

# Acupuncture: A Promising Approach for Comorbid Depression and Insomnia in Perimenopause

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**Abstract:** Comorbid depression and insomnia are ubiquitous mental complaints among women going through the perimenopausal stage of life and can result in major decline in quality of life. Antidepressive agents combined with/without hypnotics, and/or hormone therapy are currently the most common treatment for perimenopausal depression (PMD) and insomnia (PMI). Balancing the benefits of these pharmacotherapies against the risk of adverse events (AEs) is a difficult task for both clinicians and women. There has been a growing body of research regarding the utilization of acupuncture for treatment of PMD or PMI, whereas no studies of acupuncture for comorbid PMD and PMI have appeared. In this review, we summarize the clinical and preclinical evidence of acupuncture as a treatment for PMD or PMI, and then discuss the potential mechanisms involved and the role of acupuncture in helping women during this transition. Most clinical trials indicate that acupuncture ameliorates not only PMD/PMI but also climacteric symptoms with minimal AEs. It also regulates serum hormone levels. The reliability of trials is however limited due to methodological flaws in most studies. Rodent studies suggest that acupuncture prolongs total sleep time and reduces depression-like behavior in PMI and PMD models, respectively. These effects are possibly mediated through multiple mechanisms of action, including modulating sex hormones, neurotransmitters, hypothalamic-pituitary-adrenal axis/hypothalamic-pituitary-ovary axis, oxidative stress, signaling pathways, and other cellular events. In conclusion, acupuncture is a promising therapeutic strategy for comorbid depression and insomnia during perimenopause. Neuroendocrine modulation is likely to play a major role in mediating those effects. High-quality trials are required to further validate acupuncture's effectiveness.

**Keywords:** acupuncture, perimenopause, insomnia, depression, comorbid, mechanisms

## Background

Perimenopause is a universal phenomenon that marks a mid-life transition from fertility to infertility in women's lives.<sup>1</sup> It is a stage during which women are particularly vulnerable to the onset of depression,<sup>2-4</sup> even without any previous history of depressive disorders.<sup>2</sup> A large quantity of studies also link both insomnia and vasomotor symptoms (hot flushes and night sweating) to perimenopausal depression (PMD),<sup>3,5,6</sup> while insomnia is correlated more strongly and consistently with depression than vasomotor symptoms are.<sup>7-9</sup> The prevalence of comorbid depression and insomnia in perimenopause is approximately 31.5%.<sup>9</sup>

## The Comorbidity of Perimenopausal Insomnia and Depression is More Than a "Domino" Effect

The interaction between depression and insomnia, and its contribution to psychosomatic impairments, is clear.<sup>10</sup> In comparison to women without sleep disturbances, women

with sleep disturbance are 10 times more likely to experience depression; and women with depression are more vulnerable to insomnia, particularly waking during the night and having difficulty falling asleep again.<sup>11,12</sup> In various insomnia patterns, depression is highly associated with difficulty falling asleep and waking up earlier than desired.<sup>10</sup> Women in the menopausal transition are at increased risk for sleep-disordered breathing, which can also contribute to both depressed mood and poor sleep.<sup>3</sup> In light of the actigraphy data, perimenopausal insomniacs with comorbid depression show longer sleep onset latency, shorter sleep duration, and lower sleep efficiency (but not number of awakenings or wakefulness after sleep onset), in comparison to women with insomnia only.<sup>10</sup> Depression and insomnia are not only a mental burden for perimenopausal women but they also increase the difficulty of treating menopause-related somatic issues such as cardiovascular disease and osteoporosis.<sup>13</sup> Anticipation of symptom self-healing might be futile as untreated PMD can increase medical morbidity after menopause, including risks of endocrine and cardiovascular disease.<sup>14</sup>

It is challenging to find an established theoretical basis for interpreting intertwined phenomenon of insomnia and depression as women transit menopause, although the two are commonly co-encountered.<sup>4,11</sup> Two kinds of “domino” theory are sometimes asserted to partially explain this bidirectionality, or even link this bidirectionality to vasomotor symptoms: 1) PMD due to climacteric vasomotor symptoms or other psychosocial risk factors decreases sleep quality and quantity and 2) frequent night hot flushes may be tied to disrupted sleep patterns, and in turn, trigger the development of depressive symptoms.<sup>4,5</sup> The complicated interrelationships between these three symptoms (depression, insomnia, and vasomotor complaints), however, may far exceed the “domino” explanation, because not all women with hot flushes develop depression, insomnia, or both; and many perimenopausal women suffer from depression and/or insomnia in the absence of hot flushes.<sup>10</sup>

## Current Management Strategies for Comorbid Depression and Insomnia During Perimenopause

It is imperative for women in mid-life to find effective strategies to manage comorbid depression and insomnia, and maximize their well-being. Because of the co-occurrence or overlap, interdependent and interactional relationship,<sup>6,15</sup> management of insomnia is also recommended as part of treatment for PMD, in “Guidelines for the Evaluation and

Treatment of Perimenopausal Depression” issued by the Board of Trustees for The North American Menopause Society (NAMS) and Mood Disorders Task Force of the National Network of Depression Centers (NNDC).<sup>6</sup> According to NAMS and NNDC, antidepressants and cognitive behavioral therapy (CBT) are the front-line antidepressant treatments for PMD.<sup>6</sup> However, antidepressant medications have some relatively minor adverse events (AEs) that include but are not limited to dryness of mouth, digestive upsets, drowsiness, and fatigue, and some more major AEs such as rapid weight gain and sexual dysfunction.<sup>5,16–18</sup> Similarly, sedatives and hypnotics have side effects that patients may find uncomfortable<sup>19</sup> and are not recommended for longer term treatment of insomnia. CBT is highly recommended for the treatment of both depression and insomnia, but an impediment to its wider utilization is a lack of suitably trained psychologists.<sup>20</sup> Hormone replacement therapy (HRT) can be an effective treatment for perimenopausal syndrome, while it is not FDA-approved to treat perimenopausal mood disturbance.<sup>6</sup>

Complementary and alternative medicine (CAM) has many proponents and supporters<sup>3</sup> and has been sought to treat depression<sup>16</sup> and insomnia<sup>19</sup> associated with perimenopause. As previously reported, during peri- to post-menopause up to 50% of the women worldwide seek assistance from CAM approaches, including herbal medicine, yoga, massage therapy, dietotherapy, as well as acupuncture for symptomatic relief.<sup>3,21</sup> Acupuncture has a long tradition of usage for the treatment of various menopause-related symptoms, including PMI and PMD, dating back thousands of years.<sup>22</sup> Its clinical efficacy has been investigated for natural menopause and chemical-/surgery-induced menopause.<sup>22</sup> It has also been reported that menopausal women sustaining insomnia as a major complaint tend to select CAM approaches, particularly body therapies, as their first choice of remedy.<sup>23,24</sup> A menopausal epidemiological study carried out in the US indicated that in women who primarily used alternative therapies including acupuncture to manage menopause-related depression, 1.0% were completely symptom free, 84.6% made symptoms get a little to a lot better, 12.5% showed no change in symptoms, and 1.9% reported the worsening of symptoms, which was slightly less effective than the conditions in women who primarily used antidepressive or anti-anxiety agents for menopause-related depression (5.6% were completely symptom free, 88.6% made symptoms get a little to a lot better, 3.9% showed no change in symptoms, and 1.9% reported the worsening of symptoms).<sup>25</sup> However, due to the limited evidence and

uncertainty about its effectiveness and mechanism of action in physiological terms, acupuncture is still striving for general scientific recognition and support.

This review aims to summarize and assess existing clinical and preclinical evidence of acupuncture as a treatment for perimenopausal insomnia and depression, as well as discuss the potential mechanisms involved. We aim to provide an evidence-base for decision-making for clinical practitioners to recommend (or for perimenopausal to women select) acupuncture as a potential therapy.

## Effects and Safety of Acupuncture on Depression and Insomnia

Acupuncture is one of the simplest, popular, and safest CAM procedures.<sup>19,26,27</sup> It is derived from Traditional Chinese Medicine (TCM) and has a history of use in medicine of at least 4000 years under the influence of oriental philosophical theories.<sup>28</sup> It is a clinical treatment modality in which targeted proposed specific locations of the body, the acupuncture points (also called acupoints) have thin, solid, metallic needles inserted deeply for therapeutic purposes. The therapeutic efficacy is more effectively manifested when the pierced needles are manipulated manually with slight rotation (back-and-forth motion) and/or pistoned (up-and-down motion) or other complex combinations (manual acupuncture, MA), or are stimulated by the electric current via an impulse generator (electroacupuncture, EA).<sup>27–30</sup> As illustrated in neuroimaging reports, acupuncture can cause a wide array of central nervous system (CNS) responses involving the hippocampus, amygdala, cerebellum, hypothalamus, and other limbic structures.<sup>31</sup> Dysfunction or disorder in these cerebral regions has been previously implicated in the development of depression<sup>32,33</sup> and/or insomnia.<sup>34,35</sup> Both clinical and basic studies indicate these two forms of acupuncture (MA and EA) are different with regard to outcomes and underlying physiological mechanisms, it is however difficult to conclude which one is more efficacious.<sup>29</sup> Furthermore, patterns of usage of MA or EA usually vary by condition treated, stimulus demand, and/or acupuncturist preference.<sup>29</sup>

Patients are attracted to acupuncture in part by its reputation for being low-risk. Several prospective surveys with large sample sizes have suggested that acupuncture-related AEs mainly involve minor local reactions at the site of needling, such as bruising, pain, or minor bleeding, and the incidence of these events is generally very low (no more than 3%).<sup>36,37</sup> No serious AEs requiring hospital visits or resulting in permanent disability or death have been reported from

acupuncture.<sup>36,37</sup> Twelve prospective studies involving several Asian and European countries validated that the incidence of the acupuncture-related serious AEs (ie, life threatening, hospital admission required or prolongation of existing hospital stay, persistent or significant disability or incapacity, death, etc) was estimated to be 0.55 per 10,000 patients, and 0.05 per 10,000 treatment sessions.<sup>32,38</sup> Given its non-pharmacological basis, acupuncture also obviates the concerns with respect to toxicity and AEs that commonly occur when using hypnotics/sedatives, such as hangover, tolerance, increased alertness, and even endocrinological, hematological or cardiovascular events,<sup>39</sup> and concerns regarding common side effects of contemporary antidepressive agents, such as dry mouth, cardiovascular/gastrointestinal side effects, seizure, bleeding, sexual dysfunction, weight gain, and even suicidality.<sup>40</sup> Acupuncture also does not increase the metabolic burden of the liver and kidney. It is thus a potentially safe, promising and attractive remedy in the management of comorbid depression and insomnia associated with perimenopause. But, the question remains as to whether it is really effective?

As of March 2019, there were at least 31 systematic reviews and/or meta-analyses (SRs/MAs) regarding acupuncture treatment for depression.<sup>41</sup> As of September 2018, there were at least 34 SRs/MAs regarding acupuncture treatment for insomnia.<sup>30</sup> Although the included primary randomized controlled trials (RCTs) are less than well-powered and have some methodological flaws, the available evidence is in favor of acupuncture's effectiveness and safety, and supports it as a monotherapy or adjuvant therapy for patients with depression or insomnia, particularly those who are intolerant to Western medications.<sup>30,41</sup> In China, acupuncture has even been added as a routine remedy in the latest Guidelines for the Diagnosis and Treatment of Insomnia formulated by the Chinese Sleep Research Society (CSRS).<sup>30</sup> The clinical guidelines issued by the Canadian Network for Mood and Anxiety Treatments (CANMAT) Depression Work Group recommended acupuncture as a third-line treatment with "Level 2 Evidence" for the adjunctive treatment of mild-to-moderate depression.<sup>41,42</sup>

## How is Acupuncture for Perimenopausal Depression and Insomnia Conceptualised in TCM

TCM looks upon human life as a holistic, dynamic, spiritual, and functional unity, and the development of disease mainly as the result of a disordered state of the human

functional balance (imbalance in the forces between Yin and Yang).<sup>26,28,43</sup> Therefore, the basic protocol of preventing and/or treating disease in TCM is to restore the imbalance state and achieve Yin-Yang harmony via various remedies (eg, herbal medicine, acupuncture, moxibustion, Tui-na, etc) depending upon the individual and the malady.<sup>26,28,43</sup>

In clinical setting, acupuncture is ubiquitously applied based on the basic theory of TCM, which emphasizes the concept of “syndrome pattern”.<sup>44</sup> “Treatment based on Syndrome Differentiation” is the essential principle of TCM. That is, patients are classified into different TCM syndrome patterns according to their clinical symptoms and signs, and then corresponding treatments, including acupuncture, are prescribed.<sup>44,45</sup> According to the concept and theory of TCM gynecology, all perimenopausal diseases and disorders including PMI/PMD can be classified into the main category of “Juejing-Qianhou-Zhuzheng” (绝经前后诸症, meaning “symptoms and signs associated with perimenopause”, which is similar to “perimenopausal syndrome” in Western medicine) for treatment.<sup>46</sup> In light of different symptoms, patients with PMI/PMD are generally further divided into different syndrome patterns within the scope of perimenopausal syndrome, and then receive corresponding TCM therapies. This strategy is the embodiment and process of “Treatment based on Syndrome Differentiation”. PMI/PMD is usually classified into different syndrome patterns in different published studies.<sup>47,48</sup> Based on bibliometric analysis,<sup>47,48</sup> we listed the top six syndromes of each of these two disorders and the proportion of patients in each pattern, respectively (see Table 1; organs in the syndrome pattern correspond to the TCM understanding). It is interesting to identify that in three out of nine patterns, PMI and PMD overlap. The pattern with the highest proportion of patients in both conditions is consistent, that is, the pattern of “depression of Liver and deficiency of kidney”. Given that TCM prescriptions (eg, acupuncture, herbal medicine, etc) are highly dependent on patterns, establishing standardized pattern classifications of PMI/PMD is essential for research and improved clinical practice.

Despite a lack of standardized pattern classification, perimenopausal symptoms including PMI/PMD are closely related to liver and kidney in TCM clinical practice.<sup>47,49</sup> Hence, herbal medicines (or acupoints) associated with regulating liver (or Liver Meridian of Foot-Jueyin) and kidney (or Kidney Meridian of Foot-Shaoyin) are often selected for treating depression and insomnia associated with perimenopause.<sup>47,49</sup> Smoothing liver (smooths liver and regulates Qi) and nourishing kidney (nourishes kidney

and enriches essence) are regarded as the general principles for perimenopausal disorders.<sup>47,49</sup>

## Evidence from Clinical Trials

Does the existing clinical evidence support acupuncture as a safe and effective therapy for comorbid PMI and PMD, and is the evidence reliable? To answer this question, a comprehensive literature search with no restrictions for research types was carried out. Unfortunately, no RCTs, cohort studies or case studies within this theme were retrieved, reflecting a significant research and practice gap. Our team thereby is currently carrying out an RCT focusing on this theme. This trial has been registered in the Chinese Clinical Trial Registry (No. ChiCTR2100043054), and the results are expected to be published in 2022. However, we retrieved many RCTs and some SRs/MAs focusing on acupuncture treatment for PMD alone or PMI alone. Those SRs/MAs involved several modified modalities of acupuncture for which mechanisms of action differ from those for MA/EA and were not discussed in this review; therefore, only eligible original RCTs in those SRs/MAs were extracted.

Our team has published two SRs/MAs<sup>19,50</sup> within related fields (15 RCTs in SR/MA of PMI; 25 RCTs in SR/MA of PMD) where we covered our retrieval strategy in detail (retrieval in 2020), as well as our quality evaluation and interpretation of the evidence. Based on updated retrieval (July 2021), we have included more RCTs recently published (22 RCTs of PMI; 25 RCTs of PMD). The critical information and major findings of each RCT were extracted and summarized in Table 2. The results of meta-analyses cited from our SRs/MAs are displayed in Table 3, and detailed analysis process can be referred to in our published articles.<sup>19,50</sup> Given that this review is not an SR, a narrative summary on the findings followed by comments on the methodology and implications for future research of these studies is provided. We expect that these summaries will help clinicians and policymakers judge the role of acupuncture, and its potential and feasibility for the management of depression and insomnia associated with perimenopause.

## Effectiveness and Efficacy of Acupuncture for PMI and PMD

We classified the retrieved RCTs into two categories: acupuncture as an independent or as an adjuvant to standard care in the management of PMI/PMD.

**Table 1** Common TCM Syndrome Patterns of PMI and PMD

Syndrome Patterns	Major Symptoms	Tongue	Pulse	Ratio	
				PMI	PMD
Depression of liver and deficiency of kidney	Insomnia or dreamful sleep, depressed mood, fatigue, chest distress and preference for sighing, hot flushes and sweating, frequent urination or dribbling urination	Red tongue with little coating	Stringy and thready or stringy and rapid	60.78%	30.42%
Liver depression and spleen deficiency	Depression or irritability, poor sleep, poor appetite, abdominal distension, loose stool	White coated tongue	Stringy and slow	24.02%	–
Stagnation of Qi due to depression of liver	Depression or irritability, preference for sighing, hypochondrium distress and/or pain, distending pain of breasts	Thin whitish coating of the tongue	Stringy	–	18.80%
Imbalance between heart-Yang and kidney-Yin	Irritability and insomnia, palpitation, dizziness and tinnitus, loss of memory, dry mouth, soreness and weakness of waist and knees	Red tongue with little coating	Thready and rapid	–	13.46%
Spleen-kidney Yang deficiency	Insomnia due to nocturia, soreness and weakness of waist and knees, chilly sensation and the cold limbs, diarrhea before dawn or loose stools, edema in the extremities	Pale and slight corpulent tongue with whitish and slippery fur	Deep and retarded without strength	4.31%	–
Deficiency of both kidney Yin and kidney Yang	Poor sleep, sometimes hot flushes and sweating and sometimes chilly sensation and the cold limbs, soreness and weakness of waist and knees, dizziness and tinnitus	Pale tongue with thin coating	Stringy and thready	4.31%	–
Heart-Gallbladder Qi deficiency	Palpitation, timidity, feeling fearful, difficulty in falling asleep, tendency to sleep lightly, nightmares, depressed mood, short of breath, spontaneous perspiration	Pale tongue with whitish coating	Stringy and thready	3.70%	6.72%
Heart-spleen deficiency	Insomnia, dreamful sleep, worry beyond measure, palpitation, poor appetite, loose stool, fatigue, sallow complexion, loss of memory	Pale tongue with whitish coating	Thin and weak	2.87%	6.11%
Hyperactivity of fire due to Yin deficiency	Vexation, irritable and depressed mood, dry mouth, tidal reddening of the cheeks, dysphoria in chest palms-soles	Red tongue with little coating	Stringy and rapid	–	4.65%

Table 1 is not a direct quote from any paper, but is compiled by us from data in two published papers (Ref 47 & 48 of this manuscript); Similarly, Table 3 is compiled by us from data in two published papers (Ref 19 & 50 of this manuscript); The rest of the tables and figures are original and do not require reference. 47 and 48.

