Combination Treatment With Quetiapine in Bipolar Disorder Patients

TO THE EDITOR: In their article, published in the April 2009 issue of the *Journal*, Trisha Suppes, M.D., Ph.D., et al. (1) concluded that quetiapine plus lithium or divalproex caused a significant risk reduction in the time to recurrence of any mood event compared with placebo and lithium or divalproex in bipolar patients. We feel that the design, methodology, data analysis, interpretation, and writing of the study need to be examined critically before the clinician can extrapolate these findings to the usual clinical situation.

First, with the exception of rapid cyclers, there was no information about the number and frequency of prior episodes and residual symptoms of the patients entering the randomization phase. This information would have been helpful as well as controlling statistically for the effect of prior and residual symptoms, since it is well known that frequency of past episodes and residual symptoms are strong predictors of future episodes (2, 3). Second, it was not clear why the patients were started on a quetiapine-mood stabilizer combination immediately in the pre-randomization phase. The authors may wish to provide a rationale or evidence supporting this decision. Third, two-thirds of the pre-randomization patients discontinued during the pre-randomization phase for a number of reasons, including lack of therapeutic response, developing an adverse event, and lost to follow-up. Could it be possible that the remaining patients, who did eventually proceed to the randomization phase, represented a group favorably predisposed to the quetiapine combination? Fourth, the authors may wish to discuss the limitation that there was no structured interview used to ascertain the index episode; rather, at times it was left to the medical judgment of the clinical investigator. Fifth, it would have strengthened the study if an increase of lithium/divalproex dose could have been included in the definition of a "mood event," since this is what would be done first in clinical situations of recurrence. Sixth, although the authors only mentioned the hazard ratios, the median ratio of time to recurrence in the quetiapine group versus the placebo group could give additional meaning regarding the actual magnitude of the difference (4). Last, the findings regarding the metabolic side effects of the quetiapine combination should have been mentioned in the conclusion section of the abstract.

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Maintenance Treatment for Patients With Bipolar Disorder

TO THE EDITOR: We read the study by Dr. Suppes et al. (1) with a great deal of interest and wish to raise concerns about the methodology. The authors evaluated the efficacy and safety of the combination of quetiapine with lithium or divalproex relative to monotherapy with lithium or semisodium valproate in maintenance treatment for patients with bipolar I disorder.

Randomized controlled trials are usually cited as the gold standard for detecting the efficacy of results. However, they often can be flawed in design and are not immune to bias.

First, in this study, 1,953 patients received open-label quetiapine. However, only 628 patients were randomly allocated for maintenance treatment. This indicates that only one-third of the patients were selected for maintenance therapy, which raises the possibility of selection bias. In this regard, Healy (2) stated that company sponsored clinical trials invariably recruit samples of convenience, which by definition do not actually sustain extrapolation to normal clinical practice.

Second, the authors used a wide range of exclusion and restricted inclusion criteria, which minimized the generalizability of the results.

Finally, although both arms received active treatment, the authors failed to perform power calculation, and they did not justify the sample size, which is also a requirement of the Consolidated Standards of Reporting Trials guidelines (3).

We would appreciate clarification of these issues raised.

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