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. *(J Clin Psychiatry 2004;65[suppl 15]:21–24)*

The use of lithium or valproate as first-line treatment for acute episodes of bipolar disorder has been standard for decades, but up to 40% of patients respond poorly to monotherapy with either agent, and many have clinically significant symptoms of mania after 3 weeks of therapy with a mood stabilizer.[1,2] As a result, many authorities on bipolar disorder recommend initiating treatment with combination therapy or moving expeditiously to combination therapy if monotherapy with a mood stabilizer does not yield satisfactory results. Unfortunately, relatively few controlled clinical trials have examined the safety and efficacy of the various combinations commonly employed.[2] This article will review the findings of those studies that have been conducted and will suggest some principles and practices to bear in mind when considering combination therapy.

SELECTING A COMBINATION TREATMENT REGIMEN

The factors to weigh when selecting a combination-therapy regimen are similar to those that should be assessed in choosing any treatment for bipolar disorder: onset and mechanisms of action, probability and expected extent of response, and safety. Mechanisms of action, for example, are important in terms of a drug's effects on the dominant features of a given patient's bipolar disorder, comorbidities, and concomitant pharmacologic therapies.

Another important factor in selecting a combination regimen is the possible side effects of each drug involved. A therapeutic regimen that is difficult for patients to tolerate will decrease the probability of adherence. However, because drugs used in combination therapy typically are administered at lower dosages than those employed for monotherapy, adverse events may be less frequent and less severe. Several clinical studies examining combination therapy suggest that employing 2 or more drugs in a single therapeutic regimen does not increase the burden of adverse events.[1,2,6]

Other factors to be considered when selecting a specific combination therapy include whether the combination meets the criteria for evidence-based medicine and which of the 2 methods of combination therapy should be employed. Table 1 explores these issues.

Before moving to combination therapy by adding an adjunctive agent to a drug already being taken (as opposed to simultaneous initiation of 2 or more agents), the clinician first should ensure that the dosage of the first drug has been optimized. With mood stabilizers and some other agents, optimization of dosage entails confirming that the blood drug level is in the therapeutic range and, in some cases, higher than the normal effective serum level (although still within the therapeutic range).[4]

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

Based in part on a presentation at the National Summit Meeting of the Bipolar Care OPTIONS initiative, which was held September 4–6, 2003, in Washington, D.C., and supported by an unrestricted educational grant from Janssen Medical Affairs, L.L.C.

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

Combination (cotherapy): concurrent use of 2 or more drugs
Add-on: drug B is added to drug A
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

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[4] 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."[4(p4)] The guideline states, "Of the atypical antipsychotics, there is presently more placebo-controlled evidence in support of olanzapine and risperidone."[4(p9)] In less severe mania, the guideline advises that combination treatment with a mood stabilizer and an antipsychotic should be initiated if monotherapy 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[5] 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,[1,2] or valproate to an antipsychotic.[6] 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.[7,8]

Combination Treatment of Bipolar Depression

For acute depressive episodes, the APA guideline[4] 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 combination therapy for severely ill patients, although only a limited amount of clinical data is available to support this approach. The addition of lamotrigine, bupropion,* or paroxetine* may be considered when depressive episodes do not respond to optimal doses of first-line therapy. The next step for patients who have breakthrough depressive episodes is adjunctive treatment with an antidepressant or an antipsychotic. Depressive episodes with a psychotic feature usually require adjunctive antipsychotics.[4]

Few placebo-controlled, blinded, randomized trials of combination therapy have been conducted for the treatment of bipolar depression. Consequently, the superiority of combination therapy with 2 mood stabilizers or a mood stabilizer and an antidepressant over mood stabilizer monotherapy has not been established definitively.[9] However, Nemeroff et al.[10] demonstrated that if doses of lithium produce serum levels < 0.8 mEq/L, the addition of antidepressants yielded a combination regimen that was more effective than lithium alone. The combinations tested, lithium plus imipramine* or paroxetine, were equally effective.[10] Paroxetine has been associated with relatively low rates of switching from depression to mania or hypomania when used in combination therapy with a mood stabilizer.[10,11] In another study,[9] the combination of lithium and divalproex was as effective as a combination of a mood stabilizer plus paroxetine, although patients experienced more side effects with the mood stabilizer combination. The greater amount of side effects with the mood stabilizer combination led to a higher rate of patients quitting treatment, which implies that the addition of an antidepressant may be more effective for the acute treatment of bipolar depression.[9]

Lamotrigine has been studied extensively in a variety of bipolar disorder–related conditions and has been shown to be effective both as monotherapy and in combination treatment of acute bipolar depression. The agent does not appear to induce mania or hypomania. To prevent the serious rashes that can be a side effect of lamotrigine, dosing escalation should be gradual when the agent is given with valproate.[12]

Combination Therapy With Atypical Antipsychotics or Antidepressants

Treatment with the atypical antipsychotics olanzapine or risperidone plus a mood stabilizer has been demonstrated to be superior to treatment with a mood stabilizer alone.[1] When used in combination with valproate or lithium in the treatment of patients partially unresponsive to monotherapy with a mood stabilizer, olanzapine improved patients' Young Mania Rating Scale (YMRS) scores significantly ($p = .003$) more than monotherapy. Combination therapy with olanzapine also achieved significant ($p < .001$) improvements on Hamilton Rating Scale for Depression scores compared with monotherapy. Treatment-related side effects that were significantly

