Author's response to reviews

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

Authors:

Su Hee Jang (jangsuhe@gmail.com)
Dong Il Kim (obgykdi@hanmail.net)
Min-Sun Choi (sunny8830@dongguk.ac.kr)

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

I have carefully read the note and have made the following comments and changes. We may have missed out on changes that should be made. If so, let us know and we will correct them as soon as possible.

Thank you for taking your time to look over the research. We are honored to be a part of BMC.

Here are the responses to the review:

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

The amendments made by the authors have considerably improved the quality of this review.

We appreciate your compliment. Thank you!!

1. ABSTRACT
   i) It is stated in the last sentence of the Methods section that ‘study outcomes were presented as mean differences’. Yet this is not made clear in the tables. It would appear that data are end-of-treatment scores. This needs to be clarified both in the tables and the abstract.

   We realized we haven’t changed the ABSTRACT. It’s corrected as,
   Study outcomes were presented as the improved rate (%) and or end-of-treatment scores.

   Outcome is now more clear by adding: (end-of-Tx score) in the tables next to the outcome heading..

   ii) Under ‘Results’, it is stated that herbal medicine significantly improved PMS/PMDD symptoms. However it is not clear if this refers to all the herbal interventions reviewed.

   We have mentioned that not all herbal medicine significantly improved as,

   In herbal medicine, studies on Vitex agnus castus, Hypericum perforatum, Xiao yao san, Elsholtzia splendens, Cirsium japonicum, and Ginko biloba L. were identified. Experimental groups with Acupuncture and herbal medicine
treatment (all herbal medicine except Cirsium japonicum) had significantly improved results regarding their PMS/PMDD.

iii) The ‘Conclusions’ section needs to give more of an overview of the study findings (before discussing limitations), implications of findings as well as recommendations.

The following is now added. Thank you!!

Acupuncture and herbal medicine in premenstrual syndrome and premenstrual dysphoric disorder showed 50% reduction in symptoms or better than the initial state. In one study, the outcome resulted in 77.8% reduction of the symptoms after 2~4 acupuncture treatment sessions. In both acupuncture and herbal medical interventions, there has been no serious adverse events reported proving the safety of the intervention with more than 50% relief in much of the symptoms for the most of the interventions.

2. Background. Several other reviews have been conducted of these interventions. It is not clear why only the review by Kim et al is referenced. (See below)

We have made clear of the reason why Kim’s review has been mentioned as,

As for the most recent systematic review and a meta-analysis of complementary and alternative medicine on PMS and PMDD, Kim et al. [6] in 2011 showed favorable results.

3. Data extraction: As recommended previously, the ingredients of the formulations Xiao Yao San (ie Radix Bupleuri (Chai Hu), 3g, Radix Glycyrrhizae (Gan Cao), 3g, Rhizoma Atractylodis Macrocephalae (Bai Zhu), 1.5g, Radix Albus Paeoniae Lactiflorae (Bai Shao), 6g, Tuber Curcumae (Yu Jin), 6g, Bulbus Fritillariae Cirrhosae (Chuan Bei Mu), 6g, Rhizoma Acori Graminei (Shi Chang Pu), 6g, Rhizoma Cyperi Rotundi (Xiang Fu), 6g, Pericarpium Citri Reticulatae Viride (Qing Pi), 6g, Fructus Citri Aurantii (Zhi Ke), 6g, Radix Angelicae Sinensis (Dang Gui), 10g, Sclerotium Poriae Cocos (Fu Ling), 10g, Rhizoma Gastrodiae Elatae (Tian Ma), 5g) and Dan Zhi Xiao Yao San (Dan Pi (Cortex Moutan) 68.2 mg, Zhi Zi (Fructus Gardneiae) 68.2 mg, Chai Hu (Radix Bupleuri) 68.2 mg, Dang Gui (Radix Angelicae Sinensis) 68.2 mg, Bai Shao (Radix Alba Paeoniae) 68.2 mg, Bai Zhu (Rhizoma Atractylodis Macrocephalae) 68.2 mg, Fu Ling (Poria) 68.2 mg, Gan Cao (Radix Glycyrrhizae) 22.6 mg). The authors of these articles could be contacted if there is uncertainty regarding the exact formulations used. If they cannot be contacted, it should be stated what the normal ingredients are, but that this could not be verified as no response was forthcoming from the study authors.
The following has been added to clarify the ingredients. Thanks!!