**Table 2** Summary of Clinical Trials Investigating the Effects and Safety of Acupuncture on PMI and PMID

Author/Year	Study Groups/No. of Participants	Disease (Diagnostic System)	TCM Syndrome Pattern	Acupuncture Interventions	Acupoints	Controls	Outcome Measures	Results (Compared with the Control Group) at Post-Treatment	Follow-Up	Adverse Events
Fu et al 2017 <sup>51</sup>	- MA/n=37 - placebo-MA/n=37	PMI (ICSD-3)	NR	20 min/day for 10 sessions	BL18, BL23, GB25, LR14	Streitberger placebo-needle control	PSQI, ISI, PSG (SOL, TST, WASO, SE, Ari, NI%, N2%, N3%, REM%)	(i) Lower PSQI and ISI in MA group (ii) Shorter SOL and WASO, longer TST, higher SE, lower Ari, lower NI%, and higher REM % in MA group; no differences in N2% and N3% between two groups	No follow-up	- MA/n=0 - placebo-MA/n=4 (worsening of insomnia)
Wang 2015 <sup>52</sup>	- EA/n=30 - placebo-EA/n=30	PMI (ICSD-3)	NR	30 min/day, 3 days/week for 8 weeks	BL15, BL18, BL23, CV3, CV4, CV6, CV12, EX-HN3, GV3, GV4, GV14, GV20, HT7, KI3, LR3, PC6, SP6, ST36	Streitberger placebo-needle control	PSQI, MRS, Men-QoL	No differences in PSQI, MRS and MEN-QoL between two groups	(1) No difference in PSQI and Men-QoL between two groups at 4-week follow-up (2) Lower MRS in EA group at 4-week follow-up	No adverse events
Lin et al 2017 <sup>53</sup>	- MA/n=33 - waitlist-control/n=32	PMI (CCMD-3, CDTE-TCM)	NR	30 min/day, 3 days/week for 4 weeks	CV4, CV6, CV12, EX-HN3, GV20, GV24, HT7, PC6, SP6, ST36	Waitlist	PSQI, KI	Lower PSQI and KI in MA group	No follow-up	NR

Li et al 2020a <sup>54</sup>	- EA/n=42 - placebo-EA/n=42	PM1 (ICSD-3)	Kidney Yin/ Yang deficiency	- 30 min/day for 18 days (3 days/week for 4 weeks + 2 day/ week for 2 weeks + 1 day/ week for 2 weeks) - continuous wave, 2.5 Hz, 4-5 mA	BL23, CV4, CV6, EX, EX-HN3, GV4, GV20, GV24, HT7, KI3, KI7, SP6	Streitberger placebo- needle control	PSQI, MEN- QoL, Actigraphy (TST, WASO, SE, ATs, AA), ISI, SAS, SDS	(i) Lower PSQI, ISI, MEN-QoL, SAS in EA group; no differences in SDS between two groups (ii) Longer TST, higher SE, and less AA in EA group; no differences in ATs and WASO between two groups	Lower PSQI and Men-QoL in EA group at 4- and 12- week follow- ups	- EA/n=2 [mild bleeding (1); mild pain (1)] - placebo-EA/n=1 (mild pain)
Wang et al 2015 <sup>55</sup>	- MA/n=33 - sham-MA/n=33	PMD (CCMD-3)	NR	30 min/day, 3 days/week for 8 weeks	KI6, LU7, PC6, SP4	Sham-MA [shallow puncture (2.5-5 mm), no De-qi, no retention of the needle]	SDS, Men- QoL	Lower SDS and Men-QoL in MA group	(i) Lower SDS in MA group at 4- week follow-up (ii) no difference in Men-QoL between two groups	NR

(Continued)

Table 2 (Continued).

Author/Year	Study Groups/No. of Participants	Disease (Diagnostic System)	TCM Syndrome Pattern	Acupuncture Interventions	Acupoints	Controls	Outcome Measures	Results (Compared with the Control Group) at Post-Treatment	Follow-Up	Adverse Events
Li 2015a <sup>56</sup>	- EA/n=30 - sham-EA/n=30 - Escitalopram/n=30	PMD (ICD-10)	NR	- 30 min/day, 3 days/week for 12 weeks - dense-sparse wave, 10/50 Hz, 0.5–1 mA	CV4, EX-CA1, EX-HN3, GV20, LI4, LR3, SP6, ST25	(i) Sham-MA [shallow puncture (3 mm), no De-qi, no current output] (ii) Escitalopram 10 mg/day for 12 weeks	HAMD, Men-QoL, FSH, E2, LH	(i) Lower HAMD and Men-QoL in EA group, compared with sham-EA; no differences in HAMD and Men-QoL between EA and escitalopram groups (ii) No differences in FSH, LH and E2 levels between two groups (vs sham-EA or vs escitalopram)	(i) Lower HAMD in EA group in 4-week and 12-week follow-ups (vs sham-EA); no difference in HAMD between EA and escitalopram groups in 4-week and 12-week follow-ups (ii) Lower Men-QoL in EA in 4-week follow-up (vs sham-EA or vs escitalopram); Men-QoL from low to high (EA < escitalopram < sham-EA) at 8-week and 12-week follow-ups	- EA/n=2 (hematoma) - sham-EA/n=0 - Escitalopram/n=25 [fatigue (17); headache (2); sleep disturbance (7); dizziness (7); palpitation (4); sweating (10); dry mouth (14); constipation (8)]



Ma 2017 <sup>97</sup>	- EA/n=37 - Prognova + Medroxyprogesterone acetate/n=36	PMI (CCMD-2-R)	NR	- 30 min/day, 3 days/week for 12 weeks - sparse-dense wave, 2/15 Hz	CV4, EX-CA1, EX-HN3, HT7, SP6, ST25	A total of 3 treatment cycles. Each treatment cycle includes Prognova 1mg daily for 21 consecutive days (with Medroxyprogesterone acetate 10mg daily added from day 14 to day 21) and then stop medication for 7 days	PSQI, KI, Men-QoL, FSH, E2	(i) Lower PSQI in EA group; no differences in KI and Men-QoL between two groups (ii) No differences in FSH level between two groups; higher E2 level in EA group	(i) Lower PSQI in EA group at 12-week follow-up (ii) No differences in KI MENQOL, and FSH and E2 levels between two groups	- EA/n=3 [hematoma (2); mild dizziness (1)] - Prognova + Medroxyprogesterone acetate/n=4 [breast tenderness (2); mild headache (1); colporrhagia (1)]
Chen et al 2013 <sup>57</sup>	- EA/n=38 - Alprazolam/n=32	PMI (DSM-IV)	NR	- 30 min/day for 20 days (7 days off every 10 days) - continuous wave, 0.7 Hz	EX, GV20, HT7, KI3, KI7, KI10, LR3, PC6, SP6, SP9, SP10	Alprazolam 0.4 mg/day for 20 days	AIS	Lower AIS in EA group	No follow-up	- EA/n=0 - Estazolam/n=8 (development of drug dependence after treatment)
Luo 2020 <sup>58</sup>	- MA/n=30 - Estazolam/n=30	PMI (CCMD-3, CDTE-TCM)	Incoordination between heart and kidney	30 min/day, 5 days/week for 12 weeks	BL15, BL23, BL62, EX, EX-HN1, GV20, KI3, KI6, PC6, SP6	Estazolam 1 mg/day, 3 days/week for 12 weeks	PSQI	No differences in PSQI between two groups	No follow-up	- MA/n=0 - Estazolam/n=5 [dizziness (2); nausea and vomiting (2); skin rashes (1)]
Du et al 2017 <sup>59</sup>	- EA/n=41 - Estazolam/n=41	PMI (CCMD-3)	NR	- 30 min/day, 6 days/week for 4 weeks - continuous wave, >50 Hz	PC6, SP6, Sishenzhen (1.5 Cun apart from GV20), Dingshenzhen (0.5 Cun up to EX-HN3, and 0.5 Cun up to GB14)	Estazolam 1 mg/day, 7 days/week for 4 weeks	PSQI, KI, WHOQOL-BREF, FSH, E2	(i) Lower PSQI and KI, and higher WHOQOL-BREF in EA group (ii) Higher E2 levels, and lower FSH levels in EA group	No follow-up	- EA/n=6 (mild tension before EA) - Estazolam/n=26 [dizziness (26); daytime sleepiness (26)]

(Continued)

Table 2 (Continued).

Author/Year	Study Groups/No. of Participants	Disease (Diagnostic System)	TCM Syndrome Pattern	Acupuncture Interventions	Acupoints	Controls	Outcome Measures	Results (Compared with the Control Group) at Post-Treatment	Follow-Up	Adverse Events
Kang 2015 <sup>60</sup>	- MA/n=31 - Estazolam/n=33	PMI (CCMD-3)	Heart and Gallbladder Qi deficiency	40 min/day, 6 days/week for 4 weeks	EX, EX-HN1, GB13, GB15, GV16, GV20, GV24, scalp acupoint (1 Cun up to GB15)	Estazolam 1 mg/day, 7 days/week for 4 weeks	PSQI, KI	Lower PSQI and KI in MA group	No follow-up	- MA/n=0 - Estazolam/n=1 (mild nausea)
Lai 2016 <sup>61</sup>	- MA/n=34 - Eszopiclone/n=33	PMI (CCMD-3)	Incoordination between heart and kidney	30 min/day, 6 days/week for 3 weeks (acupuncture on specific time)	BL62, KI6, LU7, SI3	Eszopiclone 3 mg/day, 7 days/week for 3 weeks	PSQI, KI	(i) Lower KI in MA group; no differences in PSQI between two groups	No follow-up	- MA/n=2 (hematoma) - Eszopiclone/n=3 [dizziness (1); dry mouth (2)]
Li 2014 <sup>62</sup>	- MA/n=120 - Estazolam/n=120	PMI (CCMD-3)	NR	30 min/day for 30 days	SP6, SP8, Shenguan (Tianhuangfuxue)	Estazolam 2 mg/day for 30 days	PSQI	Lower PSQI in MA group	No follow-up	NR
Li et al 2018a <sup>63</sup>	- MA/n=60 - Alprazolam/n=62	PMI (CDTE-TCM)	NR	30-40 min/day, 5 days/week for 9 weeks	BL13, BL15, BL17, BL18, BL20, BL23, HT7	Alprazolam 0.4-0.8 mg/day, 7 days/week for 9 weeks	PSQI, FSH, E2, LH	(i) Lower PSQI in MA group (ii) Higher E2 levels, and lower FSH and LH levels in MA group	Follow-up 30 days; NR for valid data	NR
Lu et al 2014 <sup>49</sup>	- MA/n=52 - Estazolam/n=52	PMI (CCMD-3, ICD-10)	NR	30 min/day for 30 days	CV12, EX-HN1, GB20, GV20, HT7, LR3, LR14, SP6, SP15	Estazolam 1 mg/day for 30 days	PSQI	Lower PSQI in MA group	No follow-up	NR

Ma 2014 <sup>64</sup>	- EA/n=45 - Estazolam/n=45	PMI (CCMD-2)	Any TCM syndrome pattern according to CDTE-TCM	- 30 min/day, 3 days/week for 4 weeks - continuous wave, >50 Hz	PC6, SP6, Sishenzhen (1.5 Cun apart from GV20), Dingshenzhen (0.5 Cun up to EX-HN3, and 0.5 Cun up to GB14)	Estazolam 1 mg/day, 7 days/week for 4 weeks	PSQI, HAMD	Lower PSQI and HAMD in EA group	No follow-up	No adverse events
Qin 2018 <sup>65</sup>	- MA/n=34 - Estazolam/n=33	PMI (CCMD-3, ICD-10)	Deficiency of kidney and hyperactivity of liver	30 min/day, 5 days/week for 4 weeks	BL17, BL18, BL23, EX, EX-HN1, GV20, KI3, LR3	Estazolam 1-2 mg/day, 7 days/week for 4 weeks	PSQI, HAMA MSMSMS (REM%)	(i) Lower PSQI in MA group (ii) Higher REM % in MA group	No follow-up	- MA/n=3 (hematoma) - Estazolam/n=7 [dizziness (2); daytime sleepiness (2); fatigue (3)]
Yang et al 2017 <sup>66</sup>	- MA/n=81 - Estazolam/n=81	PMI (CCMD-2)	Liver and kidney Yin deficiency	30 min/day, 15 days/month (one treatment every other day) for 3 months	CV12, HT7, KI3, PC6, ST36, ST40, four scalp acupoints (middle 1/3 of frontal apical band, posterior 1/3 of frontal apical band, anterior 1/3 of skull base band, middle 1/3 of skull base band)	Estazolam 1 mg/day, 10 days/month for 3 months	PSQI, FSH, E2, LH	(i) Lower PSQI in MA group (ii) Higher FSH levels, and lower E2 and LH levels in MA group	No follow-up	NR
Zhang et al 2017 <sup>67</sup>	- MA/n=31 - Estazolam/n=30	PMI (DTICA, CDTE-TCM)	Six syndrome patterns with liver as the core	30 min/day, 5 days/week for 4 weeks	BL17, BL18, EX, EX-HN1, GV20, LR3	Estazolam 1 mg/day, 7 days/week for 4 weeks	PSQI, KI, HAMA, HAMD	Lower PSQI, KI, HAMA and HAMD in MA group	No follow-up	- MA/n=1 (hematoma) - Estazolam/n=4 [dizziness (2); fatigue and daytime sleepiness (2); memory loss (2)]
Yan et al 2021 <sup>68</sup>	- MA/n=42 - Estazolam/n=43	PMI (CCMD-3)	NR	30 min/day, 7 days/week for 12 weeks	CV4, CV6, GV20, GV24, HT7, SP6	Estazolam 1 mg/day, 7 days/week for 12 weeks	PSQI, Men-QoL	Lower PSQI and Men-QoL in MA group	No follow-up	- MA/n=4 [dizziness (3); hematoma (1)] - Estazolam/n=3 [dizziness (1); fatigue and daytime sleepiness (2)]

(Continued)

Table 2 (Continued).

Author/Year	Study Groups/No. of Participants	Disease (Diagnostic System)	TCM Syndrome Pattern	Acupuncture Interventions	Acupoints	Controls	Outcome Measures	Results (Compared with the Control Group) at Post-Treatment	Follow-Up	Adverse Events
Li et al 2018b <sup>69</sup>	- EA/n=116 - Escitalopram/n=105	PMD (DSM-V, ICD-10)	NR	- 30 min/day, 3 days/week for 12 weeks - dilatational wave, 50 Hz, 0.5–1 mA	CV4, EX-CA1, EX-HN3, GV20, LI4, LR3, SP6, ST25	Escitalopram 10mg/day for 12 weeks	HAMD, Men-QoL, FSH, E2, LH	(i) No differences in HAMD and Men-QoL between two groups (ii) No differences in FSH, E2 and LH levels between two groups	(i) Lower HAMD in EA group at 4- and 12-week follow-ups (ii) Lower Men-QoL in EA group in 4-, 8-and 12-week follow-ups	- EA/n=14 (hematoma) - Escitalopram/n=18 (dizziness, palpitation, stomachache)
Chi et al 2011 <sup>70</sup>	- MA/n=30 - Fluoxetine/n=30	PMD (CCMD-3)	NR	30 min/day for 4 weeks	EX-HN1, EX-HN3, GV20, KB, LR3, LRI4, SP6, ST36	Fluoxetine 20 mg/day for 4 weeks	HAMD	Lower HAMD in MA group	No follow-up	- MA/n=0 - Fluoxetine/n=3 [dizziness (1); nausea (2)]
Deng 2008 <sup>71</sup>	- MA/n=29 - Deanxit/n=29	PMD (ICD-10)	NR	20–30 min/day, after 3 consecutive days of treatment, once treatment every 3 days for total 4 weeks	CV3, CV4, CV6, CV10, CV12, KI17, Qipang (0.5 Cun beside CV6), Xiafengshidian (1 Cun below and beside ST26)	Deanxit 20mg/day for 4 weeks	HAMD, KI, 5-HT	(i) No differences in HAMD and KI between two groups (ii) No differences in 5-HT levels between two groups	(i) Lower HAMD in MA at 2-week follow-up (ii) No difference in HAMD between two groups at 4-week follow-up (iii) No difference in KI between two groups at 2-and 4-week follow-ups	- MA/n=3 [changes of character of stool (2); palpitation (1)] - Deanxit/n=32 [changes of character of stool (6); dry mouth and halitosis (9); dysphoria (6); dreaminess (6); breast distending pain (5)]
Dong 2015 <sup>85</sup>	- MA/n=30 - Nilestriol + Fluoxetine/n=30	PMD (CCMD-3, CDTE-TCM)	NR	30 min/day for 30 days	BL13, BL15, BL17, BL18, BL20, BL21, BL23	Nilestriol 2mg/15days for 30 days + Fluoxetine 20mg/day for 30 days	HAMD	Lower HAMD in MA group	No follow-up	NR

