

Drug Combinations for Mania

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With the release of new medications into the armamentarium for the treatment of bipolar disorder, clinicians are required to make prudent treatment decisions in light of insufficient research data for patients with a difficult-to-control illness. Increasingly, clinicians are turning toward a combination or adjunctive treatment out of necessity. Many studies suggest effectiveness of add-on agents in patients with mania who are unresponsive to one or more drugs, while only a limited number of controlled trials actually compare one particular combination regimen to another. Despite this lack of data, there has been no lack of advice for the clinician from clinical recommendations in the form of expert treatment guidelines to case reports describing suggestive findings from the off-label use of newer agents. With a particular emphasis on the treatment of mania, this article reviews the clinical data on the individual agents of foreseeable use in combination treatment for bipolar disorder. We suggest beginning with an agent of established effectiveness when combining medications for the treatment of bipolar disorder.
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For many years lithium and the antipsychotic medications were the only available pharmaceutical agents for the treatment of acute mania. Of these, the antipsychotics were generally recommended for only acute management of agitated manic symptoms, often in hospitalized patients, with the suggestion that they be discontinued as patients entered the maintenance phase of treatment. Carbamazepine joined this group in the 1970s, valproate about a decade later, and in recent years, many more agents have found their way into the armamentarium for the treatment of mania, some quite justifiably and others more questionably so.

Early papers demonstrating lithium's acute and prophylactic therapeutic effect in bipolar disorder showed it to have a remarkably robust antimanic effect. In John Cade's

landmark first report¹ of the use of lithium in psychiatric patients, 10 out of 10 patients with mania experienced resolution of their symptoms on lithium—some for the first time in years. Evidence for lithium's antidepressant effect² and prophylaxis against recurrence³ followed quickly. As decades passed, however, it became clear that a significant portion of patients do not have complete control of their symptoms on lithium therapy alone, with breakthrough manic and depressive symptoms not uncommon. But treating breakthrough symptoms by the addition of other agents to lithium, such as antidepressants for depressive symptoms and antipsychotics for manic symptoms, has presented the clinician with a dilemma: antidepressants pose the risk of inducing manic symptoms⁴ and the typical antipsychotics impose a significant side effect burden, including the risk of tardive dyskinesia.

It is no surprise, then, that many clinicians now reach for newer agents in addition to more traditional drugs, such as newer generation anticonvulsants and the atypical antipsychotics, in their efforts to treat their patients with difficult-to-control illness. Inevitably, there are patients in whom combinations of agents seem both necessary and appropriate.⁵ Unfortunately, there are almost no clinical research data to guide the clinician in the choice of agents for combination treatment. Although there are any number of well-designed studies demonstrating that the addition of a particular agent is helpful in bringing about amelioration of symptoms in patients who have not responded to one drug, very few studies compare one particular combination of agents to another.

Despite this lack of data, there has been no lack of advice for the clinician. Published treatment recommen-

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dations from the American Psychiatric Association⁶ and guidelines such as the Expert Consensus Guidelines published in *Postgraduate Medicine*⁷ draw on the knowledge of experienced clinical scientists to set out algorithms and detailed recommendations for treatment. While undoubtedly valuable, experience cannot substitute for controlled data. When opinion is couched in terms of official or expert recommendations, however, it may seem to carry something approaching the legitimacy and authoritativeness of objective findings.

Other sources of information on pharmaceuticals for American psychiatrists are the ubiquitous continuing medical education (CME) events, usually sponsored by the pharmaceutical industry, which often describe clinical studies of off-label uses of agents. Despite the very preliminary nature of some of the studies of, for example, newer anticonvulsant medications for the treatment of bipolar disorder, these essentially unproven agents find their way into the combination regimens of many patients with bipolar disorder. Of greater concern, however, is the substitution of unproven agents for proven ones based on insufficient data as well as combinations of agents that do not include any drugs with a proven track record in treating this potentially devastating illness.

We now review clinical research data on the individual ingredients of combination treatments for bipolar disorder with an emphasis on the treatment of mania, but with an eye toward longer term treatment issues and prophylaxis.

