Acupuncture for perimenopausal depression
A protocol for a systematic review and meta-analysis
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Abstract
Background: Depression is one of common disease in the female perimenopausal period. It deprives women of their right to work and live normally, and even destroys the happiness of their families. Acupuncture is a promising treatment for perimenopausal depression.

Methods: Cochrane Central Register of Controlled Trials (CENTRAL), PubMed, EMBASE, China National Knowledge Internet (CNKI), Chongqing VIP (CQVIP), Wanfang Data, and on-line trial registries such as ClinicalTrials.gov (ClinicalTrials.gov/), European Medicines Agency (EMA)(www.ema.europa.eu/ema/), WHO International Clinical Trials Registry Platform (www.who.int/ictrp) will be searched from establishment of the database until Oct. 2018. There are no restrictions on the language of publication. The randomized controlled trials of acupuncture (electroacupuncture and manual acupuncture) for perimenopausal depression will be included, and all articles will be screened and collected by 2 reviewers independently. Revman 5.3.5 software will be used for meta-analysis. The specific process will refer to the Cochrane Handbook for Systematic Review.

Results: The efficacy and safety of acupuncture for perimenopausal depression will be comprehensively assessed from the outcomes, including the effective rate, HAMD score, estrogen level and incidence of adverse events.

Conclusion: This systematic review will provide evidence for whether acupuncture can improve perimenopausal depression.

Ethics and dissemination: There is no requirement of ethical approval, and the review will be reported in a peer-reviewed journal.

Abbreviations: CI = confidence interval, HAMD = Hamilton depression scale, MD = mean difference, OR = risk ratio, SMD = standardized mean difference.

Keywords: acupuncture, perimenopausal depression, randomized controlled trial, systematic review

1. Introduction
Depression symptoms are main clinical manifestations of perimenopausal depression. The specific manifestations are that the patient’s happiness index declined, depression, despair, even suicidal tendency, and often accompanied by dysfunction symptoms of endocrine and autonomic nervous. However, there is no clear understanding of the etiology of perimenopausal depression,[8,9] which is generally believed to be related to marriage, family, economic status and education level. According to the high incidence of perimenopausal depression and the characteristics of hormone fluctuations during this period, more and more scholars believe that the cause for the high incidence of depression in perimenopausal period may be related to the large fluctuations of hormones. But how hormone fluctuations contribute to the heightened risk is not fully understood, researchers speculate that it may involve intrinsic functional connectivity.[9,10] Therefore, in addition to psychotherapy and antidepressants, hormone replacement therapy (HRT) and antidepressant combined with HRT are also used for the treatment of perimenopausal depression. However, it is controversial that HRT for perimenopausal depression.[11] HRT of any form is an ineffective antidepressant in women who are well into the postmenopausal period.[12,13] Moreover, the efficacy of antidepressant drugs also cannot meet the patient’s expectations, and side effects such as dry mouth, fatigue, drowsiness, weight gain, and sexual dysfunction, often lead to poor patient compliance.[14,15]

In China, acupuncture is one of the most common therapeutic methods for perimenopausal depression. As well as the medical
reports on acupuncture for perimenopausal depression have gradually increased in recent years. However, there is a lack of systematic review and meta-analysis. The research will objectively assess the evidence from clinical randomized controlled trials (RCTs) on acupuncture for perimenopausal depression.

2. Methods

2.1. Registration

This systematic review protocol has been registered on PROSPERO as CRD42018114506. In this paper, the protocol will be performed using the methods introduced in the Cochrane Handbook for Systematic Reviews of Intervention[16] and reported according to the PRISMA-P guidelines.[17] If we will reﬁne procedures described in this protocol, we will document the amendments in the PROSPERO database and disclose them in future publications related to this meta-analysis.

2.2. Eligibility criteria for considering studies

2.2.1. Types of studies. All randomized controlled trials (RCTs) on acupuncture for perimenopausal depression will be included, regardless of whether the blind method is used or not. Language and publication time are unlimited. Small sample size (n < 10) and repeatedly published articles should be excluded.

2.2.2. Types of participants. Perimenopausal women diagnosed with depression are included. The time range of perimenopausal period is based on the 2012 criteria of the North American Menopause Society.[18] And the diagnosis of depression should meet one of the criteria of ICD-10[19] DSM-5[20] and CCMD-3.[21] Patients with other serious diseases such as heart disease, stroke, and severe skin problems will be excluded. Baseline is uniform for all participants in each RCT.

2.2.3. Types of interventions. The experimental group should be treated with manual acupuncture or electroacupuncture, and acupuncture points are not restricted. But acupuncture combined with drug therapy will be excluded. The control group should adopt one of the following treatment methods: antidepressant, antidepressant plus HRT, placebo, sham acupuncture. It is acceptable that the treatment lasts at least 2 weeks. In addition to intervention measures, other treatment and nursing measures should be consistent between the 2 groups.

