Author's response to reviews

Title: Effects and Treatment methods of Acupuncture and Herbal Medicine for Premenstrual syndrome/Premenstrual Dysphoric Disorder: Systematic Review

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Author's response to reviews: see over
To Whom It May Concern,

We have carefully read the reviewer’s comments and have made the following changes. We may have missed out some changes as the document Dr. Margaret Diane van Die (1st reviewer) sent us did not include track changes. [We think this is because she accepted all track changes she made on the reviewed documents prior to sending it back to us]. We would be happy to make changes again if Dr. Margaret Diana van Die re-send us the document with all track changes.

Thank you for taking your time to look over our manuscript. Responses to the reviewer’s comments are in red. Please let us know if you have any questions or concerns. Thank you.

Reviewer’s report#1(Margaret Diana van Die)

Major Compulsory Revisions:
1. It is not customary for inclusion criteria to combine RCTs and a former systematic review/met-analysis. The authors have two choices in addressing this:
   i. They can source the original studies included from the previous systematic review/met-analysis, and include the full data (ie including baseline data and end-or-treatment means/SD’s), citing these studies, or
   ii. They can omit these studies (if there is nothing to add) and refer to this review in their introduction/methods. In this case, the Methods (abstract and body of manuscript) should state that, “Studies included in the 2011 meta-analysis of acupuncture by Kim et al are not included in this review”.

   We have accepted the comment and have decided to choose the first option. We have included the full data and cited these studies in our study (please refer to Table 2 of our manuscript). Table 1, which is now Table 2, has been changed for more clear information.

2. Inclusion/Exclusion criteria: It needs to be clarified whether multi-component herbal formulations were included. It would appear that they were included, as the two Chinese herbal decoctions contain eight herbs each.

   In inclusion criteria, we have clarified this part and indicated that multi-component herbal formulations were included.

   “…the study compared acupuncture with control groups or herbal medicine including multi-component herbal formulation with placebo or pharmaceutical medicine…”

3. Data extraction:
   i. Further information should be mentioned/extracted:
condition (whether PMS or PMDD), sample size, study duration, herbal extract and dosage regimen.

ii. The omission of adverse events is a serious omission. If possible, it should be added.

iii. It is also of relevance in PMS-PMDD studies whether or not two cycles of prospective ratings were recorded prior to study entry.

i. On Data extraction, information concerning condition of PMS/PMDD, sample size, study duration, herbal extract and dosage regimen has been added and they have been noted in table 1 and 2.

ii. Thank you for pointing out this point. Per your feedback we have added adverse events.

iii. Prospective ratings are added in table 1 and 2.

Results:

4. The names of all the herbal ingredients in the two herbal formulations mentioned (Xiaoyaosan and DanZhi xiaoyaosan) need to be listed (common and Latin binomials), as well as quantities of each herb per dose/tablet.

Unfortunately, the detailed formulation is not included in the original study, however, it does mention that it is approved by TGA. Thus in data extraction section, we indicated that the two herbal granules are approved by TGA and that it is commonly accepted substances (see p.3 Data extraction).

5. The herbal extracts and the form of administration need to be stated consistently (for each study). This could be indicated in the text and/or the tables.

Thank you for pointing out this point. We have added the form of administration in Table 3.

6. There appears to be some misunderstanding of the requirements of the Risk of Bias assessment. This should include selection bias; blinding of outcome assessment; blinding of participants and personnel; attrition bias; reporting bias. The authors are referred to the Cochrane risk of bias tool available in RevMan: ms.cochrane.org/revman/download

No attempt has been made to assess the quality of the trials included.

We have included a table for Risk of bias of included RCTs as a Table according to the Cochrane risk of bias tool:

<table>
<thead>
<tr>
<th>Risk of bias across studies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adequate sequence generation</td>
</tr>
<tr>
<td>The risk of bias in the studies was variable. For adequate sequence generation, two studies used randomized block design [6, 23], one study used a computer-generated random number sequence to allocate patients to the treatment and control groups [15]. Thirteen studies had insufficient report on how their random numbers were generated [8-14,17-22] (Table 1)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Allocation concealment</th>
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<tr>
<td>In allocation concealment, two studies adequately concealed group assignments</td>
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</table>
by adopting central randomization [15, 16]. One study had the medications in identical appearance with labels A and B and identification number was noted in a protocol to allow a subsequent identification after the completion of the study and statistical analysis [19]. One study had women randomized to receive the tablet in a 1:1 ratio using a computer-generated code and they are randomly assigned [24]. On the remaining studies allocation was not reported or unclear. 

