Dr. Rickels has received honoraria from, served on the advisory board of, and served as a consultant to Pfizer. He has also received research grants from Bristol-Myers Squibb, Epix Pharmaceuticals, Genaissance Pharmaceuticals, the National Institute of Mental Health, Pamlab, Pfizer, and Wyeth Laboratories.

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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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Response to Khandaker et al. Letter

TO THE EDITOR: Dr. Khandaker et al. mention that the development of manic symptoms in the patient, which occurred after oseltamivir use, may have been a red herring in the causation. This would be difficult to conclude, since she experienced only mild upper respiratory symptoms and fever for 1 day and the fever subsided before the start of oseltamivir and onset of manic symptoms. However, she and her parents could note that there was a marked change in her personality, with elated mood, after taking oseltamivir. A previous case series showed that neuropsychiatric adverse events after oseltamivir use may start on the first day of treatment (1). The close temporal relationship between the onset of manic symptoms and the use of oseltamivir in our patient, with relatively mild upper respiratory symptoms and fever that subsided before the onset of mania, suggests that oseltamivir-induced mania was a more likely diagnosis.

Regarding the genetic difference, it has been suggested that a nonsynonymous single nucleotide polymorphism in human cytosolic sialidase is more prevalent in Asian populations. This polymorphism affects the activity of sialidase, which may cause neuropsychiatric adverse events in patients receiving oseltamivir (2). This may account for the observation that the majority of cases were reported in Japan.

Both oseltamivir and influenza have been reported to be associated with the development of neuropsychiatric events (3–5). Moreover, fatal neuropsychiatric adverse reactions after oseltamivir use have been reported (1). The aim of our case report was to encourage vigilant monitoring of the mental state of patients after using oseltamivir until we have a better understanding about the properties of this drug.

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Reprints are not available; however, Letters to the Editor can be downloaded at http://ajp.psychiatryonline.org.

Corrections

At the time the article "The Role of a Prescription in Anxiety Medication Use, Abuse, and Dependence," by Miriam C. Fenton et al., was published online on July 1, 2010 (doi: 10.1176/appi.ajp.2010.09081132), the second sentence in the Results section misreported percentages from Table 1. The sentence should have read as follows:

"As shown in Table 1,16.0% of that subgroup reported lifetime nonmedical use and 4.6% reported abuse of or dependence on these drugs."

This change was made for the online posting on August 4, 2010, and has been made for the article's print appearance in the October 2010 issue.

In the article "Early Expression of Negative/Disorganized Symptoms Predicting Psychotic Experiences and Subsequent Clinical Psychosis: A 10-Year Study" by Maria-de-Gracia Dominguez, M.D., et al. (published online July 15, 2010; doi: 10.1176/appi.ajp.2010.09060883), the middle name of the second author, Meram Can Saka, M.D., was lowercased, which could lead to indexes mistakenly including it as part of the surname. This has been corrected for the article's print appearance in the September 2010 issue and for its online posting as part of that issue, replacing the article posted July 15. The correct citation for the article is as follows:

Dominguez MDG, Saka MC, Lieb R, Wittchen H-U, van Os J: Early expression of negative/disorganized symptoms predicting psychotic experiences and subsequent clinical psychosis: a 10-year study. Am J Psychiatry 2010; 167:1075–1082

Clarification: In response to the review of his book in the March 2010 issue (Sederer L: Book Review: Treating the "Untreatable": Healing in the Realms of Madness. Am J Psychiatry 2010; 167:356–357), Dr. Steinman wishes to clarify that his book advocates the judicious use of antipsychotic medication in the treatment of patients who are delusional or have schizophrenia.