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Clinical evidence of Chinese medicine therapies for depression in women during perimenopause and menopause

Yuan Ming Di[a,1], Lingling Yang[b,1], Johannah L. Shergis[a], Anthony L. Zhang[a], Yan Li[b], Xinfeng Guo[b], Charlie C. Xue[a,b], Chuanjian Lu[b,*]

[a] The China-AustraliaInternational Research Centre for Chinese Medicine, School of Health and Biomedical Sciences, RMIT University, Bundoora, VIC, Australia
[b] Guangdong Provincial Hospital of Chinese Medicine, Guangdong Provincial Academy of Chinese Medical Sciences, and The Second Clinical College, Guangzhou University of Chinese Medicine, Yuexiu District, Guangzhou, PR China

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ABSTRACT

Background: Depression is common in women during perimenopause and menopause. Complementary therapies such as acupuncture and Chinese herbal medicine (CHM) are often utilized by these women. However, the efficacy and safety of these treatments have not been systematically evaluated.

Methods: We conducted a systematic review and meta-analysis of randomized controlled trials (RCTs). Nine English and Chinese databases were searched and search terms included perimenopause, menopause, depression, Chinese herbal medicine, acupuncture, RCTs, and their synonyms. Methodological quality was assessed using the Cochrane Risk of Bias Tool.

Results: A total of 18 RCTs were identified (6 CHM, 11 acupuncture related therapies, 1 combination of CHM and acupuncture). For Hamilton Rating Scale of Depression (HRSD) and Kuppermans Index of Menopause, tuina-massage, combined therapy of CHM plus acupuncture showed significant benefits at end of treatment compared to antidepressants. Either CHM and acupuncture reduced HRSD scores, indicating less severe depression, showing comparable effects to antidepressants.

Conclusion: CHM and acupuncture treatment in perimenopause and menopausal women resulted in reduced severity of depression. Results should be interpreted with caution given the small number of studies included in this review and further RCTs are warranted to validate findings from this review.

1. Introduction

Perimenopause, the period before and after menopause, begins with endocrine, biological and clinical changes and ends 12 months after the final menstrual period.[1–3] During these times of change, women often show clinical signs of physical, hormonal and psychological changes. Menopause symptoms include night sweating, hot flushes, vaginal dryness, breast tenderness, insomnia, migraines, and premenstrual dysphoria.[3] Psychological symptoms include mood swings and depression.

Depression is characterised by depressed mood, or a loss of interest, or loss of pleasure in daily activities for more than two weeks.[4] The onset of depression can occur at any stage of life. However, risk factors can be related to biological events such as menopause.[4,5] Around menopause women with no history of depression are two to four times more likely to report depressed mood compared to premenopausal women, [6,7] and the risk significantly increases in women with a history of depression.[7]

In terms of treatment, hormone replacement therapy (HRT) may be effective for mild to moderate depression during perimenopause,[8,9] but more severe depression requires antidepressant drugs.[10] Although the combination of antidepressants and HRT are commonly prescribed during perimenopause and menopause,[10–12] women often seek out complementary and alternative medicine, such as acupuncture and Chinese herbal medicine.

Complementary therapies are often sought to avoid side effects of HRT and antidepressants, as well as ongoing menopausal symptoms despite treatment. HRT increases the risk of venous thromboembolism[2] and causes long term adverse effects on the uterus, breast and cardiovascular system.[13] As for antidepressants, drugs such as selective serotonin reuptake inhibitors (SSRIs) have gastro-intestinal, stimulatory and sexual side effects. [14,15] The long-term use of antidepressants in

* Corresponding author at: Guangdong Provincial Hospital of Chinese Medicine, 111 Dade Road, Yuexiu District, Guangzhou 510120, China.
E-mail address: luchuanjian888@vip.sina.com (C. Lu).
[1] Co-first authors, the authors contributed equally to the manuscript.

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middle-aged women is limited by treatment emergent sexual dysfunction and weight gain. [16]

Chinese medicine has a long history of recognizing and treating depression. The word “depression” is found in medical books written before CE 618, such as The Yellow Emperor’s Classic of Medicine (*Huang Di Nei Jing* 黄帝内经). In this book it describes the negative effects emotions can have on one’s wellbeing. Depression in women was documented as early as CE 206 in the Medical Treasures of the Golden Chamber (*Jin Gui Yao Lue* 金匮要略), it is said that ‘woman with *zang zao* (a syndrome presented with sadness, tendency to cry, unstable mood and restlessness) feel sad, have a tendency to cry with no apparent cause, frequently yawn and should be treated with *Gan mai da zao tang* (a herbal formula).

To our knowledge, there are no systematic reviews on the effect of Chinse medicine for depression during menopause. This review systematically evaluates the safety and efficacy of Chinese herbal medicine and acupuncture therapies for depression and menopause related symptoms.