(Table 1)

Blinding
Blinding was evaluated separately for patients and outcome assessors. Most trials had insufficient information. For outcome assessor blinding, most studies received ratings of ‘unclear’ because of poor reporting or the self-reporting nature of the outcome measures used. One study had the patients and raters blind to drug assignment [18]. One study had the identification number in a protocol with the availability of information on the placebo and the active substance to the investigators and volunteers only after the completion of the study and after the statistical analysis was performed [19]. One study had supplies packaged in plain boxes labeled with code and study cycle number [20]. One study had all tablets coated to make them identical and were supplied in plaster packs marked with days of the week to aid compliance [21]. One study had the assignments kept in sealed, opaque envelopes until the point of analysis of data. The randomization and allocation process was performed by the principle investigator of the trial who was not involved in the process of treatment and measurement [24].

7. Discussion:
This should follow the format:
i. Restatement of principal findings
ii. Comparison with other reviews
iii. Possible Explanation/s for findings
iv. Implications
v. Limitations

We have reorganized the manuscript following the format suggested. Also, restatements of principal findings, comparison with other reviews, and explanation for findings, implications, and limitations have been reorganized.

8. Limitations:
This refers to the limitations of the RCTs evaluated, and of the current review. Eg
The points raised in the abstract regarding different endpoints, inclusion criteria, degree of symptom severity, diagnoses, etc.
Also please mention the limitations of this review. Eg much research has been conducted on phytotherapy prior to these inclusion dates.

In the limitations section, we have added limitation of the RCTs evaluated and of the current review (e.g., different endpoints, inclusion criteria, degree of symptom severity, diagnoses). Also, limitation of our review has also been included.

“…The research done had different inclusion criteria, measuring methods, degree of symptom severity, sample sizes, diagnoses, and treatment sessions. Only limited studies had two cycles of prospective ratings recorded prior to study entry for acupuncture intervention…”
9. Conclusion:
i. The conclusion and recommendations included within the body of the
discussion are overstated, and ignore the research conducted prior to these
inclusion dates (eg “No other previous evidence supports the results.” And “This
study shows that alternative medicine is as much effective as mainstream
medicine with the advantage of fewer major side effects”. The adverse events
were not addressed in this review.) This should be re-worked.
ii. The authors need to clarify the implication of the equivalence of Vitex to
fluoxetine

i. Thank you for this comment. We have removed those statements from our document. We
have addressed the adverse events in Table 2 and 3.

ii. Implication of the equivalence of Vitex to Fluoxetine has been clarified in page 8.

“…In a study done in Vitex agnus castus with Fluoxetine as control, there was no significant difference between
the two groups after the treatments [18]…”

10. The final conclusion does not really follow from the findings, since the study
did not focus on Korean herbal interventions. It should therefore be amended to
reflect the study findings.

Focus on Korean herbal intervention has been removed and we have made changes on
conclusion to reflect the overall study findings. Please refer to page 8.

Minor Essential Revisions:
11. Figure 1 (flowchart) requires further information for greater clarity. Also it
does not concur with the number of tables indicated in the tables (ie 12 studies
on herbal interventions, and four on acupuncture.) Specifically, please elaborate
the reasons for exclusion of the 24 studies, and give a breakdown of the 14
RCTs included, in terms of the number that were acupuncture studies, and the
number of herbal medicine studies. Please refer to the systematic review on-line
by Jong-In Kim et al for guidelines:
Acupuncture for the treatment of tinnitus: a systematic review of randomized
clinical trials
Jong-In Kim, Jun-Yong Choi, Dong-Hyo Lee, Tae-Young Choi, Myeong Lee,
Edzard Ernst BMC Complementary and Alternative Medicine 2012, 12:97 (17
July 2012)

Thank you for this comment; we understand the flowchart needed more clarification. Hence,
the flowchart has been clarified with more detailed information of the reasons for exclusion
of the studies. Because the studies included in the 2011 meta-analysis of acupuncture by Kim
et al are now included, number of identified citations (221 citations), included (19
RCTs)/excluded (20 studies) citations have been changed.

