

## EDITORIALS



## Treatment of Bipolar Depression

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Bipolar disorder consists of depressive episodes of low mood, difficulty in concentration and work, poor sleep, and poor appetite, as well as distinct manic episodes of expansive mood, pressured speech, overactivity, sexual excesses, aggressiveness, and little need for sleep; both types of episode may last for weeks or months. The primary goal of treatment is the prevention of these episodes with the use of mood stabilizers such as lithium, valproate, carbamazepine, and lamotrigine and some of the new atypical antipsychotic drugs such as olanzapine or quetiapine. However, when prophylaxis fails and a depressive or manic episode occurs, questions of appropriate treatment arise. Moreover, many patients cease to comply with the regimen of prophylactic mood stabilizers, go on to have a manic or depressive episode, and then present for treatment.

Conservative treatment of a depressive episode in a patient with bipolar disorder would be to initiate the use of a mood stabilizer if the patient is not taking one or to increase the dose or add a second mood stabilizer if the patient is already taking one.<sup>1</sup> A more aggressive clinical approach would be to add an antidepressant to the mood stabilizer. Depressive episodes in patients with bipolar disorder are problematic, since families are often relieved that the patients are not manic and are willing to allow conservative treatment, but the patients have symptoms that are subjectively worse during depressive episodes than during manic episodes and often request aggressive treatment. The clinical phenomenology of bipolar depression is similar to that of unipolar major depression. Thus, it has seemed reasonable to assume that antidepressants that are effective in treating unipolar major depression would be effective in treating bipolar depression as well.

Two European reviews of published studies<sup>2,3</sup> have shown that antidepressant treatment can be highly beneficial for bipolar depression, with little risk of the induction of mania. Traditionally, American psychiatrists have assumed that antidepressants are effective for bipolar depression but carry a risk of inducing mania.<sup>4</sup> Therefore, in the study by Sachs et al.<sup>5</sup> in this issue of the *Journal* — the largest study of its kind to date — it comes as a surprise that the addition of antidepressants to one or more mood stabilizers in the treatment of bipolar depression neither improved the depressive symptoms nor increased the risk of a switch to mania. These findings widen the gap between North America and Europe regarding the efficacy of antidepressants in the treatment of bipolar disorder but narrow the gap regarding the danger of mania.

The study by Sachs et al. is part of a large effectiveness study, funded by the National Institute of Mental Health, that differs from classic efficacy studies. Called the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD), it is carried out in the community with a sequential design and a large patient population that can be randomly assigned to different treatment groups at various stages in their illness, according to the principle of equipoise. The STEP-BD investigators enrolled 4360 patients; 2689 patients had at least one major depressive episode at some point during the program. Of these, only 366 were enrolled and randomly assigned to a group in the study by Sachs et al.

This low recruitment rate could be a source of bias. Patients in STEP-BD are well informed about the design of the study and their individual clinical history, as are their treating physicians. Given that most American psychiatrists believe that anti-

depressant treatment may induce mania in patients with bipolar disorder, patients with a history of a manic response to antidepressants or a history of severe mania might exclude themselves from the study either on their own initiative or on the advice of their physicians.

Bipolar disorder may be heterogeneous, as suggested by a study showing that patients in Israel had many episodes of mania and few episodes of depression but patients in Northern Europe had many more episodes of depression than episodes of mania.<sup>6</sup> Such heterogeneity could contribute to the contradictory results between the North American study by Sachs et al. and the European reviews.<sup>2,3</sup> Some American researchers have found that the response to antidepressants of patients with bipolar disorder may depend on the polarity of their most recent episode — that is, whether it was manic or depressive.<sup>7</sup> In a long-term, longitudinal follow-up study, Angst divided patients with bipolar disorder into subgroups according to whether their history consisted of mostly manic episodes or mostly depressive episodes; many clinical and treatment characteristics were found to differ according to this distinction.<sup>8</sup> Moreover, the clinical characteristics of bipolar disorder may change over time: a highly respected textbook of psychopharmacology published in 1980 by American authors<sup>9</sup> stated that “many bipolar patients experience infrequent depressive relapse,” which is very different from the clinical experience in North America today, as exemplified in STEP-BD.<sup>5</sup>