Li 2015 <sup>72</sup>	- MA/n=32 - Fluoxetine/n=32	PMD (CCMD-3)	Liver stagnation and kidney deficiency	30 min/day, 6 days/week for 12 weeks	BL15, BL18, BL23, EX-HN1, EX-HN3, GV20, GV24, PC6	Fluoxetine 20mg/day for 12 weeks	HAMD, KI	Lower: HAMD and KI in MA group	Follow-up for 12 weeks; no data of HAMD and KI global scores for follow-up	- MA/n=0 - Fluoxetine/n=8 [nausea and vomiting (2); dry mouth (1); indigestion (1); diarrhea (1); dizziness (1); headache (1)]
Ma et al 2009 <sup>73</sup>	- MA/n=30 - Fluoxetine/n=30	PMD (CCMD-3, CDTE-TCM)	NR	30 min/day, 5 days/week for 8 weeks	EX-HN1, EX-HN3, GV20, HT7, PC6, PC7, SP6, ST36	Fluoxetine 20mg/day for 8 weeks	HAMD	No differences in HAMD between two groups	No follow-up	- MA/n=0 - Fluoxetine/n=6 [nausea (2); dizziness (2)]
Niu et al 2017 <sup>74</sup>	- MA/n=41 - Fluoxetine/n=41	PMD (CCMD-3)	Stagnation of liver Qi	30 min/day, 5 days/week for 6 weeks	BL13, BL15, BL17, BL18, BL20, BL23	Fluoxetine 20mg/day for 6 weeks	HAMD	Lower PSQI in MA	No follow-up	- MA/n=7 [dizziness (2); palpitation (1); dry mouth (1); nausea (3)] - Fluoxetine/n=6 [dizziness (1); palpitation (2); dry mouth (2); nausea (1)]
Qian et al 2007 <sup>75</sup>	- MA/n=33 - Fluoxetine/n=30	PMD (CCMD-3)	NR	25 min/day, 5 days/week for 6 weeks	BL13, BL15, BL17, BL18, BL20, BL23	Fluoxetine 20mg/day for 6 weeks	HAMD	No differences in HAMD between two groups	No follow-up	- MA/n=2 [dizziness (1); palpitation (1)] - Fluoxetine/n=9 [insomnia (1); akathisia (1); dry mouth (1); nausea (1); palpitation (1); skin symptom (1); excitation and agitation (2)]
Qiang 2008 <sup>76</sup>	- MA/n=30 - Fluoxetine/n=30	PMD (CCMD-3)	NR	25 min/day, 5 days/week for 6 weeks	BL15, BL18, BL23, EX-HN1, GB20	Fluoxetine 20mg/day for 6 weeks	HAMD	No differences in HAMD between two groups	No follow-up	NR
Shi et al 2018 <sup>77</sup>	- EA/n=30 - Escitalopram/n=30	PMD (DSM- V)	NR	- 30 min/day, 3 days/week for 12 weeks - dense-sparse wave, 10/50Hz, 0.5–1.0mA	CV4, EX-CA1, EX- HN3, GV20, LI4, LR3, SP6, ST25	Escitalopram 10mg/day for 12 weeks	HAMD	Lower HAMD in EA group	Lower HAMD in EA at 4- and 12- week follow-ups	NR

(Continued)

Table 2 (Continued).

Author/Year	Study Groups/No. of Participants	Disease (Diagnostic System)	TCM Syndrome Pattern	Acupuncture Interventions	Acupoints	Controls	Outcome Measures	Results (Compared with the Control Group) at Post-Treatment	Follow-Up	Adverse Events
Sun et al 2015 <sup>78</sup>	- EA/n=21 - Escitalopram/n=21	PMD (DSM-V)	NR	- 30 min/day, 3 days/week for 12 weeks - dense-sparse wave, 10/50Hz, 0.5–1.0mA	CV4, EX-CA1, EX-HN3, GV20, LI4, LR3, SP6, ST25	Escitalopram 10mg/day for 12 weeks	HAMD	Lower HAMD in EA group	No follow-up	NR
Wang et al 2010 <sup>79</sup>	- MA/n=21 - Deanxit/n=21	PMD (CCMD-3)	NR	30 min/day, after 3 consecutive days of treatment, once treatment every 3 days for total 4 weeks	CV3, CV4, CV6, CV10, CV12, KI17	Deanxit 10 mg/day for 4 weeks	HAMD	No differences in HAMD between two groups	Lower HAMD in MA at 2- and 4-week follow-ups	- MA/n=3 [changes of character of stool (2); palpitation (1)] - Deanxit/n=15 [dry mouth and halitosis (9); dysphoria, dreaminess, or breast distending pain (6)]
Zhang 2010 <sup>86</sup>	- EA/n=44 - Nilestriol+ Fluoxetine/n=46	PMD (CCMD-3)	NR	- 30 min/day, 5 days/week for 12 weeks - dilatational wave, 8–9 mA, 6V	BL13, BL15, BL17, BL20, BL23, GV20, KI3, LR3, PC6, SP6	Nilestriol 2mg/14 days for 30 days + Fluoxetine 20mg/day for 12 weeks	HAMD, KI, FSH, E2, LH	(i) No differences in HAMD and KI between two groups (ii) No differences in FSH, LH and E2 levels between two groups	No follow-up	- EA/n=5 (sweating, dizziness, vomiting) - Nilestriol+ Fluoxetine/n=23 [dry mouth and halitosis (5); nausea (6); dysphoria (2); constipation (6); dreaminess (2); breast distending pain (2)]
Zhang 2013 <sup>87</sup>	- MA/n=94 - Premarin + Provera + Fluoxetine/n=94	PMD (CCMD-3)	NR	30 min/day, 7 days/week for 12 weeks	EX-HN1, GB13, GV20, GV24, HT7	Premarin 0.625mg/day and Provera 6mg/day + Fluoxetine 20mg/day for 12 weeks	HAMD, FSH, E2, LH	(i) Lower HAMD in MA group (ii) No differences in FSH, LH and E2 levels between two groups	No follow-up	- MA/n=2 (feeling pain when inserting needle) - Premarin + Provera + Fluoxetine/n=12 [dizziness (5); nausea and vomiting (4); hypersomnia (3)]

Zheng et al 2010 <sup>88</sup>	- MA/n=60 - Premarin + Provera + Fluoxetine/n=60	PMD (CCMD-3)	NR	30 min/day, 7 days/week for 12 weeks [needle retaining time for 8 hour in three acupoints (BL8, GV19, GV21) per session]	BL8, BL18, BL23, GV19, GV21, KI3, LR3, SP6	Premarin 0.625mg/day for 20 days + and Provera 6mg/day + Fluoxetine 20mg/day for 12 weeks	HAMD, KI, FSH, E2, LH	(i) No differences in HAMD and KI between two groups (ii) No differences in FSH and LH levels between two groups; Lower E2 level in MA group	Lower HAMD and KI in MA at 24-week follow-up	- MA/n=2 (feeling pain when inserting needle) - Premarin + Provera + Fluoxetine/n=18 [loss of appetite (5); dizziness (4); diarrhea (3); breast distending pain (3); leukorrhagia (2); spasmus (1)]
Ding et al 2007 <sup>80</sup>	- MA/n=39 - Fluoxetine/n=39	PMD (CCMD-2-R)	NR	30 min/day, 6 days/week for 4 weeks	BL15, BL18, BL20, BL23, GV20, HT7, LR3, SP6	Fluoxetine 20mg/day for 4 weeks	HAMD, KI	No differences in HAMD between two groups; Lower KI in MA group	No follow-up	NR
Li et al 2020b <sup>81</sup>	- EA/n=30 - Fluoxetine/n=30	PMD (CDTE-TCM)	NR	- 25 min/day, 3 days/week for 6 weeks - dilatational wave, 15 Hz, 1 mA	EX-HN1, EX-HN3, GV20, HT7, LI4, PC6, SP6, ST36	Fluoxetine 20mg/day for 6 weeks	HAMD, HAMA	No differences in HAMD between two groups; Lower HAMA in EA group	No follow-up	NR
Zhang 2015 <sup>82</sup>	- MA/n=29 - Deanxit/n=29	PMD (CCMD-3)	NR	30 min/day, after 3 consecutive days of treatment, once treatment every 3 days for total 4 weeks	CV3, CV4, CV6, CV10, CV12, KI17	Deanxit 20 mg/day for 4 weeks	HAMD	No differences in HAMD between two groups	Lower HAMD in MA at 2- and 4-week follow-ups	NR
Xing 2011 <sup>83</sup>	- MA/n=120 - Fluoxetine/n=120	PMD (CCMD-3)	Stagnation of liver Qi, heart and spleen deficiency; liver depression and phlegm-heat	20 min/day, 7 days/week for 6 weeks	GV26, PC5	Fluoxetine 20mg/day for 6 weeks	HAMD	No differences in HAMD between two groups	No follow-up	NR

(Continued)

Table 2 (Continued).

Author/Year	Study Groups/No. of Participants	Disease (Diagnostic System)	TCM Syndrome Pattern	Acupuncture Interventions	Acupoints	Controls	Outcome Measures	Results (Compared with the Control Group) at Post-Treatment	Follow-Up	Adverse Events
Zhou et al 2007 <sup>84</sup>	- MA/n=30 - Fluoxetine/n=28	PMD (CCMD-3)	Liver and kidney Yin deficiency, spleen and kidney Yang deficiency, stagnated Qi transforming into fire, stagnation of phlegm and Qi	30 min/day, 6 days/week for 6 weeks	BL15, BL18, BL23, EX-HN1, GB13, GV24, SP6, ST36	Fluoxetine 20mg/day for 6 weeks	HAMD, 5-HIAA, NE, DA	(i) Lower HAMD in MA group (ii) No differences in 5-HIAA and NE levels between two groups; Lower DA level in MA group	No follow-up	NR
Gao et al 2014 <sup>89</sup>	- MA + Estazolam/n=32 - Estazolam/n=32	PM1 (CCMD-3)	NR	20 min/day, 6 days/week for 4 weeks	EX-B2	Estazolam 2 mg/day for 4 weeks	PSQI	Lower PSQI in MA + Estazolam group	No follow-up	NR
Xu 2020 <sup>90</sup>	- MA + Alprazolam/n=50 - Alprazolam/n=50	PM1 (CDTE-TCM)	NR	30 min/day, 7 days/week for 9 weeks	EX-HN1, GV24, HT7, KI3, LR3, PC6, SP6, ST36	Alprazolam 0.4–0.8 mg/day, 7 days/week for 9 weeks	PSQI	Lower PSQI in MA + Alprazolam group	No follow-up	NR
Ma 2016 <sup>91</sup>	- MA + Estazolam/n=35 - Estazolam/n=35	PM1 (CCMD-3)	NR	7 days/week for 4 weeks	EX, HT7, KI3, K17, KI10, LR3, SP6, SP10, ST36	Estazolam 2 mg/day, 7 days/week for 4 weeks	PSQI, FSH, E2	(i) Lower PSQI in MA + Estazolam group (ii) Higher E2 levels, and lower FSH levels in MA + Estazolam group	No follow-up	NR
Zhu et al 2016 <sup>92</sup>	- MA + Estazolam/n=37 - Estazolam/n=37	PM1 (CCMD-3)	Heart and Spleen deficiency	20 min/day, 5 days/week for 4 weeks	CV12, EX, EX-HN1, GV20, GV24, HT7, KI3, LR3, SP9, ST25	Estazolam 1 mg/day, 5 days/week for 4 weeks	PSQI	No differences in PSQI between two groups	No follow-up	NR



Ma et al 2011 <sup>95</sup>	- EA + Paroxetine/n=55 - Paroxetine/n=50	PMD (CCMD-3)	NR	- 45 min/day, 7 days/week for 6 weeks - dilatational wave, 8-9 mA	EX-HN3, GV20, LI4, PC6, ST36	Paroxetine 10mg/day for 6 weeks	HAMD	No differences in HAMD between two groups	No follow-up	- EA + Paroxetine/n=2 [dizziness (1); nausea (1)] - Paroxetine/n=3 [dizziness (1); elevated blood pressure (2)]
Liu et al 2019 <sup>93</sup>	- MA + Sertraline/n=40 - Sertraline/n=40	PMD (CCMD-3, ICD-10)	NR	30 min/day, 3 days/week for 12 weeks	BL23, CV4, HT7, KI3, LI4, LR3, SP6	Sertraline 50mg/day for 6 weeks	HAMD, FSH, E2, 5-HT, GABA	(i) Lower HAMD in MA + Sertraline group (ii) Lower FSH level in MA + Sertraline group; higher E2, 5-HT and GABA levels in MA + Sertraline group	No follow-up	NR
Ning 2015 <sup>94</sup>	- MA + Nilestriol + Fluoxetine/n=45 - Nilestriol + Fluoxetine/n=45	PMD (Psychiatry textbook)	NR	30 min/day, 7 days/week for 12 weeks	BL13, BL15, BL18, BL20, BL23, GV20, HT7, KI3, LI4, LR3	Nilestriol 2mg/15days + Fluoxetine 20mg/day for 12 weeks	HAMD, TESS	Lower HAMD and TESS in MA + Nilestriol + Fluoxetine group	No follow-up	NR

**Abbreviations:** NR, no report; MA, manual acupuncture; EA, electroacupuncture; PM, perimenopausal insomnia; PMD, perimenopausal depression; DSM-IV, Diagnostic and Statistical Manual of Mental Disorders (Fourth Edition); ICD-10, International classification of sleep disorders (Third Edition); CCMD-2-R, revised Chinese Classification of Mental Disorders (Second Edition); CCMD-3, Chinese Classification of Mental Disorders (Third Edition); ICD-10, International Classification of Diseases (10th edition); DTICA, Guidelines for Diagnosis and Treatment of Insomnia in Chinese Adults (2012 Edition); CDTE-TCM, Criteria of Diagnosis and Therapeutic Effect of Diseases and Syndromes in TCM; PSQI, Pittsburgh Sleep Quality Index; ISI, Insomnia Severity Index; AIS, Athens Insomnia Scale; KI, Kupperman Index; MRS, Menopause Rating Scale; Men-QoL, Menopause-Specific Quality of Life; HAMA, Hamilton Anxiety Scale; HAMD, Hamilton Depression Scale; SAS, Self-Rating Anxiety Scale; SDS, Self-Rating Depression Scale; WHOQOL-BREF, World Health Organization's quality of life scale-brief form questionnaire; TESS, Treatment Emergent Symptom Scale; PSG, polysomnography; MSMSMS, micromovement sensitive mattress sleep monitoring system; SOL, sleep onset latency; WASO, wake after sleep onset; TST, total sleep time; SE, sleep efficiency; ATs, awakening times; AA, average awakening; ArI, arousal index; REM, rapid eye movement; NI (2, 3, 4), 1st(2nd, 3rd, 4th) period of non-rapid eye movement sleep (NREM); FSH, follicle-stimulating hormone; LH, luteinizing hormone; E2, estradiol; 5-HT, 5-hydroxy tryptamine; NE, norepinephrine; DA, dopamine; GABA, gamma-aminobutyric acid; six syndrome patterns with liver as the core [liver stagnation (stasis); excessive liver fire due to emotional suppression; deficiency of kidney and hyperactivity of liver; liver depression invading the stomach; liver depression invading the heart]; five TCM syndrome patterns according to CDTE-TCM [excessive liver fire due to emotional suppression; disturbance of Heart due to phlegm heat; Yin deficiency leading to excessive fire; Heart and Spleen deficiency; Heart and Gallbladder Qi deficiency]; BL8, Luoque; BL13, Feishu; BL15, Xinsu; BL17, Geshu; BL18, Ganshu; BL20, Pishu; BL21, Weishu; BL23, Shenshu; BL62, Shenmai; CV3, Zhongji; CV3, Zhongji; CV4, Guanyuan; CV6, Qihai; CV10, Xiwuan; CV12, Zhongwan; EX, Anmian; EX-B2, Jiaji; EX-CAI, Zigong; EX-HN1, Sishencong; EX-HN3, Yintang; GB13, Benshen; GB14, Yangbai; GB15, Toulinqi; GB20, Fengchi; GB25, Jingmen; GV3, Yaoyangguan; GV4, Mingmen; GV14, Dazhui; GV16, Fengfu; GV19, Houding; GV20, Baihui; GV21, Qianting; GV24, Shenting; GV26, Shuigou; HT7, Shenmen; KI3, Taixi; KI6, Zhaohai; KI7, Fuliu; KI10, Yingu; KI13, Qixue; KI17, Shangqu; LI4, Hegu; LR3, Taichong; LR14, Qimen; LU7, Lieque; PC5, Jianshi; PC6, Neiguan; PC7, Daling; SI3, Houxi; SP4, Gongsun; SP6, Sanyinjiao; SP8, Diji; SP9, Yinlingquan; SP10, Xuehai; SP15, Daheng; ST25, Tianshu; ST26, Wailling; ST36, Zusanli; ST40, Fenglong.

**Table 3** Results of Meta-Analyses for Existing RCTs

Comparison	Study (n); Participants (n)	Outcomes	Mean/Std. Mean Difference IV, Random, 95% CI	P
Acupuncture vs waitlist-control or placebo-/sham- acupuncture	RCTs (n = 4); PMI women (n = 283) RCTs (n < 3, no meta-analysis); PMD women (n = 126)	PSQI	MD = -4.03, 95% CI (-6.85, -1.21)	<0.01
Acupuncture vs hypnotic	RCTs (n = 12); PMI women (n = 1204) RCTs (n = 4); PMI women (n = 274)	PSQI KI	MD = -2.24, 95% CI (-3.13, -1.36) MD = -5.95, 95% CI (-10.68, -1.21)	<0.01 0.01
Acupuncture vs antidepressant/antidepressant + HRT	RCTs (n = 2); PMD women (n = 1842) RCTs (n = 3); PMD women (n = 169) RCTs (n = 6); PMD women (n = 504) RCTs (n = 3); PMD women (n = 341) RCTs (n = 5); PMD women (n = 410)	HAMD at post-treatment HAMD at 2-week follow-up HAMD at 4-week follow-up HAMD at 12-week follow-up KI	SMD = -0.54, 95% CI (-0.91, -0.16) SMD = -0.64, 95% CI (-0.95, -0.33) SMD = -1.36, 95% CI (-2.72, 0.00) SMD = -2.73, 95% CI (-6.14, 0.67) MD = -2.80, 95% CI (-5.60, -0.01)	<0.01 0.01 0.05 0.12 0.05
Acupuncture + hypnotics vs hypnotics	RCTs (n = 4); PMI women (n = 308)	PSQI	MD = -2.80, 95% CI (-4.23, -1.37)	<0.01
Acupuncture + antidepressant/antidepressant + HRT vs antidepressant or antidepressant + HRT	RCTs (n = 3); PMD women (n = 275)	HAMD at post-treatment	SMD = -0.82, 95% CI (-1.07, -0.58)	<0.01

**Note:** Data from references 19 and 50.

**Abbreviations:** PSQI, Pittsburgh Sleep Quality Index; KI, Kupperman Index; HAMD, Hamilton Depression Scale; HRT, hormone replacement therapy.

