

## Drug Combinations for Bipolar Spectrum Disorders: Evidence-Based Prescribing or Prescribing-Based Evidence?

Stephen M. Stahl, M.D., Ph.D.

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**Issue:** *Most patients with a bipolar spectrum disorder are treated with 2 or more drugs in combinations that are sometimes rational and evidence-based and sometimes not.*

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**T**reatment of bipolar spectrum disorders today is a hot topic, with many new agents now available and many new combinations being touted. However, clinical practice may not always be “in synch” with clinical research, since the treatment of bipolar spectrum disorders with monotherapies as well as with combinations of drugs may now be the least evidence-based area of psychopharmacology practice.<sup>1,2</sup>

### Evidence-Based Prescribing

The best evidence for efficacy of agents for bipolar spectrum disorders is for monotherapies, especially for acute mania (e.g., lithium, atypical antipsychotics, divalproex) and for maintenance (lithium, olanzapine, and lamotrigine).<sup>3</sup> Recently, numerous combinations have been studied, especially lithium or divalproex combined with an atypical antipsychotic

for acute mania or fluoxetine combined with olanzapine for bipolar depression (Table 1).<sup>3</sup> However, recent analysis of prescribing trends shows that the monotherapies and combinations actually utilized in clinical practice are not those that are the most evidence based.<sup>1,2</sup> For example, there is more gabapentin prescribed for bipolar disorder than lamotrigine, even though there is little compelling evidence for gabapentin’s efficacy in bipolar disorder and the FDA has approved lamotrigine for the treatment of bipolar disorder.<sup>1,2</sup> Thus, up to half of bipolar patients receiving combination therapy are given anticonvulsants (such as gabapentin or topiramate) that are not well documented to work for bipolar disorder.<sup>1-3</sup> Why?

### Prescribing-Based Evidence

To facilitate learning, I have attached whimsical names to all the prudent options available to the prescriber to treat bipolar spectrum disorders while the experts clarify the data and remove the controversy (Table 1).

**Anticonvulsants:** Perhaps one of the reasons so many anticonvulsants that are not well documented to have efficacy in bipolar disorder are nevertheless prescribed so often in bipolar disorder is due to the mistaken as-

sumption that if a drug is an anticonvulsant, it must work like any other anticonvulsant.<sup>5</sup> However, it appears that only some anticonvulsants,<sup>5</sup> particularly those with actions on voltage sensitive sodium channels, may be effective for bipolar disorder. Those agents without convincing efficacy should get no respect. (I call these “Rodney Dangerfield combos.”)

**Antidepressants:** One area in which there is evidence but also controversy is in the use of antidepressants for bipolar disorder. Some experts, for example in the Boston area,<sup>6</sup> believe that antidepressants should be added sparingly (the formula “Boston bipolar brew”), or not at all, to prevent the triggering of mania, hypomania, rapid cycling, or mixed states; whereas other experts, including several from California,<sup>7</sup> believe that antidepressants can be cautiously added for bipolar patients in the depressed state if they are already taking other mood stabilizers and not responding to them (a “California careful cocktail”) (Table 1). Experts, including some from Tennessee,<sup>8</sup> have shown that augmentation of an antidepressant with an atypical antipsychotic can result in simultaneous stabilization of activation yet elevation of mood in patients with treatment-resistant<sup>8</sup> or bipolar depression<sup>9</sup> (the “Tennessee mellow afterburner”).

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*From the Neuroscience Education Institute in Carlsbad, Calif., and the Department of Psychiatry at the University of California San Diego.*

*Reprint requests to: Stephen M. Stahl, M.D., Ph.D., Editor, BRAINSTORMS, Neuroscience Education Institute, 5857 Owens Street, Ste. 102, Carlsbad, CA 92009.*

**Lamotrigine:** Despite the recent approval of lamotrigine for the treatment of bipolar disorder, there are very few studies of its combination with other approved agents, such as lithium, divalproex, and atypical antipsychotics. Many clinicians combine these agents already, because it seems rational to combine an agent that works best from “above” to reduce and prevent mania, such as divalproex or lithium, with an agent that works best from “below” to reduce and prevent depression (or “La-Li,” “La-Do,” and “La-Li-Do”).