The risk of inducing mania after antidepressant treatment for bipolar disorder is another widely held belief in American psychiatry that was not supported in the study by Sachs et al. The antidepressants used inhibited either serotonin reuptake or dopamine reuptake; noradrenergic-reuptake inhibitors, noradrenaline-serotonin-reuptake inhibitors, or classic tricyclic antidepressants may induce mania at a higher rate.<sup>4</sup>

Lamotrigine is an anticonvulsant agent that large trials have shown to be efficacious as prophylaxis for bipolar depression, although the size of the benefit for mania is small.<sup>10</sup> A large controlled study of acute bipolar depression did not show a significant difference in the response rates to lamotrigine monotherapy and placebo with regard to the key outcome measure, although some benefits were shown for secondary measures.<sup>11</sup> In a smaller study of refractory bipolar depression,

Frye et al. found significant improvement with lamotrigine monotherapy as compared with placebo.<sup>12</sup> However, such effects of antidepressants might be less robust in an add-on clinical situation in which the patient has had a depressive breakthrough despite treatment with another mood stabilizer, as did most of the patients of Sachs et al.

Strongly held beliefs about the efficacy of antidepressants in treating bipolar depression,<sup>2,3</sup> and their equally powerful risk of inducing mania,<sup>4</sup> will not be put to rest by the study by Sachs et al. Their results will lead to less use of antidepressant medication in patients with bipolar depression, but treatment will continue to be individualized. Without ignoring the importance of data from randomized, controlled trials in resolving clinical controversy, it is critical to note that many patients are not recruited into trials, especially patients at both extremes: those with the most severe symptoms or violent or suicidal behavior and those with mild or spontaneously remitting symptoms. A patient's clinical history and past response to treatment will probably remain important factors in treatment decisions for this highly recurrent and heterogeneous illness.

Almost 90% of the patients in the study by Sachs et al. were using a mood stabilizer at randomization. Thus, the study does not address the possibility that antidepressants can cause mania in patients with bipolar depression in the absence of a mood stabilizer. Clinicians should continue to be vigilant about checking for a history of mania before initiating antidepressant therapy in patients with depression. If the depression is severe, electroconvulsive therapy is indicated for bipolar depression.<sup>13</sup> In my own practice, patients with bipolar disorder who have a history of mild mania and severe or lengthy depression are treated with antidepressants; patients with histories of life-threatening mania are almost never treated with antidepressants. Given the low response rate of patients with bipolar depression — whether or not they received antidepressants — in the trials by Sachs et al. and others, further study of newly suggested treatments such as inositol<sup>14</sup> and n-3 fatty acids<sup>14</sup> is needed. Definitive answers to many questions will require study designs, and perhaps new ethical consent tools, that can capture data for a larger and more representative sample of the various subgroups of patients with bipolar disorder.

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## Cardiovascular Risks of Antiretroviral Therapy

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Treatment with potent antiretroviral therapy has transformed human immunodeficiency virus (HIV) infection from a rapidly fatal disease into a chronic illness that some patients can live with for more than two decades. However, shortly after antiretroviral therapy was introduced, there were several reports of acute myocardial infarction and premature atherosclerotic vascular disease among young patients receiving such treatment.<sup>1</sup> Attention quickly focused on the protease inhibitors, with speculation that lipodystrophy and its associated metabolic disorders, including hyperlipidemia and insulin resistance, were increasing the cardiovascular risk.

These findings were alarming, and a flurry of research reports and editorials created a sense of an impending “epidemic” of cardiovascular disease, described by one writer as a “clockwork bomb” that might explode.<sup>2</sup> Adding to the fire were reports from observational studies suggesting that the risk of myocardial infarction was higher among patients receiving antiretroviral

therapy and particularly that the use of protease inhibitors might increase cardiovascular risk.<sup>3</sup> However, the data were not consistent, and the largest study, the Veterans Affairs Quality Enhancement Research Initiative for HIV, reported that rates of hospital admission for cardiovascular disease declined after the introduction of antiretroviral therapy, that the number of deaths from cardiovascular causes did not increase, and that specific classes of antiretroviral drugs were not related to cardiovascular risk during a mean follow-up of 15 months.<sup>4</sup> Unfortunately, the association between antiretroviral therapy and cardiovascular disease remained uncertain because several of these studies had methodologic limitations, including incomplete case ascertainment, incomplete data regarding exposure to antiretroviral therapy, and a low number of cardiovascular events.<sup>3,4</sup>

Recently, several well-designed prospective studies have shed some light on the complex interactions among the use of antiretroviral ther-