Letters to the Editor

Monotherapy Antidepressant Treatment is Not Associated With Mania in Bipolar I Disorder

TO THE EDITOR: While impressed with the creativity of the study by Alexander Viktorin, M.Sc., et al. (1), published in the October 2014 issue of the *Journal*, regarding the risk of transition to mania during antidepressant treatment in bipolar I disorder, we disagree with their conclusions, especially the conclusion that antidepressants are associated with mania.

We disagree that there is "an increased risk of manic switch among patients with bipolar disorder on antidepressant monotherapy." The authors report a hazard ratio of 2.83 for mania in patients taking antidepressants alone compared with those taking antidepressants with a mood stabilizer. With an uncorrected p value of 0.028 for the hazard ratio (and multiple hypothesis tests), the event rate is so low as to leave great uncertainty about whether this is a true effect and what is its actual magnitude. On closer examination, the increase in *absolute* risk associated with antidepressant monotherapy in this study is small and not likely clinically significant. Of 1,117 patients, only 10 additional cases of mania were found during monotherapy antidepressant treatment compared with the period without antidepressant treatment, a 0.9% increase in absolute risk. Using the number needed to harm, 112 patients would need to be treated with monotherapy antidepressants before a single one would develop mania. This would be considered insignificant even in a well-controlled, randomized trial. For comparison, the number needed to harm for metabolic abnormalities associated with atypical antipsychotics (often used for bipolar depression) has been estimated at 6 for quetiapine and 10 for olanzapine/fluoxetine (2). While evidence of efficacy in bipolar depression for some atypical antipsychotics is much more substantial than that for antidepressants, so are their risks.

Furthermore, if one is to conclude from this study that monotherapy antidepressants increase mania risk in bipolar I disorder patients, then one must also conclude that antidepressants are *protective* against mania. After all, with a hazard ratio of 0.68, the risk of mania for patients taking antidepressants long-term compared with those not taking antidepressants was actually *reduced* by 32%.

It is argued that the within-subjects design controls for confounding, but this assumes that the pattern of illness remains constant over time within any patient. These results may still represent confounding by indication. Registries and electronic health records represent powerful but not infallible tools for pharmacovigilance; confounding must be considered in any nonrandomized design.

Perhaps confirmation bias inadvertently led the authors to interpret their data in line with what is already conventional wisdom: that antidepressants increased risk of mania—and to deemphasize the much stronger association that they report in their study: that antidepressant use in bipolar I disorder prevents mania. Examining the same data, we conclude that neither finding is likely related to the properties of antidepressants themselves. The data certainly do not support the notion that monotherapy antidepressant treatment is unsafe in bipolar I disorder. The risks (or benefits) of antidepressant use in bipolar I disorder, particularly relative to potentially more harmful strategies, remain uncertain.

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Response to Ostacher et al.

TO THE EDITOR: Dr. Ostacher et al. raise important points regarding our study of the risk for treatment-emergent switch to mania when bipolar disorder patients are prescribed antidepressants. Their first point is with regard to the group receiving antidepressant monotherapy. They have noticed that the risk for switch was low in absolute terms. In fact, they argue that the number needed to harm is so high that there is no basis to suggest that antidepressants are unsafe to use in bipolar disorder. While we acknowledge that our study does not justify the conclusion that antidepressant monotherapy in

bipolar disorder is generally unsafe—there might very well be patients with bipolar disorder in whom antidepressant monotherapy can be safely used—the number needed to harm that Dr. Ostacher et al. have calculated is not representative for the whole population of bipolar disorder patients. We namely show, in Table 4 of our article, that participants in the antidepressant monotherapy group were 6.5 times less likely to experience manic episodes than those in the group treated with a mood stabilizer prior to antidepressant treatment. This classic example of "confounding by indication" suggests that patients were on antidepressant monotherapy because they were considered less likely to experience manias in the first place. Second, because of limitations in register data, our study mainly captured severe manic episodes but lacked, for example, primary care data. If we would have been able to also capture milder episodes, the number needed to harm would have been lower. Third, study participants in the monotherapy group were censored if a mood stabilizer was dispensed after the antidepressant because it was unclear how it should be interpreted: it might signify the start of prophylactic treatment in a stable patient, but it could also reflect a measure taken when signs of mania surfaced. If we would have interpreted a mood stabilizer prescription during antidepressant treatment as a sign of treatment-emergent mania, the hazard ratio would have risen to 16.3 (95% confidence interval [CI]=7.2–37.2) in the 0- to 3-month period and to 11.7 (95% CI=5.1–26.9) in the 3- to 9-month period after the antidepressant prescription. These things considered, the number needed to harm is likely to be lower if an unselected group of patients with bipolar disorder would receive antidepressant monotherapy.

The authors' second point is with regard to patients on mood stabilizers, in whom we actually found a decreased mania rate during antidepressant treatment. Dr. Ostacher et al. suggest that "confirmation bias" led us to deemphasize this finding because it contradicts conventional wisdom. We agree that we interpreted this finding cautiously. While we certainly find the idea that antidepressants together with a mood stabilizer might decrease the risk of mania interesting and worthy of follow-up, it is a new and unexpected finding that needs to be replicated before any firm conclusions can be drawn.

Dr. Ostacher et al. overlook the main finding in our study, which was that the two studied groups differed. While we found an increased rate of mania in the group treated with antidepressant monotherapy, we found no evidence of treatment-emergent mania when patients on mood stabilizer medication received antidepressant treatment (in fact, the mania rate decreased, as pointed out by Dr. Ostacher et al.). Hence, although our study provided evidence that some bipolar disorder patients switch to mania when treated with antidepressant monotherapy, the main point was that this risk can be countered by mood stabilizers. As to the question whether antidepressant use in bipolar disorder on balance is beneficial or harmful, we concur with Dr. Ostacher et al. that it remains uncertain.

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Evidence-Based Medicine and Clinical Expertise

TO THE EDITOR: The article by Delbert G. Robinson, M.D., et al. (1), published in the March 2015 issue of the *Journal*, on prescriptions in first-episode schizophrenia spectrum disorders addresses a relevant topic. The result that 39.4% of the sample (for whom prescriptions deviated from guidelines) "might have benefitted from changes in their psychotropic medication prescriptions" is self-evident—anyone "might benefit" from a medication change, including the remaining 60.6% with guideline-compatible prescriptions. The authors seem to make the assumption that prescribing according to guidelines is better than deviating from them. Their data, however, do not address this question. Their article illustrates how evidence, once built into guidelines, is usually expected to inform health policy. Deviation from guidelines is judged a priori as poor practice requiring remediation, not as informed clinical judgment. In the National Institute of Mental Health's Recovery After an Initial Schizophrenia Episode (RAISE)-Early Treatment Program (ETP) study, the most problematic prescriptions were for olanzapine or multiple antipsychotics. These are identified as primary targets for improving treatment, requiring educational efforts. In other words, deviation from guidelines is explained by gaps in knowledge. I suggest an alternative interpretation. Physicians in the RAISE-ETP study likely knew that olanzapine or multiple antipsychotics are not first-line treatments, in any condition. They also likely had *clinical reasons*, good or bad, for taking what were *thoughtful* decisions. In order to complement complex Bayesian correlations, I therefore suggest asking physicians directly about the reasons underlying their clinical decisions.

REFERENCE

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