Author’s response to reviews

Title: The effects of antipsychotic medications on microbiome and weight gain in children and adolescents

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Author’s response to reviews:

Dear Editorial board,

We thank the reviewers once again for highlighting the requested changes in order to improve our manuscript. We believe that the revised version is now stronger and indeed improved. Our changes and additions can be easily seen in the text as we used "track changes".

Please see our specific answers to the points raised by reviewer #2:

1) The following statements need support from the literature:

a.) "Interestingly, not all patients suffer from SGA- induced weight gain, suggesting that there may be additional factors that determine susceptibility"

The phrasing was changed to "not all patients suffer from the same extent of SGA-induced weight gain" and a relevant reference was quoted.

b.) "Furthermore, the metabolic effects of SGAs in children and adolescents may lead to cardiac disease including both cardia arrhythmia and cardiovascular ischemic disease"
We have revised this sentence to state "Furthermore, a fear of SGAs raising risk for cardiac disease (e.g. cardia arrhythmia and acute coronary syndrome) has been suggested", and have added several references to base this saying.

2) In the section on gherlin and leptin hormonal signaling, it's good to see the mechanisms discussed and authors speaking to pre-clinical studies, but this section is missing clinical studies/the focus should shift beyond rats (this is the bottom of page 11).

This section was elaborated and now mentions several human studies with appropriate references as well.

3.) The section "Mechanisms by which atypical APs induce weight gain" is good and has improved, but subheadings in this section would be nice now given that there are many different mechanisms discussed. For example, the first part could have a heading of "peptide hormones influencing SGA weight gain", next section could be "genetic determinants of AP weight gain", etc.

Subheadings were added as suggested, improving the flow and clarity of this paragraph.

4.) The section titled "The gut-brain axis connects between the gut microbe and psychiatric disorders" is improved, but is missing mention of youth/adolescent studies, which is the focus population of the paper.

Although very few studies on youth/adolescents exist in this field, we have enhanced this section a bit to include the studies we found.

5.) The section on the role of the immune system needs work, it is pretty superficial given how much is established between the GMB and immunity. The other thing is that these sections again should connect/mention studies of youth and adolescent patients.

While this section is not the main aspect of the current review and has extensively been reviewed elsewhere, we enhanced and added more details on the pathways connecting depression- gut microbiota-immunity.

6.) In the section on current directions for alleviating SGA-induced weight gain, the author's should mention some off label medications that are used, like topiramate, and on-label GLP-1RA.

The medications suggested now appear clearly in the text together with their description and mention of clinical trials (including in children and adolescents when available).

7.) The table reporting human studies needs a column for mean age and %male or females.
We have revised Table 1 to now include these parameters.

We hope to have answered all questions and comments.

Sincerely,

Hadar Neuman