.,[21] who studied the efficacy of paroxetine and imipramine versus that of placebo as an adjunct to lithium in 1 of the trials reviewed by Sachs.[17] In this double-blind, placebo-controlled study, patients were assigned to paroxetine (N = 35), imipramine (N = 39), or placebo (N = 43) in addition to lithium. According to change from baseline to endpoint scores on the Hamilton Rating Scale for Depression and the Clinical Global Impressions Illness Severity (CGI-S) scale, the differences in overall efficacy between the antidepressants and placebo were insignificant. Paroxetine was associated with a lower incidence of adverse effects—including treatment-related manic emergence—than imipramine. However, when the sample was segregated by high (> 0.8 mEq/L) or low (≤ 0.8 mEq/L) serum lithium levels, both antidepressants were found to be superior to placebo in patients with low serum lithium levels. Antidepressant therapy might be clinically useful for patients who cannot tolerate high serum lithium levels. Overall, the combination of a mood stabilizer and an antidepressant is not recommended as a foundational treatment; instead, monotherapy treatment with a mood stabilizer should probably be initiated first.

Although these studies showed no benefit of adding some antidepressants to mood stabilizers to treat the depressive episodes of bipolar disorder, studies have shown benefits with the particular combination of the antidepressant fluoxetine and the second-generation antipsychotic olanzapine. Tohen and colleagues[22] undertook an 8-week, double-blind, randomized controlled trial, included in the meta-analysis,[17] in which patients were assigned to receive placebo (N = 377), olanzapine (N = 370), or the olanzapine-fluoxetine combination (N = 86). The results showed olanzapine superior to placebo, and combination therapy superior to not only placebo but also to olanzapine monotherapy. The remission rates were 48.8% for the combination group, 32.8% for the olanzapine group, and 24.5% for the placebo group. Also, time to remission was shorter for the olanzapine group versus the placebo group (57 days versus 59 days) and significantly shorter for the combination group versus the placebo group (42 days versus 59 days, $p < .001$).

Lamotrigine, an anticonvulsant approved for maintenance treatment in bipolar disorder, appeared promising in

Figure 3. Pooled Response Rates From 4 Acute Bipolar Depression Studies[a,b]



[a]Reprinted with permission from Sachs.[17]
[b]Response rates defined as ≥ 50% decrease in depression rating.

an early study as an acute monotherapy for bipolar depression.[23] However, 4 of 5 subsequent multicenter, randomized, double-blind, placebo-controlled studies[24] of lamotrigine in acute bipolar depression were negative. In a pooled analysis[25] of all 5 studies, the Montgomery-Asberg Depression Rating Scale (MADRS) response rate (at least 50% reduction in baseline score) for lamotrigine (49.5%) was significantly greater than for placebo (41.4%, $p = 0.01$).

In a randomized, double-blind trial[26] of lamotrigine monotherapy (N = 205) versus the olanzapine-fluoxetine combination (N = 205), the combination therapy showed a significantly greater improvement than that of lamotrigine on the study's primary outcome scale—change from baseline on the CGI across the 7-week treatment period ($p = .002$)—and also a significantly shorter time to response ($p = .010$). However, with response defined as a 50% or greater decrease in MADRS scores, this superiority fell to the level of a trend ($p < .073$). Treatment-emergent mania was low for both groups. Patients taking combination treatment experienced more adverse effects than those taking lamotrigine. Somnolence, increased appetite, dry mouth, sedation, weight gain, and tremor occurred more frequently with the combination ($p < .05$), and total cholesterol, weight, and triglyceride levels were elevated in combination-treated patients while being lowered in lamotrigine-treated patients. Thus, the benefit of added efficacy with the olanzapine plus fluoxetine combination compared to lamotrigine needs to be weighed against the risk of adverse effects.

A STEP-BD study[27] examined patients with treatment-resistant bipolar depression. Patients (N = 66) were in a depressive episode that was nonresponsive to a combination of a mood stabilizer plus 1 or 2 antidepressants. Participants were randomly assigned to adjunctive treatment for 16 weeks with lamotrigine, inositol, or risperidone in addition to the mood stabilizer and 1 or 2 antidepressants. Overall there was a low recovery rate, but recovery tended to be more frequent with lamotrigine (23.8%) compared to risperidone (4.6%), and intermediate with inositol (17.4%). Small sample size limited the interpretation of these findings. Although some second-generation antipsychotics seem to have some antidepressant effects, particularly as adjunctive treatments in acute unipolar major depressive disorder, the same does not appear to be true of risperidone in acute bipolar depression. A larger study is needed to confirm these results.