The authors of the research has changed their email addresses and because they were no longer listed at the facility mentioned in the article, exact formulation could not be verified. The general ingredients of Xiao Yao San are Chae Hu (Radix Burpleuri) 75 mg, Bai Zhu (Rhizome Atractyloides macrocephalae) 75 mg, Fu Ling (Poria) 75 mg, Dang Gui (Radix Angelicae sinensis) 75 mg, Bae Shao (Radix Paeoniae alba) 75 mg, Shen Jiang (uncooked Rhizoma Zingiberis) 50 mg, Bo He (herba Menthae haplocalycis) 50 mg, Zhi Gan Cao (honey fried Radix Glycyrrhizae uralensis) 25 mg, and the general ingredients of Dan Zhi Xiao Yao San are Mu Dan Pi (Cortex Moutan) 68.2 mg, Zhi Zi (Fructus Gardneiae) 68.2 mg, Chai Hu (Radix Bupleuri) 68.2 mg, Dang Gui (Radix Angelicae sinensis) 68.2 mg, Bai Shao (Radix Paeoniae alba) 68.2 mg, Bai Zhu (Rhizoma Atractyloides macrocephalae) 68.2 mg, Fu Ling (Poria) 68.2 mg, Gan Cao (Radix Glycyrrhizae) 22.6 mg.

RESULTS
4. The information under the headings ‘Synthesis of Results (two places) belongs in the Methods section.

Synthesis of results section is now omitted and the following sentence is now under Search strategy in the Methods section. Thank you!!

Data were recorded and assessed using Excel 2007 FOR WINDOWS version.

5. The number of studies and different interventions could be written as the first sentence of the respective paragraphs.

In both acupuncture and herbal interventions, first sentences have been added as: ‘ (Thank you!!)

**Acupuncture interventions**

Eight studies and 9 different interventions were identified.

**Herbal interventions**

Eleven studies and 7 different interventions were identified.

6. FLOWCHART

“6 citations identified form other sources” should be defined – were these identified as a result of hand-searching reference lists of journal articles?

Reference has been added within the flowchart. As,

See Reference
7. TABLE 2
i) It is not clear why there are two rows for reference 10 (studies 3 -4), and what
the different data represent (under the heading ‘Outcome’). Outcomes need to be
specified as they are reported in table 3 for greater clarity.

To clarify this confusion,,

It is because one is on acupuncture and the other is of
moxibustion. The results of the two are not the same. Thank you~!! If
further correction is needed, let us know!!

ii) It is not clear whether the sample size is for the treatment arm only. The
column heading needs to reflect this.

The sample size for the control group is mentioned unde r
“Control” heading as n of CG (=number of Control Group).

iii) Were the data available for studies 5 – 9 in this table? If so, this should be
included. If not, ‘n/a’ should be included.

We have included n/a. Thank you very much!!

iv) What were the medications used as comparators in studi es 6 – 9?

Medications are now included. Thank you!!

Medication - Progestin (medroxyprogesterone, 6 mg daily) (30)
Medication - medroxy-progesterone 4 mg, diazepam 2.5mg twice daily (31)

8. TABLE 3
Please clarify whether ‘Outcome’ refers to ‘end-of-treatment scores unless
otherwise stated’, or mean differences, as stated in your abstract.

It is now clear that it is of ‘end-of-treatment scores’

Outcome (Improved rate or end-of-Tx score)

9. TABLE 4. The heading is confusing. “Significant result (%)… The results are
non-significant”

IT IS NOW REVISED TO:
The results were presented to reflect the results for symptom clusters.

10. DISCUSSION: The discussion should be a synthesis of the results rather than a restatement of findings. For example, the strength of the evidence for the different interventions should be made apparent to the reader, and:

i) The first paragraph and sentence 1 of the second paragraph belongs to the introduction.

The first paragraph has been deleted.

ii) the findings of this study should be compared with comparable reviews on these interventions – including (but not restricted to) the following:

This part has been added @ (vi) part!! Thank you!!

