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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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Response to Rickels Letter

TO THE EDITOR: We thank Dr. Rickels for reminding us of his early and important work in this area, which further highlights the porousness of the double-blind study. Indeed, as we pointed out, some of these concepts date back more than 25 years. In a previous draft of our commentary, we remarked on the curious point that such concepts seem to be rediscovered every decade or so.

Dr. Rickels also asserts his belief that alternative strategies, such as multiple raters or active placebos, will not be effective in preserving the blind. Certainly, one size does not fit all in a clinical trial design. However, given that existing trial design guidelines advocate these strategies, we might hope for an empirical study before dismissing them out of hand.

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Mania in a Patient With H1N1: Is Oseltamivir the Culprit or a Red Herring?

TO THE EDITOR: In the March 2010 issue of the *Journal*, Lily N.L. Ho, M.B.Ch.B., et al. (1) reported on a case of an 18-year-old woman who developed symptoms of mania after the first day of a 5-day course of oseltamivir for influenza A (H1N1). However, the patient's history indicated that oseltamivir may have been a red herring in the causation of mania. Although symptoms of mania started after the first day of treatment with oseltamivir, they did not subside until 30 days after discontinuation, despite treatment with a high-dose antipsychotic and mood stabilizer. This is unlike many drug-induced psychosis cases, where symptoms subside soon after the withdrawal of the offending drug (2).

A more likely explanation for mania in this case is the combination of influenza and high fever (39.4 °C) in an individual at high risk for bipolar disorder (a positive family history) and at an age close to the mean age of onset of the illness. Viral infections have been widely reported to be associated with mood disorders (3), and influenza has been associated with both depression and mania (4, 5).

As part of collaboration between the National Centre for Immunisation Research and Surveillance and the Australian Paediatric Surveillance Unit, in 2009 we studied 226 consecutive hospital admissions of children aged <15 years with laboratory confirmed influenza (86% H1N1). In total, nearly one-half (46.5%) of those with confirmed influenza were treated with oseltamivir. None of the patients developed any neuropsychiatric adverse events following treatment. In three cases (1.3%), confusion was part of the presenting symptoms of influenza. One of these cases was treated with oseltamivir for 5 days without any exacerbation of the confusion.

Ho et al. suggested that Chinese or Japanese ancestry may be related to developing neuropsychiatric adverse events of oseltamivir. However, this is unlikely, since no clinically relevant differences in the plasma pharmacokinetics of oseltamivir and its active metabolite oseltamivir carboxylate have been noted between Japanese and Caucasian adults or children (6). Moreover, there is evidence to suggest that neuropsychiatric adverse events in Japanese children with influenza occurred before starting oseltamivir, and these events were similar to those occurring after treatment. This is consistent with previous findings that influenza itself is associated with higher risk of neuropsychiatric events. Analysis of medical records in the United Kingdom General Practice Research Database showed significantly higher adjusted relative risk (1.75) of such symptoms in influenza patients than in the general population, an analysis performed when antivirals were seldom used (6). Therefore, general practitioners and psychiatrists should be watchful for psychiatric complications following influenza and other viral infections, particularly in predisposed individuals.

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