Making Optimal Use of Combination Pharmacotherapy in Bipolar Disorder

Charles L. Bowden, M.D.

Because patients with bipolar disorder often do not respond sufficiently to treatment with 1 mood stabilizer, psychiatrists frequently employ combination therapy and add antipsychotics, antiepileptics, or antidepressants to mood stabilizers. Combination therapy can be more effective than monotherapy in controlling breakthrough or treatment-resistant episodes. For example, atypical antipsychotics have been shown to be effective adjunctive treatments for mania and for patients with psychotic symptoms during a depressive episode, while the combination of a mood stabilizer and lamotrigine or an antidepressant has been found to control bipolar depression. The American Psychiatric Association guideline for the treatment of bipolar disorder recommends optimizing individual medications before switching to combination therapy. Selecting a combination treatment regimen with an acceptable side effect profile is critically important because patients may discontinue therapy they cannot tolerate. Agents should be added carefully, with continued monitoring of adverse effects. Physicians should give patients only as much medication as needed.

From the Department of Psychiatry, University of Texas Health Science Center at San Antonio, San Antonio.

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Corresponding author and reprints: Charles L. Bowden, M.D., Department of Psychiatry, University of Texas Health Science Center at San Antonio, 7703 Floyd Curl Dr., San Antonio, TX 78229 (e-mail: bowdenc@uthscsa.edu).
Table 1. Treatment Considerations: Types of Combination Therapy for Bipolar Disorder

<table>
<thead>
<tr>
<th>Combination (cotherapy): concurrent use of 2 or more drugs</th>
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<tr>
<td>Add-on: drug B is added to drug A</td>
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<td>Evidence-based combination therapy: At least 1 randomized, placebo-controlled study has reported a specific combination to be superior to a comparator on some measure of efficacy for patients with clearly described characteristics</td>
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Combination Therapy for Bipolar Mania

Combination therapy can be used as the initial treatment for severe episodes of bipolar mania. In such cases, the American Psychiatric Association (APA) Practice Guideline for the Treatment of Patients With Bipolar Disorder recommends a combination of lithium or divalproex plus an antipsychotic agent, which may be necessary for severely ill or agitated patients. The APA guideline recommends the use of atypical antipsychotics rather than typical antipsychotics “because of the more benign side effect profile of atypical antipsychotics.” The guideline states, “Of the atypical antipsychotics, there is presently more placebo-controlled evidence in support of olanzapine and risperidone.” In less severe mania, the guideline advises that combination treatment with a mood stabilizer and an antipsychotic should be initiated if mono-therapy with a mood stabilizer is ineffective or if a patient experiences a breakthrough manic episode or psychotic symptoms.

Psychotic symptoms (e.g., delusions or hallucinations) are common among patients with bipolar disorder. An evaluation of the patient population of the Stanley Foundation Bipolar Network concluded that 67% of patients with bipolar I disorder and 59% of all patients with bipolar disorder have a history of psychotic symptoms. If a patient has psychotic symptoms at the time of diagnosis or develops psychotic symptoms after mood stabilizer treatment has been started, an antipsychotic should be added. Atypical antipsychotics are as effective as conventional antipsychotics and are better tolerated. Most studies indicate that an atypical antipsychotic and a mood stabilizer are a more effective therapy than a mood stabilizer alone. Good evidence is available for adding an antipsychotic to lithium or valproate, or valproate to an antipsychotic. Carbamazepine’s use in combination therapy for mania can be problematic due to its many drug interactions, most notably a reduction of serum levels of concomitantly administered antipsychotic drugs.

Combination Treatment of Bipolar Depression

For acute depressive episodes, the APA guideline recommends lithium or lamotrigine as first-line treatment. Initial antidepressant monotherapy is not recommended because of the risk for precipitating a switch to mania. Some clinicians initiate lithium-antidepressant combi-
higher in the olanzapine group versus the monotherapy group included somnolence, dry mouth, weight gain, and tremor.

Combination therapy with risperidone and lithium or divalproex also produced significantly greater reductions (p = .009) in YMRS scores than monotherapy with a mood stabilizer. On the Clinical Global Impressions scale, 53% of patients receiving risperidone–mood stabilizer combination therapy had ratings of much improved or very much improved, compared with 30% of patients receiving a mood stabilizer plus placebo (p = .002). The most common adverse events with risperidone–mood stabilizer treatment were somnolence, headache, dyspepsia, extrapyramidal symptoms, and dizziness.

Adjunctive treatment with quetiapine plus a mood stabilizer has shown promise in adolescent mania and in adult mania, for which combination therapy with quetiapine produced a response on YMRS scores that was significantly greater (p = .005) than that for placebo and a mood stabilizer. Suppes et al. reported that the addition of clozapine to treatment as usual with lithium, valproate, or carbamazepine was superior to treatment as usual alone in a small-scale study with 38 patients with bipolar disorder or schizoaffective disorder. With response defined as a 30% improvement from baseline on the Brief Psychiatric Rating Scale, 65% of clozapine plus treatment-as-usual patients met the criterion for response at 3 months and 82% met it at 6 months. In contrast, 48% of treatment-as-usual patients fulfilled the response criterion at 3 months and 57% did so at 6 months.