Vitex agnus castus (VAC) chaste tree have been proven in animal and clinical trials of dopaminergic effects and its efficacy has been investigated the most on PMS of its effectiveness [17]. Hypericum perforatum influences the serotonergic system and suppresses proinflammatory cytokine levels [33]. It demonstrates to be an effective treatment for depression which is one of the symptoms of mood-related PMS symptoms [20]. Duvan et al., investigated oxidant/antioxidant status in PMS and found that increased oxidative stress and reduced anti-oxidant capacity may occur in PMS and imbalance of oxidant/antioxidant systems may be a cause or the consequence of the various stress symptoms in PMS [36]. Elzholtzia splendens contains volatile oil and flavonoids and studies have reported that it had effects on reducing inflammation and fever [34]. According to Zou Y et al., antioxidant mechanism of Hypericum perforatum attributed to its free radical scavenging activity, metal-chelation activity and reactive oxygen quenching activity that may lead to reducing PMS symptoms [35]. According to McKenna DJ, antioxidant property of Ginkgo biloba leads to exhibit therapeutic activity in congestive symptoms of premenstrual syndrome [37]. Ginkgo biloba L. is rich in flavonoid glycoside and terpene lactone [26] and a published placebo-controlled trial on the efficacy of Ginkgo for the treatment of PMS was effective against the congestive symptoms of PMD [38]. Bioflavonoids, an active ingredient of Ginkgo is known as stress modulator which explains the usage of Ginkgo as an anxiolytic medicine for PMS [26]. Hence, treatment targeting these mechanisms may exert their benefits in PMS/PMDD by correcting underlying dysfunctions.

iii) the studies with which findings are compared should be referenced.

Yes!!

iv) The authors should include the strengths of the current study (and what it contributes to the literature that the other reviews did not include).
This review shows wide spectrum of traditional treatment methods which does not limit to one method of CAM, but acupuncture and herbal medicine combined, thus give greater idea of what to expect in treating PMS/PMDD with traditional medicine. Also, by examining the best treatment methods for specific symptoms by reviewing the improved rate categorized by symptoms, it may be a used as a guideline in treatment method selection for different occurring symptoms personalized to each PMS/PMDD patients.

v) The sentence “In acupuncture studies, more than five studies have been excluded…” should be deleted. This is covered by flowchart and search limits in results section. The following sentence may be relevant if rewritten: eg “Our findings were consistent with case studies examining herbal interventions and acupuncture. (refs)”

It is now revised as,

All acupuncture interventions, the outcome results showed improvements better than the control groups thus our findings were consistent with case studies examining herbal interventions and acupuncture.

vi) Findings should be explained with reference to known mechanisms of action of the herb/s. ie Based on current knowledge of mechanisms of Vitex, Hypericum, Ginkgo etc., why might these be effective in PMS/PMDD (1 sentence each). The indications for the multi-component formulations could be given (eg liver chi stagnation causing psychological dysphoria etc/ liver-spleen dishormony, which manifests as symptoms such as…….). With regard to the TCM understanding, a further sentence could be added at the end of the paragraph, such as “Hence, treatment targetings these meridians/points/syndromes, may exert their benefits in PMS and PMDD by correcting underlying dysfunctions.”

It is now revised with more references supporting the results. J
It is same with (ii)

