Traditional Chinese Herbal Medicine for Perimenopausal Depression of Chinese Women: A Meta-analysis

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Objective: The objective of this study is to evaluate the effectiveness and safety of traditional Chinese herbal medicine (TCHM) in treatment of perimenopausal depression (PD) in China. Methods: To identify randomized controlled trials, an electronic search has been conducted through databases as follows: PubMed, the Cochrane Central Register of Controlled Trials, Web of Science, Chinese Biological Medicine Database, China National Knowledge Infrastructure Database, Chinese Scientific Journal Database, and WanFang Digital Periodicals Database. Methodological quality was evaluated by Cochrane Collaboration’s tool which is able to assess the risk of bias in Review Manager Software. What’s more, meta-analysis was performed by using Cochrane Collaboration’s RevMan 5.2 software, (Nordic Cochrane Centre, Cochrane Collaboration, Copenhagen, and Denmark). Dichotomous data were analyzed by using relative risk (RR) and 95% confidence interval (CI). Continuous variables were analyzed using weighted mean differences (WMDs) and 95% CI. Subgroup analysis was performed by the type of medicine which was used in the experimental group. Results: This meta-analysis includes 11 randomized control trials with 818 patients. Compared to the control group (RR: 1.14, 95% CI: [1.03, 1.26], P = 0.009 and WMD: −2.09, 95% CI: [−3.58, −0.18]), the experimental group had a significant higher clinical efficacy rate and relatively lower Hamilton Depression Rating Scale (HAM-D) score. For clinical efficacy rate, the results varied depending on the detail treatment measures of the experimental group. In the experimental group with TCHM, no significant difference was observed (RR: 1.14, 95% CI: [0.97, 1.33]), while in the experimental group combined with western medicine, a significant difference in the clinical efficacy rate between the experimental group and control group showed up (RR: 1.15, 95% CI: [1.01, 1.32], P = 0.04). For the HAM-D score, subgroup analyses revealed that the pure TCHM therapy was not associated with significant HAM-D score reduction compared to the control group (WMD: −2.48, 95% CI: [−6.00, 1.03], P = 0.17). However, in the experimental group where western medicine was added to, the HAM-D score decreased statistically compared to the control group (WMD: −1.88, 95% CI: [−3.58, −0.18], P = 0.03). There is no serious adverse event in both groups. Conclusions: Combination therapy of TCHM and western medicine is more effective in treating PD in terms of clinical efficacy rate. However, the results should be interpreted with caution due to the mediocre methodological quality of the included trials.

Keywords: Meta-analysis, perimenopausal depression, randomized controlled trial, traditional Chinese herbal medicine

INTRODUCTION

The perimenopausal year refers to the period when women’s menstrual cycle becomes irregular, generally between the age of 45 and 49. Perimenopause has been recognized as a time when women are at risk of new onset and recurrence of major depression recently. As one symptom of reproductive hormone change, perimenopausal depression (PD) is one type of mood disorder. Moreover, untreated depression at this time may not only causes depressive illness[1] but also leads up to sleep disorders, cardiovascular disease, diabetes, and osteoporosis.[2]

Antidepressant medication, as the core of PD treatment, plays a vital role on selective serotonin reuptake inhibitors to improve mood situation. Besides, estrogen replacement as an adjunctive therapy has also been practiced in clinic.[3]

In recent years, a number of clinical trials have been conducted to test whether the traditional Chinese herbal medicine (TCHM)

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is efficient for the treatment of PD. However, these studies were published in Chinese and could not be accessed by non-Chinese speaking doctors. The purpose of this study is revealing the effectiveness of TCHM as treatment of PD.