2. Methods

We implemented the methods outlined in the Cochrane Handbook for Systematic Reviews of Interventions 5.1. [17] Nine databases were searched from their inceptions to February 2018. English databases were searched by JS, these included Allied and Complementary Medicine Database (AMED), Cochrane Central Register of Controlled Trials (CENTRAL) on The Cochrane Library, Cumulative Index of Nursing and Allied Health Literature (CINAHL), Excerpta Medica Database (EMBASE), and PubMed. Chinese databases were searched by LLY, these included BioMedical Literature (CBM), China National Knowledge Infra-structure (CNKI), Chongqiong VIP (CQVIP) and Wanfang. Search terms were grouped into three blocks: 1) intervention (including acupuncture, Chinese herbal medicine, tuina, cupping); 2) clinical condition (including menopause, perimenopause, depression, depressive disorder, unipolar depression, major depression, major depressive disorder); and 3) trial design (including clinical trial, random, control). Complete lists of search terms are available from the authors. Reference lists of review articles were checked for additional references.

Randomized controlled trials of any duration published in English or Chinese were included. Trial participants were adult women during perimenopause or menopause, with a diagnosis of major depressive disorder based on clinical guidelines from the World Health Organisation, USA and China.[4,18,19] Participants diagnosed with other types of depression, such as bipolar depression, dysthymia, depression or depressive symptoms caused by other mental disorders, physical disorders, another medical condition or the effects of a substance were excluded.

Included interventions were Chinese herbal medicine (CHM), acupuncture and *tuina*-massage. Comparators were antidepressants; studies were excluded if they did not specify which antidepressants were used. Pre-specified outcomes measures included clinician rated and self-rating depression severity scales, Kupperman menopausal index (KI), number of participants who relapsed or achieved remission, quality of life, functional capacity (eg. social adjustment scales), suicide rate and adverse events.

Search results were synthesized by removing duplicates, followed by screening of titles and abstracts by LY, YMD and JLS. Full texts were obtained and screened by two reviewers (LY and YMD). Eligible studies satisfying the inclusion criteria were extracted using EpiData software (EpiData Association, Odense, Denmark). LY and YMD extracted and double-checked the data from included articles to obtain information on authors, publication year, title, journal, location, study design, diagnostic criteria, sample size, dropouts, age, gender, intervention, control, treatment duration, outcome measures, and adverse events. Discrepancies were discussed with a third reviewer (JLS). Risk of bias was assessed independently by two reviewers (LY and YMD) using the risk of bias assessment tool from the Cochrane Handbook.[17] Disagreements were resolved by a third reviewer (JLS). Publication bias was assessed using Funnel plots and Egger's test in Stata 14 software. When necessary, included study authors were contacted by email or telephone to obtain additional data, if no response is received after four week, the unknown information was marked as not available.

Studies were grouped for pooling based on comparable interventions and controls. Meta-analysis was conducted in Stata 14 software using published data from the included studies.

Between group differences and within group changes were assessed using random effect model. Continuous outcome data was analysed with mean difference (MD) and 95% confidence intervals (CI). When different versions of Hamilton Rating Scale for Depression (HRSD) was reported, standardised mean difference (SMD) was used. For dichotomous outcome data, risk ratios (RR) and 95% CIs are reported. A formal test for heterogeneity using the I^2 statistic is included for each meta-analysis. An I^2 score greater than 50% was considered to indicate substantial heterogeneity. Pre-defined subgroup analyses included participant characteristics and study design, such as treatment duration, specific antidepressants, low risk of bias of sequence generation, and different versions of outcome measures. Frequently used herbs and acupuncture points are also reported to provide potential research direction for future studies.

3. Results

3.1. Characteristics of included studies

Database searches identified 30,733 citations. Based on our selection criteria, 18 studies were included.[20–37] Six studies evaluated CHM, 11 evaluated acupuncture therapies, and one evaluated a combination of CHM and acupuncture (Fig. 1). All clinical trials were conducted in China and published from 2007 to 2017. Studies enrolled a total of 1,195 female participants and the sample sizes ranged from 30 to 240. Participants' age ranged from 40 to 60 years old, all diagnosed with perimenopause or menopause. Treatment duration ranged from four to 12 weeks. Antidepressant controls such as SSRIs were fixed-dose recommended in clinical guidelines.[38–40]

All studies evaluated depression severity during perimenopause or menopause assessed by the HRSD, a clinician rated scale used to measure depression severity in adults.[41] Severity of menopause symptoms was assessed by the KI[42] in six studies.[20,22,23,25,34,35] One study[29] reported results from the Menopause-Specific Quality of Life (MENQOL) questionnaire.[43] Other pre-specified outcomes were not assessed in the included studies. Adverse events were reported in 11 studies.

Five studies evaluated CHM alone compared to SSRIs and one study assessed CHM combined with SSRI compared to SSRIs. Comparator SSRIs were fluoxetine[21–23,25] and paroxetine.[20] One study compared CHM plus fluoxetine to fluoxetine alone.[24] All CHM treatments were orally administered decoctions and six distinct formulae were used. Herbal ingredients in the formulae overlapped in the included studies and common herbs in three or more studies were *Epimedium brevicornum* Maxim. (Chinese name: Xian ling pi), *Bupleurum chinense* DC. (Chai hu), *Curculigo orchioides* Gaertn. (Xian mao), *Cornus officinalis* Sieb. Et Zucc. (Shan yu rou), *Ligusticum chuangxiong* Hort. (Chuan xiong), *Angelica sinensis* (Oliv.) Diels (Dang gui) and *Anemarrhena asphodeloides* Bge. (Zhi mu).

