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Trainees and Collaborations With Industry

TO THE EDITOR: As a recent graduate of residency and fellowship in psychiatry, I read the article by David B. Merrill, M.D., et al. (1) with great interest. I struggled to define my relationship with the pharmaceutical industry throughout residency, as did most of my classmates in our program at Cambridge Hospital. I have not chosen a research-focused career, and I have great admiration for those who struggle to find funding and collaborate with industry. However, I do have one question that I was unable to answer from reading the article: What ultimately happened to the authors' finding that the study drug, aripiprazole, and control drug, haloperidol, showed no significant difference in efficacy? They refer to a study, but there is no corresponding publication citation.

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Response to Malik et al. and Brewer Letters

TO THE EDITOR: We thank Dr. Malik et al. and Dr. Brewer for their thoughtful comments. Dr. Brewer inquires about the fate of the study in which we reported a post hoc analysis of a large industry-sponsored trial that compared aripiprazole and haloperidol for the treatment of schizophrenia. Our analysis found that the apparent superiority of aripiprazole among patients early in the course of their illness was likely due to substantial side effects in the haloperidol-treated group, perhaps as a result of excessive dosing of haloperidol in the parent trial. We submitted our paper to several journals before it was recently accepted for publication (1). The difficulty of publishing negative results is a well-established phenomenon in clinical trial research in general (2) and for psychiatric trials in particular (3), and it is a primary source of publication bias. Nonpublication of negative results may be a result of authorial or organizational reluctance to submit negative findings, or a relative undervaluing of such studies by reviewers or editors.

We commend Dr. Malik et al. for the creative ways in which they teach residents in their program about the ethical challenges of interacting with the pharmaceutical industry.

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Electroconvulsive Therapy for Catatonia

TO THE EDITOR: We applaud the excellent care described by Marc H. Zisselman, M.D., and Richard L. Jaffe, M.D., (1) in their Clinical Case Conference published in the February 2010 issue of the *Journal*. Their case presentation and discussion highlight important issues in the recognition and urgent, definitive treatment of catatonia in a young patient. We would like to suggest an alternative ECT treatment procedure when urgent/emergent situations, such as the one described, occur. Since the most effective ECT is indicated, stimulus dosing should be high and consideration should be given to inducing two seizures per ECT session (en bloc ECT) until clinical improvement is apparent (2). Although the authors commented that the initial stimulus setting of 20% of the device maximum was higher than would have been prescribed by the half-age method (3), this was still very conservative. We would recommend liberal stimulus dosing, with the goal of inducing the most powerful and well-generalized seizures possible. The rationale for conservative stimulus dosing in routine ECT is to minimize effects on cognition, a consideration that does not apply to the use of ECT as a life-saving treatment in a seriously catatonic patient. While one cannot argue with the excellent outcome in the case presented in the *Journal,* we feel it is important for readers to understand that in most similar situations, every effort should be made to maximize the efficacy of the ECT administered in order to ensure the quickest and most robust clinical response. The medical sequelae of prolonged catatonia can be very serious. Early, definitive intervention offers the patient the best chance of full recovery.

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Response to Kellner et al. Letter

TO THE EDITOR: We appreciate the opportunity to respond to Kellner et al.'s comments underscoring the clinical urgency associated with the treatment of acute catatonia and important aspects of ECT stimulus dosing in this syndrome.

Our stimulus setting for the initial treatment took into account the recommendations of the half-age formula but also accounted for other factors that may have affected seizure threshold. Our patient's age and gender may have reduced her seizure threshold, while recent benzodiazepine treatment, possible dehydration, and use of bilateral electrode placement may have raised it. These complexities preclude a precise dosage determination. Furthermore, Kellner et al.'s suggestion that a more aggressive (suprathreshold) stimulus would have produced a more therapeutic seizure reflects research relevant to unilateral ECT treatment (1). There is no evidence that suprathreshold bilateral ECT yields a more rapid or robust clinical response. The suggestion of en bloc ECT in this setting is interesting but not one we would currently endorse. The evidence base for this treatment approach is anecdotal and includes cases of neuroleptic malignant syndrome. The only prospective, randomized comparison of single- and double-ECT stimulations studied treatment-resistant depressed populations (2). Indeed, catatonic patients are often exquisitely responsive to ECT and may even show response after one treatment (3), making the initial administration of multiple seizures unnecessarily aggressive.

A further variation in treatment not mentioned by Kellner et al., the application of daily rather than thrice weekly treatments for the acutely ill woman, could not be undertaken due to cardiac complications associated with the initial treatment. Interdisciplinary re-evaluation and further consent discussion were necessary before ECT treatment could recommence. The most important factor preventing a more rapid intervention was the legal hurdle of obtaining emergency guardianship. The process took 20 days and might have been further prolonged if an involved, reliable caregiver had not been available. Aggressive legal action and a responsive judicial system are often the most crucial aspects of urgent care.

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Medication Guesses in Double-Blind Studies

TO THE EDITORS: In their commentary published in the March 2010 issue of the *Journal*, Roy H. Perlis, M.D., M.Sc., et al. (1) should be commended for reminding us of the possible role that correct medication guesses may have in interpreting study results obtained with antidepressants in double-blind trials. Often in these days, when reading "new" kernels of wisdom, I experience a *déjà vu* phenomenon: Have I not seen similar data a long time ago? In fact, in the early 1960s, we published our first paper on doctor medication guesses (2). The results were based on data from several double-blind anti-anxiety studies. After 4 weeks of treatment, in these early days of psychopharmacology, we conducted primarily 4-week anxiety and depression trials; a total of 156/231 (68%) patients who were receiving active drugs were guessed to have been receiving an active drug, and 75/148 (51%) patients receiving placebo were guessed to have been receiving an active drug (χ^2=11.93). Improvement played a big role in these ratings. At the same time period, 73% of improved but only 32.0% of unimproved patients were guessed to have been receiving active medication.

In our second study (3), we had data available from a 6-week anxiety trial. Adverse events became important modifiers, but only at 6 weeks, not earlier. Irrespective of the treatment received, physicians guessed significantly more often that patients with adverse events were receiving an active drug (N=20/22) relative to patients not reporting adverse events (N=68/116; χ^2=7.01). After 6 weeks of treatment, medication guesses correlated with global improvement (r=0.65) and with adverse events (r=0.65). The multiple r between medication guesses and both global improvement and adverse events was 0.87. These data made us conclude that early improvement and, to a lesser extent, adverse events exert influence on physicians' medication guesses during a double-blind controlled study.

And while I agree with Perlis et al. that to include medication guesses into future study designs should be seriously considered, I do not believe that either the use of two raters or the use of active placebos are recommendations that would lead to improved trial methodology.

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