Reviewer's report

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

Version: 0 Date: 28 Nov 2018

Reviewer: Luc Van Gaal

Reviewer's report:

This review was completed by A. Verhaegen and L. Van Gaal

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

* Summary:
This article reviews the effects of second-generation antipsychotics (SGAs) on gut microbiota, especially in children and adolescents. SGAs are known to have major metabolic side effects, including weight gain and an increased risk for diabetes, dyslipidemia and an increased cardiovascular risk. This risk seems higher when SGAs are used in children and adolescents mainly in first time use in contrast to recurrent use.

The mechanism by which SGAs cause weight gain is still not fully known.

The last years much attention has been given to the effects of the alterations in gut microbiota and microbiota diversity and the effects on weight. The relatively new concept of gut-brain axis tries to unravel the pathways involved in the metabolic effects of gut microbiota and their metabolic effects.

The contribution of SGAs on microbiota alterations and the association with weight gain has been described in adult patients. In this paper, the authors review the effects in children and adolescents.

* Relevance of the topic:
SGAs are commonly used in children and in adolescents, not only to treat major psychotic diseases but also for personality disorders and behavioural problems. The potential side effects thus involve a large number of patients. The attention for the gut-brain axis and effects of gut microbiota on metabolism is actually exploding with many research papers on this subject.

Since SGAs reveal their weight gaining and metabolic side effects more in children and adolescents as compared to adults, and since metabolic side effects in younger patients might expand to adult live, the subject of this paper is relevant.

* Review items:
In general:

- The article has many major grammatical and linguistic errors which should be corrected.

- The content of the article in general is good, but some aspects should be further worked out:

  o The principal pathways of the gut-brain axis

  o What is the role of GLP-1 (in rats SGA's have shown to decrease GLP-1 -is this secondary vs primary)

  o The figure gives a summary of effects -should be further detailed since only some pathways are shown

  o Do the authors think that the effect on the microbioma is causal to the weight gaining effect or more to the other secondary side effects as diabetes and CV risk? How do you explain the very early weight gain of SGA's (within 1 month) by the differences in the microbioma?

  o The hypothetically dual effect of serotonin as a cause and consequence of microbioma change is mentioned, are their also other pathways (e.g. chronic low grade inflammation/depression and effects on HPA axis and its possible relation with microbioma)

  o more hypothetically: Are there at this moment already predictive and/or therapeutic options to prevent or reverse weight gain - could these drugs/methods have an effect on gut microbioma e.g. effect of metformin.

  o I miss a concept on which to build for future research and/or practical measures to take

Structure:

- The article should be better structured

  o In the chapter "Atypical psychotics and weight gain in children and adolescents" - try to keep general effects of the SGA's and the mechanisms /influences on the different neurotransmitters separate. These should be mentioned in the chapter on the mechanisms.

  o Since the general mechanism of the SGA's side effects are not the core of this paper, try to write this in a more descriptive and general way - especially putting an accent on those mechanisms that might be influenced by the changes in microbiota (e.g. the effects on the neurotransmittors, GLP-1,…)

  o Chapter on microbiota and obesity

    - First describe the effects of microbiota on metabolic side effects in a first "subchapter" - which microbial changes cause which effect (as far as known) - what is the difference between microbial change and diversity (this might be important in children) - effects in children and adults where known
Then describe the potential mechanisms by which microbiota exert their side effects in a more mechanistic chapter. Here you could include the dual effects of microbiota on psychiatric disorders as cause/consequence (serotonin hypothesis; but also inflammation/depression hypothesis).

What is the effect of SGA's on microbiota and vice versa in a third chapter.

Special considerations in adolescents and children.

Other more details to be looked at and/or corrected:

Line 53: Type 1 diabetes or Type 2 diabetes??

Line 66-71: to be rewritten - is twice the same.

Line 81-83: meaning??

Line 112: Insulin sensitivity index - (not insulin secretion sensitivity)

Line 117-122: what is effect of prolactin in cardiac risk factors. Cardiac arrhythmia and CV ischemic diseases have different pathogenetic mechanisms - should be further commented on.

Line 127: what is a hypothalamic-liver axis?

Line 161: microorganism composition of the gut???

Line 168 - CV mice??

Line 214-216: the design of the study is not clear - first observational, second longitudinal data to be provided.

References:
Numerical reference is not correct (ex. in the introduction reference 34 in the first sentence)
References do not always refer to the sentence (eg. Ref 28 in line 127)
references are not always correctly inserted in the text.

Structural and linguistic comments on the paper:
Parts of the paper have been displaced eg. line 28-34: should be omitted
Line 24-26: should be formulated differently
Language difficulties: eg. line91 - H1 receptors, correlated with... should be formulated differently.
Line 94: reduce thermogenesis and decrease lipolysis in brown AT, while increasing…
And many more
In general the paper should be corrected by a native English speaker.

Quality of written English
Please indicate the quality of language in the manuscript:

Not suitable for publication unless extensively edited

**Declaration of competing interests**
Please complete a declaration of competing interests, considering the following questions:

1. Have you in the past five years received reimbursements, fees, funding, or salary from an organisation that may in any way gain or lose financially from the publication of this manuscript, either now or in the future?

2. Do you hold any stocks or shares in an organisation that may in any way gain or lose financially from the publication of this manuscript, either now or in the future?

3. Do you hold or are you currently applying for any patents relating to the content of the manuscript?

4. Have you received reimbursements, fees, funding, or salary from an organization that holds or has applied for patents relating to the content of the manuscript?

5. Do you have any other financial competing interests?

6. Do you have any non-financial competing interests in relation to this paper?

If you can answer no to all of the above, write 'I declare that I have no competing interests' below. If your reply is yes to any, please give details below.

'I declare that I have no competing interests'

**Statement on potential review bias**
Please complete a statement on potential review bias, considering the following questions:

1. Did you co-author any publication with an author of this manuscript in the last 5 years?

2. Are you currently or recently affiliated at the same institution as an author of this manuscript?

If you can answer no to all of the above, write 'I declare that I did not publish with these authors in the last 5 years and also meet the affiliation criteria". If your reply is yes to any, please give details below.

1. Did you co-author any publication with an author of this manuscript in the last 5 years?
I agree to the open peer review policy of the journal. I understand that my name will be included on my report to the authors and, if the manuscript is accepted for publication, my named report including any attachments I upload will be posted on the website along with the authors' responses. I agree for my report to be made available under an Open Access Creative Commons CC-BY license (http://creativecommons.org/licenses/by/4.0/). I understand that any comments which I do not wish to be included in my named report can be included as confidential comments to the editors, which will not be published.

I agree to the open peer review policy of the journal