12. Results:
There is a lot of data to report. So sub-headings should be employed to facilitate
For easy reading and clearer organization, tables 2, 3, 4 have been revised. We also included abbreviations underneath each table. Moreover, acupuncture interventions, herbal interventions and the result have been sub-divided for clear understanding.

13. The number of studies reporting on each intervention should be included (in brackets after the intervention, or in text).

Per your comments, we included the number of studies reporting on each intervention in brackets after each intervention. Ex. Acupuncture interventions (8 studies, 9 different interventions), Herbal interventions (11 studies, 7 different interventions).

14. References need to be included after every mention of a result. Again the authors are directed to the on-line review for an example of this:
Acupuncture for the treatment of tinnitus: a systematic review of randomized clinical trials
Jong-In Kim, Jun-Yong Choi, Dong-Hyo Lee, Tae-Young Choi, Myeong Lee, Edzard Ernst BMC Complementary and Alternative Medicine 2012, 12:97 (17 July 2012)

Thank you for this comment. We have included references after every mention of a result throughout the entire manuscript.

15. The authors state that, “The percentage reduction was defined as difference in symptom score between the final score after treatment and symptom score at baseline” i. Do the authors mean this was divided by the baseline score? ii. If this was calculated by the authors it belongs in METHODS section.

Thank you for pointing this out. We moved this part to the methods section. Under Data extraction subheading, the following section has been added:
Calculation for reevaluation The outcomes were re-evaluated using the following valuation:
Significant result (%) = (baseline score-post treatment score)/baseline score) x100. Further evaluation of across studies on the efficacy of treatments on re-evaluated scores by symptoms was additionally analyzed. (please refer to table 4)

16. The outcomes could be further sub-divided to assist the reader: For example, as well as the broad headings of acupuncture and herbal medicine already employed, each section could be further sub-divided into overall symptoms, physical symptoms, and psychological symptoms.

Thank you for this suggestion. We had initially thought about sub-dividing as you suggested, however, we found limitation in doing so because not all studies used the same scales and measurements. Therefore, dividing them into overall, physical and psychological symptoms could cause some confusion. We hope you understand this issue.

17. The range of improvement should be included, and ii. It should be specified unambiguously how this compares to the comparator/s.
We included the range of improvement per your suggestion. Please see Table 2 and 3.

18. References:
In the reference list, please be consistent with listing under surname.

Thank you pointing this out; we corrected references 5,9,10,16,17,19,20,21,24,25,26 to be consistent with authors’ surnames.

19. Table 2:
1. Please include sample size and duration of treatment for each study. The control should be included for Ref 15.
2. The heading ‘Time’ should be altered to ‘Frequency’
3. Abbreviations used in the table should be expanded underneath the table.
4. It appears that study 12 the analysis of a sub-population of study 12. This needs to be stated within the manuscript as well as highlighted in the table.

Please note, Table 2 is now Table 3.
1. Thank you for your suggestions. Sample size and duration of treatment have been included. Control for Ref 15 has been included.
2. The heading has been changed to ‘Frequency’ from ‘Time’.
3. Abbreviations have been expanded underneath the table.
4. We are not sure if we understand this comment. Could you clarify please? Once you clarify, we would be happy to make necessary changes.

20. Table 3 i. need to be more clearly labelled. Eg Percentage reduction in symptoms by intervention.
ii. Further information is needed for the reader to determine whether a result was non-significant or not reported. Eg NS or NR.
iii. Abbreviations used should be clarified underneath the table.
iv. The presentation of results in Table 3 suggest that many symptoms demonstrated the same percentage reduction. If this is due to the RCTs reporting results for symptom clusters, it would be clearer if the results were presented to reflect that, or if it were stated in the text.