2.2.4. Types of outcome measures

2.2.4.1. Primary outcome. (1) Effective rate. The criteria for effective treatment are based on the HAMD score reduction rate of more than 25%,[22] (2) HAMD score. The lower the HAMD score was, the more significant the interventions had.

2.2.4.2. Secondary outcome. Estrogenic hormone level (FSH, E2, LH), HAMD score during follow-up period, incidence of adverse events.

2.3. Search methods for identifying the studies

2.3.1. Data sources and searches. Cochrane Central Register of Controlled Trials (CENTRAL), PubMed, EMBASE, China National Knowledge Internet (CNKI), Chongqing VIP (CQVIP), Wanfang Data, and on-line trial registries such as ClinicalTrials.gov (ClinicalTrials.gov/), European Medicines Agency (EMA) (www.ema.europa.eu/ema/), WHO International Clinical Trials Registry Platform (www.who.int/ictrp) will be searched from establishment of the database until Oct. 2018. There is no restriction on the language of publication.

The key search terms used are [(“perimenopause” OR “chronic” OR “menopause” OR “premenopause” OR “postmenopause”) AND (“depression” OR “depressive disorder” OR “melancholia”) AND (“acupuncture” OR “electroacupuncture” OR “needle” OR “acupoint” OR “acupuncture point”) AND (“randomized controlled trial” OR “randomized clinical trial”).

2.4. Study selection and data extraction

Two reviewers (Xiao Xiao and Jiayuan Zhang) independently screen and collect articles. Whether an article will be included or excluded according to the above criteria. The reasons for excluding any article should be noted. If there are different opinions between 2 reviewers, it shall be resolved by discussion or seeking help from a third reviewer (Yuxia Jin). If the consensus still cannot be reached, the dispute shall be settled by contacting the original author for original data. The specific process of study selection is shown in Fig. 1.

After the articles included are ultimately determined, a predefined data template will be prepared, which includes following information: characteristics of the study, participants, intervention, outcome measures, adverse events, and follow-up date. The template is presented to 2 reviewers (Xiao Xiao and Jiayuan Zhang), who will independently extract and code the data based on the template respectively. Finally, the data obtained by the 2 reviewers will be checked each other. If there is a dispute, discussion will be the best way to solve it. If the data are missing, it can be obtained by contacting the original author or transformation of existing data.

2.5. Assessment of risk of bias

Two researchers (Xiao Xiao and Yunxia Wang) assess the risk of bias independently, using a collaboration tool recommended by the Cochrane Handbook 5.1.[23] There are 6 points that should be evaluated: random allocation, allocation concealment, blinding, incomplete outcome data, selective outcome reporting and other biases. Disagreement will also be settled by discussion.

2.6. Data analysis

2.6.1. Date synthesis. RevMan 5.3.5 software provided by Cochrane collaboration (www.cochrane.org) will be used to conduct meta-analysis and synthesis. Risk ratio (OR) and 95% confidence interval (95% CI) will be used for dichotomous variable; mean difference (MD) and 95% conﬁdence interval (95% CI) will be used for continuous variable; standardized mean differenc (SMD) and 95% confidence interval (95% CI) will be used for continuous variable when the units are different. It is considered statistically signiﬁcant when P < .01.

2.6.2. Assessment of heterogeneity. In order to assess heterogeneity, we use the chi-square test and I² statistic. When I² > 50% or P < .10, it indicates that the heterogeneity exceeds the acceptable range. If the heterogeneity is small, in the acceptable range (P > .10, I² < 50%), the fixed effect model is used for data analysis; otherwise, the random effect model is used.

2.6.3. Subgroup analysis and sensitivity analysis. Subgroup analysis and sensitivity analysis will also be employed to explore the possible causes of heterogeneity. Subgroup analysis will be
based on possible factors that may lead to heterogeneity, such as intervention measures (electroacupuncture and manual acupuncture), control measures, length of treatment or quality of articles, etc. If quantitative synthesis is not appropriate, we will conduct a narrative synthesis.

2.7. Assessment of publication bias

If more than 10 articles are included, publication bias will be analyzed by visual inspection of funnel plots. A symmetrical distribution of funnel plot data indicates that there is no publication bias.

2.8. Confidence in cumulative evidence

GRADE system will be used for assessing the strength of the body of evidence. \cite{23} According to the grading system, the quality of evidence will be rated high, moderate, low and very low.

3. Discussion

Depression is one of common diseases in the perimenopausal female. For its treatment, psychological counseling and antidepressant drug are the main methods. Acupuncture is a common treatment for depression in China, and according to a survey conducted in the United States, depression ranks second among the top 10 indications of acupuncture. \cite{24} Therefore, acupuncture is a promising treatment for depression. Acupuncture has the advantages of simple, convenient, cheap and fewer side effects, so it is easily accepted by patients. But is acupuncture effective for hormone-fluctuating perimenopausal depression? This study will
conduct a meta-analysis of related RCTs, and provide the current evidence on the efficacy and safety of acupuncture for perimenopausal depression, so as to better guide clinical practice.