In the first category, six RCTs confirmed significant improvements acupuncture produced on sleep duration and quality<sup>51-54</sup> as well as depressed mood,<sup>55,56</sup> when compared with waitlist or placebo controls. Thirteen RCTs compared the effects between acupuncture and various hypnotics including Estazolam, Alprazolam, and Eszopiclone.<sup>49,57-68</sup> All these studies reported that acupuncture reduced global scores of Pittsburgh Sleep Quality Index (PSQI)/Athens Insomnia Scale (AIS) more effectively than hypnotics, except for two trials<sup>58,61</sup> that reported the sleep-promoting effects between the two therapies were equivalent. Twelve out of these 13 trials employed the PSQI as an outcome measure, and the results of meta-analysis favored acupuncture [MD = -2.24, 95% CI (-3.13, -1.36), *p* < 0.01]. Twenty-one RCTs compared the effects between acupuncture and antidepressants including escitalopram, fluoxetine, and deanxit,<sup>56,69-84</sup> or the effects between acupuncture and antidepressants combined with HRT.<sup>85-88</sup> All trials adopted the Hamilton Depression Scale (HAMD) as an outcome measure. The results of meta-analysis favored acupuncture in reducing the HAMD global scores [SMD = -0.54, 95% CI (-0.91, -0.16), *p* < 0.01]. Some of these RCTs also reported that the effects of acupuncture remained no weaker than those of Western medications at 2-, 4-, and 12-week follow-ups, suggesting an intermediate- to long-term antidepressive efficacy of acupuncture (Table 3).

In the second category, the meta-analysis pooled the effects of four RCTs<sup>89-92</sup> and supported a better effect of acupuncture combined with hypnotics in reducing PSQI global score, in comparison with hypnotics alone [MD = -2.80, 95% CI (-4.23, -1.37), *p* < 0.01]. Two RCTs<sup>93,94</sup> indicated that acupuncture combined with antidepressants produced lower HAMD scores than antidepressants alone. Although another RCT<sup>95</sup> found no statistically significant differences in HAMD scores between the two therapies at post-treatment, the clinical effectiveness rate (calculated based on the HAMD reduction rate) favored the combination therapy (acupuncture + Paroxetine 90.91% vs Paroxetine alone 78.00%). The meta-analysis based on these three RCTs favored the combination therapy in reducing HAMD global scores as well [SMD = -0.82, 95% CI (-1.07, -0.58), *p* < 0.01] (Table 3).

### Safety of Acupuncture for PMI and PMD

The incidence of AEs associated with each intervention in the included RCTs is summarized in Appendix 1 (in order of highest % for acupuncture). Consistent with the

previous studies that acupuncture is safe to manipulate,<sup>36,37</sup> there appears to be few risks associated with utilizing acupuncture in the management of PMI/PMD as the AEs caused by acupuncture were minimal and very mild. Hematoma (7.72%), the most frequent complaint, usually faded within a few days.<sup>19,50</sup> The incidence of other acupuncture-related AEs was less than 4%, with the exception of sweating (6.76%). The latter however is likely to be related to menopause rather than acupuncture as this is a common symptom for perimenopausal women.<sup>13,96</sup> The incidence and severity of AEs associated with psychotropic agents (hypnotics or antidepressants) far exceeded those of acupuncture. The most common of these were daytime sleepiness and/or fatigue (29.38%), breast tenderness (22%) and night-time sleep disturbance (18.18%). These findings are noteworthy given the problem of PMI/PMD and suggest that some of these treatments may exacerbate rather than alleviate the symptoms. Only one RCT<sup>97</sup> used HRT alone as a control but still identified at least three types of AEs.

These findings are highly supportive of the use of acupuncture as a therapeutic strategy in PMI and/or PMD. The data suggest that it does not matter whether the therapeutic effect of acupuncture is better or only equivalent to that of HRT and/or hypnotics/antidepressants, acupuncture can be supported as a front-line, first-choice therapeutic because of its exemplary safety profile.

## Implications for Clinical Practice

This section discusses the meaningfulness and feasibility of acupuncture for PMI and PMD. In addition to improving sleep or depression outcomes, acupuncture also showed positive effects on indices of climacteric symptoms (ie, Kupperman Index, Menopause Rating Scale, etc), quality of life in menopause (ie, Menopause-Specific Quality of Life, World Health Organization's quality of life scale-brief form questionnaire, etc), and/or anxiety symptoms (ie, Hamilton Anxiety Scale, etc). (Tables 2 and 3) These findings suggest that women with PMI/PMD as their chief complaint benefited from acupuncture in a broad range of signs and symptoms associated with life change. This finding is consistent with the "holistic medicine" concept highlighted in the TCM, which views the body as a complete entirety.<sup>43,44,98</sup> "Healthy" in TCM does not simply mean "disease free"; it means that all Zang and Fu (organs), meridians and collaterals are working in harmony, and the flow of Qi, blood and body fluids is at ease, and emotions and spiritual state are in balance.<sup>26,28,43</sup> In terms of TCM theory, a diseased condition is not only a

problem in a local part of the body but a local reflection of disharmony of the entire body.<sup>43,44</sup> Hence, TCM therapies generally address a diseased condition (condition with an imbalance between Yin and Yang) by regulating and mobilizing the entire body rather than just regulating a single factor (one symptom or one part/organ of the body).<sup>43,44,98</sup> As suggested, any potential climacteric condition (eg, nocturnal hot flushes, chronic pain, neuropsychiatric problems, etc) that may adversely affect sleep and/or mood should be considered when menopausal women seek medical advice.<sup>23</sup> This circumstance is in line with the "holistic medicine" theory of TCM, which makes acupuncture more worthy of being recommended.

Limited evidence suggests acupuncture is likely to have an add-on effect to hypnotic and/or antidepressive drugs. However, in seven trials focusing on acupuncture combined with standard care, only one study<sup>95</sup> reported the AEs; no trials included follow-up (Tables 2 and 3). Consequently, the safety and long-term effects of this integrative remedy is still less well understood. Consumers who are not familiar with acupuncture may not be willing to give up drug-based medicines immediately.<sup>19</sup> Whether reduced use of conventional drugs can be made up by the addition of acupuncture is a topic with important clinical significance because reduction of dosage in conventional drugs means fewer risks of side effects. Likewise, this add-on effect of acupuncture is also of importance in personalized medicine. Given the efficacy for all therapies may be hampered by the fact that women respond differently to each, acupuncture is ideal to be recommended as the first therapy in a layered approach, so that if acupuncture is ineffective then lower dose Western medication (eg, HRT, psychotropic agents, etc) could be tried in combination with the acupuncture prior to direct usage of pharmacotherapy or higher dose of pharmacotherapy. This treatment strategy may be particularly suitable for those women with PMI/PMD who are intolerant of drugs.

Acupoint selection is one of the decisive factors affecting the clinical effectiveness of acupuncture.<sup>99</sup> As illustrated in Table 2, the three most commonly used acupoints for PMI were Sanyinjiao (SP6), Baihui (GV20), and Shenmen (HT7), while the three most commonly used acupoints for PMD were GV20, SP6, and Yintang (EX-HN3). According to "Indications of Acupuncture Points [GB/T 30233-2013]" (National Standard of People's Republic of China, 2013 Version),<sup>100</sup> GV20, HT7, and EX-HN3 are classic acupoints for the treatment of psychiatric and psychological disorders. SP6 is the preferred acupoint for gynaecological disorders, and together with HT7, it promotes sleep. Based on TCM

syndrome patterns, for any deficient patterns, the Back-shu are used as these acupoints where the Qi of the internal organs is accumulated, and are used to strengthen the corresponding organs.<sup>100</sup> Ganshu (BL18), the Back-shu of liver, as well as Shenshu (BL23), the Back-shu of kidney, were selected in many trials (Table 2), which is consistent with the aforementioned findings that smoothing liver and nourishing kidney is the general principle for all perimenopausal disorders. In treating comorbid PMI and PMD, practitioners are hence recommended to select Back-shu of liver and kidney, and/or acupoints of Liver Meridian of Foot-Jueyin and Kidney Meridian of Foot-Shaoyin, in addition to the classical acupoints utilized for mental disease/disorders. Both MA and EA showed significant clinical benefits for PMI/PMD (Table 2). However, no study has compared MA with EA. The differences in clinical effects and underlying mechanisms of MA and EA should be explored in future clinical trials and animal studies.

Our comprehensive retrieval of literature failed to identify any RCT carried outside of China, reflecting the extremely inadequate awareness and attention paid to acupuncture in PMI/PMD management among Western researchers, despite well-documented evidence supporting the growing widespread use of CAM therapy for psychiatric complaints among Western populations.<sup>23,101</sup> Meanwhile, some surveys alluded that most Western women may also underestimate the value and role of acupuncture as a management strategy for PMI and/or PMD. As reported, only 4.8% women in Australia have visited an acupuncturist due to menopausal symptoms;<sup>102</sup> In the UK, 6.4% climacteric women utilize aromatherapy, reflexology, or acupuncture to reduce symptoms.<sup>103</sup> This review thereby is expected to evoke awareness of the potential of acupuncture among both perimenopausal women and clinicians working in this field (ie, gynaecologists, psychiatrists, and naturopaths) in Western countries. Given all the participants in the included RCTs were Chinese women, generalizing the currently optimistic results to women of other races requires some further evidence.<sup>104</sup> According to the differences in awareness, perception, and tolerance of acupuncture between Westerners and Chinese, limited modification to the nature acupuncture prescription/protocol summarized in published Chinese studies may also enhance the acceptance and applicability of acupuncture among Western perimenopausal women.

Another issue that has not yet been addressed is whether interventions can be provided during pre-menopause to prevent or reduce the occurrence of PMI and/or PMD. Women with a history of depression<sup>105</sup> or experiencing stressful

events<sup>6</sup> at pre-menopause are at high risk for PMD. Women with a history of severe premenstrual syndrome and/or psychological disturbances may benefit from preventive treatments for reducing the likelihood of PMI or ameliorating the symptoms.<sup>10</sup> These women may be a target group for preventive acupuncture (also called “acupuncture pre-treatment”), which is in line with the idea of “preventive treatment of disease” (治未病, prevent individuals from being trapped by diseases) in TCM theory.<sup>44</sup> Despite the lack of direct evidence, acupuncture pre-treatment may have positive preventive effects for perimenopausal symptoms. Most research in this area has been based on animal models. Acupuncture pre-treatment was observed to reduce oxidative stress levels,<sup>106,107</sup> inhibit the hyperactivity of hypothalamic-pituitary-ovary (HPO) axis,<sup>106</sup> as well as regulate the inflammatory response and disorders of the immune system<sup>108</sup> in either ageing female rats or rats that were ovariectomized to mimic menopause. Li et al reported that EA pre-treatment (EA was provided 10 days before chronic stress) effectively prevented the depression-like behavior of rats after undergoing chronic unpredicted mild stress (CUMS).<sup>109</sup>

## Implications for Research

The data from the few clinical trials discussed here appears to be promising, it is however too early to draw any definitive conclusions. Many RCTs have missing components in their methodology, which dilutes and weakens the quality of evidence, and may hinder the development of acupuncture as a form of evidence-based healthcare for comorbid depression and insomnia during perimenopause.

We have summarized the common deficiencies among these RCTs and listed the potential negative consequences in Table 4. Detailed assessment and analysis on quality of evidence is described in our published SRs/MAs.<sup>19,50</sup> As reported, poor-quality acupuncture studies usually show a higher proportion of positive results than high-quality studies.<sup>104</sup> Well-designed trials with robust methodology and high-quality reporting quality are warranted in future research.

## Underlying Mechanisms of Acupuncture's Effects Against Depression and Insomnia During Perimenopause

It is challenging to explore the mechanisms underlying the effects of acupuncture on depression and insomnia during

**Table 4** Common Defects of Study Design and Reporting Quality Among Current RCTs

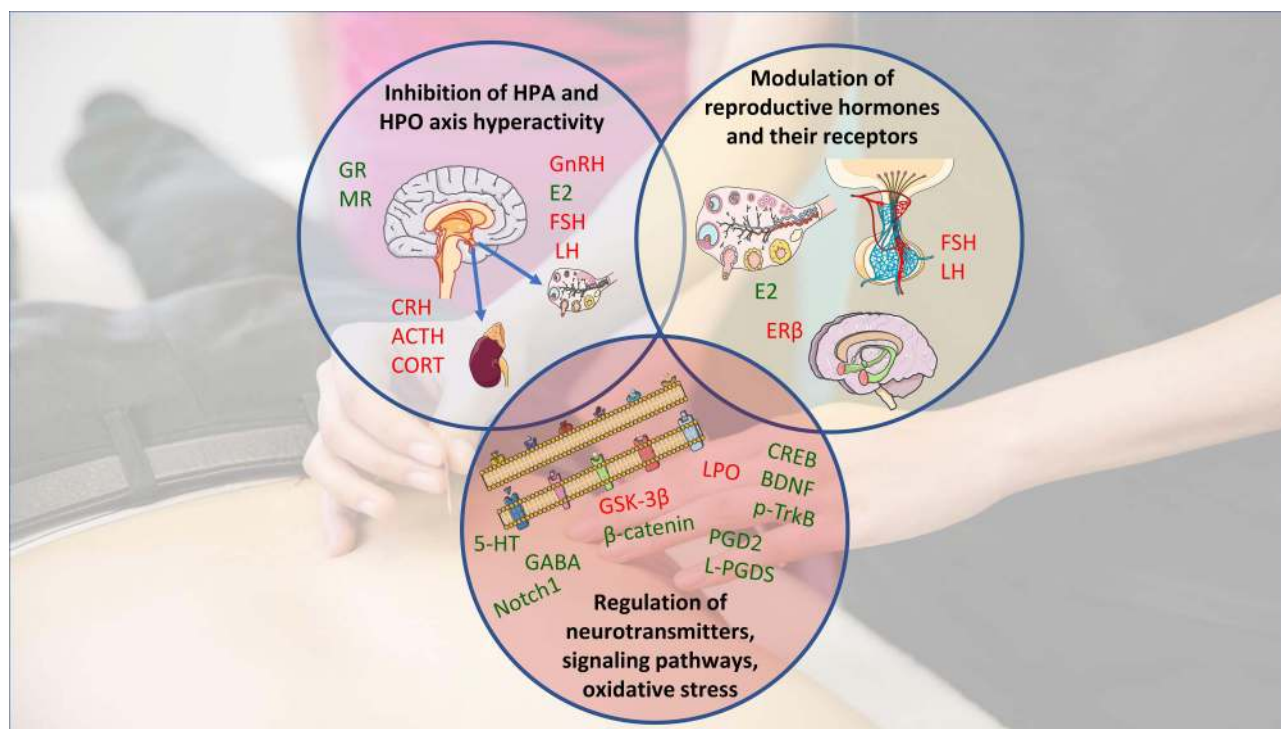
Items	Limitations	Potential Negative Consequences
Study design	Lack of appropriate sample size estimation	Diminishment of credibility of the results; reduction in likelihood of finding an effect of the treatment
	Lack of sham-/placebo- acupuncture as parallel control in trials comparing acupuncture with Western medications	Potential bias and uncertainty on the placebo effects of acupuncture
	Without appropriate statistics (ie intention-to-treat analysis, etc) for data of those withdrawal/dropout patients	Increased risk of an overestimation/underestimation of the efficacy of acupuncture or Western medications
	Lack of follow-ups	Unable to evaluate medium- and long- term effects/safety of acupuncture
	Objective indices (ie, polysomnography, actigraphy, etc) is seldom used in PMI studies	(i) Unable to understand the effects of acupuncture on sleep architecture (ii) A biased judgement or even a question on acupuncture's real efficacy due to a mismatch between the subjective and objective sleep-wake duration
	No discussion of the effects of acupuncture responding to specific/each TCM syndrome pattern (all TCM syndrome patterns are mixed for efficacy assessment)	Difficult to judge the real therapeutic effect of acupuncture
Reporting quality	Lack of reports on if or how allocation concealment and blinding of patients/ outcome assessments are performed	Inadequate blinding is associated with an exaggeration of the estimated efficacy
	Lack of description and in-depth analysis of the specific causes of withdrawal/ dropout	Unable to understand patient's compliance and acceptance of acupuncture, placebo or Western medications
	Protocols and/or registration Information are not always available	Greatly weakens the reliability of the evidence
	Incomplete descriptions of needling details and/or treatment regimen, as well as acupuncturists' background	(i) Poor reproducibility of the trial results (ii) Hinder the clinical promotion of effective acupuncture prescription

the transition to menopause in only RCTs. To enhance our understanding, investigation via animal studies is a valuable option. Together with clinical findings, animal studies can shed light on the mechanisms of action of acupuncture (Figure 1) as well as give an insight into the direction of further research. Findings of animal studies are summarized in Table 5.

