What exactly is a mood stabilizer?

L. Trevor Young, MD, PhD

Department of Psychiatry, University of Toronto, Toronto, Ont.

Two decades ago, there was 1 drug in the mood stabilizer category: lithium carbonate.[1] Carbamazepine was used in refractory cases and in a small number of specialty clinics. Valproate was entering the scene as a novel and effective mood stabilizer. Since then, it seems that every new anticonvulsant is evaluated for its mood-stabilizing properties. More recently, the atypical antipsychotic drugs have emerged as promising treatments for bipolar disorder, and the evidence supporting their efficacy rivals that of anticonvulsant medications. Other agents, such as calcium-channel blockers, have also been evaluated but have shown little evidence of mood-stabilizing properties. Guidelines for the treatment of bipolar disorder now focus on lithium, a selected number of anticonvulsants and an increasing number of atypical antipsychotic drugs as the principal agents.[2] How does the finding that seemingly disparate classes of medication have a common domain of efficacy shape our definition of what constitutes a "mood stabilizer" and our understanding of their mechanisms of action?

There has been substantial debate about the definition of a mood stabilizer.[3] In general, these definitions are based on antimanic, antidepressant and prophylactic properties to varying degrees, and they usually require 2 of the 3 effects. If we apply such a definition to the agents listed here, more differences than similarities emerge.[2] Lithium remains the gold standard, but patient selection is probably the most important variable in ensuring its effectiveness, because patients with a classic course of illness, family history and good interepisode functioning show the best response.[1] Nonetheless, most patients, regardless of their subtype of illness and clinical features, are exposed at some point in their treatment to lithium. It may indeed become more widely prescribed because of its antisuicide effects, including its ability to prevent suicide in patients who do not have a complete response to the drug.[4] Although valproate remains a widely prescribed agent, it seems to be of limited value in bipolar depression, particularly as monotherapy. Carbamazepine remains an often-underused treatment option that may have a broad range of efficacy. Lamotrigine is the only newer anticonvulsant that is supported by unequivocal evidence as a treatment for bipolar disorder but with its effects, for the most part, limited to the depressed phase and perhaps rapid cycling in patients with type II bipolar disorder. Gabapentin and topiramate were found to be ineffective in bipolar disorder in randomized clinical trials. Atypical antipsychotics as a class have been shown to be effective antimanic agents and their prophylactic and antidepressant effects continue to be studied, with particularly good evidence for olanzapine from randomized clinical trials[5,6] and for clozapine, at least from open-label studies.[7] The diversity of the agents and the differences in their clinical profiles make it hard to generalize across the agents and determine what distinguishes them as mood stabilizers. Does this call into question our somewhat ambiguous definition of a mood stabilizer?

Correspondence to: Dr. L. Trevor Young, Centre for Addiction and Mental Health, 250 College St., Toronto ON M5T 1R8; fax 416 260-4189; trevor_young@camh.net

Medical subject headings: anticonvulsants; antipsychotic agents; bipolar disorder; carbamazepine; drug therapy; lithium; valproic acid.

J Psychiatry Neurosci 2004;29(2):87-8.

It may be that overlapping mechanisms of action underlie the mood-stabilizing properties of the agents described here. There has been much progress over the past decade in elucidating the mechanism of action of mood-stabilizing drugs, in particular, lithium and valproate.[8] It is interesting that these 2 drugs share many common targets. Both have wide effects on signal transduction pathways within the cell, and both regulate the expression of a number of important target genes such as *BCL-2* and *GRP78*, which are important in preventing cell death and toxicity. More recently, cellular biology has shown that both lithium and valproate have robust neuroprotective effects after a variety of insults both in cultured cells and in intact animal models.[8] The overlap of targets between these 2 diverse agents is remarkable and, in my view, quite unexpected. Carbamazepine shares some, but not all, these effects, whereas lamotrigine has not been studied widely enough for one to draw many conclusions. Even less is known about the atypical antipsychotics, although several laboratories have published data on the neuroprotective effects of these latter agents, which have some broad similarities to those of both lithium and valproate.[9] If regulation of signal transduction and its downstream effects is the way in which mood stabilizers work, we are left with a very incomplete picture, particularly for the atypical antipsychotics in contrast with the rather impressive data on their clinical effects.

Where do we go next? From a clinical point of view, it seems likely that with more time the picture will become more complex and that specific patient variables in this heterogeneous disorder may be predictive in choosing the right agent for a specific patient. Furthermore, defining a drug as a mood stabilizer may be less relevant than the clinical profile of a specific agent. For instance, certain agents may be more helpful for the depressive part of the illness, namely, lamotrigine, and others for mania, namely, valproate. Such distinctions may be more definitive than assigning drugs to the broader category of mood stabilizers. At a mechanistic level, the shared targets of lithium and valproate remain very intriguing. A concerted effort should be made to understand whether these targets are shared by other agents, such as lamotrigine and atypical antipsychotics. It is also possible that the biologic targets of these agents may show similar variation based on their clinical differences.

Competing interests: Dr. Young is in the speaker's bureau for Eli Lilly, AstraZeneca and GlaxoSmithKline.

References

1. Geddes JR, Burgess S, Hawton K, Jamison K, Goodwin GM. Long-term lithium therapy for bipolar disorder: systematic review and meta-analysis of randomized controlled trials. *Am J Psychiatry* 2004;161(2):217-22.
2. American Psychiatric Association. Practice guideline for the treatment of patients with bipolar disorder (revision). *Am J Psychiatry* 2002;159(4 Suppl):1-50.
3. Bauer MS, Mitchner L. What is a "mood stabilizer"? An evidence-based response. *Am J Psychiatry* 2004;161(1):3-18.
4. Muller-Oerlinghausen B, Berghofer A, Ahrens B. The antisuicidal and mortality-reducing effect of lithium prophylaxis: consequences for guidelines in clinical psychiatry. *Can J Psychiatry* 2003;48(7):433-9.
5. Tohen M, Ketter TA, Zarate CA, Suppes T, Frye M, Altshuler L, et al. Olanzapine versus divalproex sodium for the treatment of acute mania and maintenance of remission: a 47-week study. *Am J Psychiatry* 2003;160(7):1263-71.
6. Tohen M, Vieta E, Calabrese J, Ketter TA, Sachs G, Bowden C, et al. Efficacy of olanzapine and olanzapine-fluoxetine combination in the treatment of bipolar I depression. *Arch Gen Psychiatry* 2003;60(11):1079-88.
7. Suppes T, Webb A, Paul B, Carmody T, Kraemer H, Rush AJ. 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(8):1164-9.
8. Coyle JT, Duman RS. Finding the intracellular signaling pathways affected by mood disorder treatments. *Neuron* 2003;38 (2):157-60.
9. Wei Z, Mousseau DD, Richardson JS, Dyck LE, Li XM. Atypical antipsychotics attenuate neurotoxicity of beta-amyloid(25-35) by modulating Bax and Bcl-X(l/s) expression and localization. *J Neurosci Res* 2003;74(6):942-7.