Regarding antidepressant-induced mania, two studies comparing antidepressants without mood stabilizer to no treatment (placebo only) reported no mania in any patients: an oddity, if true, since it would suggest that even spontaneous mania did not occur while those patients were studied or that perhaps manic symptoms were not adequately assessed. As described, another study preferentially prescribed lithium more in the antidepressant group (3), providing possibly unequal protection against mania. Although the olanzapine-fluoxetine data suggest no evidence of switching while using antipsychotics, in our reanalysis of the lithium-plus-paroxetine (or imipramine) study, there was a threefold higher manic switching rate with imipramine versus placebo (risk ratio= 3.14), with asymmetrically positively skewed confidence intervals (0.34–29.0). Combined with other studies reviewed that showed higher tricyclic antidepressant switching rates than other antidepressants, attention to this heterogeneity suggests that one cannot rule out antidepressant switching.

Finally, these short-term (up to 10 weeks) studies are only relevant, if at all, to the acute depressive episode. Contrary to the highly selective review in the discussion, they do not provide any evidence to support long-term maintenance use of antidepressants in bipolar disorder, which was previously shown ineffective in multiple randomized clinical trials in a systematic review (5).

In summary, our critique touches partly on the validity of this meta-analysis, but more importantly, on its generalizability due to unexplored heterogeneity. Apparent agreement among studies hides major conflicting results between the only adequately designed study using the most proven mood stabilizer, lithium, and the rest. It would appear that the rosy conclusions of the meta-analysis are premature when the clinical options involve use of proven mood stabilizers, such as lithium, with or without antidepressants.

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TO THE EDITOR: The review of antidepressants for bipolar depression by Dr. Gijsman et al. provided an excellent overview of the randomized, controlled trials in the literature. However, the presented data all reflect acute antidepressant treatment response, with the longest study duration (10 weeks). Bipolar disorder is a chronic, relapsing condition, with an etiology likely distinct from that of unipolar depressive disorder, for which current antidepressants were specifically developed. Treatment approaches applied to alleviate symptoms during acute exacerbations may have significant impact on the long-term course of the illness. The authors did not present evidence that the long-term outcomes are favorable with antidepressant treatment; thus, their conclusion to challenge the APA practice guideline for recommending lithium or lamotrigine as first-line treatment for bipolar depression is unfounded.

There are long-term (of 11–24 months) prospective, placebo-controlled (1–3), naturalistic prospective (4, 5), and retrospective studies (6)—excluded categorically from the current review—showing that antidepressant exposure is associated with worse long-term outcomes in patients with bipolar disorder, apart from the concern for acute mania. Developing treatment guidelines requires an integration of all available data.

The question of whether bipolar depression responds best to adding a mood stabilizer or an antidepressant may be amenable to investigation by a long-term practical clinical trial. This model of structuring studies to compare relevant alternative interventions in diverse, real-life patient populations and practice settings is gaining support from research decision makers. Current data on antidepressants in bipolar depression do not justify changing the APA treatment guidelines.

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TO THE EDITOR: The conclusion of a recently published review and meta-analysis by Dr. Gijsman et al. of antidepressant