Vitex agnus castus (VAC) chaste tree have been proven in animal and clinical trials of dopaminergic effects and its efficacy has been investigated the most on PMS of its effectiveness [17]. Hypericum perforatum influences the serotonergic system and suppresses proinflammatory cytokine levels [33]. It demonstrates to be an effective treatment for depression which is one of the symptoms of mood-related PMS symptoms [20]. Duvan et al., investigated oxidant/antioxidant status in PMS and found that increased oxidative stress and reduced anti-oxidant capacity may occur in PMS and imbalance of oxidant/antioxidant systems may be a cause or the consequence of the various stress symptoms in PMS [36]. Elzholtzia splendens contains volatile oil and flavonoids and studies have reported that it had effects on reducing inflammation and fever [34]. According to Zou Y et al., antioxidant
mechanism of Hypericum perforatum attributed to its free radical scavenging activity, metal-chelation activity and reactive oxygen quenching activity that may lead to reducing PMS symptoms [35]. According to McKenna DJ, antioxidant property of Ginkgo biloba leads to exhibit therapeutic activity in congestive symptoms of premenstrual syndrome [37]. Ginkgo biloba L. is rich in flavonoid glycoside and terpene lactone [26] and a published placebo-controlled trial on the efficacy of Ginkgo for the treatment of PMS was effective against the congestive symptoms of PMD [38]. Bioflavonoids, an active ingredient of Ginkgo is known as stress modulator which explains the usage of Ginkgo as an anxiolytic medicine for PMS [26]. Hence, treatment targeting these mechanisms may exert their benefits in PMS/PMDD by correcting underlying dysfunctions.

vi) The implications of the equivalence to fluoxetine need to be explained. Is fluoxetine of proven efficacy in PMS/PMDD? If so, then equivalence to fluoxetine is actually a positive finding. (The also implies the word ‘However’ should be removed from the sentence relating to this finding in the results section, as it does not contrast with other positive findings).

Yes!! It may be great to add some supporting evidence!! Thank you.

According to Wood et al. [31], 20mg doses per day of fluoxetine reduced behavioral symptoms in 75% of cases and physical symptoms in 40%. Study done by Diegoli et al. [32] also observed 20mg of fluoxetine per day had the remission rate of 65.4% which was the best rate compared with other drugs such as pyridoxine, alprazolam, and propranolol. According to the Diegoli et al. [32], fluoxetine was more effective for treating isolation, confusion, crying, depression, weight loss, and emotional instability, thus equivalence to fluoxetine is actually a positive finding.

vii) the quality of the studies should be commented on (by referring back to the risk of bias assessment, as well as power, sample sizes, etc).

It is now revised.

As for the quality of the study, on the review of acupuncture treatments, the sample sizes varied ranging from 7 to 35, and 17 to 101 on herbal treatments which shows much difference in the size between trials, however, all included studies except for the study on Xiao Yao San met Jadad scale criteria on herbal treatment [39].

ix) The meaning of the sentence, “On the contrary, at least 4 trials…… a limitation on such wider experience in literature” is unclear.

I hope this is clearer!! Thank you J

Much of the researches were done one time only for each intervention which is difficult to state it is significantly meaningful. On the contrary, on the effectiveness of Vitex Agnus castus performances respect with placebo has been under research for at least 4 different trials. The review lack the quality
evaluation of trials included in the review on Vitex Agnus castus and it does not include one significant trial on Vitex Agnus castus.

x) The clause, “therefore conclusions about their efficacy many not speak for all alternative therapies” is self-evident and should be deleted.

It is now deleted.

11. CONCLUSION: Bearing in mind what clinicians and future researchers will want to know,
i) Can you draw any conclusions regarding the overall findings? Was the evidence for any intervention more convincing that for others? (ie greater number of studies, better methodological quality, larger sample sizes, longer treatment duration?)

Overall, in acupuncture treatment, it can be concluded that the safety of the treatment has been proven by no report of major adverse events, treatment sessions as few as 2~4 sessions show 77.8% reduction in the symptoms and since much more treatments such as 30 sessions does not increase the degree of the symptom relief, frequency of the treatment does not affect the outcome result. Also, there was no difference between luteal phase and follicle phases in the treatment result thus the sessions may not be limited only to during the luteal phase. In herbal treatment, there have been no serious adverse events reported which in turn proves its safety with the recommended dosage. Majority of the duration of the study was for 2 to 3 menstrual cycles with the relief of PMS/PMDD symptoms however further investigation is needed for the maintenance of the relief state.

ii) Summarize the main limitations of these studies. As mentioned by Reviewer 2, the main limitation appears to be that most interventions had only one study conducted on them.

Even though much study has been done prior to these inclusion dates as mentioned above, large-scale, multicenter randomized, double-blind and placebo-controlled clinical researches are needed to support the results since most interventions had only one study conducted on them

ii) Can you make specific recommendations for future research based on the limitations of these studies?

