## Methodological Concerns in a Trial of Ziprasidone and Olanzapine

TO THE EDITOR: In their randomized, double-blind trial comparing ziprasidone and olanzapine for the treatment of acutely ill inpatients with schizophrenia or schizoaffective disorder, George M. Simpson, M.D., et al. (1) provided important information showing that olanzapine-treated patients have a greater risk of weight gain and lipid abnormalities than patients treated with ziprasidone. However, the dosing protocol in this study raised a number of questions. First, there appeared to be a potential for unblinding. Each blister pack of study medication was labeled "A," "B," or "C," corresponding to a "low," "medium," or "high" dose of each drug. All ziprasidone-treated patients were to receive the "high" dose at the end of 1 week, whereas the olanzapine-treated patients received the "medium" dose. During the trial, the treating clinician would need to know the current dose classification each week to decide whether it should or could be increased or decreased. A "medium" dose after the end of the first week would clearly indicate olanzapine treatment, whereas a "high" dose would indicate ziprasidone treatment. It is possible that unpublished procedures were used to prevent this potential problem. If so, knowledge of these procedures would be helpful in interpreting the results of the trial.

A second concern with regard to the dosing protocol is one that is not uncommon in trials sponsored by pharmaceutical companies, that of a suboptimal dose of a comparator drug. In this trial, the patients could receive a maximum olanzapine dose of only 15 mg/day, although the product labeling recommended doses up to 20 mg/day (2). The patients received 10 mg/day at the end of 1 week, and the mean dose of olanzapine throughout the trial was only 11.3 mg/day. In contrast, ziprasidone was titrated to the maximum dose recommended by the product labeling (3), 160 mg/day, by the third day of the trial. In order to reduce bias in studies comparing drugs of a sponsor and competitor, available doses should include the entire range recommended by the product labeling.

### References

1. Simpson GM, Glick ID, Weiden PJ, Romano SJ, Siu CO: Randomized, controlled, double-blind multicenter comparison of the efficacy and tolerability of ziprasidone and olanzapine in acutely ill inpatients with schizophrenia or schizoaffective disorder. Am J Psychiatry 2004; 161:1837–1847
2. Package insert for Zyprexa. Indianapolis, Eli Lilly and Company, 2001
3. Package insert for Geodon. New York, Pfizer Inc, 2004

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TO THE EDITOR: I read with interest the study by Dr. Simpson and colleagues comparing ziprasidone to olanzapine for the treatment of schizophrenia. I commend the authors for completing a head-to-head study that provides some important safety data. However, the study has two important limitations that limit its interpretation.

First, the olanzapine dosing was excessively restricted with respect to the upward titration rate (5 mg/day on days 1 and 2; 10 mg/day on days 3–7) and the maximum dose allowed (15 mg/day). The authors' argument that this dosing schedule is consistent with the package insert is weak. This dosing schedule falls within the low range of the guidelines on the package insert, which was based on studies performed about 10 years ago and submitted for approval to the Food and Drug Administration. Since that time, there have been many more studies and a vast amount of clinical experience to suggest that a significantly faster upward titration rate and a higher maximum dose often are needed to adequately treat acutely ill schizophrenia patients (1). Therefore, the approach chosen by the authors was biased against finding efficacy in the olanzapine group.

Second, the vast majority of patients in both groups were treated with lorazepam in addition to the antipsychotic. Why were such high rates of lorazepam allowed? Granted, acutely psychotic patients often benefit from a benzodiazepine. But because a major goal of the study was to compare the efficacy of ziprasidone versus olanzapine, then the high rate of use of lorazepam limited the interpretation of the results. Benzodiazepines help to enhance sleep and reduce agitation and anxiety, thus interfering with the interpretations regarding efficacy of the antipsychotics. Furthermore, benzodiazepines suppress antipsychotic-induced movement disorders such as akathisia, thus limiting the interpretation of the results regarding these adverse events.

In summary, this was not simply a study of ziprasidone versus olanzapine; it was a study of ziprasidone plus lorazepam versus suboptimally dosed olanzapine plus lorazepam.

### Reference

1. Kinon BJ, Ahl JSV, Hill AL, Buckley PF: Dose response and atypical antipsychotics in schizophrenia. CNS Drugs 2004; 18:597–616

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## Dr. Simpson Replies

TO THE EDITOR: I thank Drs. Carnahan, Perry, and Ross for their comments on our study and welcome the opportunity to discuss the issues they raise regarding drug administration, concomitant medication, and dosing.

Drs. Carnahan and Perry comment that the medication labeling—"A," "B," and "C," denoting "low," "medium," and "high" doses—would alert investigators at day 7 to treatment assignment because all patients randomly assigned to ziprasidone received 80 mg b.i.d. (the "high" dose) on days 3 to 7 and all patients randomly assigned to olanzapine received 10 mg/day (the "medium" dose). The "A," "B," and "C" labeling was, in fact, employed only during the flexible-dose weeks of the study (weeks 2 to 6). During days 1 to 2 and days 3 to 7, when fixed doses were administered, the medication cards did not contain this labeling. During both the fixed titration and flexible-dose phases of the study, the patients in the two treatment arms received identical quantities of medication of identical appearance; in the olanzapine group, placebo capsules were employed to simulate twice-a-day dosing. For example, a subject who was assigned to olanzapine at 10 mg/day would have received the same number of identical-appearing capsules twice a day as a subject who was assigned to ziprasidone at 80 mg b.i.d. with this "double-dummy" design.