Bipolar Maintenance

As of mid-2008, there were 4 approved monotherapy treatments (lithium, lamotrigine, olanzapine, and aripiprazole), and only 1 approved combination treatment (quetiapine combined with lithium or valproate) for the longer-term treatment of bipolar disorder, despite the use of diverse combinations in clinical practice being very common.

Quetiapine combined with lithuim or valproate was recently approved for bipolar maintenance treatment, based on two 24-month, multicenter, randomized, double-blind, placebo-controlled adjunctive quetiapine (added to lithium or divalproex) longer-term treatment studies[28] of patients with bipolar I disorder with a recent manic, mixed, or depressive episode. Combining the results from these trials, adjunctive quetiapine (N = 646) compared to adjunctive placebo (N = 680) yielded significantly lower overall (19.3% versus 50.4%), depressive (10% versus 27%), and manic relapse rates (all $p < .0001$).

Clozapine, another second-generation antipsychotic, is approved by the FDA for treatment-resistant schizophrenia but is not approved for treating bipolar disorder. Clozapine has been studied by Suppes and colleagues[29] and was found to be effective as an add-on therapy for patients with treatment-resistant bipolar disorder or schizoaffective disorder. In this study, treatment-resistant patients were randomly assigned to receive clozapine augmentation to treatment as usual (N = 19) or treatment as usual without clozapine (N = 19). After 1 year, the adjunctive clozapine group had greater improvement from baseline in ratings on the Brief Psychiatric Rating Scale and the CGI than the

Table 1. Boxed Warnings for Drugs Used in Treating Bipolar Disorder

Agent	Boxed Warning
Lithium	Toxicity at doses close to therapeutic levels
Valproate	Hepatotoxicity, teratogenicity, and pancreatitis
Lamotrigine	Serious rash
Carbamazepine	Serious rash, aplastic anemia, and agranulocytosis
Second-generation antipsychotics	Increased mortality in elderly patients
Antidepressants	Suicidality in children, adolescents, and young adults

treatment-as-usual group, and a sustained mood-stabilizing effect was observed. Clozapine carries the risk of significant side effects, including agranulocytosis, which requires weekly blood monitoring. Importantly, the mean dosage used to treat bipolar disorder (234 mg/day) was much lower than that used for schizoaffective patients (623 mg/day). Clozapine could constitute an important option for patients with very treatment-resistant bipolar disorder.

In the maintenance phase[30] of the above-mentioned acute trial[26] comparing the olanzapine plus fluoxetine combination with lamotrigine monotherapy, among patients in remission (MADRS ≤ 12) after the 7-week acute phase, depressive relapse (MADRS > 15) rates were similar with the olanzapine plus fluoxetine combination (13.7%, 13/95) and lamotrigine (18.2%, 14/77). Treatment-emergent affective switch rates were similarly low with the olanzapine plus fluoxetine combination (5.0%, 10/202) and lamotrigine (7.3%, 14/191). The olanzapine plus fluoxetine combination compared to lamotrigine yielded less insomnia, but more other adverse effects, including somnolence, increased appetite, dry mouth, sedation, weight gain, and tremor, and incidence of treatment-emergent cholesterol ≥ 240 (15.9% versus 3.7%) and clinically significant (> 7%) weight gain (33.8% versus 2.1%).

The use of adjunctive antidepressants in the longer-term treatment of bipolar disorder is even more controversial than in the treatment of acute bipolar depression. These agents have been seen as temporary adjuncts for administration during acute bipolar depression and are best avoided in the longer term due to efficacy and tolerability (i.e., treatment-emergent affective switch) concerns. Indeed, a review of 7 controlled trials[31] involving 363 bipolar disorder patients indicated that adding antidepressants to lithium did not confer enhanced prevention of depression and that antidepressant monotherapy, and perhaps adding an antidepressant to lithium, increased treatment-emergent affective switch.

