Author's response to reviews

Title: The Self-reported Montgomery-Asberg Depression Rating Scale is a useful evaluative tool in Major Depressive Disorder

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Author's response to reviews: see over
Dear Doctor Alam,

Re: Manuscript 1184896948197653

As instructed, this cover letter is a point-by-point response to the reviewer’s comments, the comments from the editorial board member, and your comments.

It is divided into four sections:
1. Our responses to the Editorial Board Member’s comments
2. Our responses to questions raised in your second email of September 18, 2008
3. Our responses to the comments from Reviewer 1, Leon Flicker
4. Our responses to the comments from Reviewer 2, Kenneth Kobak

We have uploaded the revised manuscript via the BMC website and hope that we have correctly reformatted the document to conform to BMC style.

1. Responses to the Editorial Board Member’s Comments:

Comment 1. As mentioned in the manuscript, there is increasing focus on evaluating and using self-report measures in clinical trials, as an adjunct to interviewer-rated scales, so I think it is important to validate these scales. In this regard, in addition to the self-rated Hamilton raised by Reviewer 2, I would also ask the authors to describe the QIDS-SR since it was recently validated in the influential STAR*D trial.
Response: Thank you. We have amended the text to include mention of the QIDS-SR and the HDI among the principal PRO scales and have referenced both accordingly.

Comment 2. The MADRS was specifically developed as a rating scale that would be more sensitive to change in clinical trials than the Hamilton and others. Therefore, validating a self-rated version should, by definition, be done in the context of a clinical trial, since the most important characteristic is the sensitivity to change.
Comment 3. In raising the last point, however, I do not think that the authors have adequately addressed the sensitivity to change in their validation. They have focused too narrowly on the sensitivity and specificity of the MADRS-S to detect remission as defined by the MADRS. I would have expected an analysis of the correlation of change score on the MADRS-S with change score on the MADRS.
Response to both: In assessing sensitivity over changes, our main concern was to focus on clinical relevance of scales. While MADRS and MADRS-S total score have different numbers of items, and therefore different ranges (i.e. 0-60 for MADRS and 0-27 for MADRS-S), it seems more appealing for us to focus on “Perceived remission” by defining the optimal threshold value for MADRS-S. This explains why we focus on this kind of analysis.
Comment 4. In addition, the authors have not adequately described the rationale behind their analysis and the results in the section on Evaluative Ability (which is why Reviewer 1 in point 4 believed this section should be deleted). In the original trial, the MADRS differentiated between the two drugs in efficacy (i.e., that escitalopram was superior to citalopram). Therefore, if the MADRS-S is sensitive to change, it should also discriminate between the two drugs. That's the reason that the authors reported the differences in change scores, response and remission between the two drugs using the MADRS-S. However, the data from the MADRS should also be presented (as a comparison) and the effect size of the MADRS-S should be compared to the effect size found with the MADRS.

Response: We have rewritten the “Evaluative ability” section to read as follows: “When comparing the antidepressant effects of the two therapeutic strategies of the trial, we found that the mean MADRS-S score changes from baseline were in favour of escitalopram (-9.9 ± 5.1 for escitalopram versus -8.6 ± 5.9 for citalopram), the mean difference of 1.3 (standard error of 0.7) being statistically significant (p=0.046). As a comparison, a mean MADRS difference of 2.1 was found between escitalopram and citalopram (p<0.05).

Perceived response, defined as a reduction of at least 50% of the baseline MADRS-S score, and perceived remission, defined using the optimal cut-off value of 5 found in the ROC analysis, were also significantly in favour of escitalopram (Figure 2). Perceived response rates were 66.4% and 53.9% for escitalopram and citalopram, respectively (p=0.033). Perceived remission rates were 49.6% and 37.6% for escitalopram and citalopram, respectively (p=0.043). As a comparison, response rates based on investigators’ ratings of the MADRS were 76.1% for escitalopram and 61.5% for citalopram (p=0.009); remission rates were 56.1% and 43.6% for escitalopram and citalopram, respectively (p=0.040).”

