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

based and open to everyone interested (http://www.psychiatry.ox.ac.uk/balance).

On the relationship between systematic reviews and clinical guidelines, we are understandably very pleased that Dr. Hirschfeld et al. have already noticed our review, and we look forward to the next update of the APA guideline for bipolar disorder. We agree that developing treatment guidelines requires the updating and integration of all available data. When this leads to different conclusions by different consensus groups, it means—in the absence of obvious cultural or legal constraints—either that the evidence has been selectively evaluated or there is simply too little evidence to make better than an opinion-led summary. For example, lamotrigine was recommended for the acute treatment of bipolar depression by the APA bipolar disorder guideline on the basis, at that time, of just one available study in which lamotrigine was more effective than placebo on a secondary—not the primary—outcome measure. Since then, the results of two other acute studies have also become available, and they were both negative (3).

In the case of short-term treatment of bipolar depression with antidepressants, we stand by our conclusion that the available evidence supports their efficacy. Their use in bipolar I patients should normally be accompanied by a mood stabilizer (4). The need for further independent studies remains and could meet many of the apparent differences of interpretation raised by our eminent colleagues.

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Extended-Release Divalproex Sodium for Patients With Side Effects From Delayed-Release Divalproex Sodium

TO THE EDITOR: We read with interest the article by Franca Centorrino, M.D., et al. (1). For similar reasons—enhanced patient compliance resulting from once-daily dosing and the potential for greater tolerability because of less peak-trough blood-level fluctuation—we also performed a pilot switching study that we presented at the 2001 APA annual meeting and would like to share with your readers.

Ten patients with bipolar I or bipolar II disorder (some with other axis I or axis II comorbidity) who exhibited side effects that limited their compliance or tolerability to delayed-release divalproex sodium were switched to the once-daily extended-release formulation. The patients were switched based on bioavailable dose data and available tablet strength. In two multiple-dose studies, the average bioavailability of extended-release divalproex given once daily was 81%–89% relative to delayed-release divalproex tablets given b.i.d. (2). The patients were evaluated over 12 weeks to monitor their clinical status (Clinical Global Impression and Global Assessment of Functioning scales), and side effects were measured with a 7-point Likert rating scale. No additions, deletions, or dose changes of concomitant medications occurred in any patients during the 12-week observation period. Laboratory assessments included baseline and follow-up divalproex blood levels, liver function tests, and CBCs. Our case series was unblinded, open label, and naturalistic. All patients were maintained in their usual outpatient treatment settings, with no alteration in the type or frequency of their clinic appointments.

Six male and four female patients ages 27 to 52 who were currently taking divalproex for a DSM-IV diagnosis of bipolar I, bipolar II, or schizoaffective disorder were followed. This study was approved by the Aurora Healthcare Institutional Review Board, and all subjects provided appropriate informed consent. All patients had liver function tests with results within normal limits and had no history of hepatitis, pancreatitis, or hematological abnormalities. All patients had at least one side effect attributed to divalproex (namely, gastrointestinal discomfort, sedation, weight gain, or tremor) that prompted their desire to switch to a potentially more tolerable extended-release formulation.

Our 12-week follow-up results substantiated that extended-release divalproex was effective (nine of 10 patients showed equal or mildly improved clinical status), well tolerated (five of 10 had reductions in side effects), and led to enhanced medication compliance in certain individuals. Pharmacokinetic data from extended-release divalproex studies suggest that its peak and trough blood levels do not fluctuate significantly compared to the conventional divalproex formulation (2). Peak levels may be associated with increased side effects, and adequate trough levels are thought to affect the efficacy of divalproex. Thus, the extended-release formulation of divalproex (which has a more level steady-state curve) may confer the dual advantage of lesser side effects (tolerability) and more sustained efficacy.

Studies have suggested that noncompliance with pharmacological treatments for bipolar disorders is as high as 50%, and compliance increases as the number of daily doses decreases (3). Thus, once-daily dosing should improve patient compliance and, consequently, may improve treatment outcomes. This may be especially important in the treatment of individuals with bipolar disorder, for whom noncompliance often not only precipitates acute decompensation but also leads to the development of a more intractable disease pattern or loss of responsiveness to previous regimens (e.g., lithium). Our open pilot findings add to the growing literature (4) that supports the safety and efficacy of extended-release divalproex sodium in psychiatric patient populations, and we hope that it stimulates more rigorous controlled clinical trials.