

Dear Reviewers and Editors,

Thank you very much for the time to review our manuscript:

Title: Effects of acupressure treatment on depression: a systematic review and meta-analysis

Journal: World Journal of Psychiatry

Review ID: 05429012

We have revised the manuscript according to your comments, and listed the responses point-to-point here for your kind consideration:

Response to Reviewer #1:

1. Depression is classified into moderate and severe depression. in addition to the status of having no depression according to depression scales. It is not clear if acupressure treatment was effective in severe or moderate depression scales.

Response: Thank you very much for the comment. There are 14 trials included in our systematic review and meta-analysis, ten of them focused on mild-to-moderate depressive symptoms comorbid with chronic diseases (secondary depression), and three trials were in participants with mild-to-moderate depression (primary depression). We have conducted meta-analysis for both primary depression and secondary depression, and found significant improvements of acupressure in both conditions. Our findings suggested that acupressure is significantly effective for mild-to-moderate secondary depression. However, the effectiveness on moderate or severe primary depression is not certain due to little evidence available. We added a paragraph in the Discussion (*please refer to the paragraph 2 in Discussion*), and listed it as one of the limitations (*Please refer to the paragraph 3 in Limitations*).

2. It is not reported which parts of depression domains were affected by acupressure treatment across various studies.

Response: We have checked all the articles included in our review, and found none of them mentioned the effects of acupressure on depression domains. We have mentioned in the Discussion that future research may focus on the effects of acupressure for specific symptom domains of depression (*please refer to the paragraph 2 in Discussion*).

3. Regarding mechanisms of acupressure treatment, it is not mentioned about any mechanisms. I think that there must be some measurements including serotonin, dopamine, or other neurochemicals involved.

Response: Thank you very much for the comment. It is important to mention the potential mechanisms of acupressure for depression. However, only one trial in our review mentioned the potential neural mechanisms of acupressure. We have searched

related literature on studies of acupuncture, which shares the same traditional Chinese medicine theory with acupressure but uses different manipulation techniques (acupuncture uses needle while acupressure uses finger). We found that in both animals and human studies antidepressant effects of acupuncture are likely the result of the interaction in between multiple targets and levels in neural system. Acupuncture not only improves monoamine neurotransmitters, inhibits the hyperactive HPA axis, but also activates neurotrophic pathways, improves hippocampal neurogenesis, and inhibits inflammatory cytokines. We have added this information in the Discussion (*please refer to the paragraph 8 in Discussion*).

4. It is difficult to reach conclusions regarding acupressure treatment in improving depression status. Accordingly, my decision is "major corrections" are required according to previous notes.

Response: Thank you very much for the opportunity to revise. Our findings suggested that acupressure treatment is significantly associated with improvements in mild-to-moderate depressive status. However, further evidence is needed to confirm if acupressure leads to improvement in moderate-to-severe depression. We have made major corrections in the manuscript to interpret our findings.

Response to Reviewer #2

1. Most acupuncture related studies are TAU or sham controlled, which is nice. However, the exact techniques of acupuncture were less undermined, for instance, some studies using acupressure only.

Response: Thank you very much for the comment. We agree that the exact techniques of acupressure treatment were less undermined in the articles included in our review. We have put it as one of the limitations of the present study (*Please refer to the paragraph 4 in Limitations*).

2. Patients with depression can be further classified into primary vs secondary, or into other different depression subtypes which can be grouped into major depression disorder or bipolar depression.

Response: Thank you very much for the comment. There are 14 trials included in our systematic review and meta-analysis, ten of them focused on mild-to-moderate depressive symptoms comorbid with chronic diseases (secondary depression), and three trials were in participants with mild-to-moderate depression (primary depression). We have conducted meta-analysis for both primary depression and secondary depression, and found significant improvements of acupressure in both conditions. Our findings suggested that acupressure is significantly effective for mild-to-moderate secondary depression. However, the effectiveness on moderate-to-severe primary depression is not certain due to little evidence available. We added a paragraph in the Discussion (*please refer to the paragraph 2 in Discussion*), and listed it as one of the limitations (*Please refer to the paragraph 3 in Limitations*).

3. The therapeutic composition of acupoints are also wide and inclusive, the author might notice the meaningful comparisons between these cited RCT studies.