Comment 5. The other points raised by Reviewer 1 will be easily addressed and explained by the authors.

Response: Thank you. We have provided our responses in a separate section entitled “Responses to Reviewer 1.”

Comment 6. Reviewer 2 notes that the authors should include two other papers about the MADRS-S - I agree, but reference 14 in the manuscript is incorrect and actually should be the second paper (Svanborg & Asberg, J Affec Dis, 64, 2001).

Response: Thank you. The additional article has been included and reference 14 has been corrected.

Comment 7. Finally, although the authors note no competing interests, they should mention that the original trial was funded by H. Lundbeck and that they were the principal investigators of that trial.

Response: Thank you. We have added this information to the competing interests section.

2. Responses to Dr. Alam’s comments received in a second email dated September 18, 2008.

Responses to Dr Sabina Alam’s enquiries raised in her second e-mail sent on September 18, 2008.
We notice that you are reporting a randomised controlled trial but have not cited a trial registration number. Please could you clarify if you had obtained a trial registration number for this study, and if so could you include this number in the abstract of your manuscript.

RESPONSE: The original RCT was not registered. Results were subsequently published in the IJCP: Moore N, Verdoux H, Fantino B: Prospective, multicentr, randomized, double-blind study of the efficacy of escitalopram versus citalopram in outpatient treatment of major depressive disorder. *Int Clin Psychopharmacol* 2005, 20: 131-7.

***Ethics and Informed Consent***

RESPONSE: The text has been amended to include statements indicating that informed consent was obtained from all participants in the original clinical trial and that the trial met ethical standards as stipulated by the Helsinki Agreement.

***Competing interests***

RESPONSE: The Competing Interests statement has been removed from the title page and inserted between the Discussion and Authors' contributions sections.

***Authors' contributions***

RESPONSE: An Authors' Contributions section has been created and placed before the Acknowledgements and Reference list.

***Acknowledgements –***

RESPONSE: The acknowledgements section has been removed from the title page and placed between the Author’s Contribution section and the reference list.

Please list the source(s) of funding for the study, for each author, and for the manuscript preparation in the acknowledgements section.

RESPONSE: A sentence has been added to the acknowledgements section and additional information added to the competing interests section.
Responses to Reviewer 1

This study uses secondary analyses of a randomized trial of citalopram versus escitalopram to evaluate a diagnostic instrument, a self administered form of the MADRS, the MADRS-S. Although the authors claim that they used standard methods, they have not referenced the standard methodology for diagnostic tests e.g. see Whiting P et al, BMC Medical Research Methodology 2003, 3:25.

Response: The Whiting article contains the QUADAS checklist and we have taken this into consideration and understand the reviewer’s intention in raising this point. Our use of the word “standard” in the abstract may have been too vague and open to misinterpretation. Consequently, we have modified the methods section of the manuscript to read: “…evaluate the validity, reliability and sensitivity to change of the MADRS-S using psychometric methods”.

1. What was the independent gold standard? Was it the physician administered MADRS? Does this not represent incorporation bias?

Response: The reviewer is correct in saying that the independent gold standard was the physician administered MADRS scale. However, we do not think this introduces an incorporation bias for the following reasons:
- As stated in the “Assessments” section (“Patients & Methods” paragraph), patients were asked to fill in the MADRS-S before any clinical assessments took place. Therefore, patients’ perceptions of their own disease were not influenced by the interview-based MADRS assessment.
- Secondly, the objective was not to verify a diagnosis of MDD made using the MADRS by employing a patient-reported version of the scale. The objective was to check whether or not the self-reported version of the MADRS was sensitive to change through assessment of its psychometric properties.

2. The patients are limited to the age group 18-65 years and are inadequately described. Was the spectrum of patients limited in other ways? Were they deliberately screened for physical illness? Would not this assist a scale that measures somatic symptoms of depression?