In further research, comparison between the frequency, dosage, treatment duration for each intervention on each PMD/PMDD symptoms may lead to much specific guidance in clinical setting.

12. REFERENCES:
i) Authors should be listed by surname, initial.

We have corrected the ref. and corrected the list by surname, initial.
ii) According to the requirements of the journal, either all authors should be listed, or the first three followed by et al. Referencing style should be followed consistently.

All authors have been listed and the style is not consistent. Thanks.

13. Points not addressed from previous review:

i) “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.” This refers to the extract such as is given in the Ma and He studies, for example (VAC BNO 1095), as well as the mg/day and any information given regarding standardization. (Eg the Canning study on Hypericum states “900 mg/day (standardized to 0.18% hypericin; 3.38% hyperforin)” Sufficient information should be provided to allow clinicians and other researchers to establish phytoequivalence with a different product.

All the information in the original paper has been included in the table. Those not specifically mentioned are marked as N/A. Thank you!!

ii) Results section: 17. The range of improvement should be included, and ii. It should be specified unambiguously how this compares to the comparator/s. (ie were all the interventions significantly superior to the controls?)

YES!! It would be much more professional to add them. It is revised.

Acupuncture treatment using SP6 CV6 as the main points had MSSL 16.78 at the initial point which was reduced to 7.56 that the end of the session [8]. Treatment using DU20, LI4, H3, REN3,4,6, PE6, GB34, UB23 had 77.8% reduction at the end of the trial [9]. Hand acupuncture and moxibustion treatments had MSSL 20.63 and 20.65 at the initial point which was reduced to 3.94 and 3.40 that the end of the session [10]. Back-shu points and Point-thought-point techniques, electroacupuncture on scalp, treatment using BL17,18,20,23 and GV20, Ex-HN2,3 all had better outcome than the control group [11-5].

iii) 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. The authors are directed to: van Die MD, Burger HG, Teede HJ, Bone KM. Vitex agnus-castus Extracts for Female Reproductive Disorders: A Systematic Review of Clinical Trials. Planta Med 2012. (Free on PubMed)

It is now added in the herbal intervention part and the table. Thank you!

One study on Vitex agnus castus is the analysis of a sub-population of a
systematic review on clinical trials [18,27].

iv) As previously noted, the standard of English expression obscures the meaning. The recommended changes from the previous review should be implemented, or the services of a proof editor sought. Spelling of the herbs should be checked throughout and corrected where necessary. Consistency with use of Latin binomials or common names is recommended.

It has been reviewed by another reviewer for English language correction and the spellings of the herbs are carefully rechecked. Thank you!!

v) ‘PMS’ should be changed to read ‘PMS/PMDD’ throughout the document.

Yes! We have changed PMS to PMS/PMDD. Thanks.

Reviewer’s report#2 (Fabio Facchinetti)

Compulsory Revision

1) statements in the points 1 and 2 of the Author's letter response to my criticisms have to be included in the manuscript as "limitations" since Authors are unable to specifically answers to my requests. Specifically, lack of quality evaluation of trials included in the review and lack to include one significant trial on Agnus Castus.

It has been included as ‘limitations’ as,

We have tried to evaluate the effective acupuncture and herbal medical treatment methods for PMS/PMDD by reviewing RCTs. Although the risk of bias was conducted for all reviewed included trials, lack of quality of trials with reference to any particular method may limit the quality of the review.

The review lack the quality evaluation of trials included in the review on Vitex Agnus castus and it does not include one significant trial on Vitex Agnus castus.

Those researches conducted within the inclusion dates that are not included in this review have been excluded at the electronic database search stage. A study done by Kilicdag EB on Fructus agni casti and bromocriptine for treatment of hyperprolactinemia and mastalgia published in 2004 has also been excluded due to the above reason.

Editorial comments,

- Please remove your figure from your manuscript. Figures that are uploaded into our submission system are automatically incorporated into the end of your manuscript file when the PDF version generates.
I have removed the figure from the manuscript.

We have made as much corrections as possible as the reviewers and editor has suggested, however, there may have been some parts we have missed. Should there be further corrections needed, let us know! We will gladly make those changes for smooth process and as for this is our first time, we are very excited!

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