Please note Table 3 is now Table 4.
i. iii The labels have been clarified by adding abbreviations underneath the table and we have added the types of symptoms by clusters on the right hand corner of the table for easy read.
ii. We have added notes so the readers can better understand the result.
iv. Also, we have merged the improved rate by clusters for some. For example, in the cluster of pain for acupuncture treatment, we have put one improved rate for all the sub types of pain.

21. Use of English:
Please refer to the returned manuscript for corrections to use of English in track changes mode.

Thank you for sending the revised manuscript. We understand we need to do track changes for all the changes we hereby make in our transcript. However, we are not sure if the reviewer kept all the track changes in the document when sending it back to us (as we do not
see those marked changes in the document the reviewer sent us). If the reviewer would like to send another one with track changes, please let us know.

Reviewer's report#2(Fabio Facchinetti)

1 The main issue is that authors evaluated quality of trials but we are not informed of the method they use, nor there is a reference to a particular method.

The authors tried to review the effects and treatment methods for PMS and PMDD rather than the quality of the trials, thus the quality of the trials vary depending on the method each researcher used. Therefore, the methods each researcher used were not informed in this paper.

Methods they have used on trials are not specifically mentioned except for the frequency of the treatment sessions and the points they have used. Thus we have included as much information as possible with the given information. If there needs more revision, please let us know. Thank you.

2 This study has not been included. Authors should state reasons. Kilicdag EB, et al. Fructus agni casti and bromocriptine for treatment of hyperprolactinemia and mastalgia. Int J Gynecol Obstet 2004; 85: 292–293.

Although this study, Kilicdag EB, et al. Fructus agni casti and bromocriptine for treatment of hyperprolactinemia and mastalgia. Int J Gynecol Obstet 2004; 85: 292–293, may be related to PMD/PMDD and the context qualify for the issue the paper deals with, it was not included in this paper because the search engine did not include any words from the title of this research. The search terms we used for this study is as follow:

premenstrual syndrome acupuncture, premenstrual syndrome alternative medicine, premenstrual syndrome herbal medicine, premenstrual syndrome CAM, premenstrual dysphoric disorder acupuncture, premenstrual dysphoric disorder alternative medicine, premenstrual dysphoric disorder herbal medicine, premenstrual dysphoric disorder CAM for Pubmed. Search terms Premenstrual syndrome (Korean and English) and premenstrual dysphoric disorder (Korean and English) were used for the remaining search.

Because the study deals with Fructus agni casti, it has much value to be included, unfortunately, it was not found with the limited search terms we had used. Thank you for reminding us that the search term ought to be more comprehensive for future research.

3 For several acupuncture methods or herb remedies only one RCT is available, therefore conclusions about their efficacy is limited. On the contrary at least 3 trials support Vitex Agnus castus performances respect with placebo. Such wider experience in literature has to be acknowledged.

Thank you for pointing this out. As for the acknowledgement of the availability of the RCT trials as you have mentioned, we have added a note on Discussion Limitation as,

Although acupuncture and herbal medicine are largely practiced amongst Eastern medical doctors, there were limited RCTs available in this research, therefore conclusions about their efficacy may not speak for all alternative therapies. Much of the researches were done one time only for each intervention which is difficult to state it is significantly meaningful. On the contrary at least 4 trials support Vitex Agnus castus performances respect with placebo, thus there was a limitation on such
Editorial comments,

1 We note that your manuscript was submitted to us as a Database article. However, we do not feel that it qualifies as this article type, and we are therefore consider your manuscript as a Research Article. Please note that this will not affect the review process of your submission in any way.

We have resubmitted the manuscript under Research Article as you have suggested. Thank you for considering our manuscript as a Research Article.

2 Please remove your Tables from your uploaded figures, and instead include them in your manuscript file, as per our formatting guidelines.

We have included Tables in the bottom of our manuscript and removed them from figures file.

We have made revisions per reviewers’ constructive and helpful feedback. We hope these revisions have made our manuscript stronger. Thank you for your suggestions and comments. If there are any other revisions we should make please let us know. Thank you once again.

Sincerely,

Su Hee Jang
Doctor of Korean Medicine
Under graduate program, Dept. of Korean Gynecology at Dongguk University,
Under residency program at Nazareth Oriental Medical Hospital