A total of 11 studies investigated the effect of acupuncture and *tuina*-massage (massage on acupuncture points or meridians). Eight studies compared acupuncture with SSRIs.[26–32,36] Two RCTs compared acupuncture to HRT plus fluoxetine,[33,35] and one study compared *tuina*-massage to HRT plus fluoxetine.[34] The studies used 29 acupuncture points and frequently used points in four or more studies included BL18 *Gan shu*, BL23 *Shen shu*, DU20 *Bai hui*, BL15 *Xin shu*, *Si shen cong*, LR3 *Tai chong*, and BL20 *Pi shu* (Table 1).

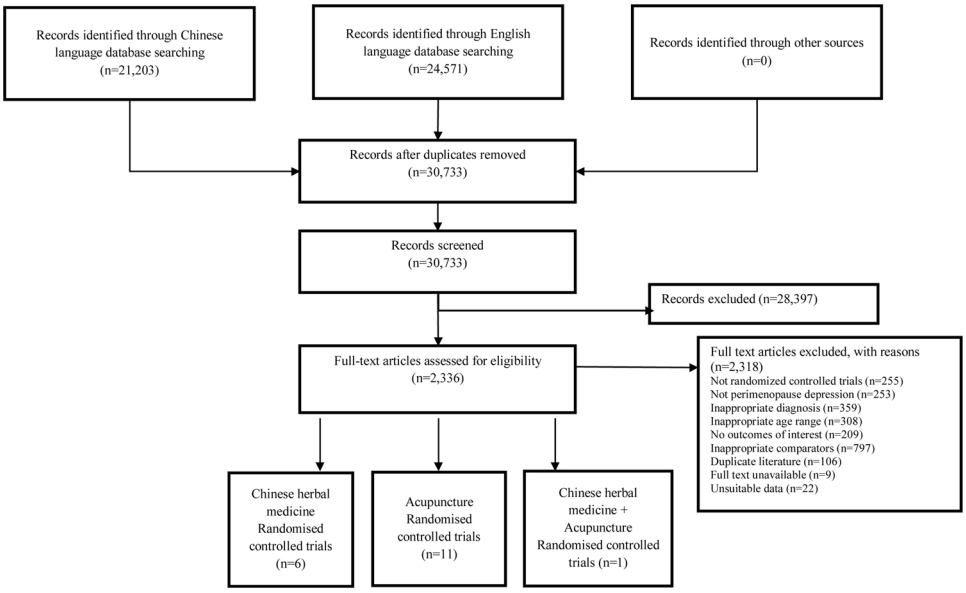

Fig. 1. Flow chart of study selection process.

3.2. Risk of bias

All 18 studies were described as randomized. However, only seven (38.9%) provided information on an appropriate method of sequence generation. One study (5.6%) described the method of allocation concealment, while 17 (94.4%) did not provide details and were judged to be at unclear risk of bias. Blinding of participants, personnel and assessors were judged at low risk of bias in one study and the remaining 17 studies were judged at high risk of bias, as the interventions were clearly different and no mention of blinding was mentioned. Outcome data were available for the included studies therefore they were assessed at low risk of bias for this domain. Selective outcome reporting was judged at unclear risk for all included studies because study protocols were not available. Risk of bias assessment is presented in Table 1.

3.3. Effects of intervention

3.3.1. Chinese herbal medicine

Five studies (380 participants) assessed the effects of CHM for depression compared to SSRIs.[20–23,25] At the end of treatment (EoT), there was no significant difference between the CHM group and SSRIs in terms of HRSD scores (SMD -0.28 [-0.90, 0.34]; I^2 = 87.1%). Change scores within groups showed that both CHM and antidepressants improved HRSD scores when baseline data was compared to EoT (Table 2, Fig. 2).

KI was assessed by four studies (n = 320) and there was a significant difference between the CHM group and the antidepressant group at EoT (MD -5.02 [-8.33, -1.72]; I^2 = 82.3%).[20,22,23,25] Change scores within groups were also significant in both groups.

One study including 72 participants assessed the effects of CHM plus fluoxetine compared to fluoxetine alone.[24] HRSD scores were not significantly different between the groups (MD -0.46 [-0.93, 0.01]).