Antidepressant monotherapy with tricyclic antidepressants (TCAs) or monoamine oxidase inhibitors (MAOIs) is associated with risk for mania induction in more than one third of bipolar patients. Treatment with antidepressants (e.g., TCAs, MAOIs, tetracyclics, nomifensine, and sulpiride) also has been related to a change from antidepressants (TCAs) or monoamine oxidase inhibitors (MAOIs) to a mood stabilizer.2 On the Clinical Global Impressions scale, 53% met the criterion for response at 3 months and 82% did so at 6 months. In contrast, 48% of treatment-as-usual patients fulfilled the response criterion at 3 months and 57% did so at 6 months.

**Implementing combination therapy**

Effectively treating patients with bipolar disorder requires that the physician possess a clear rationale and solid evidence for therapeutic decisions. The best available evidence for the effectiveness of combination therapy supports the strategy of add-on therapy rather than cotreatment, although there are instances when the need for rapid control of acute episodes requires simultaneous initiation of 2 or more agents. Starting agents sequentially enables clinicians to better identify the drug responsible for a positive or negative effect.

During the introduction of an agent, the new drug should be titrated to a therapeutic level; the physician then should wait for the patient to respond before making other changes. If the patient responds, the next step is to taper off ineffective or poorly tolerated medications, continue partially effective preexisting medications, and continue to assess the need for each component of combination therapy. Key recommendations for the use of combination therapy in bipolar disorder are presented in Table 2.

**Caveats for combination therapy**

Although combination therapy has been shown to be beneficial in treating patients with bipolar disorder, it presents its own set of complications. Combination therapy can make it difficult to identify which drug is causing improvement, adverse effects, or pharmacokinetic difficulties. Before prescribing a combination regimen, physicians should evaluate the proposed regimen and review potential adverse effects or pharmacokinetic difficulties.

Tolerability should be as important a consideration as efficacy in choosing medications. Combinations during maintenance therapy can lead to symptoms that are misinterpreted as manifestations of bipolar disorder rather than as adverse events. To help maintain the effectiveness of therapy, physicians should question patients regularly about side effects. For many patients, the adverse effect profile of some antipsychotics warrants reducing dosage or discontinuing the drug following control of an acute episode. However, the lower doses of drugs that usually are employed in combination therapy may help to mitigate the severity of side effects.

The use in combination therapy of some types of drugs should be limited. For example, more than 1 antipsychotic
Table 3. Possible Adverse Effects of Combination Maintenance Therapy of Bipolar Disorder

<table>
<thead>
<tr>
<th>Mood disturbances</th>
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<tr>
<td>Mood destabilization</td>
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<tr>
<td>Hypomania</td>
</tr>
<tr>
<td>Anergy</td>
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<tr>
<td>Impaired mentation</td>
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<tr>
<td>Weight gain</td>
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<tr>
<td>Sedation</td>
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<tr>
<td>Increases in lipoproteins</td>
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<tr>
<td>Skin disorders</td>
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<tr>
<td>Risk for serious rash with addition of new medications (especially with lamotrigine, which carries the risk for causing the potentially fatal Stevens-Johnson syndrome, and carbamazepine)</td>
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or anxiolytic should not be used concurrently. Some of the more problematic adverse effects in combination maintenance therapy are presented in Table 3.

Physicians should be careful to prescribe only as many drugs as needed for another reason: combinations can result in very high drug costs. The more drugs used, the higher the cost to the patient, which could force patients with inadequate medical insurance to abandon therapy. In weighing the cost-effectiveness of a drug or other therapy, consider not only its expense but also the costs—both economic and psychosocial—that may result from inadequate treatment. Each patient should take as much medication as needed, but never more than needed.

However, the potential benefits of combination therapy compensate for the associated risks. Combinations of 2 or more therapeutic agents have been demonstrated to be more efficacious than monotherapy in treating bipolar mania and depression. Careful selection of the various agents used in a combination regimen as well as close patient monitoring for side effects and adherence can help ensure that a combination regimen is both safe and effective.

*These agents are not approved by the Food and Drug Administration for the treatment of bipolar disorder.

Drug names: bupropion (Wellbutrin and others), carbamazepine (Epitol, Tegretol, and others), clozapine (Clozaril and others), divalproex (Depakote), imipramine (Tofranil and others), lamotrigine (Lamictal), olanzapine (Zyprexa), paroxetine (Paxil and others), quetiapine (Seroquel), risperidone (Risperdal).

REFERENCES

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