**Author contributions**

Xiao Xiao, Qi Zhang designed the systematic review. Qi Zhang is the guarantor of the article. The protocol was drafted by Xiao Xiao. Qi Zhang revised the manuscript. Xiao Xiao and Jiayuan Zhang will screen the titles, abstracts, keywords of all retrieved records and extract data independently. Xiao Xiao and Yunxia Zhang will assess the ROB independently. Yuxia Jin arbitrated in cases of disagreement and ensured the absence of errors. All review authors approved the publication of the protocol.

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**Methodology:** Xiao Xiao.

**Project administration:** Xiao Xiao, Qi Zhang.

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**Supervision:** Qi Zhang.

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**Writing – review & editing:** Xiao Xiao.

**References**

[1] Mousavi S, Charterji S, Verdes E, et al. Depression, chronic diseases, and decrements in health: results from the World Health Surveys. Lancet (London, England) 2007;370:851–8.

[2] Wememberger AH, Ghedemah M, Martinez AM, et al. Trends in depression prevalence in the USA from 2005 to 2015: widening disparities in vulnerable groups. Psychological medicine 2018;48:1308–15.

[3] Luck T, Then FS, Engel C, et al. The prevalence of current depressive symptoms in an urban adult population. Psychiatr Prax 2017;44:148–53.

[4] Sassarini DJ. Depression in midlife women. Maturitas 2016;94:149–54.

[5] Parker G, Brotchie H. Gender differences in depression. Int Rev Psychiatry (Acharingdon, England) 2010;22:429–36.

[6] de Kruijf M, Spijker AT, Molendijk ML. Depression during the perimenopause: a meta-analysis. J Affect Disord 2016;206:174–80.

[7] Li RX, Ma M, Xiao XR, et al. Perimenopausal syndrome and mood disorders in perimenopause: prevalence, severity, relationships, and risk factors. Medicine 2016;95:e4466.

[8] Menard C, Hodes GE, Russo SJ. Pathogenesis of depression: insights from human and rodent studies. Neuroscience 2016;321:138–62.

[9] Fisher PM, Larsen CB, Beliveau V, et al. Pharmacologically induced sex hormone fluctuation effects on resting-state functional connectivity in a risk model for depression: a randomized trial. Neuropsychopharmacology 2017;42:446–53.

[10] Gordon JL, Girder SS, Meltzer-Brody SE, et al. Ovarian hormone fluctuation, neurosteroids, and HPA axis dysregulation in perimenopausal depression: a novel heuristic model. Am J Psychiatry 2015;172:227–36.

[11] Craig MC. HRT should be considered as first line therapy for perimenopausal depression: AGAINST: More clinical trials are needed. BJOG 2016;123:1011.

[12] Studd J. HRT should be considered as first line therapy for perimenopausal depression: FOR: Estrogens are the first line treatment for perimenopausal women. BJOG 2016;123:1011.

[13] Gordon JL, Girder SS. Hormone replacement therapy in the treatment of perimenopausal depression. Curr Psychiatry Rep 2014;16:317.

[14] Ashton AK, Jamerson BD, W LW, et al. Antidepressant-related adverse effects impacting treatment compliance: Results of a patient survey. Curr Ther Res Clin Exp 2005;66:94–106.

[15] de las Cuevas C, Penate W, Sanz EJ. Risk factors for non-adherence to antidepressant treatment in patients with mood disorders. Eur J Clin Pharmacol 2014;70:89–98.

[16] Higgins JPT, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. Available from http://handbook.cochrane.org. Accessed September 5, 2018.

[17] Shameer M, Mohr D, Clarke M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. BMJ (Clinical research ed) 2015;350:g7647.

[18] Harlow SD, Gass M, Hall JE, et al. Executive summary of the stages of reproductive aging workshop + 10: addressing the unfinished agenda of staging reproductive aging. J Clin Endocrinol Metab 2012;97:1159–68.

[19] Saxena S, Saraceno B. The ICD-10 classiﬁcation of mental and behavioural disorders. WHO; 1993.

[20] Association AP. Diagnostic and statistical manual of mental disorders (DSM-5®). American Psychiatric Pub; 2013.

[21] Psychosis Branch of Chinese Medical Association. The Chinese Classiﬁcation and the Diagnose Criterion of Mental Disorder (CCMD-3)(in Chinese). Jinan: Shandong science & technology press; 2001.

[22] Stefan L, Henn F, Rolf E, et al. What does the HAMD mean? J Affect Disord 2005;86:96–106.

[23] Guyatt GH, Oxman AD, Vist GE, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. BMJ (Clinical research ed) 2008;336:349–51.

[24] Wang H, Yang G, Wang S, et al. The most commonly treated acupuncture indications in the united states: a cross-sectional study. American J Chin Med 2018;46:1–33.