Drug-Induced Switching in Bipolar Disorder
Epidemiology and Therapeutic Implications

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Summary

The use of antidepressants in patients with unipolar depression is associated with a negligible rate of switching into mania. In contrast, in patients with bipolar disorder, even those treated concomitantly with a mood stabiliser, such switching appears to represent a greater problem. Preliminary evidence from some controlled studies suggests that antidepressants may double the incidence of a switch, from some 25% in patients receiving placebo to 50% in those receiving tricyclic antidepressants. Other series in patients with rapid cycling bipolar disorder suggest an even higher switch rate; however, only about one-third of the observed switches are likely to be attributable to the antidepressant (i.e. unrelated to the natural course of illness).

In addition to these phenomena, cycle acceleration has been observed consistently in a subgroup of patients with bipolar disorder who are receiving maintenance treatment with tricyclic antidepressants, and this has been verified by periods of discontinuation and reintroduction of the drug. Cycle acceleration appears to occur in approximately one-fifth of patients with refractory bipolar illness.

Given these potential liabilities, it is unclear as to what is the most judicious treatment algorithm to follow for the bipolar patient with depression that is breaking through treatment with a mood stabiliser. In the absence of adequate studies, our own algorithm is to use antidepressants judiciously in nonrapid cycling patients, but to relatively avoid them in rapid and ultra-rapid cyclers. Instead, we
prefer to use adjunctively a second mood stabiliser prior to the introduction of a unimodal antidepressant. Systematic controlled clinical trials are eagerly awaited, comparing not only the acute antidepressant efficacy of the newer antidepressants, but their liability in causing a switch or cycle induction when introduced into long term prophylaxis.

With the advent of a series of new potential mood stabilising agents, direct comparison of the addition of a second mood stabiliser with that of a unimodal antidepressant will help establish the comparative risk : benefit ratios of these differential approaches. It is also hoped that clinical and biological markers of differential antidepressant responsivity will ultimately be identified and help to refine the process of choosing the best antidepressant modality for depression breaking through prophylaxis with mood stabilisers in patients with bipolar disorder.

Perhaps it is most appropriate to begin this review with a caveat: there are relatively few data on the magnitude of the problem of drug-induced switching in bipolar disorder. Patients with bipolar depression have been systematically excluded from most pharmaceutical industry-sponsored trials designed to bring antidepressants to market, and there have been no large-scale studies of antidepressants in combination with mood stabilisers for bipolar depression since the early 1980s. Nonetheless, we will attempt to review the data that do exist in this regard, and suggest how it might be interpreted in relationship to current clinical therapeutics. However, in doing so, we acknowledge from the outset that the conclusions and our interpretations of them must, of necessity, be highly provisional, and a more complete database upon which to base these judgements in clinical practice is eagerly awaited.

In addition, it is apparent that the pharmacotherapeutic 'scene' in bipolar illness is rapidly changing and evolving. Treatment of bipolar illness is no longer limited to lithium carbonate augmented with antipsychotics and benzodiazepines for breakthrough manic episodes, and tricyclic antidepressants (TCAs) or monoamine oxidase inhibitors (MAOIs) for depressive episodes. A whole host of potential antidepressants for bipolar illness has emerged from the work in unipolar depression. Equally promising is the emergence of a variety of treatment options in pharmacoprophylaxis with putative mood stabilising agents other than lithium, including carbamazepine and valproic acid (sodium valproate).[1]

The availability of these options has also vastly complicated the methodological horizon, wherein appropriate study designs are endlessly argued over and difficult to fund. The field is further mired in controversy by the decision of the American Psychiatric Association not to include antidepressant-induced mania as bipolar illness in DSM-IV.[2] This further confuses any potential data collection process in relationship to the ultimate outcome of patients who have their first episode of hypomania or mania while receiving antidepressants.

In this review, we will refer to a ‘switch’ into mania or hypomania as an isolated episode emerging during treatment with an antidepressant, and ‘cycling’ or ‘cycle acceleration’ as an increase in episode frequency occurring with maintenance treatment.

1. Controversies Regarding the Existence of Drug-Induced Switching

Angst[3] has presented data showing that even after 3 episodes of major depression, some 29% of patients with bipolar disorder may still be incorrectly diagnosed as having a unipolar illness. Therefore, the stage is immediately set for controversy, as it is unclear whether a switch during antidepressant treatment is a natural statistical expectation or whether the antidepressant was some-