Reviewer’s report

Title: Predictors of the effectiveness of an early medication change strategy in patients with Major Depressive Disorder

Version: 2 Date: 05 Sep 2018

Reviewer: Keltie McDonald

Reviewer's report:

The authors report an interesting investigation of predictors of remission in patients with Major Depressive Disorder (MDD), who participated in a randomised-controlled trial of early medication change (EMC) versus treatment as usual (TAU). The authors have demonstrated a good rationale for the study in the background section. While the study did not show significant differences between the treatment groups, after controlling for multiple tests, there were some apparent trends that may warrant further investigation. This study adds to the literature aimed to improve our understanding of predictors of treatment response. However, the document needs substantial editing to improve clarity and readability. There are many run on sentences, and corrections of grammar, use of punctuating, and phrasing are necessary. Furthermore, areas of the document need to be updated to improve consistency within the document and with other literature. Specific queries and recommendations are below:

1. The authors have used non-improvers, non-responders, and non-remitters seemingly interchangeably throughout the document, which can be confusing. I recommended that the authors select one (define it) and use it consistently throughout.

2. The endpoint, remission, has been defined as a HAM-D17 score < 7 points after 8 weeks. My understanding is that remission is typically considered a score of less than or equal to 7. Why was <7 chosen?

3. The first analysis (Table 2) examined the effects of treatment group, predictor, and the interaction of treatment group and predictor on remission. None of the interactions were significant, so it seems unnecessary to further explore these associations using Chi-squared tests. This appears to be a repeat of the same analysis, only using a different measure of association and without the correction for multiple comparisons.

4. Why were the secondary analyses not corrected for multiple comparisons as well? Although the analysis was exploratory, issues with multiple comparisons still apply.

5. Table 1 (page 9).

   i. For items described in terms of n(%). The denominator for the percent appears to be inconsistent. For example, 55 females out of 97 EMC patients = 57%, but 78
melancholic MDD out of 97 EMC patients = 80% (versus 22% reported in the text). Please clarify.

ii. For items described in terms of (+/- SD). Is this mean +/- SD or median +/- SD or something else? Also, ensure consistency of reporting.

iii. It is unclear to me what is meant by 1st episode/recurrent MDD. Aren't these two different groups of patients, and wouldn't 100% of patients fit into these two categories? Or is this the proportion of 1st episode patients only?

6. Table 2 (pages 10-11). I don't think it is necessary to report both the regression coefficient and OR as they provide equivalent information. I suggest just including the OR for simplicity.

7. I could not recreate the Bonferroni-Holm adjusted p-values provided in Table 2. For example, if listed in ascending order, rank 1 would correspond to p=0.019 (Atypical MDD, treatment group). Given 36 comparisons, the adjusted p-value should be:

\[
\text{Adjusted p-value} = (C-i+1) \times p = (36-1+1) \times 0.019 = 0.684.
\]

The corresponding adjusted p-value reported was 0.228. This p-value would correspond to only 12 comparisons. Were the adjustments made by groups?

While this does not change the interpretation of results, it is important that the methods are clear. Please clarify your calculations in the methods section.

Are the methods appropriate and well described?
If not, please specify what is required in your comments to the authors.

No

Does the work include the necessary controls?
If not, please specify which controls are required in your comments to the authors.

Yes

Are the conclusions drawn adequately supported by the data shown?
If not, please explain in your comments to the authors.

Yes

Are you able to assess any statistics in the manuscript or would you recommend an additional statistical review?
If an additional statistical review is recommended, please specify what aspects require further assessment in your comments to the editors.
I am able to assess the statistics

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Please indicate the quality of language in the manuscript:

Not suitable for publication unless extensively edited

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