## Modulation of Reproductive Hormones and Their Receptors

The established association between fluctuating hormonal milieu and sleep as well as mood is one explanation for the development of insomnia and/or depression during perimenopause.<sup>2-4,13,110</sup> The endocrine system is regarded as one of the principal intrinsic factors affecting women's sleep and mood during their reproductive life span.<sup>1,14,96</sup> As estrogen is involved in the regulation and stabilization of the circadian rhythm system, its physiological fluctuation as well as a decreased sensitivity to estrogens in the hypothalamus during perimenopause contributes to circadian rhythm disturbances, and possibly the subsequent development of PMI.<sup>4</sup> Woods et al investigated 286 women approaching menopause by

establishing a mixed effects model, and found that in addition to age, crucial factors influencing sleep included the usage of exogenous hormones and women's endogenous reproductive hormone levels.<sup>111</sup> The former can be used to explain the improvement that HRT produces in terms of PMI; and the latter may be a pathway to understand the possible mechanism underlying the benefits of acupuncture. That is, acupuncture moderates estrogen level in perimenopausal women as shown in Table 2. Likewise, the changing hormonal milieu also contributes to the depressive symptoms in women who are in menopausal transition.<sup>112</sup> Some longitudinal analyses have suggested the correlation between reproductive hormones [eg, estradiol (E2), follicle-stimulating hormone (FSH), luteinizing hormone (LH), etc] levels and sleep disturbances<sup>1</sup> or depressive symptoms<sup>112</sup> in perimenopause. Increased FSH levels are correlated with trouble staying asleep, while decreased E2 levels are correlated with both difficulty in falling and staying asleep.<sup>1</sup> A strong linkage between frequent nocturnal awakenings and altered sex hormone levels (increments in FSH, and decrements in E2 and estrone) were reported in both the Study of Women's Health Across the Nation (SWAN) and the Seattle Midlife Women's Health Study (SMWHS).<sup>10</sup>



**Figure 1** Potential mechanisms by which acupuncture may improve perimenopausal depression and insomnia. Manual- and/or electro-acupuncture may alter hypothalamic-pituitary-adrenal and -ovarian hyperactivity; modulate reproductive hormones and their receptors, or regulate neurotransmitters, signaling pathways, and oxidative stress. Green indicates an upregulation/increase by acupuncture (↑); red indicates a downregulation/decrease (↓). Acupuncture may also improve perimenopausal depression and insomnia by improving vasomotor symptoms, while this indirect effect is not shown. Images are adapted from Servier Medical Art under Creative Commons CC-BY license. **Abbreviations:** HPA, hypothalamic-pituitary-adrenal; HPO, hypothalamic-pituitary-ovary; GR, glucocorticoid receptor; MR, mineralocorticoid receptor; GnRH, gonadotropin-releasing hormone; E2, estradiol; FSH, follicle-stimulating hormone; LH, luteinizing hormone; CRH, corticotropin-releasing hormone; ACTH, adrenocorticotropic hormone; CORT, cortisol; ER $\beta$ , estrogen receptor beta; 5-HT, 5-hydroxytryptamine; GABA, gamma-aminobutyric acid; CREB, cAMP-response element-binding protein; BDNF, brain-derived neurotrophic factor; p-TrkB, phosphorylated-TrkB; PGD-2, prostaglandin D2; L-PGDS, lipocalin-type prostaglandin D synthase; LPO, lipid peroxidation; GSK-3 $\beta$ , glycogen synthase kinase-3 beta.

The alteration of reproductive hormone levels due to ovarian aging also contributes to vasomotor symptoms via at least three pathways: 1) slight increases in core body temperature; 2) altered thermal threshold/resetting and narrowing of the thermoregulatory system; and 3) a decreased thermoneutral zone in the brain.<sup>13,110</sup> The latter two alterations can reduce women's ability to tolerate nocturnal hot flashes and subsequently cause sleep disruption.<sup>110</sup> An interesting finding is the inconsistent results in the links between different sleep indexes and FSH. Data from SWAN showed a relationship between the increased FSH over time and more slow wave sleep (SWS) recorded by polysomnography (PSG), which contrasts with findings correlating hormone fluctuation with subjective sleep indexes.<sup>10</sup> Among women with PMI, Fu et al also observed that acupuncture induced reductions in both wake after sleep onset (WASO) and arousal index (ArI),<sup>51</sup> which were negatively correlated with E2 levels but positively correlated with FSH.<sup>113</sup> Estrogen is a mood-elevator as well, and its effect on emotional functions is partly mediated by the amygdala and hypothalamus.<sup>114</sup> New onset of PMD was strikingly associated

with increased FSH and LH levels.<sup>112</sup> Decreasing E2 levels that occur approaching menopause are weakly linked to more depressive symptoms.<sup>115</sup> Exogenous estrogen (in the form of E2) has also been shown to be related to the reduction of PMD.<sup>114</sup> Among women without a history of depression, high variability in levels of FSH, LH, and E2 is linked to increased prevalence of PMD.<sup>3</sup>

Many clinical and animal studies cited in this review have confirmed the regulation of serum sex hormone levels by acupuncture (Tables 2 and 5). Despite the lack of correlational analysis, almost all studies showed a consistent trend—the amelioration of PMI and/or PMD produced by acupuncture, along with increments in circulating E2 and/or decrements in FSH and LH levels. Researchers thereby inferred that the improvement of PMI/PMD by acupuncture might be achieved via the modulation of expression of one or more of these three hormones.<sup>116–119</sup>

The estrogen receptors (ER $\alpha$  and ER $\beta$ ) are closely related to the pathophysiology of climacteric-related neurological and psychiatric illness,<sup>120</sup> and their aberrant

**Table 5** Summary of Animal Studies Determining the Mechanisms Underlying Acupuncture on PMI and PMD

Author/Year	Animals	Disease Models	Methods of Modeling	Study Groups/No. of Participants	Interventions	Acupuncture Protocol	Acupoints	Outcome Measures	Results
Cao et al 2019 <sup>152</sup>	SD rats, 280–320g, 12 months	PMI	(i) OVX (ii) Electrical stimulation	- EA/n= 12 - Model/n= 12 - Sham-surgery/n= 12	- EA/OVX + electrical stimulation + EA - Model/OVX + electrical stimulation - Sham-surgery/sham-OVX + electrical stimulation	- 20 min/day for 14 days - Dense wave, 50Hz	SP6	(i) MER (REM, SWS) (ii) 5-HT, 5-HIAA, 5-HT1A in hippocampus	(i) EA increased REM and SWS (ii) EA increased 5-HT and 5-HT1A levels; no significant change in 5-HIAA level
Cao et al 2020 <sup>136</sup>	Wistar rats, 230–270g, 5–7 months	PMI	(i) OVX (ii) Electrical stimulation	- EA/n= 10 - Model/n= 10 - Sham-surgery/n= 10	- EA/OVX + electrical stimulation + EA - Model/OVX + electrical stimulation - Sham-surgery/sham-OVX + electrical stimulation	- 15 min/day for 21 days - Dense wave, 50Hz	EX-HNI, HT7	(i) MER (TST, REM, SWS, LS) (ii) L-PGDS, PGD2, PGE2 in CSF (iii) GABA in VLPO	(i) EA increased REM, SWS; no significant change in TST and LS (ii) EA increased L-PGDS and PGD2 levels; no significant change in PGE2 level (iii) EA increased GABA level
Jin et al 2010 <sup>89</sup>	SD rats, 230–270g, 3 months	PMI	(i) OVX (ii) Electrical stimulation	- EA/n= 30 - Model/n= 30 - Sham-surgery/n= 30	- EA/OVX + electrical stimulation + EA - Model/OVX + electrical stimulation - Sham-surgery/sham-OVX + electrical stimulation	- 30 min/day for 7 days - Continuous wave, 15Hz, 2mA	BL23, SP6	(i) SOL and TST (ii) Heat-resistant time (iii) Energy (iv) Times of locomotor activity	(i) EA increased TST and reduced SOL (ii) EA increased heat-resistant time (iii) EA increased energy (iv) No significant change in times of locomotor activity (v) The earlier the intervention of EA in the perimenopausal period, the better the effect

(Continued)

Table 5 (Continued).

Author/Year	Animals	Disease Models	Methods of Modeling	Study Groups/No. of Participants	Interventions	Acupuncture Protocol	Acupoints	Outcome Measures	Results
Jin et al 2011 <sup>190</sup>	SD rats, 150–180g	PMI	(i) OVX (ii) Electrical stimulation	- EA/n= 30 - Model/n= 30 - Sham-surgery/n= 30	- EA/OVX + electrical stimulation + EA - Model/OVX + electrical stimulation - Sham-surgery/sham-OVX + electrical stimulation	- 30 min/day for 7 days - Continuous wave, 15Hz, 2mA	BL23, SP6	(i) SOL and TST (ii) Heat-resistant time (iii) Energy	(i) EA increased TST and reduced SOL (ii) EA increased heat-resistant time (iii) EA increased energy (iv) The earlier the intervention of EA in the perimenopausal period, the better the effect
Xie 2013 <sup>116</sup>	SD rats, 216–245.8g, 6–8 weeks	PMI	OVX	- EA/n= 25 - Model/n= 25 - Sham-surgery/n= 25 - Sham-EA/n= 25	- EA/OVX + EA - Model/OVX - Sham-surgery/sham-OVX - Sham-EA/OVX + sham-EA	- 15 min/day for 7 days - Continuous wave, 2Hz	BL23, EX	(i) EEG/EMG recording systems for rats and mice (WASO, REM, NREM) (ii) Serum FSH, E2 (iii) Estrogen receptor in VLPO and TMN (iv) Weight	(i) EA increased NREM, and reduced WASO and REM (ii) EA increased E2 and decreased FSH levels (iii) No significant change in estrogen receptor (iv) EA reduced weight
Yu 2012 <sup>117</sup>	SD rats, 230–270g, 6–8 weeks	PMI	OVX	- EA/n= 12 - Model/n= 12 - Sham-surgery/n= 12 - Sham-EA/n= 12	- EA/OVX + EA - Model/OVX - Sham-surgery/sham-OVX - Sham-EA/OVX + sham-EA	- 15 min every other day for 7 days - Continuous wave, 2Hz	EX	(i) EEG/EMG recording systems for rats and mice (WASO, REM, NREM) (ii) Serum FSH, E2, LH	(i) EA increased NREM and reduced WASO; no significant change in REM; EA alleviated sleep fragmentation during the daytime (ii) EA increased E2 and reduced FSH levels; no significant change in LH level



Yang 2017 <sup>121</sup>	SD rats, 230–270g, 6–8 weeks	PMI	OVX	- EA/n= 40 - Model/n= 40 - Sham-surgery/n= 40 - Sham-EA/n= 40	- EA/OVX + EA - Model/OVX - Sham-surgery/ sham-OVX - Sham-EA/OVX + sham-EA	- 15 min/day for 7 days - Continuous wave, 15Hz	BL23, EX	(i) EEG/EMG recording systems for rats and mice (WASO, REM, NREM) (ii) serum E2 and 5-HT (iii) Adrenocortical E2 (iv) Hypothalamic 5-HT, NE, ER- $\alpha$ mRNA, ER- $\beta$ mRNA	(i) EA increased NREM, and reduced WASO and REM; EA alleviated sleep fragmentation during the daytime (ii) EA increased E2 and 5-HT levels (iii) EA increased E2 level (iv) EA increased 5-HT, and decreased NE and ER $\beta$ mRNA; no significant change in ER $\alpha$ mRNA
Jing et al 2020 <sup>174</sup>	SD rats, 190–210g, 56–62days	PMD	(i) OVX (ii) CUMS	- EA/n= 10 - Control/n= 10 - Model/n= 10 - Sham-surgery/n= 10 - Clomipramine/ n= 10	- EA/OVX + CUMS + EA - Control/no treatment - Model/OVX + CUMS - Sham-surgery/ sham-OVX + CUMS - Clomipramine/ OVX + CUMS + Clomipramine	- 20 min/day for 28 days-isperse- dense wave, 4/ 20Hz, 18V	BL23, GV20, SP6	(i) Behavioral tests (OFT, SPT) (ii) Serum E2, LH, GnRH (iii) GSK-3 $\beta$ mRNA, $\beta$ -catenin mRNA in hippocampus (iv) $\beta$ -Catenin protein, p- $\beta$ -catenin protein in hippocampus	(i) EA improved rats' depression-like behavior in behavioral tests (ii) EA increased E2, and decreased LH and GnRH levels (iii) EA decreased GSK-3 $\beta$ mRNA and increased $\beta$ -catenin mRNA expression (ii) EA increased $\beta$ -catenin protein and decreased p- $\beta$ -catenin protein expression
Guo et al 2019 <sup>145</sup>	KM mice, 18–22g	PMD	(i) OVX (ii) CUMS	- EA/n= 10 - Control/n= 10 - Model/n= 10 - Clomipramine/ n= 10	- EA/OVX + CUMS + EA - Control/no treatment - Model/OVX + CUMS - Clomipramine/ OVX + CUMS + Clomipramine	- 20 min/day for 28 days- disperse-dense wave, 2/10Hz, 18V	BL23, GV20, SP6	(i) Behavioral tests (FST, IAT, ADE, TSE) (ii) Serum E2, FSH, LH (iii) 5-HT, NE, DA in hippocampus	(i) EA improved mice' depression-like behavior in behavioral tests (ii) EA increased E2 and decreased LH and FSH levels (ii) EA increased 5-HT, NE and DA levels

(Continued)

Table 5 (Continued).

Author/Year	Animals	Disease Models	Methods of Modeling	Study Groups/No. of Participants	Interventions	Acupuncture Protocol	Acupoints	Outcome Measures	Results
Seo et al 2018 <sup>170</sup>	SD rats, 250–300g	PMD	OVX	- EA/n= NR - Model/n= NR - Sham-surgery/n= NR - Sham-EA/n= NR	- EA/OVX + EA - Model/OVX - Sham-surgery/sham-OVX - Sham-EA/OVX + sham-EA	60 seconds/day for 4 days	SP6	(i) Behavioral tests (FST, OFT, EPM) (ii) E2 and estrogen receptor expression in plasma and hippocampus (iii) BDNF and p-TrkB receptor in hippocampus (iv) NPY in hippocampus	(i) EA improved rats' depression-like behavior in behavioral tests (ii) no significant change in E2 level or estrogen receptor expression (iii) EA increased BDNF and p-TrkB receptor levels (iv) EA increased NPY levels
Deng et al 2017 <sup>185</sup>	SD rats, 190–210g, 56–62days	PMD	(i) OVX (ii) CUMS	- EA/n= 12 - Control/n= 12 - Model/n= 12 - Clomipramine/n= 12	- EA/OVX + CUMS + EA - Control/no treatment - Model/OVX + CUMS - Clomipramine/OVX + CUMS + Clomipramine	- 20 min/day for 28 days-disperse-dense wave, 4/20Hz, 18V	BL23, GV20, SP6	(i) Behavioral tests (FST, OFT) (ii) MAP-2, Notch1, Jagged1, Hes1 in hippocampus (iii) MAP-2 mRNA, Notch1 mRNA, Jagged1 mRNA, Hes1 mRNA in hippocampus	(i) EA improved rats' depression-like behavior in behavioral tests (ii) EA increased MAP-2 protein and Notch1 protein levels, and decreased Jagged1 protein and Hes1 protein levels (iii) EA increased MAP-2 mRNA and Notch1 mRNA expression, and decreased Jagged1 mRNA and Hes1 mRNA expression
Deng 2017 <sup>177</sup>	SD rats, 190–210g, 56–62days	PMD	(i) OVX (ii) CUMS	- EA/n= 10 - Control/n= 10 - Model/n= 10 - Sham-surgery/n= 10 - Clomipramine/n= 10	- EA/OVX + CUMS + EA - Control/no treatment - Model/OVX + CUMS - Sham-surgery/sham-OVX + CUMS - Clomipramine/OVX + CUMS + Clomipramine	- 20 min/day for 28 days-disperse-dense wave, 4/20Hz, 18V	BL23, GV20, SP6	(i) Behavioral tests (FST, OFT, SPT) (ii) GSK-3β, β-catenin in hippocampus (iii) β-catenin protein, p-β-catenin protein in hippocampus (iv) GSK-3β mRNA, β-catenin mRNA in hippocampus	(i) EA improved rats' depression-like behavior in behavioral tests (ii) EA decreased GSK-3β and increased β-catenin contents (iii) EA increased β-catenin protein expression; no significant change in p-β-catenin protein expression (iv) EA decreased GSK-3β mRNA and increased β-catenin mRNA expression

Huangfu 2018 <sup>129</sup>	SD rats, 190–210g, 56–62days	PMD	(i) OVX (ii) CUMS	- EA/n= 10 - Control/n= 10 - Model/n= 10 - Clomipramine/ n= 10	- EA/OVX + CUMS + EA - Control/no treatment - Model/OVX + CUMS - Clomipramine/ OVX + CUMS + Clomipramine	- 20 min/day for 28 days- disperse-dense wave, 4/20Hz, 18V	BL23, GV20, SP6	(i) Behavioral tests (FST, OFT, SPT, TSE) (ii) Glucocorticoid receptor, mineralocorticoid receptor in hippocampus	(ii) EA improved rats' depression-like behavior in behavioral tests (ii) EA increased glucocorticoid receptor and mineralocorticoid receptor levels
Jiang 2017 <sup>124</sup>	SD rats, 190–210g, 56–62days	PMD	(i) OVX (ii) CUMS	- EA/n= 12 - Control/n= 12 - Model/n= 12 - Sham-surgery/n= 12 - Clomipramine/ n= 12	- EA/OVX + CUMS + EA - Control/no treatment - Model/OVX + CUMS - Sham-surgery/ sham-OVX + CUMS - Clomipramine/ OVX + CUMS + Clomipramine	- 20 min/day for 28 days- disperse-dense wave, 4/20Hz, 18V	BL23, GV20, SP6	(i) Behavioral tests (FST, SPT, TSE) (ii) Serum E2, FSH, LH, GnRH, CRH, ACTH, CORT, $\beta$ -EP	(i) EA improved rats' depression-like behavior in behavioral tests (ii) EA increased E2 and $\beta$ -EP, and decreased FSH, LH, GnRH, CORT, ACTH and CRH levels
Jiang et al 2017 <sup>127</sup>	SD rats, 190–210g, 8–9 weeks	PMD	(i) OVX (ii) CUMS	- EA/n= 12 - Control/n= 12 - Model/n= 12 - Sham-surgery/n= 12 - Clomipramine/ n= 12	- EA/OVX + CUMS + EA - Control/no treatment - Model/OVX + CUMS - Sham-surgery/ sham-OVX + CUMS - Clomipramine/ OVX + CUMS + Clomipramine	- 20 min/day for 28 days- disperse-dense wave, 4/20Hz, 18V	BL23, GV20, SP6	(i) Behavioral test (SPT) (ii) Serum E2, LH, GnRH, $\beta$ -EP	(i) EA improved rats' depression-like behavior in behavioral test (ii) EA increased E2 and $\beta$ -EP, and decreased LH and GnRH levels

(Continued)

Table 5 (Continued).