**Atypical antipsychotics:** The atypicals that have been marketed the longest, especially olanzapine and risperidone, are especially well established as efficacious in clinical practice, particularly for bipolar mania and particularly in combination with lithium and divalproex.<sup>3</sup> Now the newer atypical antipsychotics are emerging, and not just for acute mania, but also for depression associated

with bipolar I, bipolar II, and treatment-resistant depression.<sup>3</sup> Thus, the new FDA approvals for bipolar mania for quetiapine and ziprasidone and pending for aripiprazole mean the possibility of adding new options to the treatment formula for bipolar spectrum disorders, including some with less risk of weight gain and perhaps diabetes.<sup>10</sup> Any of these atypicals can be added to lithium, lamotrigine, or divalproex, including for complicated cases that do not respond to 1 or 2 agents (e.g., “Quel kit” for combinations with Seroquel/quetiapine; “Able stabilizer” for combinations with Abilify/aripiprazole; and “Jiminy Crickets” for combinations with ziprasidone [zipa-li and zipa-li-do-la]).

**Summary**

Current treatment of bipolar disorder is an area of unmet need that multiple new agents, alone and in combination, are beginning to meet.

**Table 1. Drug Combinations for Bipolar Spectrum Disorders, Including Treatment-Resistant Depression<sup>a</sup>**

Combination	Popular Name
<b>Evidence-Based Prescribing</b>	
Lithium with any atypical antipsychotic (especially olanzapine, risperidone, and quetiapine)	“Atypical-lithium combo”
Divalproex with any atypical antipsychotic (especially olanzapine, risperidone, and quetiapine)	“Atypical-Depakote combo”
Lithium augmentation of antidepressants	“Classical combo”
Atypical antipsychotic augmentation of antidepressants (especially olanzapine augmentation of fluoxetine)	“Tennessee mellow afterburner”
Olanzapine-fluoxetine combination	“Symbyax”
<b>Prescribing-Based Evidence</b>	
Lamotrigine-lithium	“La-Li”
Lithium-Depakote (divalproex)	“Li-Do”
Lamotrigine-Depakote (divalproex)	“La-Do”
Lamotrigine-lithium-Depakote (divalproex)	“La-Li-Do”
Any combination of mood stabilizers not including an antidepressant	“Boston bipolar brew”
Any combination of mood stabilizers that does include an antidepressant	“California careful cocktail”
Any combination containing ziprasidone (Geodon; e.g., zipa-li-do-la; i.e., ziprasidone, lithium, divalproex, and lamotrigine)	“Jiminy Cricket”
Any combination containing Seroquel (quetiapine)	“Quel kit”
Any combination containing Abilify (aripiprazole)	“Able stabilizer”
Any combination containing an anticonvulsant with little or no evidence of efficacy in bipolar disorder (“Can’t get no respect”; e.g., gabapentin, topiramate)	“Rodney Dangerfield combo”

<sup>a</sup>Adapted with permission from Stahl.<sup>3,4</sup>

**REFERENCES**

1. Stahl SM, Grady MM. Is the use of antiepileptic drugs and antipsychotics in bipolar disorder and schizophrenia evidence-based and cost-effective? [poster] Presented at the 42nd annual meeting of the American College of Neuropsychopharmacology; December 7–11, 2003; San Juan, Puerto Rico
2. Cutler AJ. Clin Psychiatry News 2004;32:1–18
3. Stahl SM. Essential Psychopharmacology: The Prescriber’s Guide. New York, NY: Cambridge UP; 2004
4. Stahl SM. Essential Psychopharmacology. 3rd ed. New York, NY: Cambridge UP. In press
5. Stahl SM. J Clin Psychiatry 2004;65:738–739
6. Sachs GS. J Clin Psychiatry 2003;64(suppl 8):35–40
7. Post RM, et al. Bipolar Disord 2003;5:396–406
8. Shelton RC, et al. Am J Psychiatry 2001;158:131–134
9. Tohen M, et al. Arch Gen Psychiatry 2003;60:1079–1088
10. Consensus development conference on antipsychotic drugs and obesity and diabetes. J Clin Psychiatry 2004;65:267–272

**Take-Home Points**

- ◆ Treatment of bipolar spectrum disorders currently includes reducing and preventing mania, hypomania, depression, and dysthymia, as well as mixed, rapid cycling, and treatment-resistant states.
- ◆ Mood stabilizers for these conditions now include lithium, atypical antipsychotics, some but not all anticonvulsants, and, controversially, antidepressants.
- ◆ Although most patients with a bipolar spectrum disorder receive 2 or more psychotropic drugs, only a few of these combinations have been extensively studied.
- ◆ As more evidence is being generated, especially with combinations of 3 or more agents, prescribers must weigh the risks and benefits of commonly utilized combinations, noting how to dose and how to augment with a rational mixture of empirically useful and potentially synergistic mechanisms of action.