Reviewer’s report

Title: Clinical and metabolic response to vitamin D plus probiotic in schizophrenia patients

Version: 1 Date: 29 Dec 2018

Reviewer: Darryl Eyles

Reviewer’s report:

I gather this paper was previously reviewed and I have been drafted as an additional external reviewer?

This is a small randomised placebo controlled trial to see if a supplement could affect well described metabolic syndrome in schiz patients.

Met syndrome is a major problem in both the onset and treatment of schiz particularly affected by the use of anabolising 2nd gen antipsychotics

The primary data that these supplements attenuated some of the metabolic syndrome in these patients is not that surprising. Indeed the rising evidence that Vit D modulates gut biome and therefore probably patient immune responsivity may represent an interesting therapeutic potential.

Q1 However the reduction (although quite small) in PANSS is definitely a new outcome. Could the authors explain why the BPRS in that case remained unaffected? Also I (and the authors agree) note that BPRS scores and PANSS were substantially lower in the active arm at baseline in table 3? Surely this totally biases study outcome? I am not sure "adjustment for baseline"  is what is required rather a better randomisation " I think this is THE MAJOR ISSUE in this whole manuscript.

Could the authors comment?

Q2 So which one was it? The probiotic or the D that affected PANSS so positively? This should be discussed in the light of the work cited from Jones et al.,

Q3 Body weight did not vary over the 12 weeks? Was there an expectation it would given the other metabolic outcomes? Would this take longer?

Q4 Ref 19 Jones et al., used L. reuteri NCIMB 30242 to increase 25OHD. Is that anything like the probiotic use here?

Statement: - One real opportunity missed here is an analysis of 16s RNA of fecal matter pre and post intervention.
It would be fascinating to know what microflora change had occurred in the probiotic group and correlate this with individual clinical outcome. Hopefully this will be done in future studies.

General comments

Although the paper is understandable there are still occasional English expression errors even in the abstract. The discussion in particular would benefit from another English speaker reviewing text.

Please remove naive statements like this in the intro "Oxidative stress and increased inflammatory cytokines play a critical role in the inflammatory processes leading to the development of schizophrenia" We have NO idea what causes schizophrenia despite many of us spending our lives working on the biology of this condition.

Please also drop the Patrick/Ames references to 5-HT. The comments about Vit D and 5-HT are I'm afraid alos naïve.

Tryptophan hydroxylase is not special in response to VDREs. Virtually every gene has VDRE sites of D activation (the authors themselves say there are 900). If you want to pick a neurotransmitter try Dopamine for instance. The enzyme for its production Tyrosine hydroxylase which is both more relevant to schiz and also has D responsive elements. Patrick and Ames have also NOT shown any brain related function in their FASEB review that is "improved". Please removes or delete this part of the discussion it detracts.

"One participant in the supplemented group and 4 in the placebo group dropped out for personal reasons" This is NOT what Fig 1 shows?

**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?**
If an additional statistical review is recommended, please specify what aspects require further assessment in your comments to the editors.

I am able to assess the statistics

**Quality of written English**

Please indicate the quality of language in the manuscript:

Needs some language corrections before being published

**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.

No

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/](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.