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

treatment of bipolar depression is "at odds" (according to the review) with the recommendation of the APA Practice Guideline for the Treatment of Patients With Bipolar Disorder (1) to use lithium or lamotrigine as a first-line treatment for bipolar depression. Instead, the review recommends a combination of a mood stabilizer and an antidepressant.

The APA practice guideline was developed in 2001 and published in April 2002. Every effort was made to ensure that the guideline's recommendations were based on evidence available at the time. The recommendation for lithium or lamotrigine was based on the positive results of controlled monotherapy trials of these agents in the treatment of bipolar I depression. In 2001, the controlled data on antidepressants in combination with a mood stabilizer did not support efficacy for bipolar depression. A positive fluoxetine-olanzapine study (2) had not been completed, and no statistically significant difference in efficacy was observed in the placebo-controlled study of paroxetine and a mood stabilizer (3).

A second noted difference between the review by Dr. Gijsman et al. and the APA guideline regards the recommendation to select specific antidepressants as part of combination therapy. The APA guideline recommended the use of agents for which there were controlled data and for which low rates of switching had been found.

Since the guideline's publication in April 2002, a substantial amount of controlled research has emerged on the treatment of bipolar disorder, including the acute treatment of depression, the acute treatment of mania, and maintenance and prophylaxis. APA practice guidelines are revised at regular intervals, about every 5 years, depending on available resources. Between revisions, in an effort to keep recommendations current and useful, the project now publishes "guideline watches." Watches briefly describe major developments in the scientific literature that could lead clinicians to treat patients in a manner different from what the guidelines recommend. They are published online at http://www.psych.org/psych_pract/treatg/pg/prac_guide.cfm. We look forward to updating the bipolar disorder guideline in the near future.

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Dr. Gijsman and Colleagues Reply

TO THE EDITOR: We thank our correspondents and appreciate their points of view; we will address three independent concerns in their correspondence.

Regarding meta-analysis and heterogeneity, we agree with Drs. Ghaemi and Goodwin that meta-analysis can be seen as an "observational study of studies" simply because one can only include the trials that have happened to be performed and written up. However, the benefit of random assignment certainly is not lost with meta-analysis because it preserves the unbiased estimate of treatment effect from each randomized trial and estimates a weighted mean treatment effect. Heterogeneity is the situation in which there are genuine differences underlying the results of studies (1). In our review, there was evidence of heterogeneity on the outcome of "clinical response" in the comparison of antidepressants versus placebo. However, the direction of the treatment effect is the same for all studies, limiting the clinical implications of the heterogeneity (1).

Drs. Ghaemi and Goodwin argue that the effect of antidepressants might be smaller in studies in which all patients concurrently used lithium, and they suggest that this is caused by the antidepressant effect of lithium. They also argue that in one trial, the differential use of lithium may have positively influenced the effect of antidepressants, but the particular figures they give appear to be misquoted.

We think their explanation is unlikely because the proportion of responders in the comparison group is not larger in studies with concurrent use of lithium, as would be expected under their hypothesis. Moreover, on a priori grounds, we think the concurrent use of lithium is unlikely to be a major issue between the trials. Most patients had already been taking lithium for some time at random assignment; they were not, for the most part, assigned to it as a new treatment.

As to long-term outcomes, we acknowledge, with Drs. Ghaemi and Goodwin and Drs. Fetter and Askland that our review included only short-term studies, and we did not draw any conclusions about the longer-term risk of antidepressants to induce mania or rapid cycling. Instead, we said, "Given the limited evidence, there is a compelling need for further studies with longer follow-up periods and careful definition and follow-up of emerging mania and partial remission" (p. 1537).

In the long-term treatment of patients with bipolar disorder, the combination of lithium plus a tricyclic antidepressant was associated with more manic relapses (although not statistically significant) only in the controlled study by Quitkin and Kane (1981) but actually not in the controlled study by Prien et al. (1984). The study by Altshuler et al. (2) was a naturalistic study, indicating that stopping antidepressants in patients who were also using mood stabilizers was associated with more depressive relapses; this finding is often interpreted as favoring the long-term use of antidepressants in at least some patients.

We are currently piloting a trial from Oxford comparing any selective serotonin reuptake inhibitor with lamotrigine in bipolar depression. We aim to randomly assign as many patients as possible and to follow them for up for 12 months. Recruitment for this BALANCE-2 trial is worldwide and web