Reviewer’s report

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

Version: 2 Date: 08 Sep 2018

Reviewer: Nicholas Mischel

Reviewer's report:

General comments:

This post-hoc analysis of a large (for psychiatry) completed clinical trial investigating different medication strategies for patients who respond early or not to first-line anti-depressant therapy is well-conceived and appropriate in scope. There is reasonable rationale for this analysis. There is an issue with the statistical analysis. There is an issue in the abstract and the full manuscript with inappropriate reporting of uncorrected p values as evidence, albeit labelled as "preliminary". It's my view, shared by many, that uncorrected p values are irrelevant at best and misleading at worst in cases of multiple comparisons. Any inferences drawn from these data are similarly irrelevant or misleading.

Background:

Well-written with a clear and reasonable hypothesis made explicit.

Methods:

The issue with the statistical analysis relates to the corrections for multiple comparisons. Is each predictor considered a discrete "subtype" in the analysis? More detail is required with respect to if corrections were made for the entire set of "subtypes", in this case corrected for 12 comparisons within the entire "family" of variables/predictors. The term family is used to refer to the statistical convention of calling a related set of variables, age/sex/race for example, a "family" and the use of corrections for multiple comparisons to decrease the "family-wise error rate" (FWER).

It appears that in this analysis, all variables were included within a family of 12 or so variables. It is possible that this approach unnecessarily increases the chance of a Type 2 error by considering all variables/predictors as members of one "family" rather than separating them into the families/sets that were determined a-priori and listed under "Possible predictors of treatment outcome". It is my opinion that the more appropriate approach would be to analyse each of the four sets independent from each other, correcting for the number of comparisons performed within only each of the four sets rather than the grand total number of comparisons. It is possible that there is a signal in the MDD atypical subtype that is being missed since the analysis described here corrects for >10 comparisons rather than the four comparisons done within melancholic vs. anxious vs. atypical vs. suicidal set/family of predictors.
If I am mistaken regarding how the corrections for multiple comparisons were done, I apologize. In any case please be more descriptive in the manuscript or in a supplement regarding the how the number of comparisons was determined in post-hoc statistical correction procedures.

Results:

Related to the above issues, the resulting analysis of the predictors are not listed according to the four priori determined sets that are listed under "Possible predictors of treatment outcome". Please reformat the tables to group these families/sets of predictors with one another and specify families/sets with sub-headings. As mentioned above, it is not appropriate to highlight or discuss any uncorrected p value in a multiple comparison procedure due to the problem of multiplicity making such values irrelevant and/or misleading. Any odds ratio reported in the abstract or text should include the 95% confidence interval in parentheses beside it and only corrected p values.

It is not clear if or how the presence and severity of psychiatric somatic symptoms like irritable bowel, palpitations, headache, impacted the CIRS score relative to the presence and severity of non-psychiatric medical comorbidities like diabetes, heart disease, kidney disease, etc. If possible, report the presence and level of psychiatric somatic symptoms and any somatic symptom disorders in your cohort and account for this in the analysis.

Discussion/Implications/Limitations/Conclusions:

This will need to be re-written based on the feasibility and results of the analyses requested above.

**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.

No

**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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Acceptable

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