Can Discontinuation Trials Inform the Use of Antidepressants in Depressed Children?

TO THE EDITOR: In their randomized discontinuation trial, published in the April 2008 issue of the *Journal*, Graham J. Emslie, M.D., et al. (1) demonstrated that depressed children and adolescents who receive continuation treatment with fluoxetine will remain in remission longer than those whose treatment is discontinued after 12 weeks. Although the trial was rigorously conducted and reported, we have concerns regarding the choice of design, which is not applicable to all depressed children and adolescents, including those who recover spontaneously. Discontinuation trials apply only to patients who respond to medication, and they can be difficult to identify in practice (2).

To establish the practical benefits of a treatment in populations with high spontaneous response rates (e.g., children, adolescents), a different design is needed in which all patients are randomly assigned to active treatment or placebo and followed for the full study duration. This strategy, also known as the classic two-arm parallel randomized controlled trial, has been used to definitively establish the efficacy of selective serotonin reuptake inhibitors in depressed adults for up to 9 months (3). Until similar trials have been conducted in children and adolescents, long-term treatment decisions will be based on a select study population of patients who respond to drug treatment. Little guidance is provided for the identification and management of those who recover without drug therapy.

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Dr. Emslie Replies

TO THE EDITOR: We appreciate the comments submitted by Drs. Deshauer and Grimshaw and agree that the study design they propose would answer thought-provoking questions regarding the long-term risks and benefits of antidepressants and placebo. However, it would not address the question we attempted to answer in our study. A randomized discontinuation design intends to assess whether—in this case—12 weeks of treatment with an antidepressant are adequate to prevent relapse. We have already demonstrated that fluoxetine is more effective than placebo acutely in three separate studies (1–3). These previous studies, along with multiple other factors, will be used to inform clinicians about whether to initiate treatment with an antidepressant. This study, on the other hand, was intended to inform clinicians about how long to continue antidepressant treatment once it has been initiated.

To assume that discontinuation trials apply only to patients who respond to drug therapy, as suggested by Drs. Deshauer and Grimshaw, is clearly incorrect. The placebo response rates in the acute fluoxetine trials ranged from 33%–37%. Therefore, it can be argued that a similar percentage of the youths who were treated openly during the acute phase of our study were, in fact, patients who responded to placebo. Unfortunately, there currently is no definitive method to identify these patients. While the classic two-arm parallel group design may have been conducted in studies of adults with depression, the majority of adult trials that have attempted to answer the question of relapse prevention utilized the Food and Drug Administration recommended discontinuation design, such as the one used in our study.

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Considerations Regarding the Use of Metformin With Olanzapine

TO THE EDITOR: In the study conducted by Ren-Rong Wu, M.D., et al. (1), published in the March 2008 issue of the *Journal*, the effect of dose was successfully controlled by assigning the two study groups (olanzapine plus metformin group and olanzapine plus placebo group) to the same dosages. However, although the groups' baseline and endpoint scores on the Scale for the Assessment of Positive Symptoms and Scale for the Assessment of Negative Symptoms did not differ, it might have been necessary to adjust the olanzapine dosage

based on the patients' clinical presentations. The difference in the Treatment Emergent Symptom Scale scores during the follow-up visits was not reported, which exposed patients to two medications with potentially serious adverse reactions without clinical evaluation.

Two inclusion criteria were 1) no antipsychotic treatment for at least 3 months before enrollment in the study—not antipsychotic naive—and 2) first psychotic episode of schizophrenia. However, the tables in the article indicated that the mean duration of illness was 6.8 years for the metformin group and 7.6 years for the placebo group.

Reporting the completer analysis eliminated the randomization effect. Simultaneously, in the intent-to-treat analysis, the authors used the last observation carried forward method. Although widely accepted, this method remains biased (2). Last observation carried forward assumes that responses following dropout remain constant at the last observed value. In this instance, special attention should be given, since the longer a patient is treated with olanzapine, the more weight the patient is likely to gain. Dr. Wu et al. demonstrated this in their study when the difference in weight gain diverged after 8 weeks of follow-up. In relying on this supposedly more conservative statistical method, the effect of metformin may have been overestimated.

Metformin is known to attenuate weight gain by reducing caloric intake (3). Accordingly, reduced caloric intake is a potential mediator in the association between metformin use and weight loss but is also an independent cause of weight loss. In the study conducted by Dr. Wu et al., there were no data pertaining to caloric intake difference between the two study groups at baseline or follow-up. Monitoring caloric intake but not necessarily controlling for it may help better explain this association.

Although no serious adverse events were reported in the active treatment group, one must consider that metformin is stamped with a black box warning as a result of the feared, albeit debated (4), lactic acidosis. A thorough risk-benefit assessment should be undertaken when considering the use of metformin to prevent the metabolic derangement associated with olanzapine as opposed to resorting to a more benign atypical antipsychotic agent. Justifying the use of this combination in antipsychotic-naive patients with a first psychotic episode seems to be a more challenging task.

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Olanzapine Treatment and Weight Gain: Considering the Lipid Side Effects of Antipsychotics

TO THE EDITOR: Dr. Wu et al. presented a remarkable pharmacological intervention trial in which metformin administration attenuated several common side effects of olanzapine. Metformin is an appealing option, given 1) the ease of its administration, 2) its relative safety, and 3) the familiarity with its use from a primary care perspective. However, it is important to be familiar with its side effect profile, which may include lactic acidosis.

As the authors thoroughly addressed, most of the metabolic effects of olanzapine are a result of increased weight and increased insulin resistance. However, there are other clinically relevant disturbances such as lipid abnormalities—mainly an increase in triglyceride levels—which require mandatory monitoring (1). This issue was not addressed by the authors.

The Chinese patients in the study had an average body mass index of 21.32. Our heavier outpatients in the United States are even more likely to benefit from a metformin regimen because of the likelihood of higher baseline glucose and insulin measurements (2).

Several other clinical features of the study differed from the clinical characteristics of patients in the United States. First, one can argue that the Chinese patients received both pharmacological and lifestyle modification, since the study indicated that they had at least 30 minutes of daily exercise, which is not equivalent to that of the average schizophrenia patient in the United States. Second, and most relevant to the metformin findings, is the low caloric intake, which was 1,900–2,200 calories per day. The average man in the United States consumes 2,600 calories per day, and thus such a regimen would represent a significant reduction in caloric intake for U.S. patients. Even in an outpatient metformin and lifestyle intervention study (3), Dr. Wu et al. acknowledged that it was not necessary to change the daily caloric intake. Only the nutrient proportion needed to be altered in order to adhere to American Heart Association guidelines. One might speculate that the appetite stimulating properties of olanzapine were constrained by this dietary restriction.

Dr. Wu et al. succeeded in emphasizing the effect of olanzapine on body weight and glucose metabolism, along with the benefits of metformin treatment, to address these issues (3). However, they did not mention the option of antipsychotic treatment with a more favorable lipid side effect profile, such as aripiprazole, ziprasidone, or paliperidone extended-release (4).

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