Author/Year	Animals	Disease Models	Methods of Modeling	Study Groups/No. of Participants	Interventions	Acupuncture Protocol	Acupoints	Outcome Measures	Results
Jing et al 2018 <sup>178</sup>	SD rats, 180–220g, 17 weeks	PMD	(i) OVX (ii) CUMS	- EA/n= 12 - Control/n= 12 - Model/n= 12 - Clomipramine/ n= 12	- EA/OVX + CUMS + EA - Control/no treatment - Model/OVX + CUMS - Clomipramine/OVX + CUMS + Clomipramine	- 20 min/day for 28 days-disperse-dense wave, 2/10Hz, 18V	BL23, GV20, SP6	(i) Behavioral test (TSE) (ii) E2, NE in hippocampus (iii) DKK1, LRP-5, LRP-6 in hippocampus	(i) EA improved rats' depression-like behavior in behavioral test (ii) EA increased E2 and NE levels (iii) EA decreased DKK1, and decreased LRP-5 and LRP-6 expression
Zhou et al 2015 <sup>146</sup>	SD rats, 220–260g	PMD	(i) OVX (ii) CUMS	- MA/n= 9 - Model-1/n= 9 - Model-2/n= 8 - Sham-surgery/n= 6 - Nifedriol + Fluoxetine/n= 9	- MA/OVX + CUMS + MA - Model-1/OVX + CUMS - Model-2/OVX - Sham-surgery/sham-OVX - Nifedriol + Fluoxetine/OVX + CUMS + Nifedriol + Fluoxetine	20 min/day for 21 days	BL23, GV20, SP6	(i) Behavioral test (OFT) (ii) 5-HT, NE, DA in hypothalamus	(i) MA improved rats' depression-like behavior in behavioral test (ii) MA increased 5-HT level; no significant changes in NE and DA levels
Shi et al 2012 <sup>147</sup>	SD rats, 300–350g, 4 months	PMD	(i) OVX (ii) CUMS	- MA/n= 10 - Model/n= 5 - Sham-surgery/n= 5 - Estradiol benzoate/n= 10	- MA/OVX + CUMS + MA - Model/OVX + CUMS - Sham-surgery/sham-OVX + CUMS - Estradiol benzoate/OVX + CUMS + Estradiol benzoate	30 min/session, once session every 2 days for total 30 sessions	CV4, CV6, LI4, LR3, PC6, SP6, ST36	(i) Serum E2 (ii) 5-HT in hypothalamus	(i) EA increased E2 level (ii) EA increased 5-HT level

Sun 2009 <sup>118</sup>	(i) SD rats, 250–300g, 11–15 months (n=45) (ii) Young SD rats, 150–200g, 4 months (n=10)	PMD	CUMS	- EA/n= 15 - Model/n= 15 - Clomipramine/n= 15 - Young/n= 10	- EA/CUMS + EA - Model/CUMS - Clomipramine/CUMS + Clomipramine - Young/CUMS	- 20 min/day for 7 days- disperse-dense wave, 4/20Hz, 2V	BL18, BL23, GV20, SP6	(i) Behavioral tests (OFT) (ii) Serum E2, NE	(i) EA improved rats' depression-like behavior in behavioral test (ii) EA increased E2 and NE levels
Wang et al 2016 <sup>171</sup>	SD rats, 220–260g, 17weeks	PMD	(i) OVX (ii) CUMS	- EA/n= 10 - Control/n= 10 - Model/n= 10 - Clomipramine/n= 10	- EA/OVX + CUMS + EA - Control/no treatment - Model/OVX + CUMS - Clomipramine/OVX + CUMS + Clomipramine	- 20 min/day for 28 days- disperse-dense wave, 2/10Hz	BL23, GV20, SP6	(i) Behavioral test (OFT) (ii) CREB, BDNF in hippocampus	(i) EA improved rats' depression-like behavior in behavioral test (ii) EA increased BDNF and CREB levels
Wu 2012 <sup>148</sup>	(i) SD rats, 260–471g, 11–13 months (n=73) (ii) Young SD rats, 140–191g, 4 months (n=20)	PMD	CUMS	- EA/n= 18 - Model/n= 19 - Clomipramine/n= 18 - Herbal medicine/n= 18 - Young/n= 20	- EA/CUMS + EA - Model/CUMS - Clomipramine/CUMS + Clomipramine - Herbal medicine/CUMS + XiaoYao-Pill - Young/CUMS	- 20 min/day for 10 days- disperse-dense wave, 2/15Hz, 2V	BL18, BL23, GV20, SP6, ST36	(i) Behavioral test (OFT) (ii) Serum E2 (iii) 5-HT2A mRNA, p-ERK 1/2 in hippocampus	(i) EA improved rats' depression-like behavior in behavioral test (ii) EA increased E2 level (ii) EA decreased 5-HT2A mRNA expression; EA increased p-ERK 1/2 expression

(Continued)

Table 5 (Continued).

Author/Year	Animals	Disease Models	Methods of Modeling	Study Groups/No. of Participants	Interventions	Acupuncture Protocol	Acupoints	Outcome Measures	Results
Zhang 2009 <sup>128</sup>	(i) SD rats, 250–300g, 11–15 months (n=45) (ii) Young SD rats, 150–200g, 4 months (n=10)	PMD	CUMS	- EA/n= 15 - Model/n= 15 - Clomipramine/n= 15 - Young/n= 10	- EA/CUMS + EA - Model/CUMS - Clomipramine/CUMS + Clomipramine - Young/CUMS	- 20 min/day for 7 days-continuous wave, 20Hz, 2V	BL18, BL23, GV20, SP6	(i) Behavioral test (OFT) (ii) Serum E2 (iii) $\beta$ -EP in hippocampus	(i) EA improved rats' depression-like behavior in behavioral test (ii) EA increased E2 level (iii) EA increased $\beta$ -EP level
Zhao et al 2011 <sup>149</sup>	(i) SD rats, 260–471g, 11–13 months (n=66) (ii) Young SD rats, 140–191g, 4 months (n=20)	PMD	CUMS	- EA/n= 15 - Model/n= 18 - Clomipramine/n= 17 - Herbal medicine/n= 16 - Young/n= 20	- EA/CUMS + EA - Model/CUMS - Clomipramine/CUMS + Clomipramine - Herbal medicine/CUMS + XiaoYao-Pill - Young/CUMS	- 20 min/day for 28 days	BL18, BL23, GV20, SP6, ST36	(i) Behavioral test (OFT) (ii) Serum 5-HT, HDL	(i) EA improved rats' depression-like behavior in behavioral test (ii) EA increased 5-HT and HDL levels
Song et al 2021 <sup>119</sup>	KM mice, 18–22g, 5–6 weeks	PMD	(i) OVX (ii) Ice-water swimming stimulation (I-WSS)	- EA/n= 10 - Control/n= 10 - Model/n= 10	- MA/OVX + I-WSS + MA - Control/I-WSS - Model/OVX + I-WSS	- 30 min/day, 6 days/week for 4 weeks	CV4, KI3, KI15, SP6, SP10, ST36	Serum E2	EA increased E2 level

**Abbreviations:** NR, no report; PM1, perimenopausal insomnia; PMD, perimenopausal depression; MA, manual acupuncture; EA, electroacupuncture; OVX, ovariectomy; CUMS, chronic unpredictable mild stress; MER, multichannel electrophysiological recordings; SOL, sleep onset latency; TST, total sleep time; WASO, wake after sleep onset; REM, rapid eye movement; NREM, non-rapid eye movement; LS, light sleep; SWS, slow wave sleep; FSH, follicle-stimulating hormone; LH, luteinizing hormone; E2, estradiol; CSF, cerebrospinal fluid; VLPO, ventrolateral preoptic; TMN, tuberomammillary nucleus; PGD2, prostaglandin D2; PGE2, prostaglandin E2; L-PGDS, lipocalin-type prostaglandin D synthase; GABA, gamma-amino butyric acid; 5-HT, 5-hydroxytryptamine; 5-HIAA, 5-hydroxyindole acetic acid; NE, norepinephrine; DA, dopamine; ER- $\alpha$ , Estrogen receptor- $\alpha$ ; ER- $\beta$ , Estrogen receptor- $\beta$ ; GnRH, gonadotropin-releasing hormone; GSK-3 $\beta$ , glycogen synthase kinase-3 $\beta$ ; p- $\beta$ -catenin, phosphorylated  $\beta$ -catenin; BDNF, brain-derived neurotrophic factor; NPY, neuropeptide Y; MAP-2, microtubule-associated protein-2; CRH, corticotropin-releasing hormone; ACTH, adrenocorticotropic hormone; CORT, cortisol;  $\beta$ -EP, beta-endorphin; DKK1, Dickkopf1; LRP-5, low density lipoprotein receptor related protein 5; LRP-6, low density lipoprotein receptor related protein 6; CREB, cyclic-AMP response binding protein; p-ERK 1/2, phosphorylated-extracellular regulated kinase 1/2; HDL, high-density lipoprotein; CUMS, chronic unpredictable mild stress; SPT, sucrose preference test; OFT, open field test; FST, forced swimming test; IAT, independent activity test; ADE, avoiding dark experiment; TSE, tail suspension experiment; EPM, elevated plus maze; BL18, Ganshui; BL23, Shenshui; CV4, Guanyuan; CV6, Qihai; EX, Anmian; EX-HN1, Sishencong; GV20, Baihui; HT7, Shenmen; KI3, Taixi; KI15, Zhongzhu; LI4, Hegu; LR3, Taichong; PC6, Neiguan; SP6, Sanyinjiao; SP10, Xuehai; ST36, Zusanli.

expression has been linked to a variety of cancers, particularly breast and ovarian cancers.<sup>120</sup> Yang reported that successful PMI modeling resulted in an increased expression of ER $\beta$  in the hypothalamus, which was prevented by acupuncture.<sup>121</sup> This kind of aberrant expression of estrogen receptors are observed when rodents exposed to ovariectomy (OVX), modelling menopause, followed by CUMS, to induce depressive-like behaviours, as well.<sup>120</sup> These findings suggest that acupuncture may have brain-predominant effects in modulating estrogen receptors, with potential protective benefits underlying its sleep-promoting and antidepressive effects.

## Inhibition of Hyperactivity of HPA and HPO Axes

Hyperactivity of the hypothalamic-pituitary-adrenal (HPA) axis is a significant biological marker of depressive disorder.<sup>122</sup> A previous SR suggested that EA could reduce cortisol (CORT) release from the adrenal glands and thereby modify the HPA axis by downregulating the expression of corticotropin-releasing hormone (CRH) and adrenocorticotrophic hormone (ACTH) in the hypothalamus and pituitary gland, respectively, as well as decreasing the expression of CRH mRNA in the hypothalamus.<sup>123</sup> This hypothesis was tested in a PMD model by Jiang et al.<sup>124</sup> In this study, EA showed antidepressant-like effects that were no weaker than clomipramine in PMD rats, along with significant reductions in CRH, ACTH and CORT. Jiang also reported an increase in E2 and a decrease in FSH and LH levels in the rats.<sup>124</sup> The response of HPA axis can be modulated by estrogen.<sup>122</sup> Hence, Jiang's findings further support the idea that acupuncture's regulation of estrogen also contributes to its inhibition of hyperfunction of the HPA axis. This theory also partially explains the benefits of acupuncture on PMI. Since increased expression of ACTH and CORT causes an awakening effect, insomnia closely links to the hyperactivity of HPA axis as well.<sup>125</sup> Xi et al reported significant symptom-relief in chronic insomniacs who underwent acupuncture, accompanied by downregulation in serum CRH, ACTH and CORT expression.<sup>126</sup> A reciprocal relationship has been established between the HPO and HPA axes.<sup>122</sup> Acupuncture appears to suppress these two axes synchronously. In three animal studies,<sup>124,127,128</sup> EA's effects on HPO axis-related hormones was observed, including normalizing the reduced E2 and beta-endorphin as well as the increased LH and gonadotropin-releasing hormone (GnRH) in a

PMD model. The sleep-promoting benefit of acupuncture may be further explained as well because there is also an interaction between the sleep-wake cycle system and the HPO axis.<sup>113</sup> There is also an association between HPO axis and the orexin system, which is involved in the regulation of arousal and plays a cardinal role in sleep and wakefulness.<sup>113</sup>

Huangfu et al have provided further prominent evidence that the inhibition of the HPA axis by EA might also be achieved via its modulation of the glucocorticoid receptor (GR) and mineralocorticoid receptor (MR).<sup>129</sup> Disruption of GR signaling is proposed to underlie HPA axis dysregulation observed in stress-related psychiatric illness.<sup>130</sup> Huangfu reported a significant decline of both GR and MR in the hippocampus of PMD rats, which was reversed with 28-day EA (20 min per day). Along with the improvement of depression-like behavior, EA also increased the number and functional activity of neurons in the hippocampal CA3 region in this group of rats.<sup>129</sup>

## Regulation of Neurotransmitters

At the neurochemical level, several mechanisms of sleep-wakefulness control and emotion regulation have been identified. Coordination of various neurotransmitters appears to play a vital role in this regulated alternation state.<sup>131</sup> For instance, the positive regulation of estrogen in sleep and mood disorders associated with menopause<sup>114,132</sup> can be partially explained by its wide involvement in the metabolism of gamma-amino butyric acid (GABA), serotonin [5-hydroxytryptamine (5-HT)], norepinephrine, and acetylcholine.<sup>132</sup>

It is well known that GABA is the dominant inhibitory transmitter.<sup>133</sup> Decreased GABAergic activity links to a weakening of the sleep-promotion system or a strengthening of the arousal system.<sup>134</sup> As the first-line hypnotics, benzodiazepines and benzodiazepine receptor agonists (Z-drugs) act by increasing the intrinsic activity of the GABA via binding to the receptor binding region of the GABA<sub>A</sub> receptor, which in turn exerts an inhibitory and suppressing effect on the outputs to all of the major cell groups in the brainstem and hypothalamus that promote hyperarousal.<sup>134</sup> Acupuncture appears to be able to ameliorate PMI via a similar pathway. The ventrolateral pre-optic nucleus (VLPO) is a main cerebral region containing cluster of neurons essential for the initiation and maintenance of sleep.<sup>135</sup> Cao et al observed that acupuncture upregulated the GABA levels in the VLPO in a PMI rat, which was positively correlated with prolonged REM

sleep and SWS.<sup>136</sup> The same study also reported the effects of acupuncture on prostaglandin (PG) D2 system in cerebrospinal fluid. There were significant increments in lipocalin-type PGD synthase and PGD2 levels, and exiguity decrements in PGE2 levels, indicative of the multi-targeted effect of the intervention. Although acupuncture's regulation of GABA is rarely investigated in PMI-related clinical trials, many trials have reported that acupuncture up-regulated serum GABA levels in patients with primary insomnia and chronic insomnia.<sup>137,138</sup> Estrogen receptors are found throughout the brain, so estrogen shows modulatory effects on the neurotransmitter systems.<sup>5</sup> One of the interpretations for the increased risk of PMD posits that depression is caused by the impacts of E2 fluctuations on neurotransmitter systems in cerebral regions that regulate mood and emotion.<sup>8,14</sup> Dysregulation of the GABA balance between GABA<sub>A</sub> and GABA<sub>B</sub> due to hormone fluctuations also contributes to the increased vulnerability to depression during perimenopause.<sup>96</sup> Among women with PMD, the decreased GABA concentrations were found mainly in the anterior cingulate cortex, which is usually activated by diverse tasks including emotion processing and regulation and is closely associated with the occurrence and development of depression.<sup>139</sup> The GABAergic system and GABAergic neurosteroids show potential involvements in the etiology of PMD, as women whose GABARAR receptor fails to adjust to the rapid change in neurosteroid levels may be more prone to PMD.<sup>133</sup> The effect of acupuncture in reinstating reduced hippocampal GABA content in rats with depression has been widely investigated and confirmed.<sup>140,141</sup> It is worthwhile noting that the GABA system also plays a key role in restraining the HPA axis at the level of the paraventricular nucleus of the hypothalamus.<sup>133</sup> The close relationship between the hyperactivity of the HPA and HPO axes and PMI and/or PMD has been mentioned in the earlier section. Furthermore, in many animal experiments cited in this review (Table 5), ovarian hormone deprivation due to OVX evoked significantly increased serum FSH and LH levels as well as reduced serum E2 level, suggesting ovarian failure results in the exhausted hypothalamic GABA contents. The acupuncture-induced reversal of these disrupted hormone and neurotransmitter levels thereby seems to modulate the upstream factors of the HPO axis and inhibit the HPA-axis hyperactivity, potentially by reinstating the hypothalamic GABAergic neuronal function.