Of the three studies that reported on adverse events, there were no events in the CHM groups.[21,23,24] Adverse events in the antidepressant groups included nausea, vomiting, indigestion, diarrhoea, headache, dizziness, disturbed sleep, fatigue, sexual dysfunction, difficulty breathing, dry mouth, breast tenderness and breakthrough bleeding.[21,24]

3.3.2. Acupuncture

Eight studies (743 participants) assessed the effects of acupuncture compared to antidepressants.[26–32,36] When HRSD scores were assessed, there were no significant difference between the two groups (SMD -0.14 [-0.53, 0.25]; I^2 = 84.5%) (Fig. 3). Subgroup analysis of studies at low risk of bias for sequence generation, treatment duration (less than or equal to six weeks) or specific antidepressant (fluoxetine) did not show a significant difference of HRSD scores. Two studies (156 participants) with a treatment duration of 12 weeks showed significant difference in HRSD scores between the two groups (SMD -1.17 [-1.93, -0.40]; I^2 = 78.7%).[28,29] Overall, within group analysis showed significant improvements in the acupuncture and antidepressant groups (Table 2). One study of 90 participants had a follow-up of 12 weeks, no significant difference was found between groups (MD 0.33 [-0.11, 0.77]).[29] When compared with baseline, within group analysis showed significant improvement in both the acupuncture (MD -1.02 [-1.40, -0.64]) and antidepressant groups (MD -1.88 [-2.49, -1.27]).[29]

Two studies (n = 142) assessed menopause symptoms by KI.[27,28] At EoT, acupuncture significantly improved KI scores compared to fluoxetine (MD -5.45 [-10.38, -0.52], I^2 = 89.7%). Significant change in scores was also observed within groups.

One study of 90 participants assessed quality of life using the MENQOL.[29] No significant difference was found between acupuncture and escitalopram groups (MD -0.04 [-0.43, 0.35]). When compared to baseline, both group showed significant improvements in MENQOL scores at EoT. At 12 weeks follow-up, no significant difference was found between groups (MD -0.34 [-0.76, 0.08]). When compared with baseline, significant improvement was shown in both the acupuncture group (MD -0.89 [-1.25, -0.54]) and antidepressant group (MD -0.6 [-1.02, -0.18]).

Relapse rate was assessed in one study,[28] after 12 weeks of treatment and 12 weeks of follow-up, results showed that acupuncture significantly reduced relapse rate compared to fluoxetine (RR 0.21 [0.05, 0.90]).

Five studies reported on adverse events.[26,28–31] No adverse events were reported in the acupuncture group in two studies.[26,28] A total of 11 adverse events in the acupuncture group were reported in three studies,[29–31] including local bruising (2 cases), dizziness (3 cases), palpitations (2 cases), dry mouth (1 case) and nausea (3 cases). All studies reported AEs in the antidepressant group, there was a total of 108 AEs, including dizziness (11 cases), nausea (5 cases), vomiting (1 case), dry mouth (17 cases), indigestion(1 case), diarrhoea (1case), fatigue (17 cases), headache (3 cases), trouble sleeping (7 cases), palpitations (7 cases), sweating (10 case), skin problems (1), over excited

Table 1
Characteristics of included studies.

Study No.	Author, Year	No. of Participants (I: C)	Diagnostic criteria	Intervention (dosage, frequency of intake)	Control (dosage, frequency of intake)	Outcomes	Treatment duration	Risk of Bias (SG, AC, BPt, BPn, BOA, IOD, SR, Other)*
Chinese herbal medicine studies								
1	Gao N 2010	62 (31:31)	ICSD-2	Le xin tang 100ml, p.o, b.i.d	Paroxetine	HRSD, KI	12w	U, U, H, H, H, L, U, L
2	Li GY 2014	60 (30:30)	ICSD-2	Jia wei er xian tang 150ml, p.o, b.i.d	Fluoxetine	HRSD, AEs	6w	U, U, H, H, H, L, U, L
3	Xu FQ 2013	164 (82:82)	ICSD-2	Bu shen shu gan hua yu tang 150ml, p.o, b.i.d	Fluoxetine 20mg, p.o, q.d.	HRSD, KI	8w	U, U, H, H, H, L, U, L
4	Zang HL 2008	30 (18:12)	ICSD-2	Shu yu fang 100ml, p.o, b.i.d	Fluoxetine 20mg, p.o, q.d.	HRSD, KI, AEs	12w	L, U, H, H, H, L, U, L
5	Zhang Y 2013	64 (32:32)	ICSD-2	Bu shen shu gan hua ji fang 150ml, p.o, b.i.d	Paroxetine	HRSD, KI	8w	L, U, H, H, H, L, U, L
6	Zhang GQ 2009	72 (38:34)	ICSD-2	Zao ren bu xue tang plus fluoxetine 100ml, p.o, b.i.d	Fluoxetine 20mg, p.o, q.d.	HRSD, AEs	4w	U, U, H, H, H, L, U, L
Acupuncture studies								
7	Chi H 2011	60 (30:30)	ICSD-2	GV 20 Baihui 百会, EX-HN3 Yintang 印堂, EX-HN1 Sishencong 四神聪, LR14 Qimen 期门, ST-36 Zusanli 足三里, SP6 Sanyinjiao 三阴交, LR3 Taichong 太冲, KI3 Taixi 太溪 50 mins, once everyday	Fluoxetine 20mg, p.o, q.d.	HRSD, AEs	4 weeks	U, U, H, H, L, L, U, L
8	Ding L 2007	78 (39:39)	ICSD-2	BL23 Shenshu 肾俞, BL18 Ganshu 肝俞, BL21 Pishu 脾俞, BL15 Xinshu 心俞, GV20 Baihui 百会, HT7 Shenmen 神门, SP6 Sanyinjiao 三阴交, LR3 Taichong 太冲 30 mins, 6 times/week	Fluoxetine 20mg, p.o, q.d.	HRSD, KI	4 weeks	U, U, H, H, H, L, U, L
9	Li HB 2015	66 (34:32)	ICSD-2	BL23 Shenshu 肾俞, BL18 Ganshu 肝俞, BL21 Pishu 脾俞, GV20 Baihui 百会 (30 studies), EX-HN3 Yintang 印堂 (20 studies), EX-HN1 Sishencong 四神聪, GV24 Shenting 神庭, PC6 Neiguan 内关 30 mins, 6 times/week	Fluoxetine 20mg, p.o, q.d.	HRSD, KI, AEs	3 months	U, U, H, H, H, L, U, L
10	Li ZF 2015	90 (30:30)	ICD-11	CV4 Guanyuan 关元, EX-8 Zigong 子宫, ST25 Tianshu 天枢, SP6 Sanyinjiao 三阴交, LI4 Hegu 合谷, LR3 Taichong 太冲, GV20 Baihui 百会, EX-HN3 Yintang 印堂 30 mins, 3 times/week	Escitalopram 10mg, p.o, q.d	HRSD, MENQOL, AEs	12 weeks	L, L, L, L, L, L, L, U, L
11	Niu SX 2017	82 (41:41)	CCMD3	BL11 Feishu 肺俞, BL19 Geshu 膈俞, BL23 Shenshu 肾俞, BL18 Ganshu 肝俞, BL21 Pishu 脾俞, BL15 Xinshu 心俞 30 mins, 5 times/week	Fluoxetine 20mg, p.o, q.d.	HRSD, AEs	6 weeks	L, U, H, H, H, L, U, L