LITHIUM

Lithium has long been considered the “gold standard” for treatment of bipolar disorder and mania. Early placebo-controlled studies established it as an effective choice for the treatment of mania.⁸⁻¹¹ Although the time lag to the onset of antimanic efficacy is significant, there is little doubt that lithium is effective as an antimanic agent. One open study suggests that a more rapid administration of lithium (a loading strategy) may be a potentially effective means for reducing the delay in onset of lithium’s antimanic effect.¹²

In more recent studies, lithium has been the standard for comparison when evaluating the antimanic effectiveness of other medications.¹³ Open studies report lithium to be as effective as or superior to many drugs commonly prescribed for reducing mania, including divalproex, carbamazepine, olanzapine, and atypical antipsychotics.¹⁴ Several open studies suggest, however, that lithium is not as effective as some of these other agents, divalproex in particular, for treating individuals with mixed or dysphoric mania.¹⁴

ANTICONVULSANTS

Several anticonvulsants were introduced into the pharmacologic armamentarium for bipolar disorder in the late

20th century that have been shown to be effective in reducing manic symptoms, especially for patients with poor response to lithium or for those individuals unable to tolerate its side effects. Nevertheless, not all medications effective as anticonvulsants are effective for the treatment of mania.

Current data on anticonvulsants most strongly support the use of valproate and carbamazepine as acute antimanic agents. These drugs have demonstrated greater efficacy than placebo and similar efficacy to lithium in both open and controlled trials.^{13,15,16}

Valproate

To date, 2 placebo-controlled studies^{13,17} have assessed the efficacy of valproate in the acute treatment of mania. Pope et al.¹⁷ studied 36 patients hospitalized for mania in a 3-week study in which 17 patients received valproate and 19 received placebo. Although completion rates were only 24% (N = 4) and 21% (N = 4) respectively, the patients taking valproate had a 54% improvement in score on the Young Mania Rating Scale (YMRS), compared with only 5% improvement in those taking placebo (p = .003). Similarly, a 20% improvement on the Global Assessment Scale (GAS) was observed in the patients taking valproate (0% improvement for placebo), and a parallel trend of improvement for valproate patients was seen on the Brief Psychiatric Rating Scale (BPRS).

In 1994, the Depakote Mania Study Group¹³ conducted a large placebo-controlled study of acute mania in 179 hospitalized patients with bipolar I disorder, comparing valproate or lithium with placebo. While many participants withdrew prematurely from the study, fewer terminations occurred among those patients taking valproate (48%) compared with the groups taking either lithium (64%) or placebo (61%). Following 21 days of treatment, nearly half of the patients taking valproate and half of those taking lithium compared with only 25% of those taking placebo showed marked improvement (50% or greater improvement in Mania Rating Scale [MRS] score). Response to valproate was independent of previous response to lithium; however, response to lithium was significantly dependent on a previous history of lithium responsiveness. In a long-term naturalistic comparison of valproate and lithium for treating depressive symptoms of bipolar disorder, Ghaemi and Goodwin¹⁸ reported equal effectiveness and tolerability between the 2 drugs, but of note they also suggested that responders might represent distinct subgroups as each agent appeared similarly effective in non-responders to the other agent. Several studies support preferential use of valproate in dysphoric, mixed, and rapid cycling states.^{13,19}

Carbamazepine and Oxcarbazepine

Since Ballenger and Post²⁰ first recommended carbamazepine as a treatment for bipolar disorder in 1980, a

number of subsequent studies^{21,22} have reported carbamazepine as superior to placebo, although not necessarily equivalent to lithium in the short-term treatment of mania. According to a review by McElroy and Keck,²³ results from many of the controlled studies supporting carbamazepine are confounded, however, by the concomitant use of lithium or other anticonvulsants.

In 1990, Okuma et al.²¹ conducted a double-blind placebo-controlled study of 105 patients with mania whose symptoms had responded poorly despite treatment with antipsychotic medication. All the patients took haloperidol, and the sample was split into 2 equal groups with half of the patients receiving carbamazepine (400–1200 mg/day) and the other half enough lithium to obtain mean serum lithium levels of 0.46 mEq/L. On final assessment, despite medication doses resulting in relatively low serum levels, both groups showed marked-to-moderate improvement.

In an 8-week double-blind comparison of carbamazepine and lithium in 52 hospitalized patients with acute mania, Small et al.¹⁵ found equal effectiveness between the 2 drugs in reducing manic symptoms (reduction in YMRS score).

