Reviewer’s report

Title: Quetiapine Augmentation of SRIs in treatment refractory obsessive-compulsive disorder: A double-blind, randomised, placebo-controlled study

Version: 1 Date: 26 October 2004

Reviewer: Lawrence H Price

Reviewer’s report:

General

1. This industry-sponsored study utilized a double-blind, randomized, placebo-controlled, parallel-group design to examine flexible-dose quetiapine augmentation in patients with obsessive-compulsive disorder (OCD) who had failed to respond to a preceding 12-week course of open-label treatment with a serotonin reuptake inhibitor (SRI). A total of 42 patients were randomized to placebo or quetiapine for the 6-week study. The study demonstrated no significant difference in efficacy between quetiapine and placebo, with both groups manifesting significant improvement from baseline. The placebo response rate in this study makes it difficult to draw any definitive conclusions regarding the efficacy of quetiapine in this population.

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Major Compulsory Revisions (that the author must respond to before a decision on publication can be reached)

1. It is essential for the authors to provide appropriate power calculations for a study such as this, which fails to demonstrate statistically significant differences on measures that are hypothesized to be different. Given the sample size of the present study, what was its power to detect a given effect size? Alternatively, or additionally, what sample size would have been needed to detect a statistically significant difference with reasonable power?

2. Methods: In the Study Design section, in the first sentence, it is unclear what is meant by the expression “all subjects were followed up for the minimum 12-week duration…” Does this mean that all subjects were treated for the minimum 12-week duration? How was this established? By history, or were all patients actually treated by the investigators prior to randomization into the augmentation trial? What were the specific drugs used to treat patients during this preceding period? What were the means and ranges of the doses used for each drug?

3. Methods: In the Ratings section, 2nd paragraph, it is stated that treatment response was defined as either a 25% reduction in Y-BOCS score or a CGI-I rating of 1 or 2. This is a somewhat liberal definition of response, in that it allows patients to be considered responders by virtue of change on either one of two different assessment instruments. The study would be stronger if patients were considered responders by virtue of meeting both criteria.

4. Results: In the Treatment Outcomes section, paragraph 2, the figures cited for percentage reduction in the YGTSS in the last sentence appear to be inaccurate. I base this assertion on the data presented in Table 1, for YGTSS at baseline and YGTSS change at week 6. Calculation of YGTSS percentage change using these data yields a percentage change of 18.2% for quetiapine and 41.6% for placebo, in contrast to the 11.5% and 15.8% figures, respectively, presented in the manuscript.

5. Discussion: In the 1st paragraph, it is misleading to compare the response rates of the present
study with those of previous studies. In the first place, the high placebo response rate in the present sample makes it clear that the patients enrolled in this study cannot be considered similar to the patients enrolled in previous studies with a low placebo response rate. For example, in reference 21 the placebo response rate was 0%. Secondly, as noted elsewhere in this review, the criteria for response in the present study were relatively liberal. Again, for comparison, see the relatively more stringent response criteria employed in reference 21.

6. Discussion: In the 2nd paragraph, the authors try to account for their unexpectedly high placebo response rate by asserting that treatment had been insufficiently aggressive during the pre-randomization phase of this study. Again, additional data characterizing the nature and intensity of the pre-randomization treatment patients received would be extremely helpful in allowing the reader to draw his or her own conclusions.

7. Discussion: In the 3rd paragraph, it is suggested that the failure to demonstrate superior efficacy for quetiapine in this study might have been due to “relatively slow up-titration result[ing] in relatively low mean daily doses.” However, it should be noted that 75% of the quetiapine-treated patients reported sedation, with 10% of those patients dropping out of the study as a result. Thus, it is questionable whether more aggressive dosing would have been feasible. The comparison further on in this paragraph between the dosing of quetiapine in the present study and the dosing of risperidone in reference 21 is not really valid: in terms of sedation, risperidone and quetiapine are more like apples and oranges. In the 3rd line from the end of this paragraph, it is unclear what is meant by the phrase “adequately low doses.” Do the authors mean “therapeutically adequate doses”?

8. Discussion: In the 4th paragraph of this section, it is asserted that the high placebo response rate in the present study may have been due to employment of a flexible dosing schedule, and reference 36 is cited in support of this. This is a misreading of that reference. In fact, the authors of reference 36 conclude that “having a positive trial outcome [i.e., statistically significant separation of active drug from placebo] was almost twice as high in flexible dose trials (59.6%) compared to fixed dose trials (31.4%).” If anything, therefore, the findings from reference 36 (which however, involved depressed patients rather than OCD patients) suggest that the flexible-dose design used in the present study would have been more likely to have resulted in separation of quetiapine from placebo.

9. Conclusions: For the reasons discussed above, it is inappropriate to suggest that quetiapine might be effective because the response rate in the present study was similar to response rates in previous studies showing separation of active drug from placebo. Similarly, it is unclear and unconvincing that there are “indications that this treatment strategy [i.e., quetiapine augmentation] is likely to be effective;” nothing in the present study supports that assertion. The conclusion should therefore be re-written to more accurately reflect what the authors actually found in this study. Perhaps, indeed, additional study of quetiapine augmentation for OCD is warranted, but that would seem primarily to be due to the limitations of the current investigation.

Minor Essential Revisions (such as missing labels on figures, or the wrong use of a term, which the author can be trusted to correct)

1. Methods: In the Study Design section, line 2, delete the occurrence of the word “prior.” In line 3 of this section, change “support” to “supported.” In the 4th line from the end of this section, change “who” to “which.”

2. Methods: In the Statistical Analysis, the first line should be changed to read, “39 of the 42 randomized subjects successfully completed…” In the 5th line from the end of this paragraph, change “Student” to “Student’s.” There should be a period at the end of the last line.
3. Methods: In the Treatment section, in the last sentence, it is stated that subjects were withdrawn from medication after completion of the treatment phase of the study. Were subjects withdrawn from all medication or only from the augmentation medications?

4. Results: In the Study Sample Characteristics section, in lines 2 and 4, “seroquel” should be changed to “quetiapine.” In the second sentence of this paragraph, clarify that age is in years.

5. Results: In the Treatment Outcomes section, paragraph 1, 5th line from the end, there should be a space between “ratings” and “did.”

6. Results: In the Treatment Outcomes section, last paragraph, in the last sentence it is stated that responders did not differ significantly from non-responders in mean daily dosage. Does this refer to active quetiapine or to placebo?

7. Results: In the Tolerability section, in the 4th line, insert “the” between “in” and “mild.”

8. Tables: In Table 1, “Seroquel” should be changed to “Quetiapine.” As noted above, the figures presented for YGTSS percentage change appear to be inaccurate and must be corrected.

9. Figures: In all of the figures, “Seroquel” should be replaced with “Quetiapine.” In Figure 1, the data points must be re-aligned so that they correspond with the appropriate week on the abscissa. In Figure 2, “CGI-i” should be replaced with “CGI-I.” Figure 3 can be deleted.

Discretionary Revisions (which the author can choose to ignore)

1. Abstract: In the Results section, it would be extremely helpful to include the response rates for quetiapine (40%) and placebo (47.6%).

What next?: Unable to decide on acceptance or rejection until the authors have responded to the major compulsory revisions

Level of interest: An article whose findings are important to those with closely related research interests

Quality of written English: Needs some language corrections before being published

Statistical review: No

Declaration of competing interests:

Yes to Q.1: Received speaker’s honorarium form the sponsor (AstraZeneca).