Response: As stated in the Moore publication, patients’ medical history was recorded at baseline. To clarify this point we have added the following sentences in the “Study Design & Population” section (“Patients & Methods” paragraph):
“Patients meeting DSM-IV criteria for primary diagnoses of any axis I disorder other than MDD, or those with a history of mania, bipolar disorder, schizophrenia or other psychotic disorder, obsessive-compulsive disorder, cognitive disorder were not eligible for the study. Patients who met DSM-IV criteria for substance abuse or dependence within the past 12 months, or who used a depot antipsychotic within 6 months before study inclusion, or any antipsychotic, anxiolytic or anticonvulsant medications within 2 weeks before the first administration of study medication were also ineligible.”
3. Why did you measure the stability of the scale over time only in those subjects whose measures did not change?

**Response:** As for any evaluative instruments or tests, the stability over time is a mandatory property that needs to be explored. The basic idea is the following: if a scale is stable over time, then the difference in patients’ scores should be near to zero, with a small variability. But in a randomised clinical trial, it is likely to have patients whose health status improves or worsens (even over a short period of time). So, the aim of exploring the stability over time in a subpopulation of patients whose health state did not change between the two assessments is to capture the variability of the scale itself, after removing within-patient variability.

4. Repeating the data outcomes for the trial under “evaluative ability” adds nothing to this paper’s aims.

**Response:** The objective of the paper was to demonstrate, among other things, that the self-reported version of the MADRS could be used as an evaluative instrument that would assist in discriminating between therapeutic strategies. We cannot agree with this comment because, in our view, removing this part would mask arguments that support the ability of the MADRS-S to highlight differences in the disease management of MDD from the patient’s point of view.
Responses to Reviewer 2

1. Is the question posed by the authors well defined?
Yes, clearly stated.

2. Are the methods appropriate and well described?
Yes. I would include in the discussion a sentence on their thoughts on whether the fact that the patient version always went first made a difference (i.e., order effects; was counterbalancing necessary?).

RESPONSE: We have added a sentence in the discussion to describe what impact of this procedure.

3. Are the data sound?
Yes.

4. Does the manuscript adhere to the relevant standards for reporting and data deposition?
Yes

5. Are the discussion and conclusions well balanced and adequately supported by the data?
Yes, except that they say the divergence between self report and clinician in this study shows they are measuring different things. An alternative explanation is that the patient report is not equivalent to the clinician report. They should provide this as an alternative explanation.

RESPONSE: We fully agree with the reviewer’s comment. The non-equivalence of patients’ and clinicians’ reports has been added to the discussion.
In this way, I would cite work by others done comparing other versions of the self report MADRS to clinician, who found high correlations (e.g., Mundt JC, Katzelnick DJ, Kennedy SH, et al. Validation of an IVRS version of the MADRS. J Psychiatr Res 2006;40:243-246). I would also include in the discussion (or the intro) prior work done by the authors of the MADRS (i.e., Asberg) comparing the self report MADRS to the BDI (Svanborg & Asberg, J Affec Dis, 64, 2001, p. 203-216).

RESPONSE: These references have been added to the introduction and discussion sections of the manuscript.

6. Are limitations of the work clearly stated?
Yes, except as previously stated.

7. Do the authors clearly acknowledge any work upon which they are building, both published and unpublished?

Yes, though I would include in the intro a mention of the self-report HAMD (via computer and paper-pencil). There is a whole decade worth of research on this, and it is widely used in research (especially by pharma). Here are cites:


RESPONSE: We thank the reviewer for these references. They have been added to the introduction and discussion.

8. Do the title and abstract accurately convey what has been found?
Yes

9. Is the writing acceptable?
Yes

Doctor Moore and I hope that these responses answer your questions. We remain at your disposal for any and all complimentary information you may require.

With kind regards,

Bruno Fantino