Oxcarbazepine, the keto-derivative of carbamazepine, has been shown to be effective at reducing manic symptoms in at least one open study.²⁴ It has fewer drug interactions than carbamazepine and is not subject to metabolic auto-induction, making it possibly safer than carbamazepine.²⁵

Lamotrigine

The effectiveness of lamotrigine in the treatment of acute mania has been reported on in case reports, open studies, and 3 double-blind placebo-controlled studies. The results can be characterized as mixed at best. Two double-blind placebo-controlled studies reported the anti-manic effectiveness of lamotrigine as not significantly different from placebo.^{26,27} On the other hand, Ichim and colleagues,²⁸ in a small (N = 30) 4-week randomized controlled trial involving hospitalized patients with mania, found lamotrigine and lithium to be similarly efficacious, with both groups of patients obtaining similarly reduced MRS scores. Of note in this study, however, is that all patients in the lithium group received a fixed lithium dose (800 mg/day) with no titration of lithium dose according to results from therapeutic monitoring. The mean serum lithium level for the group was only 0.7 mEq/L.

Results from an open study suggest that administration of lamotrigine in patients with bipolar disorder may lead to a worsening of or the onset of manic symptoms.²⁹ In the largest controlled lamotrigine monotherapy study in bipolar depression, 8% of the patients taking lamotrigine developed manic, hypomanic, or mixed symptoms over 7 weeks, a percentage comparable with that seen for antidepressant-induced mania.³⁰ However, in an analysis of pooled data from 827 patients taking lamotrigine and 685

patients taking placebo in 8 controlled studies ranging from 3 weeks to 18 months, the risk of developing manic symptoms while on lamotrigine therapy was comparable to that of placebo.³¹

Gabapentin

A number of case reports and uncontrolled, open-label studies of gabapentin in patients with manic, mixed state, or refractory bipolar disorder suggest a beneficial effect in bipolar disorder, at least when used as an adjunctive medication.^{32–38}

Currently, only 2 controlled studies of gabapentin in bipolar disorder^{27,39} have been conducted, and in both, gabapentin was no more effective than placebo in the treatment of acute mania. In 2000, Frye et al.²⁷ conducted a placebo-controlled crossover trial comparing gabapentin, lamotrigine, and placebo and found no statistical difference in improvement rating between gabapentin (26%) and placebo (23%) after 6 weeks. The second study, carried out by Pande et al.³⁹ in 2000, found that adjunctive gabapentin was less effective than placebo in decreasing total YMRS scores.

Topiramate

While no controlled trials currently exist evaluating the use of topiramate for acute mania, the results from several open studies suggest possible antimanic efficacy as an adjunctive treatment.⁴⁰ In 1998, Marcotte⁴¹ reported that 52% (N = 23) of 44 refractory bipolar patients with manic or mixed symptoms improved while on topiramate in a 16-week open trial. In 2000, McElroy et al.⁴² conducted an open-label naturalistic study of adjunctive topiramate use in 54 outpatients with refractory bipolar disorder, of whom at the outset 30 had manic, mixed, or cycling symptoms. At week 10, of the 30 manic patients, 63% (N = 19) showed improvement as evidenced by change in YMRS score ($p = .001$). Of note, the patients lost an average of 2.4 pounds [1.1 kg] after 4 weeks, with their weight stabilizing over a period of 10 weeks. Similarly, in an open-label study of 12 manic, 5 mixed, 1 hypomanic, and 6 rapid cycling patients taking add-on topiramate, Chengappa et al.⁴³ observed 50% reduction in YMRS scores, a Clinical Global Impressions (CGI) rating of much or very much improved in 60% (N = 12) of patients, and a mean weight loss of 9.4 [4.2 kg] pounds at 5 weeks in 100% of patients.

Unlike many agents used to treat mania, topiramate does not cause weight gain as its use can, in fact, result in weight loss. The observation of topiramate's potentially beneficial effects in mania in combination with its relatively favorable side effect profile warrants further exploration of topiramate's efficacy in controlled studies.

Tiagabine

Tiagabine, a selective inhibitor of the principal neuronal GABA transporter, is a newly approved drug for the

treatment of partial seizures.⁴⁰ Over the past several years, a few preliminary, open studies investigating the efficacy of tiagabine in bipolar disorder have been conducted. Combined data from 2 very small trials (combined N = 5) using open-label, add-on tiagabine (4–12 mg/day) have suggested a reduction of both manic and depressive symptoms.^{44,45} However, data from 2 more recent open trials suggest that tiagabine has only very limited antimanic efficacy and that rapid titration can result in potentially severe side effects, including nausea and seizures. In one open study of 8 acutely manic inpatients by Grunze et al.,⁴⁶ no relief from manic symptoms was seen after 2 weeks when tiagabine was administered as monotherapy (N = 2) or as an adjunctive medication. In 2002, Suppes et al.⁴⁷ followed 17 treatment-refractory bipolar patients receiving tiagabine add-on therapy for 38 days. Four participants dropped out of treatment, 3 patients achieved significant improvement, and 10 patients showed no change or worsening.

