Author’s response to reviews

Title: Treatment of Depression with Chai Hu Shu Gan San: a Systematic Review and Meta-analysis of 42 Randomized Controlled Trials

Authors:

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Reviewer reports:

Xi Huang (Reviewer 1): The content of this submission is good and innovation, however, the authors need more and key literatures, for example: Pharmacogn Med.2014 Oct;10(40):503-8. The whole review is that this submission should be revised again.

A: Thank you for your reminder. We revised the whole review.

Joshua Rosenblat (Reviewer 2): The authors review a relevant and timely topic, namely, the antidepressant effects of Chai Hu Shu Gan San. Given the number of RCTs conducted in the area, conducting a meta-analysis is an excellent idea. However, there are a few areas that must be improved prior to publication. Areas of revision are described as follows:

- the reviewer appreciates that the authors used an English editing service, however, the writing can still be greatly improved. While the writing is mostly grammatically correct, the manuscript is written using colloquial language and must be written in a more scientific manner.

A: Thank you for your advice. We revised the English writing.

- In the abstract, the objective is not clearly stated. It appears that the objective is to determine the antidepressant effects of CHSGS. However, the overall antidepressant effect size is not stated in the abstract. Rather, only subgroup trends is stated with no p-values or confidence intervals.

A: Thank you for your advice. We revised it in the abstract.
- First paragraph of introduction is misleading stating that SSRIs and SNRIs have severe adverse effects and referencing an article about St. John's Wort, not an article about the tolerability of SSRIs and SNRIs.

A: Thank you for your reminder. We revised the part by using the other reference.

- In the intro line 30, need to substantiate claim of "satisfying clinical therapeutic efficacy" with a reference or explanation. Also, the quotation from the book is out of place and not necessary. Here too, the authors should attempt to use more scientific language, rather than making statements such as "soothes the liver."

A: Thank you for your advice. We revised the part following the reviewer’s advice.

- In methods, please clarify "depression." Are you including only major depressive disorder or also bipolar depression?

A: Thank you for your review. We revised it in the updated manuscript.

- Excluding RCTs with only one author is an odd exclusion criteria. It is a large leap to say that all RCTs with only one author listed on the publication are "fake." A single investigator may hire people to run the clinical trial without including them on the publication, especially for a small trial. As outlined, the included RCTs had weaknesses and risk for bias. I would say that a single author is a risk for bias but should not lead to complete exclusion of the trials, especially since there is such a large number of trials with only one author.

A: Thank you for your reminder. We supplemented 18 one-single author’s articles following the review’s advice in the updated manuscript.

- Please specify which authors conducted the search and reviewed the abstracts.

A: Thank you for your reminder. We revised it in the updated manuscript.

- The authors should use the random effects model for all pooling given heterogeneity of study design, regardless of I-squared values.

A: Thank you for your advice. We revised in the updated manuscript.

- Please clarify how the analysis was conducted. It appears that using an odds ratio (OR) would be more appropriate, not RR. The odds ratio can either be for remission (HAMDi in normal
range) or response (HAMD greater than 50% decreased). Please clarify and explain if you are looking at remission or response.

A: Thank you for your reminder. We revised the OR that reviewer mentioned in the paper. And most articles do not report remission or response rate, so we did not focus on them.

-Please explain the break down of why studies were excluded

A: Thank you for your advice. We revised the Flow Diagram.

-the fact that there are ZERO published studies in english or published to PubMed is a significant limitations. As the current article is written in english, it will be hard for most readers to look up the referenced studies. As a reviewer, I was not able to verify if the data was extracted correctly which greatly limits my review of the accuracy of the extracted data that the meta-analysis is based upon.

A: Thank you for your reminder. We revised in the Discussion Part in the updated manuscript.

-the results section will require much updating and it is very unclear and confusing in its current state. The main issue is that it appears that no specific a priori protocol was followed, but rather, the analysis was conducted and re-conducted to find comparisons that lead to a statistically significant finding. As the primary aim of the study is to find the antidepressant effect size of CHSGS, the primary result should be pooling together ALL studies and providing the reader with an overall antidepressant effect. Towards this end, there should be a black diamond at the bottom of the forest plot with an overall effect with 95%CI, I-squared, Z and p-value. I am not sure why this was excluded and only sub-group analyses are shown. As secondary outcomes, you may sub-categorize and determine if the effect is larger in sub-analysis compared to the pooled result of all studies, but this should not be presented as a primary outcome

A: Thank you for your advice. Since the depression and protopathy of the included articles are different, we used a subgroup analysis to present.

-as outlined in the discussion, excluding 27 RCTs simply on the basis of only having one author is a significant limitation and might have significantly biased your results.

A: Thank you for your reminder. 18 of 27 RCTs can be used and we supplemented them following the reviewer’s advice in the updated manuscript.