(*continued on next page*)

Table 1 (*continued*)

12	Qian J 2007	66 (33:33)	ICSD-2	BL11 Feishu 肺俞, BL19 Geshu 膈俞, BL23 Shenshu 肾俞，BL18 Ganshu 肝俞，BL21 Pishu 脾俞，BL15 Xinshu 心俞 30 mins, 5 times/week	Fluoxetine 20mg, p.o, q.d.	HRSD, AEs	6 weeks	L, U, H, H, H, L, U, L
13	Xing K 2011	240 (120:120)	ICD-11	GV26 Renzhong 人中，PC5 Jianshi 间使 20 min, once everyday	Fluoxetine 20mg, p.o, q.d.	HRSD	6 weeks	L, U, H, H, H, L, U, L
14	Zhou SH 2007	60 (30:30)	ICSD-2	BL23 Shenshu 肾俞，BL18 Ganshu 肝俞，BL15 Xinshu 心俞, ST36 Zusanli 足三里，SP6 Sanyinjiao 三阴交，GV24 Shenting 神庭，GB13 Benshen 本神，EX-HN1 Sishencong 神聪 30 mins, 6 times/week	Fluoxetine 20mg, p.o, q.d.	HRSD	6 weeks	L, U, H, H, H, L, U L
15	Zhang YQ 2013	188 (94:94）	ICSD-2	GV 20 Baihui 百会，GV24 Shenting 神庭，GB13 Benshen 本神，EX-HN1 Sishencong 神聪, HT7 Shenmen 神门 30 mins, once everyday	Fluoxetine, 20mg, p.o, q.d. HRT	HRSD, Aes	12 weeks	U, U, H, H, H, L, U, L
16	Zheng SH 2010 a	120 (60:60)	ICSD-2	Sishenzhen, SP6 Sanyinjiao 三阴交, BL23 Shenshu 肾俞，BL18 Ganshu 肝俞，LR3 Taichong 太冲, KI3 Taixi 太溪 30 mins, 3 times/week	Fluoxetine, 20mg, p.o, q.d. HRT	HRSD, KI, Aes	12 weeks	U, U, H, H, H, L, U, L
17	Zheng SH 2010 b	60 (30:30)	ICSD-2	Wei Jiao Tui Na therapy 20 mins, 3 times/week	Fluoxetine 20mg, p.o, q.d.	HRSD	2 months	U, U, H, H, H, L, U, L
Chinese herbal medicine plus acupuncture study								
18	Zhu HL 2013	60 (30:30)	ICSD-2	Zi shen shu gan tang 滋肾疏肝汤 (Sheng di huang 生地黄，Bai he 百合，Sha shen 沙参，Gou qi 枸杞，Shan yao 山药，Shan zhu yu 山萸肉，Han liang cao 旱莲草，Dang gui 当归，Chuan jian 川楝，Chai hu 柴胡，Xiang fu 香附，Bai shao 白芍, Yu jin 郁金、He huan hua 合欢花、Gan cao 甘草) 300ml, p.o, b.i.d BL23 Shenshu 肾俞，BL18 Ganshu 肝俞，BL15 Xinshu 心俞、GB13 Benshen 本神、神鹿、EX-HN1 Sishencong 四神聪、GV20 Baihui 百会、PC6 Neiguan 内关 30 mins, once everyday	Fluoxetine	HRSD	2 months	U, U, H, H, H, L, U, L