TYPICAL ANTIPSYCHOTICS

Until the early 1990s, typical antipsychotics, particularly haloperidol, went unchallenged as the fastest acting treatments for the agitation seen in acute mania. Neuroleptics were considered by the European community as the treatment of choice for acute mania, a practice reasonably well supported by the literature of the time,^{48,49} and justified given the relatively slow onset of lithium.⁵⁰

In a recent meta-analysis of the literature from 1980 to 1997, Tohen et al.⁵¹ found that typical antipsychotics are more frequently used in an inpatient setting, and they continue to be used widely in Europe and in the United States⁵² for the treatment of mania despite their unfavorable side effect profiles and their de-emphasis in the Expert Consensus Guidelines⁷ and other recent treatment algorithms for bipolar disorder. Valproate has a comparable time to onset of antimanic effects⁵³ and greater tolerability than the typical antipsychotics,¹³ and the newer atypical antipsychotic medications have better side effect profiles and an overall superior effectiveness to typical antipsychotics when used adjunctively with a mood stabilizer.⁵⁴

ATYPICAL ANTIPSYCHOTICS

Since the 1990s, the treatment of mania has been significantly changed by the introduction of the atypical antipsychotics. Two of these medications, olanzapine and risperidone, have been the subjects of the largest number of clinical studies.

Olanzapine

Olanzapine is currently the only atypical antipsychotic currently approved by the U.S. Food and Drug Administration for treatment of acute mania, having been shown to be superior to placebo for this indication in 2 large,

double-blind, placebo-controlled monotherapy studies. In the first study by Tohen et al. (1999),⁵⁵ reductions in YMRS scores were seen after 3 weeks in 49% of the olanzapine-treated group compared with 24% for the placebo group. A similar follow-up study⁵⁶ obtained similar results except that the olanzapine versus placebo difference in efficacy appeared after only 1 week of treatment. In both studies, the olanzapine-treated subjects had more weight gain and sedative side effects compared with placebo. While there are no controlled comparisons of olanzapine either to a typical or to another atypical antipsychotic as a monotherapy agent for bipolar mania, a retrospective chart review of 42 bipolar patients treated with adjunctive olanzapine, risperidone, or clozapine suggested similar efficacy and tolerability between the 3 atypicals.⁵⁷ Of note, olanzapine caused the greatest weight gain (greater than 10 lb [> 4.5 kg]), although olanzapine plus lithium was associated with less weight gain than was olanzapine plus divalproex.

In a double-blind, randomized controlled trial comparing olanzapine to lithium in 30 patients with mania, Berk et al.⁵⁸ found significant improvements in both groups. No significant differences in outcome between groups were recorded in the BPRS, CGI, or mania scale at 4 weeks, suggesting that olanzapine is at least as effective as lithium in the treatment of mania.⁵⁸

In a 6-week double-blind, randomized placebo-controlled study (N = 344) by Tohen et al.,⁵⁹ superior efficacy ($> 50\%$ improvement on YMRS) was achieved in the treatment of manic and mixed bipolar episodes with olanzapine plus either lithium or valproate as compared to lithium or valproate alone.

Zajacka et al.⁶⁰ published a 12-week, double-blind study following 120 bipolar patients hospitalized for acute mania, of whom 63 received valproate and 57 received olanzapine. No significant difference in efficacy was observed in the 2 treatment groups; however, valproate was associated with a better side effect profile and significantly less weight gain than was olanzapine.

Risperidone

In a 3-week controlled trial comparing risperidone monotherapy (6 mg/day) to lithium (800–1200 mg/day) or haloperidol (10 mg/day) in 45 patients with mania, treatment outcomes, evaluated by mean improvement on YMRS, were similar and significantly improved for all groups.⁶¹

A 3-week randomized, placebo-controlled study⁶² compared risperidone or haloperidol combined with lithium or valproate to placebo in 156 bipolar patients who were either in a mixed or manic episode. Nearly half of those receiving placebo or haloperidol dropped out compared to a discontinuation rate of 35% (N = 18) among the risperidone group. Efficacy of risperidone, measured by improvement of YMRS, was comparable to that of haloperi-

dol at endpoint and over time and was significantly better than that of placebo. Results were consistent for both those with and without psychotic symptoms at baseline.⁶²

Results from open studies also suggest improvement in manic symptoms in mixed and manic patients receiving risperidone plus lithium, valproate, or carbamazepine.⁶³⁻⁶⁵

TREATMENT FOUNDATIONS IN BIPOLAR DISORDER

As this review makes clear, quite a few agents have been shown to be effective for the treatment of acute mania. Many of these studies involve combinations of antimanic agents. Very few, however, were designed specifically to compare one combination to another. How, then, does the clinician go about making decisions about combination treatments in the absence of authoritative clinical data comparing various combinations? We suggest that the foundation of treatment for bipolar disorder begin with an agent of established effectiveness.

