

## Treatment of Rapid-Cycling Bipolar Disorder: Are Antidepressants Mood Destabilizers?

A century ago, rapid-cycling bipolar disorder was not observed. Either classic nosologists, such as Kraepelin, simply missed it or it did not exist. The term was first coined in the 1970s to identify lithium nonresponders in randomized clinical trials; thereafter, rapid cycling became the subject of decades of further research, which has confirmed that rapid cycling is a factor in poor prognosis. Rapid-cycling patients do worse in follow-up than patients without rapid cycling, and they are also less likely to respond to treatment. The erroneous impression then arose that anticonvulsants, such as carbamazepine or divalproex, were more effective than lithium in treating rapid cycling. The error came from comparing studies using lithium alone against studies using anticon-

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vulsants alone, without a direct comparison of the two treatments. Such comparisons need to be made head to head, in randomized studies. When these comparisons are performed with proper methods, anticonvulsants are seen to be about equivalent to lithium (i.e., ineffective) in treating rapid cycling (1, 2).

Because rapid cycling was not described until the 1970s, clinicians began speculating that psychotropics, such as antidepressants, induce rapid cycling. Is rapid cycling iatrogenic? Do antidepressants perhaps increase the risk for rapid cycling or worsen symptoms in some patients? Early reports of a possible link between antidepressants and rapid cycling were made in the 1970s by Kukopulos in Italy (3) and by Wehr et al. at NIMH (4). Later observational studies were contradictory and inconclusive (5). Yet the largest published randomized clinical trial showed that discontinuation of antidepressant medication improved refractory rapid cycling (4). This study found an association between tricyclic antidepressant treatment and rapid cycling in a double-blind, placebo-controlled on-off-on-off design, although the published report was incomplete in many details. Nonetheless, the implication, that antidepressants cause rapid cycling, was intriguing; this finding potentially gives clinicians an important tool to improve outcome in bipolar disorder: discontinuation of antidepressants. Yet this approach goes against some of the tendencies of physicians: giving, not stopping, medications to improve mental illnesses.

In this issue of the *Journal*, Schneck and colleagues report new data from the NIMH-sponsored Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD) study, in which about one-third of the patients with bipolar disorder had rapid cycling; these patients also had more recurrences in the 1-year follow up. Only 5% of these rapid-cycling patients continued to meet that definition (four or more episodes in a year) at the 1-year follow up, either because of appropriate treatment in STEP-BD or because of natural history. The major predictor of worse outcome was antidepressant use, which about 60% of the patients received, most often accompanied by mood stabilizers.

By focusing on the relationship between antidepressant use and rapid cycling, the STEP-BD study fills an important void. Not only is the study far larger (N=1,742) than any prior investigation, it is also prospective, unlike all but one prior observational study (6). Moreover, unlike that study, this STEP-BD study shows that antidepressants

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are associated with worsened course of illness even after adjustment for severity of baseline depression.

The aforementioned largest randomized clinical trial of rapid cycling (N=51), although not definitive, also indicated an association between antidepressant use and rapid cycling (4). In contrast, a recent small study (N=9) of previously untreated patients with type II rapid-cycling bipolar disorder showed benefit with citalopram (7), but that study was limited to type II bipolar illness. Further, those data do not apply to patients with refractory illness. Now the largest prospective observational study has confirmed the association of rapid cycling with antidepressant use, supporting the viewpoint that these agents can worsen overall illness, causing more mood episodes (including depression), in patients with a rapid-cycling course.

Critics may suggest that the available randomized clinical trials of maintenance treatment for bipolar disorder do not uniformly provide evidence of increased cycling rates with antidepressants. As has been discussed at length elsewhere (5), it is relevant that those trials were conducted with mostly non-rapid-cycling patients and were not powered to detect long-term worsening of mood episodes with antidepressants, compared with placebo. In the future, it will be difficult, as well as ethically challenging, to devise randomized clinical trials to test the hypothesis of worsening of rapid-cycling bipolar disorder with antidepressants. Thus, observational analyses such as this STEP-BD study will become even more influential for informing clinical care.

In my own clinical experience, most cases of refractory bipolar disorder, usually of the rapid-cycling variety, are due to the mood-destabilizing effects of antidepressants. Such patients often receive antidepressants for years, with or without mood stabilizers. They rarely receive mood stabilizers in the absence of antidepressants. If antidepressants are seen as mood destabilizers, then an adequate therapeutic trial of mood stabilizers for rapid cycling can occur only *in the absence of antidepressants*. Frequently, in patients with refractory rapid-cycling bipolar disorder, multiple trials of mood stabilizers appear to fail, as the data of Schneck et al. suggest, *because* they are evaluated with antidepressants. When antidepressants are stopped, those same mood-stabilizing agents can then be effective. Stopping antidepressants thus is the sine qua non of treating rapid-cycling bipolar disorder. Sometimes, in a minority of cases, usually with highly suicidal patients during depressive episodes, short-term antidepressant treatment may be warranted. But in most patients with rapid cycling, these mood destabilizers are best avoided.

Mood destabilization with antidepressants should be distinguished from an acute manic “switch.” Antidepressant-induced mania, or switch, is a short-term phenomenon; one might define it as happening within 2 months of the beginning of antidepressant treatment. Mood destabilization is a long-term phenomenon, reflecting more mood episodes over time than would have occurred by natural history. Antidepressants may cause long-term mood destabilization without a short-term manic switch, and vice versa. Although some agents may have low rates of acute manic switch (8), especially when used with mood stabilizers (9), the data from STEP-BD suggest that even the new generation of antidepressants can produce long-term mood destabilization.

In sum, like other results from STEP-BD, this study may be one more nail in the coffin of antidepressant use in bipolar disorder. It would seem rational to turn our attention from antidepressants toward better proven interventions, particularly psychotherapies (10), for the depressive morbidity of bipolar disorder.

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