Abbreviations: AEs adverse events; AC Allocation Concealment; b.i.d two times a day; BPt Blinding of Participants; BPn Blinding of Practitioner; BOA Blinding of Assessors; ; Ccontrol groups; CCMD3 Chinese Classification of Mental Disorders 3rd edition; HRSD Hamilton Rating Scale for Depression; I intervention groups; IOD Incomplete Outcome Data; ICD-11 International Classification of Diseases 11th Revision; ICSD International Classification of Sleep Disorders 2nd edition; KI Kuppermans Index for menopause; L Low risk of bias; ; HHigh risk of bias; p.o Per os; SG Sequence Generation; SR Selective Reporting; U Unclear risk of bias;

(2 cases), constipation (8 cases), sleepiness (2 cases), restlessness (1 case) and other unspecified symptoms(14 cases).

Two studies (318 participants) compared acupuncture to an antidepressant plus HRT.[33],[35] At EoT no significant difference was found in HRSD scores between groups (MD -1.13 [-3.22, 0.95], I^2 = 80.2%). Change scores in both the groups were significant at EoT compared to baseline (Table 2). At six months follow up, acupuncture improved HRSD scores (MD -0.74[-1.11, -0.37]).[35] Zheng SH 2010 also assessed

Table 2
Summary of results on Hamilton Rating Scale for Depression (HRSD).

Comparison	No. of studies (no. of participants)	Baseline balance	Between group comparison EoT	Within group comparison EoT: Intervention; Control (MD or SMD [95% CI], I^2%)	Between groups comparison FU Intervention; Control (MD or SMD [95% CI], I^2%)
CHM Vs. anti	5 (380)	Yes	SMD -0.28 [-0.90, 0.34]; I^2 = 87.1%	SMD -2.48 [-3.42, -1.55]*; I^2 = 91.0%; SMD -2.09 [-2.66, -1.51]*; I^2 = 76.7%)	NA
Acup Vs. anti	8 (743)	Yes	SMD -0.42 [-0.88, 0.04]; I^2 = 88.7%	SMD -2.88[-3.43, -2.33]*; I^2 = 85.3%; SMD -2.20[-3.04, -1.36]*; I^2 = 94.4%	NA
Acup Vs. anti + HRT	2 (318)	Yes	MD -1.13 [-3.22, 0.95], I^2 = 80.2%	MD 13.90 [11.20, 16.60]*, I^2 = 85.4%; MD 12.84 [8.74, 16.84]*, I^2 = 93%	MD -0.74 [-1.11, -0.37]*^

Abbreviation: Acup, acupuncture; anti, antidepressant; CHM, Chinese herbal medicine; EoT, end of treatment; FU, follow-up; therapy; NA, not applicable.
* statistically significant, $p < 0.05$.

KI. [35] When acupuncture was compared to HRT and an antidepressant, there was no significant difference between groups. However, change in KI was shown in both groups after treatment. At 6 months follow-up, acupuncture significantly improved HRSD scores (MD -0.74 [-1.11, -0.37]) and KI scores (MD -3.7 [-4.98, -2.42]) compared to control. [35] Adverse events were reported in both studies. In the acupuncture group four cases of needle pain was reported. In the control group a total of 24 adverse events were reported, including: dizziness (9 cases), nausea and vomiting (4 cases), sleepiness (3 cases), loss of appetite (5 cases), diarrhoea (3 cases), breast tenderness (3 cases), increased leucorrhoea (2 cases) and tremor (1 case).

One study (75 participants) assessed the effect of *tuina*-massage compared to antidepressants plus HRT.[34]At EoT *tuina*-massage significantly improved HRSD scores compared to control (MD -3.4 [-5.53, -1.27]). Significant improvements were also observed within groups when EoT scores are compared to baseline scores. This study also assessed KI. *Tuina*-massage significantly improved KI scores compared to antidepressant plus HRT (MD -6.09 [-8.33, -3.85]). Significant improvements were also observed within groups when EoT scores are compared to baseline scores. At 6 months follow up, tuina-massage significantly improved HRSD (MD -1.43 [-1.94, -0.92]) and KI scores (MD -8.53 [-10.12, -6.94]) compared to control. This study did not report on adverse events.

3.3.3. Chinese herbal medicine plus acupuncture

One study assessed the effects of Chinese herbal medicine combined with acupuncture compared to fluoxetine.[37] A significant difference was found between groups (MD 12.67, [7.57, 17.78]). However, baseline imbalance was detected. Changes scores were significant for the control group but not the intervention group. There were no adverse events reported in the intervention group. Five adverse events were reported in the fluoxetine group including nausea, headache, dizziness and feeling feverish.

