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To the Editors:
The authors did not present all their meaningful results.1 In the “Clinical Global Impression” section, they report that at Week 8, a larger proportion of patients were rated as “much improved” or “very much improved” on the Clinical Global Impression–Improvement Scale in the 300 (61.3%) and 600 mg/d (60.0%) compared with the placebo group (38.5%). As I calculate the $3 \times 2 \chi^2$, this array is significant ($P < 0.01$), as is 300 mg/d versus placebo ($P < 0.01$), but not for 600 mg/d versus placebo ($P = 0.13$).

Similarly, they do not present an analysis of the Clinical Global Impression–Severity Scale at Week 8. The overall $3 \times 2 \chi^2$ is significant ($P < 0.001$) as are both comparisons to placebo of 300 and 600 mg/d ($P < 0.001$).

The reader should know that the data favoring quetiapine are stronger than what the authors presented.

To the Editors:
I was puzzled by a recent article in the journal,1 which investigated the effects of quetiapine for bipolar depression, and hope that its authors can clarify a few questions.

The central issue of this letter is that the study used mixed-model, repeated-measures analysis (MMRM) to calculate effect size, as opposed to using the means and SDs provided by last-observation-carried-forward analysis (LOCF). Using MMRM analysis, the authors found an effect size of 0.61 favoring quetiapine 300 mg/d over placebo on the Montgomery-Asberg Depression Rating Scale and an effect size of 0.54 favoring quetiapine 600 mg/d on the same measure. However, if LOCF data, provided in Table 2 of the study report, are utilized to calculate effect size, the effects shrink to 0.40 for 300 mg/d and 0.37 for 600 mg/d.2 Thus, changing from a conventional LOCF approach to an MMRM approach inflated the effect sizes by 53% and 46%, respectively.

Given such a large change, it would seem appropriate for the authors to justify their use of the MMRM method and provide the means, SDs, and formula that were used to calculate effect size. In addition, the authors should also have reported the LOCF effect sizes so that the readers would have been aware of how the method impacted the findings.

To the Editors:
"Efficacy of Quetiapine Monotherapy in Bipolar I and II Depression"
A Double-Blind, Placebo-Controlled Study (The BOLDER II Study)" by Dr Thase and Colleagues

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Reply to Comments by Dr Rifkin and Dr Dawdy

To the Editors:

I wish to thank Drs Rifkin and Dawdy for their letters, which suggest that we have both underestimated and overestimated the effects of quetiapine monotherapy in our report of a randomized controlled trial of bipolar depression. For reasons that I hope are obvious, the responses that follow are mine alone and do not in any way reflect an official position of the study’s sponsor, AstraZeneca.

With respect to Dr Rifkin’s observations, it is true that alternate ways of analyzing the results on the Clinical Global Impressions (CGI) scales would have yielded a larger estimate of benefit. In reporting the primary results of this industry-sponsored study, which was primarily conducted to support a Food and Drug Administration application for quetiapine to receive approval for the specific indication of treatment of bipolar depression, we closely followed an a priori data analysis plan that did not include this method of analyzing the CGI. I agree that the CGI scales are better suited for analysis as categorical variables, as suggested by Dr Rifkin. Hopefully, this approach can be used in subsequent post hoc analyses of the pooled BOLDER data set to better describe both the magnitude and benefit of quetiapine therapy and to identify particular subsets of patients who may be more or less responsive to this therapy.

The points raised by Dr Dawdy were the topic of a flurry of Internet commentary in 2006 and 2007 and are easily answered, at least on the surface. It is my understanding that mixed model repeated measurement (MMRM) analyses were chosen to compute effect sizes in the BOLDER studies because it would permit direct comparison with the results of the study of the only other treatment approved for bipolar depression, the combination of olanzapine and fluoxetine (OFC). Thus, in plain and simple terms, we were attempting to facilitate an “apples to apples” comparison between quetiapine monotherapy and OFC. I am concerned that readers who were not part of the Internet exchange may misinterpret the tone of Dr Dawdy’s letter to suggest that there was something unseemly about the choice of MMRM over the last-observation-carried-forward (LOCF) method. There is nothing noble about the LOCF method: many biostatisticians have considered it to be obsolete for a number of years (see, for example, Lavori’s), and frankly, it is more accurate to say that the use of the LOCF approach to compute effect size deflates the true effect of a treatment than it is to say that the MMRM approach inflates that effect. It is nevertheless true that MMRM and LOCF results should not be compared, either implicitly or directly. Industry-sponsored therapeutics research is now often viewed through a cynical lens, and I regret that I did not anticipate that this concern would arise when we were writing the BOLDER II article in late 2005 and early 2006. If so, we would have reported effect sizes according to both MMRM and LOCF methods. By either metric, the effects of quetiapine were both clinically and statistically significant in the BOLDER studies and, looking across studies, seem to be comparable to both those of OFC in bipolar depression and those for conventional antidepressants in contemporary studies of major depressive disorder. Comparitive studies are now needed to prospectively confirm these early observations.

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