Lithium

Lithium has well-established efficacy for all phases of the illness: the treatment of manic as well as the depressed phases of bipolar disorder and also its proven prophylactic efficacy. The highly recurrent nature of bipolar disorder and the frequency of breakthrough symptoms in the course of illness argue for consideration of long-term treatment issues even as treatment decisions are being made for the most emergent and acute phase of the illness: mania. Lithium remains the only available antimanic agent with proven antidepressant effects. (While lamotrigine is clearly an effective antidepressant in bipolar disorder, whether it is an effective antimanic agent is much less clear.) Available studies also support the conclusion that lithium is superior to other available agents in preventing relapses of illness. The data suggesting a specific anti-suicide effect for lithium⁶⁶ also argue for the use of this agent in bipolar disorder in the absence of other overriding considerations (inability to tolerate lithium therapy, or other factors discussed below.)

Valproate and Carbamazepine

The other agents with solid data to support efficacy in several different phases of bipolar illness include valproate and carbamazepine.

Valproate, clearly an effective antimanic agent, also has data to support an antidepressant effect.⁶⁷ There is even evidence that some patients have a better antidepressant response to valproate than to lithium and that lithium-responsive and valproate-responsive patients represent separate subgroups of patients with bipolar depression.¹⁸ Whether the one available study comparing valproate to lithium for prophylaxis⁶⁸ supports its efficacy for this indication is a matter of controversy. The data supporting the

superior efficacy of valproate in rapid cycling and dysphoric mania are, however, clear.⁶⁹

Although substantial data support the use of carbamazepine for treating mania,^{15,22} depression,^{20,70} and perhaps for prophylaxis^{40,71} in bipolar disorder, it appears to be prescribed much less often for the treatment of mania than lithium or valproate. A cross-over study⁷² comparing it to lithium and a lithium/carbamazepine combination found that the combination of carbamazepine and lithium was more effective than either agent alone in preventing relapses of bipolar disorder, one of the few studies of combination treatment that examined differential efficacies of agents in this way.

Building on the Foundation

A variety of medications in several different classes have been shown to benefit manic patients who are not responding to antimanic monotherapy with lithium, valproate, or carbamazepine. The typical and atypical antipsychotic agents have been shown to be effective, and there is probably also a place for benzodiazepines in combination with other agents, at least in the acute setting for very agitated patients.⁷³ The primary cautions with lithium and antipsychotic combinations involve side effects thought to be mediated by dopaminergic systems, such as increased extrapyramidal symptoms and neuroleptic malignant syndrome. Oversedation more acutely and increased appetite and weight gain in the longer term are risks of antipsychotic and anticonvulsant combinations.

It is important to remember that concurrent administration of multiple drugs makes it difficult for the clinician to assign either the side effects or the beneficial effects that arise in the course of treatment to the appropriate drug.

SUMMARY

For many acutely manic patients, combinations of medications are critical to bring symptoms under control acutely and to prepare for outpatient management. Choosing second- and third-line medications and drug combinations will, however, depend more on clinical experience and prudence than on the scientific literature, which offers scant empirical information regarding complex regimens. Published recommendations and guidelines will offer valuable advice for making these decisions, but clinicians should familiarize themselves with the methods by which these recommendations have been developed in order to assess their validity and relevance for individual patients. More prospective and controlled studies of drug combinations are needed to adequately test the widespread practice of combined medication treatments in manic patients.

Drug names: carbamazepine (Tegretol and others), clozapine (Clozaril and others), divalproex sodium (Depakote), gabapentin (Neurontin),

haloperidol (Haldol and others), lamotrigine (Lamictal), olanzapine (Zyprexa), oxcarbazepine (Trileptal), risperidone (Risperdal), tiagabine (Gabitril), topiramate (Topamax).

Disclosure of off-label usage: The authors of this article have determined that, to the best of their knowledge, carbamazepine, gabapentin, haloperidol, lamotrigine, oxcarbazepine, risperidone, tiagabine, and topiramate are not approved by the U.S. Food and Drug Administration for the treatment of bipolar disorder.

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