Nevertheless, it may be that a minority of patients could benefit from longer-term adjunctive antidepressants. In a naturalistic (i.e., not randomized) effectiveness study,[32] only 34% (189/549) of Stanley Foundation Bipolar Network patients receiving adjunctive antidepressants for new-onset major depressive episodes continued these agents for at least 60 days. Among the small subset (15%, 84/549) achieving remission for 6 consecutive weeks (with CGI-S scores indicating no more than mild subsyndromal symptoms), continuing antidepressants more than 6 months compared to less than 6 months was associated with a lower rate of depressive relapse (36% versus 70%) with no increase in treatment-emergent affective switch. Thus, among the 15% of depressed bipolar disorder patients who attained durable remission with antidepressants, continuing these agents more than 6 months had merit.

Clearly, more randomized, controlled trials of combination treatments for the longer-term management of bipolar depression are needed.

SAFETY AND TOLERABILITY OF MEDICATIONS USED TO TREAT BIPOLAR DISORDER

Nearly every treatment used for bipolar disorder carries the possibility of serious side effects (Table 1). All mood stabilizers include boxed warnings. Part of the art of pharmacotherapy for patients with bipolar disorder is matching agents to patients' risk factors and ability to tolerate the agents. The patient's other medications should also be taken into account.

Second-generation antipsychotics, besides having a boxed warning with respect to increased cardiac or infectious disease mortality in elderly patients, also may be associated with extrapyramidal effects and risk factors for metabolic syndrome, such as weight gain.[33] Metabolic syndrome is closely associated with cardiovascular disease and diabetes,[34] and studies[35,36] have ranked the metabolic risks associated with certain antipsychotics. In general, clozapine and olanzapine are associated with the greatest weight gain and increased risk of associated metabolic disturbances; risperidone and quetiapine can produce intermediate changes in weight but discrepant results in relation to metabolic risk; and aripiprazole and ziprasidone produce minimal weight gain and little risk for metabolic disturbances.[36]

In addition to possible suicidality in young patients, antidepressants have a range of side effects (such as teratogenicity) and potential drug interactions that should be considered in combination therapy. Additional long-term studies are needed in this area to fully assess benefits and risks of combining antidepressants with other agents for bipolar disorder.

CONCLUSION

Physicians have a substantial armamentarium of agents to use for the treatment of bipolar disorder. Although successful results may be obtained with monotherapy in some patients, other patients may not respond to diverse monotherapies. By combining mood stabilizers with second-generation antipsychotics, or possibly antidepressants and second-generation antipsychotics, therapeutic synergy may be created that provides better responses for these

treatment-resistant patients. Combinations may also yield more rapid and robust responses for some patients. Using lower dosages of each of the agents may help to avoid adverse effects, yet yield greater efficacy through synergy. When using combination therapy in the management of bipolar disorder, physicians should tailor regimens to suit the individual risk factors of each patient in an effort to achieve the most robust therapeutic outcome with the fewest adverse effects.

Drug names: aripiprazole (Abilify), bupropion (Wellbutrin, Aplenzin, and others), carbamazepine (Carbatrol, Tegretol, and others), chlorpromazine (Thorazine, Sonazine, and others), clozapine (FazaClo, Clozaril, and others), divalproex (Depakote), fluoxetine (Prozac and others), haloperidol (Haldol and others), imipramine (Tofranil and others), lamotrigine (Lamictal and others), lithium (Eskalith, Lithobid, and others), olanzapine (Zyprexa), olanzapine-fluoxetine (Symbyax), paroxetine (Paxil, Pexeva, and others), quetiapine (Seroquel), risperidone (Risperdal), valproate (Depacon and others), ziprasidone (Geodon).

Disclosure of off-label usage: The author has determined that, to the best of his knowledge, bupropion, imipramine, paroxetine, risperidone, and inositol are not approved by the U.S. Food and Drug Administration for the adjunctive treatment of bipolar depression; carbamazepine is not approved for the combination treatment of bipolar disorder; clozapine, haloperidol, and perazine are not approved for the treatment of bipolar disorder; lamotrigine is not approved for the treatment of acute bipolar depression and adjunctive treatment of bipolar depression; and lithium is not approved for use in combination with antidepressants for bipolar depression.

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