**Methods**

**Search strategy**


**Study selection**

Inclusion criteria for included studies were as follows: (a) Type of study: The study claimed to be a randomized controlled trial (RCT) was included, regardless of whether it is blinded or not; (b) Type of participant: All patients, diagnosed as PD according to the accepted criteria, were included (accepted criteria: Women who have been diagnosed with menstrual disorder from 45 to 55 years old: A. Severe recurrent temper outbursts manifested verbally and/or behaviorally that are grossly out of proportion in intensity or duration to the situation or provocation. B. The temper outbursts are inconsistent with developmental level. C. The temper outbursts occur, on average, three times or more per week. D. The mood between temper outbursts is persistently irritable or angry in most of the day, nearly every day, and is observable by others. E. Criteria A-D have been present for 12 months or more. Throughout that time, the individual has not had a period for three consecutive months or more without all of the symptoms in Criteria A-D. F. Criteria A and D are present in at least two of three settings and are severe in at least one of those. G. The diagnosis should not be made for the first time before the age of 6 or after the age of 18. H. By history or observation, the onset of Criteria A-E is before the age of 10. I. There has never been a distinct period lasting more than 1 day during which the full symptom criteria, except for duration, for a manic or hypomanic episode have been met. J. The behaviors do not occur exclusively during an episode of major depressive disorder and are not better explained by another mental disorder. K. The symptoms are not attributable to the physiological effects of a substance or to another medical or neurological condition.); (c) Type of intervention: TCHM as an intervention or co-intervention with western medicines, in comparison with those receiving no treatment, placebo, or western medicines; and (d) Types of outcome measure: Effectiveness of TCHM for PD has been determined based on clinical efficacy rate and Hamilton Depression Rating Scale (HAM-D) score.

**Data extraction and methodological quality assessment**

Two authors (Ying Zhang and Lin-jie Xu) independently evaluated all trials and extracted relevant data from each study using a structured format. Disagreements were resolved by consensus, and if necessary, the third author was consulted. The following data were extracted: The number of patients in experimental group and control group, age, duration of the disease, intervention, treatment duration, etc. Risks of bias of studies were assessed according to the criteria from the Cochrane Handbook for Systematic Reviews of Interventions, version 5.1.0. (Nordic Cochrane Centre, Cochrane Collaboration, Copenhagen, and Denmark) using the Cochrane Collaboration’s tool for assessing risk of bias in Review Manager Software, version 5.2 (Nordic Cochrane Centre, Cochrane Collaboration, Copenhagen, and Denmark) by two authors independently. This judgment on the risk of bias was categorized by three levels: “high risk,” “unclear risk,” and “low risk.” Studies which met all criteria were judged as having a low risk of bias, studies which met none of the criteria were judged as having a high risk of bias, and studies with insufficient information to judge were marked as unclear risk of bias.

**Statistical methods**

Dichotomous data were analyzed using risk ratio (RR) with 95% confidence intervals, whereas continuous variables (change from baseline to the end of the treatment) were analyzed using weighted mean differences (WMD). Pooled analyses were calculated using fixed-effect models, whereas random-effect models were applied in case of significant heterogeneity across studies. Statistical heterogeneity was measured using the $I^2$ statistic. All $P$ values were two-tailed, and the statistical significance was set at 0.05. Statistical analyses were performed using the Cochrane Collaboration (Rev Man 5.2, Copenhagen, Denmark).

**Results**

Based on our inclusion criteria, 167 articles were retrieved according to the search strategy. Twenty-two trials were excluded after duplicates were removed. Through a preliminary review, 49 potential trials were identified, of which 38 were excluded for specific reasons, as listed in Figure 1. Only 11 RCTs[4–14] met our inclusion criteria.

**Characteristics of study**

A total of 818 patients were enrolled for the analysis (418 in the experimental group and 400 in the control group). All these studies were conducted in patients from People’s Republic of China. Among the 11 studies, 7 trials used TCHM alone for treatment. The rest of the trials used TCHM plus western medicine. The western medicine used in the experimental group was the same as in the control group. The duration of trials selected in this study varied from 4 weeks to 3 months [Table 1].
Quality assessment of the included studies

Cochrane risk of bias tool was used to assess the risk of bias. All 11 RCTs mentioned the word “randomization,” but only one of them described it in details. None mentioned allocation concealment or intention-to-treat analysis. None of the studies reported incomplete results. Overall, the quality of the included studies was relatively not high [Figures 2 and 3].

Clinical efficacy rate

The clinical efficacy rate refers to the ratio of effective patients to the total patients in each group. It was reported in 10 trials. After pooling these trials, we observed that there was a significant difference in clinical efficacy rate between the experimental group and the control group (RR: 1.14, 95% confidence interval [CI]: [1.03, 1.26], P = 0.009) [Figure 4]. The rate was higher in the experimental group than that in the control group.