Response: Thank you indeed for the comment. Yes, the therapeutic composition of acupoints are wide and inclusive. We listed the acupoints used in all articles (please refer to the Table 1) and found that the most commonly used acupoints for depressive symptoms were: Sanyinjiao, Shenmen, and Zusanli. We also did subgroup analysis for these three commonly used acupoints and found a large effect size for Sanyinjiao, a moderate effect size for Shenmen, and a small effect size for Zusanli (*please refer to “Effects of acupressure on depression using different acupoints in Result*). However, we noticed that the meaningful comparisons between these cited RCT studies may not be possible due to the heterogeneity of therapeutic composition of acupoints selected. We listed as one of the limitations of our study (*Please refer to the paragraph 4 in Limitations*).

4. How was the “qi” evaluated in different studies? This is also a confounding factor for further study inclusion.

Response: Thanks very much for the comment. We have checked in all studies included in our review and found none of them reported the evaluation of the “qi”. We have added a paragraph to mention the confounding factor “qi” in the Discussion (*please refer to the paragraph 2 in the page 17*).

5. There are still many other limitations of the study, where the authors might illustrate for the reader.

Response: We have added some limitations according to the above comments, e.g. the lack of evidence of acupressure for primary depression; no study measured “qi” which may be a confounding factor for the outcome; the exact manipulation techniques and acupoints selected are wide and inclusive. The future research with well-designed trials and measurements is required to provide more conclusive evidence in the use of acupressure in promoting depression (*please refer to the paragraph 5 in Discussion*).

Response to Reviewer #3:

This is a state-of-the-art systematic review and meta-analysis of the effects of acupressure in treatment of depression. The study follows PRISMA guidelines and synthesizes clear positive effects of acupressure. Authors are advised to offer comparison of acupressure effects with standard Western methods of cognitive-behavioral therapy and psychopharmacological interventions, especially in terms of efficacy and outcome. Further guidance and recommendations on the possible combinations of conventional approaches with complementary acupressure methods might be found useful.

Response: Thank you very much for the kind comments. We have revised the manuscript according to all reviewers' comments and are looking forward to your kind consideration for publication.

EDITORIAL OFFICE'S COMMENTS

(1) *Science editor:*

(1) We only accept the manuscript in MS Word format, and the manuscript in any other format will be rejected;

Response: The revised manuscript will be resubmitted in MS Word format.

(2) The authors did not provide original pictures. Please provide the original figure documents. Please prepare and arrange the figures using PowerPoint to ensure that all graphs or arrows or text portions can be reprocessed by the editor;

Response: The original pictures made by PowerPoint (for Figure 1) and Revman (for Figure 3-14) will be submitted together with the manuscript. For the Figure 2 (Funnel Plots), we entered data into an Excel file and created the figure using STATA. We submitted the original data in Excel for your review.

(3) PMID and DOI numbers are missing in the reference list. Please provide the PubMed numbers and DOI citation numbers to the reference list and list all authors of the references. Please revise throughout;

Response: All references have been revised by adding PMID and DOI numbers.

(4) The "Article Highlights" section is missing. Please add the "Article Highlights" section at the end of the main text;

Response: The 'Article Highlights' section has been added at the end of the main text.

(5) Please confirm if the figures are original. If an author of a submission is re-using a figure or figures published elsewhere, or that is copyrighted, the author must provide documentation that the previous publisher or copyright holder has given permission for the figure to be re-published; and correctly indicating the reference source and copyrights. And please cite the reference source in the references list. If the author fails to properly cite the published or copyrighted picture(s) or table(s) as described above, he/she will be subject to withdrawal of the article from BPG publications and may even be held liable.

Response: Yes, we confirm that all figures are original.

(2) *Company editor-in-chief:* I have reviewed the Peer-Review Report, full text of the manuscript, and the relevant ethics documents, all of which have met the basic

publishing requirements of the World Journal of Psychiatry, and the manuscript is conditionally accepted. I have sent the manuscript to the author(s) for its revision according to the Peer-Review Report, Editorial Office's comments and the Criteria for Manuscript Revision by Authors.

Response: Thanks very much for the conditionally acceptance. The manuscript has been revised according to all reviewers' comments and Science editor's comments and resubmitted for your kind consideration for publication.