Author’s response to reviews

Title: A randomized controlled trial of a mitochondrial therapeutic target for bipolar depression: Mitochondrial agents, N-acetylcysteine, and placebo

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Author’s response to reviews:

Dear Dr Lee,

BMC Medicine

Editor
Many thanks for your review of our submission to BMC Medicine our manuscript entitled ‘A randomized controlled trial of a mitochondrial therapeutic target for bipolar depression: Mitochondrial agents, N-acetylcysteine, and placebo’ for consideration for an original research Article.

We are appreciative of your constructive review suggestions, which we have addressed as follows:

Editorial comments:

In addition to addressing the reviewers' comments, please also address the following editorial concerns:

a.) Within the declaration 'Authors contributions', authors Chee Ng and Astrid Waterdrinker are not assigned individual contributions; please check if this is correct.

Many thanks for this pickup; this has been corrected.

b.) Additionally within this declaration, please confirm if initials 'OD' and 'OMD' refer to the same author (and thus, an author is not missing.

Many thanks for this pickup; this has been corrected.

Reviewer #1: Dan Iosifescu

This is an informative and important study testing an important hypothesis related to the role of mitochondrial active agents in bipolar (BP) depression. The study has an interesting design of testing a combined group of mitochondrial active agents versus NAC alone versus placebo. I have the following concerns and suggestions:

1. The authors need to specify how many BP I vs BP II vs BP NOS in each of the 3 study arms (in Table 1). As the authors know, treatments have had significant differences in efficacy in BP I vs BP II. Also, inclusion of BP NOS is diluting the study sample and should be described as a study limitation.

We only recruited participants with BD I and BD II; the breakdown of diagnosis has now been added as text to page 12 of the manuscript.
2. Were all study participants taking at least one mood stabilizing drug (lithium, anticonvulsant or antipsychotic), in agreement with current BP treatment guidelines? If not, how many subjects in each arm not meeting this criterion? Does this explain the small difference in the change in YMRS between groups?

The number of subjects in each arm taking baseline medications is reported on page 12. We did not specify a requirement for baseline therapy, in order to make the study as generalizable as possible. We have added "Regarding baseline mood stabiliser status, combining the three medications, 93.4% (n=169) were on at least one of the medication types, lithium, mood-stabiliser, and/or antipsychotic. There were no differences between the groups: Placebo 88.5% n=54, NAC 94.9% n=56, and CT 96.7% n=59. " to page 13 in track changes.

3. Approximately 40% of the study sample were taking natural remedies at baseline. Were those continued during the study?

Yes: this has been clarified in the revision.

4. Subjects with alcohol or drug use disorders (SUD) were not excluded, although a significant literature associates these conditions with treatment non-response in BP subjects. How many subjects met criteria for SUD's across the three study groups?

Information on alcohol and illicit SUDs have now been added to page 12 of the manuscript. It is curious that the rates of substance use were higher in the CT group, which may have adversely influenced outcomes in that group, as substance abuse predicts poorer outcomes. This is also now mentioned in the discussion.

5. Moreover, a larger proportion of subjects in the placebo group were listed as "using alcohol" than in the CT group. Could that explain the small improvement observed in the CT group? The authors need to describe what "using alcohol" means and any measures of the magnitude of alcohol and drug use across study groups. This should also be discussed as a study limitation.

Statistical examination of baseline differences is generally discouraged with the analysis of clinical trial data. On observation, there does appear to be baseline differences in the magnitude of substance use and presence of SUD (other than alcohol use disorder). This has been noted as a limitation in Discussion.
6. Given the large proportions of subjects reporting GI AEs, a breakdown of symptoms in this category by study group would be helpful (potentially added in Table 5)

This information has been added to page 20 of the manuscript. There were significant differences of the NAC group compared to the two other groups with respect to heartburn/reflux/indigestion.

7. The abstract conclusion should clarify that this is an overall negative study, with no significant differences between groups detected at the primary outcome.

This has been done as suggested.

Reviewer #2: Michele Fornaro

I enjoyed reading the present report, which is nicely and concisely written. I have only few minor remarks to prompt to the attention of the authors:

1) I not sure if they followed an ITT or a LOCF analysis.

A modified ITT was conducted; with those with post-randomisation data included in the final analysis. This information has been added to the Data Analysis section.

2) Where there any specific symptoms of depression differing between the active group vs. placebo (beyond the total score)?

As noted in the manuscript, here were no differences noted on any of the clinical measures depicted in Table 2. We did not explore individual items on the rating scales because of the risk of false positive findings with such a large number of variables.

3) I feel like the discussion is bit concise. I would suggest the authors to encompass the mitochondrial targets in bipolar depression even in comparison to standard treatments, especially lithium. You may want to refer to the following: "The Identification of Biomarkers Predicting Acute and Maintenance Lithium Treatment Response in Bipolar Disorder: A Plea for Further Research Attention" for example (https://doi.org/10.1016/j.psychres.2018.08.034).
We have expanded the discussion to add the potential role of biomarker stratification and the reference as suggested.

Yours sincerely,

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