Author’s response to reviews

Title: Rapid cycling bipolar disorder is associated with antithyroid antibodies, instead of thyroid dysfunction

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The editor
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RE: Manuscript ID BPSY-D-19-00191

Dear Professor Byrne:

Enclosed is our revised manuscript (Manuscript ID BPSY-D-19-00191). We would like to thank you and your reviewers for the very helpful comments on our manuscript. We have performed all the revisions the reviewers asked and addressed most of the reviewers’ concerns. In the revised manuscript, modified parts have been highlighted using red font. Following is a point-to-point response to the reviewers' comments.

Reviewer 1
Hossam Khalifa:

I think it is acceptable

Response: Thanks for the agreement.

-Reviewer 2

P. V. S. Magalhaes

The manuscript "Rapid cycling bipolar disorder is associated with antithyroid antibodies, instead of thyroid dysfunction" addresses an old issue regarding the relationship between rapid cycling and thyroid dysfunction in bipolar disorder. Despite its tradition, new work on this front has been scant, so investigating these associations in a large sample is wellcome.

1. It is unclear from the inclusion exclusion criteria how many patients were screened or refused to be included in the study. The authors state that the patients were inpatients or had been inpatients before, so it is not clear how they were recruited.

Response: In the revised manuscript, we have added related information about how many subjects were screened. As for the procedure of recruitment, in the raw manuscript, we had stated that "Potential participants were recommended by their treating psychiatrists, this is how we recruited the patients.

Could they be recruited in any illness phase?

Response: Yes, they were recruited in any illness phase. The proportion of patients in each phase was listed in table 1.

2. Rapid cycling was defined as four episodes in any given year during the patient's life? How was this established?

Response: if the ratio of the total number of affective episodes/the total duration of illness (year) was equal or above 4, rapid cycling was established. The related information was added in the revised manuscript.

3. Was any kind of power analysis performed to establish the sample size needed for these comparisons? What was the authors' primary outcome?

Response: We did not perform any kind of power analysis to calculate the ideal sample size before the initiation of this study since not much information about the prevalence of thyroid
dysfunction or TPO-ab positivity in BP among Han Chinese population was available at that time. That was to say, this study’s outcome was our primary outcome.

4. The authors appear to leave out of multivariable analysis the patient’s current state. This could be relevant, as antithyroid antibodies might be a marker of rapid cycling as a more enduring feature, but thyroid dysfunction per se could be related to state. In any event it would be useful to add current mood state as a covariable.

Response: We do not agree on that. First, we have analyzed the association between the prevalence of thyroid dysfunction and current states. Althouth patients with current depressive episode was less likely to have hypothyroidism compared those in remission (p=0.048, OR=0.333, 95CI%=0.099-0.998), but this association disappeared after controlling for psychopharmaceutical treatment. That was to say, the style of current state did not impose any significant impact on the thyroid function. In addition, in this study, no significant difference in the current state was found between RC and non-RC group. Therefore, we don’t think it is necessary to conduct multivariable analysis with current state as a covariable.

5. In the discussion, the authors both state that the sample is one of the largest ever and relatively small. A clear primary outcome would easily resolve this issue. All samples can be both large and small, depending on what one whishes to analyze.

Response: we agree on that all samples can be both large and small, depending on what on wishes to analyze. In this study, from the perspective of thyroid dysfunction, it comprise of one of the largest samples of BD patients ever examined. However, if in terms of antithyroid antibodies, the sample size is relatively small, considering both the prevalence of TPO-ab or Tg-ab positivity and the proportion of RC are low.

6. Finally, although people with rapid cycling are compared to people without this feature, the distinction can be subtle in some cases. Have the authors considered adding a control group consisting of people with other mental disorders or without mental disorders to further establish the specificity of the findings to bipolar disorder?

Response: It is a very constructive suggestion. Unfortunately, in this study, we did not enroll patients with other mental disorders. In the future, we would like to do so.

Alberto Bocchetta (Reviewer 3): This is an interesting paper adding new data to the existing literature.

I suggest to include the following two citations in the Discussion with a view to the emerging hypothesis of "Hashimoto's bipolar disorder", its potential mechanisms and the role of lithium, if any:


Response: we have done as you suggested. Thank you for your constructive advice.

FORMATTING CHANGES:

(1) Manuscript Body: Please note that Research articles require the following sections:

-Background
-Methods
-Results
-Discussion
-Conclusions

Response: the formatting has been changed as required

DECLARATIONS SECTION:

We note that the Declarations section in your manuscript has not been completed and may be missing information. Please read the following information and edit your manuscript accordingly. Failure to adhere to our policies may result in rejection of your manuscript.

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Response: all the required missing information about declaration has been added in the second revision of the manuscript.