4. Discussion

Through systematic and comprehensive literature search, we found 18 RCTs that assessed the effects of CHM, acupuncture, or both administered simultaneously for depression in women during perimenopause or menopause. Overall, the results suggest that CHM and acupuncture is showed improvements post treatment in reducing depression severity during menopause and perimenopause. Our results show that CHM is well tolerated, with no reports of adverse events. Further, the incidence of adverse events of acupuncture is much lower than antidepressants, which is consistent with previous reviews.[44]

There are currently no systematic reviews that assess the effect of Chinese medicine for depression during perimenopause or menopause. No previous reviews assessed the effect of CHM treatments for depression during perimenopause or menopause, the focus was on menopausal symptoms but not depression related to menopause.[45,46] There are a few acupuncture reviews on acupuncture for depression in perimenopause and menopause women.[44,47] Li 2014 evaluated the effectiveness and safety of acupuncture and moxibustion for perimenopausal depression based on 15 studies that involved 1,507 participants.[47] Huang 2011 assessed the effect and safety of acupuncture in the treatment for peri menopausal depression, a total of 13 trials involving 1057 patients were included.[44] Previous meta-analysis results showed that acupuncture plus medication (HRT, tibilone, antidepressants) or acupuncture alone is better than medication alone at both effective rate and curative rate.[44,47] Both reviews reported on curative rate, however Li 2014 did not provide details on how it was calculated.[47] We did not include this outcome in our review, as curative rate based on HRSD scores is not a valid and tested outcome. Not all studies included in previous systematic reviews are included in our review, many clinical studies using CHM or acupuncture did not clearly state which guideline the authors referred to for depression diagnosis. In our review, included studies must reference to an internationally recognised guideline to confirm the diagnosis of depression: Diagnostic and Statistical Manual of Mental Disorders,[4] Chinese Classification of Mental Disorders,[19] or the International Classification of Disease.[48]

Consistent with previous review by Huang 2011, our results showed that acupuncture compared to antidepressants reduced depression severity. Further analysis found that when HRSD scores within the acupuncture group was assessed, significant improvement was found between baseline and EoT. This shows that acupuncture is not an inferior treatment to antidepressants, instead it has comparable benefits. Similar findings were found in the CHM studies, when CHM is compared to SSRIs, although no between group differences were demonstrated, while within group analysis between baseline and EoT showed significant improvements in HRSD scores in the CHM group. These findings demonstrate that CHM or acupuncture therapies can reduce HRSD scores indicating a reduction in depression severity and symptoms of depression in patients during the perimenopause and menopause period. Significant results were also found for *tuina*-massage and when CHM was combined with acupuncture. However, the evidence is from two small studies and firm conclusion cannot be drawn.

Considering antidepressants to be an effective treatment for depression during perimenopause or menopause,[8–10,49,50] CHM and acupuncture therapies having an equivalent effect is an indicator that Chinese medicine therapies have the potential to be an alternative or adjunct therapy for depression during perimenopause or menopause.

Four CHM studies assessed KI and found positive effects at EoT, indicating that CHM is a possible therapy for general menopause symptoms. *Tuina*-massage was also found to be beneficial for KI. Although when acupuncture was compared to antidepressant and HRT, there was no significant difference between treatment groups, there were significant improvements within the acupuncture group, indicating that acupuncture can improve menopause symptoms and is not

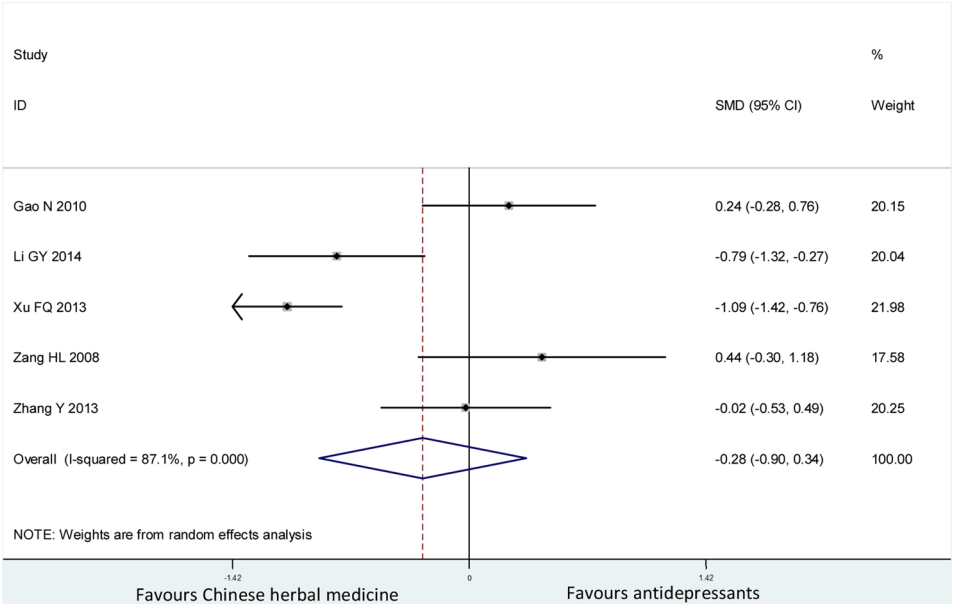

Fig. 2. Chinese herbal medicine versus antidepressants assessing the Hamilton Rating Scale for Depression for depression during perimenopause and menopause.