As with GABA system, a dysfunctional serotonergic system is another factor contributing to the development of PMD, a mechanism that is receiving increasing attention.<sup>133,142</sup> The available evidence suggests there are lower serum 5-HT levels in postmenopausal women than in regularly menstruating women,<sup>143</sup> and in comparison to the natural menopause in humans, the decline of 5-HT levels following ovariectomy is more drastic.<sup>143</sup> Selective serotonin reuptake inhibitors are one of the most frequently utilized non-hormonal substitutes for menopausal symptoms,<sup>144</sup> suggesting that serotonin is widely involved in multiple symptoms during the menopausal stage. Both the odds of PMD and the severity of PMD symptoms are negatively correlated with serotonin levels.<sup>142</sup> Both human clinical<sup>71,84,93</sup> and animal studies<sup>145-149</sup> have revealed the increases in serum 5-HT and/or hippocampal 5-HT and its major metabolites caused by acupuncture, along with decreased PMD symptoms or depression-like behaviors. In addition to the enhancement of 5-HT synthesis and the increase of 5-HT and its metabolite content in the brain and synaptic gaps, previous studies also suggested that acupuncture restored synaptic plasticity by regulating serotonin expression in the hippocampus resulting in relieved depression symptoms.<sup>123,150</sup> This process involves acupuncture-induced bidirectional regulation of the expression of serotonin transporters (5-HTTs) and serotonin-1A (5-HT1A), which then increases the expression of hippocampal galanin (Gal) and tryptophan hydroxylase (TPH) as well as restores or reverses the impairments in synaptic plasticity.<sup>123</sup> Given existing animal studies mainly focused on hippocampus, future studies within in field might benefit from some investigations of other cerebral regions important for depressive-like symptoms including amygdala and prefrontal cortex. Serotonin also plays an integral part in the process of sleep preparation, initiation, and maintenance.<sup>151</sup> In both serum and hippocampus of PMI rats,<sup>121,152</sup> researchers observed that acupuncture treatment led to increments in serotonin and its chief end-product of metabolism, accompanied by significant increases in REM and SWS. This finding is also meaningful for PMD, because these two sleep outcomes are usually shown to be less in women with depression compared with the healthy women.<sup>11</sup> Estrogen affects the serotonin system in several ways, including promoting the synthesis of serotonin by increasing the rate of degradation of monoamine oxidase (the enzyme that catabolizes serotonin), and inhibiting the reuptake of serotonin by affecting intraneuronal serotonin transport.<sup>114,153</sup> E2, for instance, is able to



stimulate the production of neurotransmitters such as serotonin and to enhance serotonergic function in depression and its treatment.<sup>114</sup> In the previous section, we displayed both clinical and animal evidence that acupuncture increased E2 levels. It is hence reasonable to summarize that acupuncture can directly elevate serotonin levels, but also indirectly strengthen the benign regulation of serotonin in sleep and mood with this increased E2.

## Reduction of Oxidative Stress Levels

Oxidative stress plays a critical part in the pathophysiology of sleep disturbance, as brain-free radicals accumulate during wakefulness and are removed during sleep.<sup>154</sup> Compared with good sleepers, insomniacs generally have much higher oxidative stress parameters.<sup>155</sup> Meanwhile, oxidative stress is a pivotal factor in ageing.<sup>156</sup> Menopause is an aging process, in which oxidative stress plays a crucial role in developing a diversity of symptoms.<sup>156</sup> The decline of estrogen during menopause results in the massive release of reactive oxygen species (ROS) and creates a pro-oxidant state,<sup>157,158</sup> which explains the association between increased oxidative stress and climacteric symptoms due to insufficient estrogen. Treatment with antioxidant estrogen has been shown to lead to a reduction in the occurrence of sleep disturbances, implying that the improvement of oxygen metabolism may be a potential management strategy for climacteric-related sleep disorders.<sup>13,159</sup> Recent study identified an evident imbalance between lipid peroxidation (LPO) and the antioxidant defense system among the menopausal insomniacs,<sup>160</sup> providing a pathogenic rationale for including drugs that inhibit LPO activation in the synthetic therapy of these patients.<sup>161</sup> A cross-sectional study involving 187 perimenopausal women also suggested that there was a positive correlation between insomnia score, menopause rating score, and LPO.<sup>157</sup> Acupuncture has been found to normalize disordered LPO processes, and prevent formation and accumulation of LPO products in sleep deprivation-associated regions of the brain, particularly hippocampus.<sup>162,163</sup> The association between menopause-related depression and oxidative stress has been identified as well. Hirose et al reported that depressive symptoms among middle-aged women were independently associated with high urinary 8-OHdG, a biomarker indicator of oxidatively damaged DNA reflecting the severity of oxidative stress.<sup>164</sup> Although there is no direct evidence investigating the effect of acupuncture on 8-OHdG in PMD populations, MA was found to improve cognitive function and mood in patients with vascular dementia, along with significant decline in urinary 8-OHdG.<sup>165</sup> The mechanisms

linking PMD to oxidative stress appear to be bidirectional: high oxidative stress may lower norepinephrine and serotonin and levels, which in turn results in depression; depression may contribute to ROS production as well as weaken the antioxidant defense system.<sup>164</sup> Tian observed striking increases in serum malondialdehyde (MDA) which is the LPO product as well as striking decreases in serum superoxide dismutase (SOD) and glutathione peroxidase (GSH-Px) which are the two major intracellular antioxidant enzymes in rats that underwent OVX, which were reversed by acupuncture.<sup>106</sup> A recent RCT revealed that EA significantly decreased level of lipid hydroperoxides, a byproduct of oxidative stress, among insomniacs.<sup>166</sup> Acupuncture was also reported to retard the drastic decline of SOD and nitric oxide synthase (NOS) levels in plasma and uterine tissues of rats naturally entering menopause.<sup>107</sup> Besides the increment of GSH-Px and SOD contents, the upregulation in expression of CuZnSOD mRNA and protein is another pathway by which acupuncture may ameliorate oxidative injuries.<sup>162</sup> These findings suggest that the antioxidant mechanism underlying acupuncture may be associated with its effects on a cluster of oxidative stress-related enzymes inducing a nonspecific response. Oxidative stress levels are also positively correlated with climacteric hot flushes,<sup>167,168</sup> a potential contributor of PMI<sup>169</sup> and PMD<sup>5</sup> as mentioned. Among women aged 45–55 years, those with hot flushes were found to show lower levels of plasma total antioxidant activity compared with women free of this symptom.<sup>168</sup> Therefore, acupuncture may also reduce hot flushes via resisting the oxidation effects, which in turn reduces PMI and PMD.

## Promotion of Signaling Pathways

The effects of acupuncture on signaling pathways have also been widely studied, providing a new perspective to understand the clinical efficacy of acupuncture at a molecular level.<sup>123</sup> We identified six animal studies involving three signal transduction pathways that revealed possible mechanisms implicated in the improvement of PMD by acupuncture.

Brain-derived neurotrophic factor (BDNF) in the hippocampus is a crucial target for the treatment of depression,<sup>170</sup> and it may be linked with the development of depression by cAMP-response element-binding protein (CREB) and its upstream pathways.<sup>140</sup> Many conventional antidepressive agents mediate antidepressant-like effects via increasing synthesis and signal transduction of cerebral BDNF expression.<sup>123,170</sup> Acupuncture appears to work on the same signaling pathway. Two studies demonstrated

that EA altered depression-like behavior in PMD rats by normalizing the downregulated expression of hippocampal CREB, BDNF, and phosphorylated-TrkB (p-TrkB) which is a high-affinity receptor of BDNF.<sup>170,171</sup> Activation of BDNF/TrkB/CREB pathway is thereby suggested as a potential mechanism implicated in the beneficial effects of acupuncture on PMD. This pathway may also link to the improvements in PMI by acupuncture. Although there is no direct evidence, Liu reported that EA improved both sleep and cognitive functions (learning and memory) in sleep-deprived rats by activating the PKA-C $\beta$ /CREB/BDNF/TrkB signaling pathway.<sup>172</sup>

Activation of the Wnt/ $\beta$ -catenin signaling pathway has moderation effect on multiple aspects of hippocampal neurogenesis, which has been linked to depressive symptoms.<sup>173</sup> Glycogen synthase kinase-3 $\beta$  (GSK-3 $\beta$ ) and  $\beta$ -catenin are key proteins of Wnt signaling, which comprise a degradation complex to phosphorylated (p)- $\beta$ -catenin to be ubiquitinated.<sup>174</sup> These critical regulatory molecules particularly GSK-3 $\beta$  and  $\beta$ -catenin are suggested to be targets and/or action modifiers of antidepressants such as lithium<sup>175</sup> and fluoxetine.<sup>176</sup> Interestingly, regulation of these proteins was also observed in two studies in which acupuncture improved depressive-like symptoms in PMD rats.<sup>174,177</sup> As reported, hippocampal mRNA and protein expression of GSK-3 $\beta$  were decreased, while mRNA and protein expression of  $\beta$ -catenin were increased after 28-days EA treatment. Another study showed that acupuncture reduced the expression of Dickkopf 1 (DKK1) and low-density lipoprotein receptor-related protein (LRP) 5/6 in the hippocampus of PMD rats.<sup>178</sup> As an endogenous inhibitor, DKK1 binds to LRP 5/6 and results in the inhibition of canonical Wnt signaling pathway.<sup>179</sup> These findings suggest that activation of the Wnt/ $\beta$ -catenin signaling pathway may be another mechanism by which acupuncture mediates antidepressant-like effects. We identified no studies investigating PMI in association with the Wnt/ $\beta$ -catenin signaling pathway, highlighting a significant gap in the literature, but Qu et al have reported that activation of this pathway enhanced hippocampal neurogenesis and improved learning and memory in sleep-deprived mice.<sup>180</sup>

The Notch signaling pathway is involved in the promotion of neurogenesis and brain plasticity.<sup>181,182</sup> Notch1 is the principal Notch receptor,<sup>183</sup> and it can interact with ligands such as Jagged1 and then trigger the release of the Notch intracellular domain.<sup>182</sup> As the major downstream target genes of Notch signaling, Hes is found to take part in the inhibition of neuronal differentiation.<sup>184</sup> Emerging evidence has shown that Notch signaling is associated with

the depression-like performance in mid-aged female rats undergoing chronic restraint stress.<sup>182</sup> Deng et al established PMD model by chronic stress and reported decreased expression in hippocampal Notch1 protein and mRNA, as well as increased expression in both hippocampal Jagged1 protein and mRNA as well as hippocampal Hes1 protein and mRNA in PMD rats, which were reversed by EA treatment.<sup>185</sup> These results imply that acupuncture can improve PMD performance, possibly by increased neurogenesis and promoted neuronal differentiation via activating the Notch signaling pathway.

## Attenuation of Vasomotor and Other Perimenopausal Symptoms

Krystal et al suggested that PMI is a vasomotor-initiated sleep disruption as it is usually triggered initially by night sweats.<sup>169</sup> Some longitudinal investigations and SRs/MAs of perimenopause have also indicated the positive correlation between vasomotor complaints and poor sleep and/or depressive symptoms.<sup>1,2</sup> In comparison with those without vasomotor symptoms, women suffering from more night sweats weekly are with more likelihood to report sleep difficulties.<sup>1</sup> Translated, women with vasomotor symptoms are more at risk for insomnia.<sup>186</sup> However, there is a theory that vasomotor symptoms are not a necessary prerequisite for PMD,<sup>13</sup> while perimenopausal women with hot flashes are indeed at higher risk of developing depression.<sup>5</sup> Moreover, women with PMD have a higher likelihood of being irritable from vasomotor symptoms and report greater severity of their hot flashes. They are also most likely to seek help from primary health care services.<sup>5</sup> Some recent evidence reveals a bidirectional relationship between PMD and vasomotor complaints.<sup>8,122</sup> It is thought that this relationship may not be simply explained by the mediating effect of sleep disruption,<sup>8,122</sup> whereas PMD and perimenopausal anxiety due to vasomotor symptoms do contribute to the impaired sleep.<sup>110</sup> Attenuation of vasomotor symptoms by acupuncture thereby partially explains why it promotes the PMI relief.<sup>186</sup> Plenty of clinical data cited in our review have shown that acupuncture significantly lowered the Kupperman Index global scores (Table 2). Hot flashes and sweating are the critical and most weighted items of the Kupperman Index scale.<sup>187</sup> Although the frequency of hot flashes and night sweats were not directly assessed in our included clinical papers, acupuncture is sure to be promising to mitigate menopausal-associated vasomotor symptoms.<sup>188</sup> As denoted in the umbrella systematic review performed by

Befus et al in 2018, evidence from RCTs supports the utilization of acupuncture as an adjunctive or stand-alone remedy option for reducing vasomotor symptoms.<sup>188</sup> Additionally, two included animal studies<sup>189,190</sup> reported that acupuncture significantly increased total sleep time and reduced sleep onset latency in PMI rats, along with enhancement of the rats' heat-resistant ability (prolongation of heat-resistant time). Accumulating evidence suggests that acupuncture-induced temperature control and reduction in hot flushes among climacteric women is achieved by elevating beta-endorphin level and suppressing GnRH secretion.<sup>191</sup> These benefits of acupuncture were validated again in PMD rats and were accompanied by a significant reduction in depression-like behavior.<sup>124,127,128</sup> Interestingly, serotonin regulates thermoregulation and peripheral vasculature.<sup>153</sup> The effect of acupuncture on serotonin may therefore explain the reduced vasomotor symptoms as well. Although there is debate available regarding acupuncture treatment for hot flushes, the controversy focuses only on its placebo effects. A comprehensive review by Ee et al suggested that acupuncture did not show better effects in comparison with sham-acupuncture,<sup>192</sup> another network meta-analysis exhibited opposite conclusion.<sup>193</sup> In comparison with no treatment, however, the benefits of acupuncture or placebo-acupuncture are clear, according to both papers.<sup>192,193</sup> In summary, reducing the sleep disruption and/or depressive symptoms by relieving hot flushes is a possible explanation for acupuncture's benefits on PMI and PMD, although further research is required.

The interdependent and interactional relationship between anxiety, depression, and insomnia has been established in women with perimenopausal complaints.<sup>6,13,15</sup> However, this relationship appears to be underestimated and does not receive adequate attention in the current research, as only 4 of the 22 PMI RCTs included emotion-related indicators<sup>54,64,65,67</sup> and none of the 25 PMD RCTs included sleep-related indicators. According to the domino theory mentioned in the previous section, the improvement of insomnia caused by acupuncture may also be one of the mechanisms of PMD remission, and vice versa. Future trials hence should be more comprehensive in their outcome tools. For instance, scales/questionnaires should cover sleep, mood, vasomotor symptoms as well as quality of life, and even consider introducing PSG/actigraphy and neuropsychological tests. With these data we will be able to appraise intricate associations between menopausal characteristics, sleep, mood, lifestyle factors, and women's expectation and experience of acupuncture,

which will further our understanding of the true role of acupuncture in perimenopause management. Animal experiments are also required to investigate the mechanisms behind acupuncture on a larger scale.

## Conclusion

Our review demonstrates that acupuncture has a positive and broad effect on PMI and PMD, being beneficial on mood, sleep, and vasomotor symptoms. Consistent data from clinical trials and animal studies support that those effects possibly are mediated through a number of mechanisms, from regulation of reproductive hormones and neurotransmitters, and inhibitions in oxidative stress and HPA and HPO axis hyperactivity, to activation and deactivation of key proteins in various signaling pathways. Neuroendocrine modulation is likely to play a major role in mediating those effects. Despite some methodological deficiencies, acupuncture could be an adjunct therapy or viable and safe option for women with comorbid depression and insomnia during perimenopause. The multifaceted effects of acupuncture on, and the TCM syndrome patterns of, PMI and PMD provide an innovative direction for future research.

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## Disclosure

None of the authors have any conflicts of interest to declare in this study.

## References

1. Kravitz HM, Joffe H. Sleep during the perimenopause: a SWAN story. *Obstet Gynecol Clin North Am.* 2011;38(3):567–586. doi:10.1016/j.ogc.2011.06.002
2. Augoulea A, Moros M, Lykeridou A, Kaparos G, Lyberi R, Panoulis K. Psychosomatic and vasomotor symptom changes during transition to menopause. *Prz Menopauzalny.* 2019;18(2):110–115.

