
Do Antidepressants Really Beget More Depressive Episodes?

To the Editor: Ghaemi et al¹ describe a randomized study as part of the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD) initiative in which euthymic patients were randomly assigned to continuation versus discontinuation of their antidepressant, but not “mood-stabilizing,” medications and were followed up to 3 years. The rather “eye-popping” result and conclusion, respectively, presented in the abstract are that “rapid-cycling course predicted 3 times more depressive episodes with antidepressant continuation” and “rapid-cycling patients had worsened outcomes with modern antidepressant continuation.”^{1(p372)}

On first blush, this would seem an important finding. However, closer inspection of the data reveals these to be unsupported conclusions. To summarize: 32 patients were randomized to antidepressant continuation, while 38 were randomized to discontinuation. Of the 32 in the continuation group, 7 (by my calculations extrapolated from Table 1) had rapid cycling, while 25 were non-rapid cycling. Of the 38 who discontinued antidepressants, 10 were rapid cycling and 28 were non-rapid cycling. There was no signal whatsoever, in either rapid-cycling or non-rapid cycling subjects, of a tendency for those who continued antidepressants to have more manic states. Not to be dismayed, the authors, in an apparent attempt to inflate the presumably horrific, rapid cycling-inducing effects of antidepressants, compare the number of *depressive* episodes per year in the resultant 4 groups. Among the continuation group, those who were rapid cycling had about 3 times as many such episodes per year as those who were non-rapid cycling.

However, this is a virtually meaningless comparison, especially if taken in isolation as the authors do. A much better comparison to look at the rapid-cycling enhancement tendencies of antidepressants would be to compare the number of episodes per year in rapid-cycling antidepressant continuation subjects (1.29) versus

that in rapid-cycling discontinuation subjects (0.82). The authors do not tell the readers whether this post hoc comparison is statistically significant, but I highly doubt that it is, considering the paltry sample sizes of the 2 groups (7 who continued antidepressants vs 10 who discontinued). Furthermore, among non-rapid cycling patients, the continuation of antidepressants appeared to be associated with an almost halving of the number of depressive episodes per year vis à vis discontinuation of antidepressants (0.42 vs 0.70).

All of these data simply make no sense: why would antidepressant continuation be protective in non-rapid cycling subjects but “depressogenic” in rapid cycling subjects? Furthermore, why would this presumed enhancement of mood episode recurrences be true only for depressions and not for manias, the latter being the heretofore feared event among the bipolar mavens who are largely against such compounds?

Finally, the sample sizes in the group in question, namely rapid-cycling subjects, are so small (7 and 10), that this trial hardly qualifies as a randomized controlled trial for *them*—at best, it is a very preliminary pilot project, the conclusions of which have been misleadingly stated in the abstract. In fact, I suspect the results in rapid-cycling patients were influenced by 1 or 2 outliers, and I challenge the authors to present data for each of these patients.

In my opinion, the readers of the *Journal of Clinical Psychiatry* were not well served by this cynically spun article.

REFERENCE

1. Ghaemi SN, Ostacher MM, El-Mallakh RS, et al. Antidepressant discontinuation in bipolar depression: a Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD) randomized clinical trial of long-term effectiveness and safety. *J Clin Psychiatry*. 2010;71(4):372–380.

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