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.[2] 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.[2]

Adjunctive treatment with quetiapine plus a mood stabilizer has shown promise in adolescent mania[13] and in adult mania,[14] 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.[15] 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.[16,17] Treatment with antidepressants (e.g., TCAs, MAOIs, tetracyclics, nomifensine, and sulpiride) also has been related to a change from a manic-depressive-euthymic course to a continuous-cycling course in one fourth of patients; about two thirds of these continuous-cycling patients had rapid-cycling courses.[18] Selective serotonin reuptake inhibitors (SSRIs) and bupropion may be less likely to cause hypomania than TCAs.[10,19] However, all antidepressants have been associated with those unwanted results, and the evidence of greater therapeutic efficacy with SSRIs or bupropion is unclear. If an antidepressant is used, short-term therapy of 1 to 6 months followed by tapering is recommended.[16]

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 cotherapy, 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.

Table 2. Making Optimal Use of Combination Therapy in Bipolar Disorder: Key Recommendations[a]

Realize that the multifaceted nature of bipolar disorder usually will necessitate combination therapy
Have a specific and clear rationale for each agent prescribed and know the evidence regarding its use alone and in combination
Place overall tolerability on par with efficacy in choosing agents and regularly question patients about side effects
In combination therapy, add agents rather than starting them simultaneously whenever possible
Employ mood stabilizers in patients with bipolar I disorder
Screen for psychosis even in the absence of mania
In weighing the cost effectiveness of a drug or other therapy, consider not only its expense but also the costs that may result from inadequate treatment
Assess the need for each component of combination therapy on a continuing basis

[a]Derived from Bowden.[3]

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

Mood disturbances
Mood destabilization
Hypomania
Obtundation
Anergy
Impaired mentation
Weight gain
Sedation
Increases in low-density lipoproteins
Increases in glucose levels
Skin disorders
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)

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

1. Tohen M, Chengappa KN, 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
2. Sachs GS, Grossman F, Ghaemi SN, et al. Combination of a mood stabilizer with risperidone or haloperidol for treatment of acute mania: a double-blind, placebo-controlled comparison of efficacy and safety. Am J Psychiatry 2002;159:1146–1154
3. Bowden CL. Combination therapy vs monotherapy for the treatment of bipolar disorder. Presented at the Bipolar Care OPTIONS South Central Regional Working Group; July 25–26, 2003; Dallas, Tex
4. American Psychiatric Association. Practice Guideline for the Treatment of Patients With Bipolar Disorder [revision]. Am J Psychiatry 2002;159 (suppl 4):1–50
5. Suppes T, Leverich GS, Keck PE, et al. The Stanley Foundation Bipolar Treatment Outcome Network, 2: demographics and illness characteristics of the first 261 patients. J Affect Disord 2001;67:45–59
6. Muller-Oerlinghausen B, Retzow A, Henn FA, et al, for the European Valproate Mania Study Group. Valproate as an adjunct to neuroleptic medication for the treatment of acute episodes of mania: a prospective, randomized, double-blind, placebo-controlled, multicenter study. J Clin Psychopharmacol 2000;20:195–203
7. Spina E, Perucca E. Clinical significance of pharmacokinetic interactions between antiepileptic and psychotropic drugs. Epilepsia 2002;43:37–44
8. Licht RW, Olesen OV, Friis P, et al. Olanzapine serum concentrations lowered by concomitant treatment with carbamazepine. J Clin Psychopharmacol 2000;20:110–112
9. 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;157:124–126
10. 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
11. Vieta E, Martinez-Arán A, Goikolea JM, et al. A randomized trial comparing paroxetine and venlafaxine in the treatment of bipolar depressed patients taking mood stabilizers. J Clin Psychiatry 2002; 63:508–512
12. Bowden CL. Lamotrigine in the treatment of bipolar disorder. Expert Opin Pharmacother 2002;3:1513–1519
13. DelBello MP, Schwiers ML, Rosenberg HL, et al. A double-blind, randomized, placebo-controlled study of quetiapine as adjunctive treatment for adolescent mania. J Am Acad Child Adolesc Psychiatry 2002;41:1216–1223
14. Mullen J, Devine N, Sweitzer D. Quetiapine adjunctive therapy for acute mania associated with bipolar disorder (SIAM). In: New Research Abstracts of the 156th Annual Meeting of the American Psychiatric Association; May 20, 2003; San Francisco, Calif. Abstract NR482: 180–181
15. Suppes T, Webb A, Paul B, et al. Clinical outcome in a randomized 1-year trial of clozapine versus treatment as usual for patients with treatment-resistant illness and a history of mania. Am J Psychiatry 1999;156:1164–1169
16. El-Mallakh RS, Karippot A. Use of antidepressants to treat depression in bipolar disorder. Psychiatr Serv 2002;53:580–584
17. Wehr TA, Goodwin FK. Can antidepressants cause mania and worsen the course of affective illness? Am J Psychiatry 1987;144: 1403–1411
18. Kukopulos A, Reginaldi D, Laddomada P, et al. Course of the manic-depressive cycle and changes caused by treatment. Pharmakopsychiatr Neuropsychopharmakol 1980;13:156–167
19. Sachs GS, Grossman F, Ghaemi SN, et al. Combination of a mood stabilizer with risperidone or haloperidol for treatment of acute mania: a double-blind, placebo-controlled comparison of efficacy and safety. Am J Psychiatry 2002;159:1146–1154