Estrogen levels and factors in Hamilton Depression Rating Scale

Data concerning estrogen levels and factors in HAM-D were extracted from two trials. A summary of these data was shown in Table 2. Overall, we observed that there was no significant difference in the estrogen levels (E2, follicle-stimulating hormone, and luteinizing hormone) between the experimental group and the control group. On the contrary, the experimental group produced a significant reduction in the anxiety, weight, cognitive disorder, sleeping disorder, and despair score in HAM-D.

Subgroup analyses

Subgroup analyses were carried out for clinical efficacy rate and HAM-D score according to whether western medicine was added in the experimental group. On the whole, no significant difference was observed in the experimental group if no western medicine was added (RR: 1.14, 95% CI: [0.97, 1.33]) [Figure 6]. When western medicine was added in the experimental group, there was significant difference in the clinical efficacy rate between the experimental group and control group (RR: 1.15, 95% CI: [1.01, 1.32], P = 0.04).
[Figure 7]. For the HAM-D score, subgroup analyses revealed that the pure TCHM therapy was not associated with significant HAM-D score reduction compared to the control group (WMD: −2.48, 95% CI: [−6.00, 1.03], P = 0.17) [Figure 8].

However, if western medicine was added in the experimental group, the HAM-D score was decreased statistically compared to the control group (WMD: −1.88, 95% CI: [−3.58, −0.18], P = 0.03) [Figure 9].
Adverse effects

There was no meta-analysis of adverse effects due to lack of adverse events reports in some of these clinical trials. Seven studies (Liu, 2007; Ni et al., 2014; Feng et al., 2014; Li et al., 2013; Shao et al., 2011; Chen et al., 2011; and Zhang et al., 2009) reported that there were mild and tolerable adverse events during the treatment. One study (Li et al., 2013) claimed that there was no difference in the number of adverse events reported between the experimental group and control group, while other six studies mentioned that there were more adverse events in the control group than those in the experimental group. The main symptoms reported were nausea, dry mouth (Liu, 2007; Shao et al., 2011; and Chen et al., 2011), headache, insomnia (Ni et al., 2014 and Zhang et al., 2009).
of depression in Parkinson’s disease. A meta-analysis also suggests that Er-xian decoction (a classic Chinese formula) has significant advantages in relieving menopausal symptoms. There are several possible explanations for the effectiveness of THCM on such diseases. First, these diseases are mood disorders, and in the theory of THCM, seven emotions (qi qing) could cause illness. For instance, rage may impair liver. According to these theories, THCM has its own methods to deal with such diseases. Second, THCM is based on the holism philosophy that attempts to bring the body, mind, and spirit into a harmony system. Thus, THCM shows especial advantages in early intervention, combination therapies, and personalized medicine.

In this review, it is safe to say that THCM demonstrates a potential beneficial effect for PD, especially when it cooperates with western medicines. This beneficial effect is not closely related to the regulation of estrogen levels. However, the systematic review could not provide sufficiently sound data.

### DISCUSSION

A meta-analysis of RCTs has been conducted to evaluate the effect of TCHM comparing with western medicine. The main result of this meta-analysis is that the positive effects of TCHM have been demonstrated as clinical efficacy rate increased and HAM-D score decreased, especially when the combination therapy of TCHM and western medicine was used. To the best of our knowledge, the current meta-analysis was the first to evaluate the effect of THCM for PD.

In the recent years, quite a few evidence-based reviews of herbs or traditional Chinese formulas on depression and menopausal symptoms have been published. A systematic review indicates that THCM is beneficial for the treatment of dizziness, and constipation (Feng et al., 2014), but all of them were tolerable and no patients withdrew because of the adverse events.

The systematic review could not provide sufficiently sound data.
due to several limitations of the included studies. First, the methodological quality of the studies in this analysis was not very high. Thus, the potential risk of bias in these trials cannot be eliminated. Moreover, it is worth noticing that only 818 patients were involved in the 11 RCTs, which justifies the performance of more large-scale RCTs for evaluating the effect of TCHM on PD patients.

**Conclusions**

In conclusion, this meta-analysis initially demonstrated the therapeutic effects of TCHM on PD. This preliminary evidence supports the continuing usage of TCHM as a potentially optimistic and reliable intervention for PD. In the future, the mechanisms of TCHM need to be explored.

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**Conflicts of interest**

There are no conflicts of interest.

**References**