Reviewer’s report


Version: 0 Date: 08 Aug 2018

Reviewer: Alexandra Maria Bodnaruc

Reviewer’s report:

Dear authors and editor,

Thank you for the opportunity to review this manuscript.

The authors presented the protocol for a review with meta-analysis of randomized controlled trials assessing the effectiveness of insulin sensitivity-enhancing lifestyle and dietary-related adjuncts in improving antidepressant treatment response.

The proposed systematic review is timely and will be useful for informing future studies and possibly clinical practice. I recommend this manuscript for publication, with several essential modifications.

Below are the recommended modifications for this manuscript.

Kind regards,

Alexandra

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Abstract:

* Line 45: I do not think the term "cohort" is appropriate in this context. Please adjust.

* Lines 48 - 50: If I understood well, the objective of your review is "to evaluate the effectiveness of insulin sensitivity-enhancing lifestyle and dietary-related adjuncts in improving antidepressant treatment response". This is not what I understand when reading the last sentence of the "Background" section of the abstract. Please adjust.

* Lines 51 - 58: The way it is actually phrased, the "Methods/design" section of the abstract seems to mainly describe the objectives (from line 51 - 55) and not the actual methodology. Please adjust.
**Background:**

* General on the whole section: The "Background" section is quite long but repetitive and not convincing enough. I believe that the subject of this review is very pertinent, but the "Background" section doesn't really convince me of that. It includes too much information on associations between IR and depression/depression treatment response and is missing/lacking explanations of mechanisms may explain that IR is more prevalent in individuals with depression or vice-versa. Why might the presence of IR in individuals with depression impair response to common pharmacological treatments? This section also misses explanations on mechanisms linking the lifestyle adjuncts to IR and depression - you only briefly mention that the lifestyle adjuncts can help to improve both insulin sensitivity and depression symptoms (this should be discussed before the discussion section). Please 1) check for repetitions, 2) explain the link between IR and depression/depression treatment response, and 3) describe (or at least mention) most common mechanisms linking lifestyle adjuncts to IR and depression.

* Lines 69 - 73: In the DMS III and IV, chronic depression is a specifier of major depressive disorder and not a diagnosis by itself. The way it is phrased it leads to thinking that chronic depression is a diagnosis by itself, and the difference between persistent depressive disorder/dysthymia and chronic depression is not apparent. Please modify this passage to improve understanding by the reader. I also suggest, once the variations in terminologies between DMS IV and V are explained, to stick to one term throughout the whole text.

* Line 84: I don't think the term "cohort" is appropriate in this context. Please adjust.

* Line 100: Influenced/undermined - please choose one term (I believe "influenced" could be better in this context).

* Lines 127 - 129: "...with insomnia being more frequently reported". While this is true, depressions that are resistant to pharmacological treatment are more likely to be atypical. Individuals with atypical depression usually experience hypersomnia. In your discussion (lines 395 - 399). You explain some potential mechanisms linking sleep to depressive symptoms, and these mechanisms have mostly been suggested in contexts of sleep deprivation. I believe it could be pertinent to explain the possible effects of both insomnia and hypersomnia on depression pathophysiological pathways.

**Objectives:**

* The last paragraph of the "Background" section and the "Objectives" section are repetitive. In the "Objectives" section you are repeating your hypothesis and are stating what the main aim of the review is twice (first sentence (lines 147 - 149) and last sentence (lines 152 - 158)). As written in lines 147 - 149, the main aim of the review is, in my opinion, very clear. The last sentence of the paragraph is confusing. When you write "the effect of the insulin sensitivity-enhancing adjuncts (exercise; probiotics; ...),
collectively, in improving depressive symptoms …", the word collectively leads to thinking that you are looking for studies with interventions including ALL the lifestyle-related adjuncts that you enumerate just before. Revising the last paragraph of the introduction and the "objectives" for clearness and conciseness (perhaps an "objectives" section isn't needed - the objectives could just be presented at the end of the "Background" section and the variables will be explained in the "Methodology" section.

Methodology:

* Lines 171 - 172: Please include an explanation (ideally a physiological one in relation to the outcome measures) for your choice of including studies with an intervention duration of 4 weeks or more.

* Lines 173 - 195: At the beginning of the section describing the intervention types, you state that all types of lifestyle and dietary-related intervention having the potential to influence IR will be considered. However, as presented in lines 173 - 195, you seem to only include 5 types of interventions. No rationale was included as to why you chose physical activity, vitamin D, zinc, probiotics and hygienic-dietary recommendations, and do not include other interventions. For example, the Mediterranean diet (*you actually mention the healthy/Mediterranean diet in the "Background" section (line 120) but not in the methodology), omega-3 polyunsaturated fatty acids, monounsaturated fatty acids, as well as magnesium also appear to impact both mood and insulin sensitivity. Therefore, if you decided to focus on the 5 selected "types" of interventions for some specific reasons, please explain why. If not, you should include all types of lifestyle-related interventions and therefore make the necessary changes throughout the manuscript (i.e., in the methodology section, but also background and discussion where you mention these specific intervention types). Since a healthy diet and physical activity are part of the hygienic dietary recommendation***, why wouldn't you also include (if any) interventions including only sleep hygiene and only light exposure? These do not have to be done altogether to have an influence on IR and depression symptoms.

*** Shouldn't it be lifestyle "hygienic" recommendation rather than "dietary"?

* Lines 196 - 201: Please include a brief explanation as to why you will only consider lithium and no other agents used as mood stabilizers for studies including bipolar depression.

* Lines 237: The search in electronic databases should be updated - the period of time between December 31st, 2017 and the future submission for publication of your systematic review is too long in my opinion. The date should be changed accordingly in the protocol.

* Lines 342 - 355: The depression type (unipolar vs. bipolar), as well as the type of medication used (antidepressant vs. antidepressant + mood stabilizer), are also possible sources of heterogeneity and subgroup analyses for these variables might be necessary.
Discussion:

* To be adjusted according to changes made in the introduction. Perhaps, this section could include more on the scientific and clinical impact of the systematic review.

**Level of interest**
Please indicate how interesting you found the manuscript:

An article of importance in its field that should be highlighted to relevant networks

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

Acceptable

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Were you mentored through this peer review?

No