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.

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Defining the Core Processes of Psychotherapy

TO THE EDITOR: Janis L. Cutler, M.D., et al. (1) presented an excellent clinical case conference comparing approaches to the treatment of an individual using three different types of psychotherapy (cognitive behavior therapy, interpersonal psychotherapy, and psychodynamic therapy). Dr. Cutler commented that cognitive behavior therapy and interpersonal psychotherapists "do not believe it necessary to explore or interpret transference" (p. 1572). We would disagree with this statement with regard to cognitive behavior therapy. As cognitive behavior therapy supervisors training psychiatry residents, we often find that supervisees and psychodynamic therapy supervisors have the perception that transference is not examined in cognitive behavior therapy. In our opinion, this is one of the major misconceptions of cognitive behavior therapy that has been identified by various experts (2–5).

Although the word "transference" is not part of the jargon of cognitive behavior therapy, examination of the cognitions related to the therapist with respect to past significant relationships is an integral part of the assessment and treatment in cognitive behavior therapy. Developing a cognitive behavior therapy case conceptualization of patients is recommended for treating every patient with cognitive behavior therapy (3); cognitive behavior therapists examine the thoughts, feelings, and behaviors related to a wide range of situations (including reactions to the therapist) and relevant childhood experiences to understand the underlying core beliefs and conditional assumptions of each patient. In addition, Beck et al. (5) stated that a cognitive therapist must be

> particularly sensitive to…the patient's hypersensitivity to any action or statement that might be construed as rejection, indifference or discouragement. The patient's exaggerated responses or misinterpretations may provide valuable insights but the therapist must be alert to their occurrence and prepare the framework for using these distorted reactions constructively.

We believe that it is important to underscore that transference issues are examined carefully, in an upfront fashion, in cognitive behavior therapy and must be an integral component of the complete management of every patient undergoing cognitive behavior therapy.

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TO THE EDITOR: The informative clinical case conference by Dr. Cutler et al. arrived at the brink of psychotherapy's current challenges but failed to take the next step into the heart of the matter. After concise descriptions of cognitive behavior therapy, psychodynamic, and interpersonal therapy by proponents of each approach, Dr. Cutler and colleagues synthesized similarities and distinctions among the three. They noted their many shared features, including the critical importance of the therapeutic alliance, and found a primary distinction in the emphasis psychodynamic psychotherapy places upon transference, which cognitive behavior therapy and interpersonal psychotherapy do not share. They noted that "common factors" account for most outcomes. Technique is important but accounts for only about 15% of outcome, with 55% of patient change attributable to patient variables (1). Dr. Cutler et al. correctly believe that there may be prescriptive approaches for specific patient characteristics, citing investigators who found that cognitive therapy works better for patients with less impaired cognitive skills, whereas interpersonal therapy works better for patients who have some social skills. There is a growing body of process research suggesting that therapists must customize their approaches to patients (2). The patient's assets and deficits are the most substantial determinants of outcome, with the therapist's skills and abilities—regardless of theoretical school—secondarily influencing outcome. The strength of the working alliance follows these key variables as a tertiary influence (3). Like the child who saw that the pompous emperor really had no clothes, process research is revealing that the schools of therapy are illusory. It is finally telling us the naked truth that patient and therapist variables are the primary keys to outcome. Findings like these compel us to describe psychotherapy as it is, by using our expanding knowledge of the human brain to describe the neural circuits of psychotherapy based upon their fundamental processes: engagement, broadening self-awareness, pattern search, change, termination, resistance, transference, and countertransference. I hope Dr. Cutler and her colleagues will build upon these neurobiological discoveries to help define psychotherapy as it is.

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