Author’s response to reviews

Title: Pharmacotherapies for fatigue in chronic liver disease (CLD): a systematic review and meta-analysis (protocol)

Authors:

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Author’s response to reviews:

Dear Dr. Chaabna:

Thank you very much for your constructive comments on our systematic review protocol. Your recommendations were very helpful and guided us in the revision of the original draft. Below are our point-by-point responses to each of your recommendations:

The authors are planning to conduct a systematic review to assess the benefits and harms of pharmacological interventions versus placebo for the management of fatigue in people with chronic liver disease. This is an interesting topic. The protocol is clear and well written.

Thank you very much for your input.

Kindly find below my comments:

I would suggest to clearly state the different steps in which the reviewers are involved (screening, extraction, quality assessment). Line 123

We have modified Line 123 accordingly. The revision clearly states the individual roles of each reviewer throughout each step of study screening, extraction, and quality assessment. The change is reflected in detail in the sections of the protocol titled 'Study selection and screening' and 'Data extraction and management.'

Line 127-133: I would suggest to extract conflict of interest statement of each study as recommended by AMSTAR.

The data extraction process for each included study will now be guided by AMSTAR 2 recommendations and will include information on conflict of interest for each study. This is clearly described in Lines 197-200 of protocol.

I suggest to assess first the forest plot in order to identify heterogeneity between studies.
Why not using tau2 and Q test to further assess the heterogeneity?

We have made the following changes to the protocol to more clearly describe how heterogeneity between studies will be identified through the assessment of the forest plot and other measures:

Heterogeneity across all the studies will be explored by using a combination of these measures:

I. Examination of forest plots and their associated outputs, e.g., Cochran’s Q

II. Determination of I2 statistic, i.e., variation in effect size due to heterogeneity (with 30% - 59%, 60%-89%, and 90% - 100% representing moderate, substantial and considerable levels of heterogeneity)

III. Determination of T2 and tau (i.e., estimate of between-study variance or measure of the dispersion of true effect sizes between studies based on the magnitude of the effect size) for determining the prediction interval.

I would suggest to use fixed-effect model for the meta-analysis only if you include in your quantitative synthesis, studies with the exact same designs (same type of CLD, duration of the therapy...). Otherwise, I would suggest only the use random-effect models.

The requested change has been made. Because we expect heterogeneity, no mention is made of the fixed-effect model. The protocol now ONLY states that a random-effect model will be used.

I would suggest to report your systematic review according to PRISMA guidelines (PRISMA 2009 and PRISMA for abstract 2013) and to provide an assessment of your future systematic review using AMSTAR tool.

The revised protocol will be reported according to PRISMA guidelines (PRISMA 2009 and PRISMA for abstract 2013). An assessment of the future systematic review will use the AMSTAR 2 tool. This information can be found in the ‘Methods/design’ section of protocol (Lines 124-134).

I have identified some typos such as in line 66. I encourage the authors to proofread the manuscript.

The typo in line 66 was corrected. Closing braces have been replaced with closing square brackets. The manuscript has also been proofread and major language edits made.

Thank you again for your feedback.

Sincerely,

Andem Effiong (and Prerna Kumari)
Dear Dr. Rodrigo:

Thank you very much for your constructive comments on our systematic review protocol. Your recommendations were very helpful and guided us in the revision of the original draft. Below are our point-by-point responses to each of your recommendations:

This protocol addresses an interesting research question. I have several comments for improvement.

Defining chronic liver disease as duration of a liver pathology greater than 6 months is a very simplistic view. There can be asymptomatic patients with ongoing liver damage at microscopic level (chronic persistent hepatitis). There needs to be a better definition of what you include as chronic liver disease. For example does it have to be confirmed by biopsy or persistent elevation of liver enzymes is enough?

You are exactly correct. We have revised the definition of what we deem chronic liver disease to reflect these valid points. We now define chronic liver disease as:

"progressive destruction of normal liver functions, commonly associated with fibrotic regeneration of the liver tissue."

And we also state that, "This review will include studies in which CLD was detected and confirmed with at least one of the following diagnostic tools: laboratory examination, liver biopsy, or radiologic imaging."

There are many aetiologies for chronic hepatitis. Giving an ad hoc list of selected aetiologies is grossly insufficient. Since you cannot list all possible causes, it may be wise to mention the broad categories and give a few examples for each.

In the revision, we mention the broad categories of chronic liver disease and give appropriate examples. Please see Lines 48-58.

I cannot understand why the authors are excluding non-pharmacological therapies. The evidence base will be more complete if these are also included in the review

We have included non-pharmacological therapies as a comparator in order to make the evidence base more robust.

There can be many confounders for fatigue such as thyroid status, anaemia, post viral infection and mental health. How do authors propose to adjust for these complexities?

We agree. In the section 'Subgroup analysis' we now describe in detail how we plan to adjust for various confounders and effect modifiers.

Lastly, the revised manuscript was proofread and major language edits were made.
Thank you very much for your feedback.

Sincerely,

Andem Effiong (and Prerna Kumari)