Reviewer’s report

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

Version: 0 Date: 24 Sep 2018

Reviewer: Dan Iosifescu

Reviewer's report:

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.

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?

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

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?

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.

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

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

Yes

**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?**
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I am able to assess the statistics

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