

Introduction

Do Some Antidepressants Work Faster Than Others?

The Role of Anticonvulsants as Mood Stabilizers

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The proceedings of this recent symposium highlight clinically important new evidence in 3 areas of bipolar disorder. Calabrese and associates provide converging evidence that rapid cycling is more common than generally recognized, marked primarily by recurrent depression, and that lithium or lithium and valproate, while quite beneficial for mania, are insufficiently or modestly effective for depression in rapid cycling. New evidence that lamotrigine may be especially beneficial for depression in rapid cycling is reviewed.

With the expanding array of Food and Drug Administration–approved and off-label medications employed in bipolar disorder, most of which are also anticonvulsant drugs, an understanding of the specific adverse effects of such agents is essential. In the management of bipolar disorder, adverse effects are of course important for safety reasons, but also because they are strong drivers of treatment adherence. Discussion of adverse effects often is given second billing in research reports and articles on clinical management. Here, Goldberg and Burdick address in detail the important subject of cognitive effects of anticonvulsant drugs. Severity of these effects varies greatly across drugs. Valproate, lamotrigine, and levetiracetam, for example, appear to have low or no cognitive adverse effects. Results are inconsistent for carbamazepine but, for the most objective measures, indicate greater deficits in sensory memory from carbamazepine than valproate. Topiramate, and for that matter lithium, is associated with frequent occurrence of cognitive adverse effects at standard doses.

A similarly detailed review of rash associated with anticonvulsants is presented by Hebert and Ralston. This provides the perspective of a dermatologist dealing with the most severe forms of dermatologic and mucous membrane adverse effects. Adverse effects from anticonvulsants that are associated with other organ systems are addressed by Swann, with attention to practical steps in managing these over time. Hirschfeld presents an up-to-date review of the evolving concept of the bipolar spectrum. Importantly, he

reviews a new, simple, self-rated scale, the Mood Disorder Questionnaire, that offers improved sensitivity in early diagnosis of bipolar disorder.

IMPROVING SENSITIVITY AND ACCURACY OF DIAGNOSIS OF BIPOLAR DISORDER

I will add here some points aimed at improving the accuracy of diagnosis of bipolar disorder. The Calabrese et al. and Hirschfeld articles indicate some of the reasons that accurate diagnosis is a challenging issue. Although the DSM system has greatly improved reliability of diagnosis across clinicians, the current criteria do not lend themselves to recognition of the early presentation of the disorder in many patients with bipolar spectrum characteristics, or to rapid-cycling patients wherein the overly restrictive time requirements of DSM-IV for an episode are at variance with the actual ways that rapid cycling usually manifests.

For some patients with bipolar disorder, the correct diagnosis is never made or only made belatedly. The largest group consists of outpatients with depressive episodes.¹⁻³ Depressed patients who have frequent depressive episodes, early-onset depression, a family history of mania, or certain prominent symptoms while depressed (e.g., motor retardation, hypersomnia) have an increased likelihood of having bipolar disorders. Additionally, many bipolar patients who acknowledge their depressive episodes are unable to recognize or recall manic or hypomanic periods. Interviews of family members and discussion with the patient of the types of symptoms that would indicate a bipolar condition are both useful strategies. A period of time is often needed for the evidence supportive or not supportive of bipolar disorder to emerge.

Table 1 shows how bipolar patients commonly present to health care providers. A wide variety of psychiatric conditions, mostly in the anxiety and depressive spectrum, could be considered by clinicians seeing such a patient. A number of general medical disorders could be considered for such complaints—an important issue, since these patients often present in the offices of general physicians. Also, patients come often with complaints about problems in relationships, drinking too much, legal troubles, or problems consequent to impulsivity. Not least, they present with no psychiatric complaint, leaving the burden of fer-

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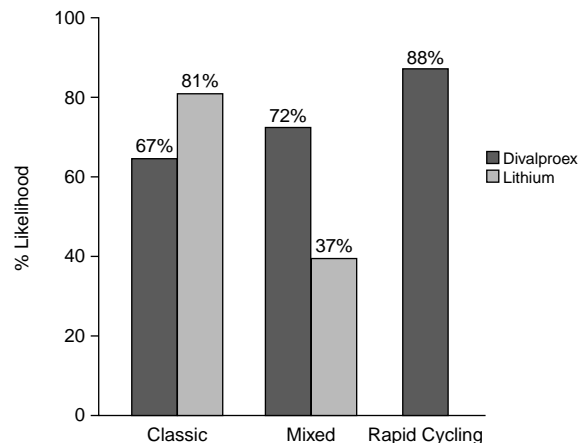
Table 1. How Bipolar Patients Present to Health Care Providers

| | |
|---------------------------------|---------------------------------|
| Being depressed | Drinking too much |
| Being anxious | Abusing drugs |
| Having mood swings | Being in trouble with the law |
| Experiencing insomnia | Having relationship problems |
| Being irritable | Having impulse-control problems |
| Experiencing low energy/fatigue | Expressing no complaints |
| Being unable to focus | |

retting out the link to a bipolar spectrum condition to the clinician.

The DSM-IV criteria for mixed mania require that symptoms of mania and depression occur every day for at least 1 week. Recent work by Swann et al.⁴ indicates that a more useful way of defining mania is as depressive mania, with 2 or more purely depressive symptoms in the context of mania. This evidence is not sufficiently conclusive to provide a new formal definition for mixed mania. However, in practice, we should be looking for mania in any patient who presents with subjective depression. Similarly, we should try to assess the degree of depression in any patient who presents with manic or hypomanic symptoms. The reason we investigate these polar opposites is because both illness course and treatment response are related to mixed manic status. The most persuasive evidence of this differential response of patients with mixed mania comes from a major study⁵ comparing divalproex, lithium, and placebo in bipolar I manic patients hospitalized for their illness. Among patients with mixed manic presentations, the response of the patients randomly assigned to lithium was approximately half that of the response rate seen among patients randomly assigned to divalproex (Figure 1). Mixed mania is also strongly associated with patients with neurologic impairment and patients with substance abuse disorders. Patients with combined mania and neurologic disorders have higher rates of mortality than do patients with major depression.⁶

Despite the evidence of the importance of depression as a predictor of illness course and treatment response in bipolar disorder, there are few adequate studies of treatments of depression in bipolar disorder. Calabrese et al. published the largest randomized, placebo-controlled parallel-group study in acutely depressed patients with bipolar disorder.⁷ Lamotrigine was superior to placebo, with improvement seen principally in affective and cognitive aspects of depression, rather than somatic symptoms of depression. Other evidence further suggests that attention to treatments for the depressive side of bipolar disorder can yield important advances. A 1997 study by Denicoff et al.⁸ compared the percentage of time that patients spent depressed and the percentage of time spent manic while treated with lithium, carbamazepine, or the combination. All 3 regimens reduced

Figure 1. Likelihood of 20% Improvement in Manic Syndrome Score in Classic Mania, Mixed Mania, and Rapid Cycling^a

^aBased on data from Bowden.⁵ Two-way analysis of variance, $p = .027$.

time spent manic. By contrast, none of the regimens reduced the percentage of time spent depressed. The results are in accord with similar findings of greater time spent depressed than manic in rapid-cycling patients treated with lithium.⁹

Taken together, these findings make a strong case that the depressive side of bipolar disorder is a central factor associated with relatively poor outcomes and that there is an urgent need for safe and effective treatments of depression in bipolar disorder.

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