Author's response to reviews

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

Authors:

Paul D Carey (pcarey@sun.ac.za)
Bavanisha Vythingum (anaidoo@wol.co.za)
Soraya Seedat (sseedit@sun.ac.za)
Jacqueline E Muller (jemuller@sun.ac.za)
Michael Van Ameringen (vanamer@mcmaster.ca)
Dan J Stein (djs2@sun.ac.za)

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Author's response to reviews: see over
Dear Colleagues

**Re: Resubmission of manuscript incorporating responses to reviewers comments**

Thank you for the review of my original submission and the opportunity to respond to the comments and recommendations made by each of the reviewers. I believe I have adequately addressed each of the matters raised by the reviewers and am certain that this has enhanced the quality of this paper. Please see my detailed responses below.

**Reviewer: Lawrence Price:**

Major compulsory revisions:
1. The appropriate analysis of sample size is now included as suggested in the section on study design.
2. Methods: The initial follow-up of patients (prior to inclusion in the study) was unclear in the previous version of this paper and this has now been more clearly defined to reflect that subjects were treated and followed up by investigators for the full duration of the 12 week SRI treatment phase prior to inclusion in this study. Furthermore, as suggested by the reviewer, details of mean dose and range for each of the SRI’s used as well as the dose for each of the study subjects are now tabulated in Table 1 and 2 respectively.
3. Methods: The reviewer helpfully points out that our determination of treatment response is fairly liberal. As such the present analysis (number of responders Table 2) reflects only those that meet criteria for response on both of the primary outcome measures (ie YBOCS reduction of 25% from baseline and an endpoint CGI-I of 1 or 2). This had the effect of reducing the number of CGI responders by 2.
4. Results: The error with respect to YGTSS percentage change is acknowledged and has been corrected accordingly in the text and Table 3.
5. Discussion: The authors agree that the similarity drawn with other studies in respect of response size for the active treatment group, is probably inappropriate. The discussion has been changed and now more clearly discusses the fact that methodological factors led to the inclusion of a distinctly different study population in that it is less refractory i.r.o number of previously failed SRI trials.
6. Discussion: The inclusion of Table 1 and 2 will now allow readers to clearly see the nature and intensity of previous treatments. We contend however that it remains likely that duration and not intensity of the SRI treatment prior to inclusion is the likely explanation for the placebo response.
7. Discussion: On the point of a “slow” up-titration rate in our study as a limiting factor, we agree with the reviewer that the levels of sedation in this sample may
well have limited a more aggressive approach. We draw a comparison with the more aggressive schedule used in the positive study by Denys (2004) in which it appeared not to have been a limiting factor, despite similar rates of sedation, and imply that this may remain an option in future work. The discussion now also more clearly states that the comparisons with other studies (McDougle) are interesting in as much as they achieved doses at which subjects responded earlier in the study.

8. Discussion: The reference in question has been removed. We still make a point however, that repeated assessments and repeated dose increases may have contributed to the high placebo response rate, though consider this less likely than some of the other reasons provided in the discussion.

9. Conclusions: The author agrees that some of the assertions in this section may be inappropriately strong and have been changed to more accurately reflect the outcome of this study.

Minor essential revisions:

1. Methods: “prior” – deleted/ “support” – sentence reworded / “who” changed to “which”
2. Methods: inserted “randomised”/ “Student” changed to “Student’s”
3. Methods: Treatment withdrawal from study medication while SRI continued has been clarified in the text.
4. Results: “seroquel” changed to “quetiapine”
5. Results: space inserted
6. Results: A correction has been made to this figure. Also the differences between mean doses for quetiapine responders and non-responders have been inserted.
7. Results: “the” inserted
8. Table headings and contents: “seroquel” changed to “quetiapine” / YGTSS figures corrected as mentioned above.
9. Figures: Reference to “seroquel” changed to “quetiapine” / Figure 2 and 3 have been deleted from this version/ data labels (weeks) in Figure 1 now aligned with data points

Discretionary revisions:
1. Number of responders have been included in the abstract as suggested.

Reviewer: Lorrin M Koran

General:
The number of previous SRI trials did not differ between responders and non-responders and did not have an effect on treatment response in our sample. This information is now reflected in the text.

“significant majority” – deleted “significant”

The author has elected not to include the data on specific symptom patterns including hoarding, but for clarity, hoarding was present in 12 subjects (4 in quetiapine group [3
responders, 1 non-responder] and 8 in the placebo group [4 responders, 4 non-responders])

As suggested by the previous reviewer, detailed information on previous SRI treatment is now provided in Tables 1 and 2.

Major compulsory revisions:
1. Typographical errors in the SD have been corrected. Numbers of subjects dosed above 200mg are now provided in the text and appear not to have rendered any additional advantage to treatment outcome. Full details of final doses are also provided in Table 2.
2. The reviewer correctly points out that a separate calculation of the treatment groups was not provided and this is now done.
3. Mean and median doses are now provided for different groups as well as for all study subjects. An error in the median value for quetiapine responders has been corrected as suggested by the reviewer.
4. Line 15 – “adequately low” – changed to “therapeutically low”
5. The reviewer suggests mentioning that “indequate duration of treatment at 200mg/day or more may have been a factor.” We agree that this is likely to be the case and this is now reflected in the discussion.

Minor essential revisions:
1. Page 4: Sentences revised
2. Page 5&6: Reasons and timing of withdrawal now stated more clearly
3. Distribution of co-morbid tics across treatment groups was contained in the original version and has not been altered.

The authors trust that all the comments by the reviewers have been addressed to the satisfaction of the reviewers and look forward to hearing from your team in this regard in the near future.

Sincerely

Paul Carey
Corresponding Author