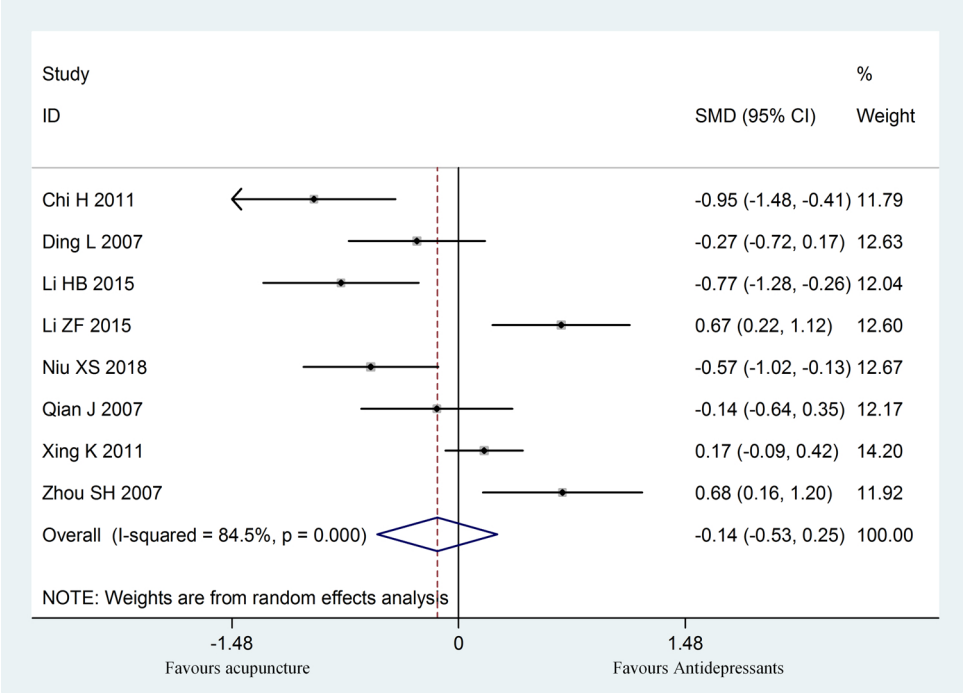

Fig. 3. Acupuncture versus antidepressants assessing the Hamilton Rating Scale for Depression for depression during perimenopause and menopause.

inferior to antidepressant and HRT combined.

Limitations of this review

This review identified 18 studies with generally small sample sizes. The included studies have methodological limitations and thus provided low quality and inconclusive evidence, a consistent finding with previous reviews on depression during perimenopause.[44,47] Heterogeneity was high, possibly arising from different herbs or acupuncture points used, dosage of herbs, different needle retention time and frequency, different treatment duration or depression severity.

Implications for future trials

We recommend future trials to follow rigorous methodology to improve overall quality including clearly describing methods of randomization, allocation concealment, methods of blinding and register the trial protocols in an internationally recognised registry.

One interesting observation was when acupuncture was compared to antidepressant plus HRT, the effect on HRSD and KI was not significant after three months of treatment but had significant long-term effects at six months follow-up. In our review, only four studies had a follow-up period, this can be incorporated into future trials to assess the long-term effect of CHM and acupuncture for depression during perimenopause and menopause periods. Therefore, it is worth assessing the long-term effects of acupuncture in the future. Further, depression is a lifelong disease and relapse often occurs, due to the nature of disease, therefore the long-term effect of Chinese medicine therapies on relapse rate should also be evaluated.

Only one included study evaluated the quality of life in this group of

participants, this outcome should be incorporated into future trials as this may produce a significant benefit in addition to the improved physical and mental effects.

Implication for practice

We observed that formula and herbs identified our review focused more on treating menopause. Previous systematic reviews on Chinese herbal medicine for depression identified the most common formulae used in the included studies being Xiao yao san, Chai hu Shu gan san and Gan mai da zao tang, and frequently used herbs were chai hu, bai shao and fu ling.[51,52] In our review, 6 herbal formula was identified, and they did not overlap with the above-mentioned formulae. Chai hu was identified as a commonly used herb across all studies in this review.

Frequently used points across included studies include BL18 *Gan shu*, BL23 *Shen shu*, DU20 *Bai hui*, BL15 *Xin shu*, *Si shen cong*, LR3 *Tai chong*, and BL20 *Pi shu*. These acupoints align with recommendations from The Standards for the Diagnosis, Syndrome Differentiation and Evaluation of the Clinical Effect for Depression Guideline[53] and can be incorporated into treatments of depression during menopause. Previous systematic reviews on acupuncture for depression did not have discussion on acupoints.[54–57]

Therefore, we recommend when menopause is complicated with depression, it may be worth modifying the treatment strategy to not only treat menopause related symptoms but also improve depression.

5. Conclusion

The included studies were published in the last 10 years; this could imply that the research on this topic using Chinese medicine therapies started to emerge in the recent years. Although Chinese medicine therapies have shown similar effect at reducing depression severity as antidepressants, there is limited evidence on the efficacy of CHM or acupuncture for depression during perimenopause and menopause. Future well designed clinical trials on CHM and acupuncture should follow rigorous methodology and reporting, using sufficient large sample sizes with follow-ups.

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Conflicts of interest

The authors declare no conflicts of interest.

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