3. Raglan GB, Schulkin J, Micks E. Depression during perimenopause: the role of the obstetrician-gynecologist. *Arch Womens Ment Health*. 2020;23(1):1–10. doi:10.1007/s00737-019-0950-6
4. Caruso D, Masci I, Cipollone G, Palagini L. Insomnia and depressive symptoms during the menopausal transition: theoretical and therapeutic implications of a self-reinforcing feedback loop. *Maturitas*. 2019;123:78–81. doi:10.1016/j.maturitas.2019.02.007
5. Gyllstrom ME, Schreiner PJ, Harlow BL. Perimenopause and depression: strength of association, causal mechanisms and treatment recommendations. *Best Pract Res Clin Obstet Gynaecol*. 2007;21(2):275–292. doi:10.1016/j.bpobgyn.2006.11.002
6. Maki PM, Kornstein SG, Joffe H, et al. Board of trustees for the North American Menopause Society (NAMS) and the Women and Mood Disorders Task Force of the National Network of Depression Centers. Guidelines for the evaluation and treatment of perimenopausal depression: summary and recommendations. *Menopause*. 2018;25(10):1069–1085.
7. Ayaki M, Tsubota K, Kawashima M, Kishimoto T, Mimura M, Negishi K. Sleep disorders are a prevalent and serious comorbidity in dry eye. *Invest Ophthalmol Vis Sci*. 2018;59(14):DES143–DES150. doi:10.1167/iovs.17-23467
8. Joffe H, Petrillo LF, Koukopoulos A, et al. Increased estradiol and improved sleep, but not hot flashes, predict enhanced mood during the menopausal transition. *J Clin Endocrinol Metab*. 2011;96(7):E1044–E1054. doi:10.1210/jc.2010-2503
9. Terauchi M, Obayashi S, Akiyoshi M, Kato K, Matsushima E, Kubota T. Insomnia in Japanese peri- and postmenopausal women. *Climacteric*. 2010;13(5):479–486. doi:10.3109/13697130903353478
10. Baker FC, de Zambotti M, Colrain IM, Bei B. Sleep problems during the menopausal transition: prevalence, impact, and management challenges. *Nat Sci Sleep*. 2018;10:73–95. doi:10.2147/NSS.S125807
11. Morssinkhof MWL, van Wylick DW, Priester-Vink S, et al. Associations between sex hormones, sleep problems and depression: a systematic review. *Neurosci Biobehav Rev*. 2020;118:669–680. doi:10.1016/j.neubiorev.2020.08.006
12. Im EO, Yang YL, Liu J, Chee W. The association of depressive symptoms to sleep-related symptoms during menopausal transition: racial/ethnic differences. *Menopause*. 2020;27(11):1315–1321. doi:10.1097/GME.0000000000001611
13. Santoro N, Epperson CN, Mathews SB. Menopausal symptoms and their management. *Endocrinol Metab Clin North Am*. 2015;44(3):497–515. doi:10.1016/j.ecl.2015.05.001
14. Miller LJ, Girgis C, Gupta R. Depression and related disorders during the female reproductive cycle. *Womens Health (Lond)*. 2009;5(5):577–587. doi:10.2217/WHE.09.44
15. Krystal AD. Depression and insomnia in women. *Clin Cornerstone*. 2004;6(1):S19–S28. doi:10.1016/S1098-3597(04)80022-X
16. Xiao X, Zhang J, Jin Y, Wang Y, Zhang Q. Effectiveness and safety of acupuncture for perimenopausal depression: a systematic review and meta-analysis of randomized controlled trials. *Evid Based Complement Alternat Med*. 2020;2020:5865697. doi:10.1155/2020/5865697
17. De Las Cuevas C, Peñate W, Sanz EJ. Risk factors for non-adherence to antidepressant treatment in patients with mood disorders. *Eur J Clin Pharmacol*. 2014;70(1):89–98. doi:10.1007/s00228-013-1582-9
18. Ashton AK, Jamerson BD, Weinstein L, Wagoner C. Antidepressant-related adverse effects impacting treatment compliance: results of a patient survey. *Curr Ther Res Clin Exp*. 2005;66(2):96–106. doi:10.1016/j.curtheres.2005.04.006
19. Zhao FY, Fu QQ, Kennedy GA, et al. Comparative utility of acupuncture and Western medication in the management of perimenopausal insomnia: a systematic review and meta-analysis. *Evid Based Complement Alternat Med*. 2021;2021:5566742. doi:10.1155/2021/5566742
20. Asnis GM, Thomas M, Henderson MA. Pharmacotherapy treatment options for insomnia: a primer for clinicians. *Int J Mol Sci*. 2015;17(1):50. doi:10.3390/ijms17010050
21. Dodin S, Blanchet C, Marc I, et al. Acupuncture for menopausal hot flashes. *Cochrane Database Syst Rev*. 2013;(7):CD007410. doi:10.1002/14651858.CD007410.pub2
22. Baumelou A, Liu B, Wang XY, Nie GN. Perspectives in clinical research of acupuncture on menopausal symptoms. *Chin J Integr Med*. 2011;17(12):893–897. doi:10.1007/s11655-011-0930-9
23. Hachul H, Oliveira DS, Bittencourt LR, Andersen ML, Tufik S. The beneficial effects of massage therapy for insomnia in postmenopausal women. *Sleep Sci*. 2014;7(2):114–116. doi:10.1016/j.slsi.2014.09.005
24. Newton KM, Buist DS, Keenan NL, Anderson LA, LaCroix AZ. Use of alternative therapies for menopause symptoms: results of a population-based survey. *Obstet Gynecol*. 2002;100(1):18–25.
25. Williams RE, Kalilani L, DiBenedetti DB, Zhou X, Fehnel SE, Clark RV. Healthcare seeking and treatment for menopausal symptoms in the United States. *Maturitas*. 2007;58(4):348–358. doi:10.1016/j.maturitas.2007.09.006
26. Cheuk DKL, Yeung WF, Chung KF, Wong V. Acupuncture for insomnia. *Cochrane Database Syst Rev*. 2012;9(9):CD005472.
27. Yeung WF, Chung KF, Leung YK, Zhang SP, Law AC. Traditional needle acupuncture treatment for insomnia: a systematic review of randomized controlled trials. *Sleep Med*. 2009;10(7):694–704. doi:10.1016/j.sleep.2008.08.012
28. Chon TY, Lee MC. Acupuncture. *Mayo Clin Proc*. 2013;88(10):1141–1146. doi:10.1016/j.mayocp.2013.06.009
29. Langevin HM, Schnyer R, MacPherson H, et al.; Executive Board of the Society for Acupuncture Research. Manual and electrical needle stimulation in acupuncture research: pitfalls and challenges of heterogeneity. *J Altern Complement Med*. 2015;21(3):113–128. doi:10.1089/acm.2014.0186
30. He W, Li M, Zuo L, et al. Acupuncture for treatment of insomnia: an overview of systematic reviews. *Complement Ther Med*. 2019;42:407–416. doi:10.1016/j.ctim.2018.12.020
31. Smith CA, Armour M, Lee MS, Wang LQ, Hay PJ. Acupuncture for depression. *Cochrane Database Syst Rev*. 2018;3(3):CD004046.
32. Femenia T, Gómez-Galán M, Lindskog M, Magara S. Dysfunctional hippocampal activity affects emotion and cognition in mood disorders. *Brain Res*. 2012;1476:58–70. doi:10.1016/j.brainres.2012.03.053
33. Hamidi M, Drevets WC, Price JL. Glial reduction in amygdala in major depressive disorder is due to oligodendrocytes. *Biol Psychiatry*. 2004;55(6):563–569. doi:10.1016/j.biopsych.2003.11.006
34. Li C, Dong M, Yin Y, Hua K, Fu S, Jiang G. Abnormal whole-brain functional connectivity in patients with primary insomnia. *Neuropsychiatr Dis Treat*. 2017;13:427–435. doi:10.2147/NDT.S128811
35. O'Byrne JN, Berman Rosa M, Gouin JP, Dang-Vu TT. Neuroimaging findings in primary insomnia. *Pathol Biol (Paris)*. 2014;62(5):262–269. doi:10.1016/j.patbio.2014.05.013
36. MacPherson H, Thomas K, Walters S, Fitter M. The York acupuncture safety study: prospective survey of 34 000 treatments by traditional acupuncturists. *BMJ*. 2001;323(7311):486–487. doi:10.1136/bmj.323.7311.486
37. White A. The safety of acupuncture—evidence from the UK. *Acupunct Med*. 2006;24(1S):53–57. doi:10.1136/aim.24.Suppl.53
38. White A. A cumulative review of the range and incidence of significant adverse events associated with acupuncture. *Acupunct Med*. 2004;22(3):122–133. doi:10.1136/aim.22.3.122
39. European Medicines Agency. *Guideline on Medicinal Products for the Treatment of Insomnia*. London: European Medicines Agency; 2011:14–16.

40. Wang SM, Han C, Bahk WM, et al. Addressing the side effects of contemporary antidepressant drugs: a comprehensive review. *Chonnam Med J.* 2018;54(2):101–112. doi:10.4068/cmj.2018.54.2.101
41. Li M, Niu J, Yan P, et al. The effectiveness and safety of acupuncture for depression: an overview of meta-analyses. *Complement Ther Med.* 2020;50:102202. doi:10.1016/j.ctim.2019.102202
42. Ravindran AV, Balneaves LG, Faulkner G, et al.; CANMAT Depression Work Group. Canadian Network for Mood and Anxiety Treatments (CANMAT) 2016 clinical guidelines for the management of adults with major depressive disorder: section 5. Complementary and alternative medicine treatments. *Can J Psychiatry.* 2016;61(9):576–587. doi:10.1177/0706743716660290.
43. Sun DZ, Li SD, Liu Y, Zhang Y, Mei R, Yang MH. Differences in the origin of philosophy between Chinese medicine and Western medicine: exploration of the holistic advantages of Chinese medicine. *Chin J Integr Med.* 2013;19:706–711. doi:10.1007/s11655-013-1435-5
44. Zheng HX. *The Basic Theory of Traditional Chinese Medicine (Tenth Edition) [Article in Chinese]*. Beijing, China: China Press of Traditional Chinese Medicine; 2016.
45. Jiang L, Liu B, Xie Q, et al. Investigation into the influence of physician for treatment based on syndrome differentiation. *Evid Based Complement Alternat Med.* 2013;2013:587234. doi:10.1155/2013/587234
46. Volker S. Globalising Chinese medical understandings of menopause. *East Asian Sci Technol Soc.* 2008;2:485–506. doi:10.1215/s12280-009-9069-6
47. Zhuo ZW, Hu L, Chen QL, Liang WN, Li CD. Study on syndrome elements and literature laws in patients with perimenopausal depression [article in Chinese]. *Trad Chin Med J.* 2019;18(1):53–58.
48. Zhang Y, Huang JS, Wu Song Y, et al. The distribution and characteristics of TCM syndromes of perimenopausal insomnia [article in Chinese]. *Trad Chin Med J.* 2013;54(18):1574–1576.
49. Lu C, Yang XJ, Hu J. Efficacy comparison between acupuncture smoothing-Liver and regulating-Spleen method and regulating Governor-Vessel method for perimenopausal insomnia [article in Chinese]. *Chin Acup Moxib.* 2014;34(8):759–762.
50. Zhao FY, Fu QQ, Kennedy GA, Conduit R, Zhang WJ, Zheng Z. Acupuncture as an independent or adjuvant management to standard care for perimenopausal depression: a systematic review and meta-analysis. *Front Psychiatry.* 2021;12:666988. doi:10.3389/fpsy.2021.666988
51. Fu C, Zhao N, Liu Z, et al. Acupuncture improves perimenopausal insomnia: a randomized controlled trial. *Sleep.* 2017;40(11):zsx153. doi:10.1093/sleep/zsx153
52. Wang WD. *Effect Comparison Between Electroacupuncture with Yin yang-Tiao heng-Tou ci Needling Method and Placebo-Electroacupuncture in Treating Perimenopausal Insomnia [Article in Chinese]* [Master thesis]. Shanghai University of Traditional Chinese Medicine; 2015.
53. Lin WX, Yin P, Xu SF. Clinical efficacy evaluation of Tiao ren-Tong du needling for perimenopausal insomnia [article in Chinese]. *Shanghai J Acup Moxib.* 2017;36(8):900–904.
54. Li S, Wang Z, Wu H, et al. Electroacupuncture versus sham acupuncture for perimenopausal insomnia: a randomized controlled clinical trial. *Nat Sci Sleep.* 2020a;12:1201–1213. doi:10.2147/NSS.S282315
55. Wang C, Bai YF, Fu WB, He YH. Clinical effect of acupuncture at four acupoints of Qijing on perimenopausal depression [article in Chinese]. *Chin J Gerontol.* 2015;35(12):3390–3392.
56. Li ZF. *Clinical Study on the Effect of Electroacupuncture on Patients with Mild to Moderate Depression in Perimenopausal Period [Article in Chinese]* [Doctorate thesis]. Guangzhou University of Chinese Medicine; 2015a.
57. Chen XL, Xu K, Qin XH. Clinical study on electroacupuncture for perimenopausal insomnia. *J Acupunct Tuina Sci.* 2013;11(6):336–338. doi:10.1007/s11726-013-0722-1
58. Luo L. *Clinical Observation on the Therapeutic Effect of Acupuncture with Tonifying Kidney and Regulating Heart Method on the Patients with Perimenopausal Insomnia [Article in Chinese]* [Master thesis]. Nanjing University of Chinese Medicine; 2020.
59. Du JL, Fan WJ, Du HJ. Clinical observation of Jin's three-needle combined with Jiaweiwumei-pill in the treatment of perimenopausal insomnia [article in Chinese]. *China Pharm.* 2017;28(8):1104–1107.
60. Kang H. *Clinical Observation of Scalp Acupuncture on the Treatment of Insomnia with Heart and Gallbladder Qi Deficiency in Perimenopausal Period [Article in Chinese]* [Master thesis]. Heilongjiang University of Chinese Medicine; 2015.
61. Lai XJ. *The Clinical Study of Using the Xu's Feitengbafa on Shenmai and Zhaohai Point on Time in Treating Perimenopausal Insomnia (Disharmony Between the Heart and Kidney) [Article in Chinese]* [Master thesis]. Chengdu University of Traditional Chinese Medicine; 2016.
62. Li YN. Effect of acupuncture “Xiasanhuang” acupoints on 120 cases of perimenopausal insomnia [article in Chinese]. *China Prac Med.* 2014;9(19):244–246.
63. Li OJ, Wang F. Acupuncture at back-shu points of five Zang, Geshu (BL 17) and Shenmen (HT 7) for the treatment of perimenopausal insomnia [article in Chinese]. *Chin Acup Moxib.* 2018a;38(5):469–472.
64. Ma GG. *Clinical Research on Perimenopausal Insomnia Treated with Jin Three-Needle Therapy [Article in Chinese]* [Doctorate thesis]. Guangzhou University of Chinese Medicine; 2014.
65. Qin YY. *Clinical Study of Acupuncture in Treating Perimenopausal Insomnia with Liver Hyperactivity and Kidney Deficiency Syndrome Pattern Based on the Theory of Treating Insomnia Based on Liver [Article in Chinese]* [Master thesis]. Chengdu University of Traditional Chinese Medicine; 2018.
66. Yang JR, Xu HY, Bai JM, Tang ZG, Lu R, Wang ZY. Scalp and body acupuncture in treating 81 cases of perimenopausal insomnia [Article in Chinese]. *West J Trad Chin Med.* 2017;30(2):4–6.
67. Zhang W, Pi Y, Chen T, Wang WW, Yang WF, Wang ZY. Clinical observation of treating perimenopausal insomnia by acupuncture based on the theory of Liver [article in Chinese]. *J Sichuan Trad Chin Med.* 2017;35(9):152–155.
68. Yan B, Ma XM, Zhou WX, Yu HB, Yang ZX. Effect of acupuncture with Tongren-Tiaodu method on perimenopausal insomnia [article in Chinese]. *Hubei J TCM.* 2021;43(5):40–42.
69. Li S, Li ZF, Wu Q, et al. A multicenter, randomized, controlled trial of electroacupuncture for perimenopausal women with mild-moderate depression. *Biomed Res Int.* 2018b;2018:5351210.
70. Chi H, Zou W. Yishen-tiaoan acupuncture therapy in the treatment of perimenopausal depression: an observation of 30 cases [article in Chinese]. *JCAM.* 2011;27(7):4–7.
71. Deng AJ. *A Randomized Controlled Clinical Trial of Bo's Abdominal Acupuncture in the Treatment of Perimenopausal Depression [Article in Chinese]* [Master thesis]. Guangzhou University of Chinese Medicine; 2008.
72. Li HB. *Clinical Observation of Acupuncture Treatment on Perimenopausal Depression with Kidney Deficiency and Liver Stagnation [Article in Chinese]* [Master thesis]. Heilongjiang University of Traditional Chinese Medicine; 2015b.
73. Ma J, Liu Z. A clinical study of acupuncture treatment on perimenopausal depression [article in Chinese]. *J Psychiatr.* 2009;22(4):276–278.
74. Niu XS, Wang P. Clinical study of acupuncture on Wangshi-Wuzangshu combined Geshu in the treatment of perimenopausal depression with stagnation of Liver Qi syndrome pattern [article in Chinese]. *Int J Trad Chin Med.* 2017;39(11):999–1002.

75. Qian J, Zhang J, Pei Y, Cheng J. Clinical observation of acupuncture on Wangshi Wuzangshu combined Geshu for perimenopausal depression [article in Chinese]. *Beijing J TCM*. 2007;26:491–492.
76. Qiang BQ. Acupuncture treatment on 30 cases of perimenopause depression [article in Chinese]. *J Shaanxi TCM*. 2008;29(7):871–872.
77. Shi J, Huang DM, Feng QF, Tang NL. Clinical observation of electroacupuncture treatment for mild to moderate depression in perimenopausal period [article in Chinese]. *China J Mod Med*. 2018;28(20):52–56.
78. Sun YJ, Tan Z, Jiang CY, Li SY. Clinical observation of electroacupuncture in the treatment of mild and moderate perimenopausal depression [article in Chinese]. *J Guangxi Univ Chin Med*. 2015;18(4):13–15.
79. Wang XY, Li XY, Deng AJ. Comparative study on abdominal acupuncture and Western medicine for treatment of perimenopause depression [article in Chinese]. *Chin Acup Moxib*. 2010;30(11):913–917.
80. Ding L, Liu B. Treatment of perimenopausal depression by acupuncture with Nourishing-Kidney-Regulating-Liver-Strengthening-Spleen-Tranquilizing-Heart method [article in Chinese]. *Chin Archiv Trad Chin Med*. 2007;25(5):1066–1067.
81. Li P, Dai W. Clinical observation of electroacupuncture in the treatment of perimenopause depression [article in Chinese]. *Clin J Trad Chin Med*. 2020b;32(3):555–558.
82. Zhang J. Comparative study on the efficacy of abdominal acupuncture and Western medicine in treating perimenopause depression [article in Chinese]. *World Latest Med Inf*. 2015;64:145.
83. Xing K. Clinical observation of 120 cases of perimenopausal depression treated by Xingshen-Jieyu acupuncture [article in Chinese]. *Matern Child Health Care China*. 2011;26(34):5373–5375.
84. Zhou SH, Wu FD. Therapeutic effect of acupuncture on perimenopausal depression and its effects on DA, NE and 5-HIAA contents [article in Chinese]. *Chin Acup Moxib*. 2007;27(5):317–321.
85. Dong Y. Clinical observation of acupuncture on beishu acupoint in the treatment of perimenopausal depression [article in Chinese]. *Jilin J Trad Chin Med*. 2015;35(3):306–308.
86. Zhang YL. *Effect of Electroacupuncture on Hamilton Score and Sex Hormone Levels in Patients with Perimenopausal Depression [Article in Chinese]* [Master thesis]. Shaanxi University of Chinese Medicine; 2010.
87. Zhang YQ. Clinical study of acupuncture treatment on 94 cases of perimenopausal depression [article in Chinese]. *Inner Mongol J Trad Chin Med*. 2013;32(11):41–42.
88. Zheng SH, Wu YT, Liao JR, Xu MZ, Hu ZN, Chen LH. Clinical study of Sishen-needle treatment on perimenopausal depression [article in Chinese]. *Liaoning J Trad Chin Med*. 2010;37(4):726–728.
89. Gao L, Niu HY. A preliminary study on clinical effects of Panlong-needling on perimenopausal insomnia [article in Chinese]. *Jilin J Tradit Chin Med*. 2014;34(1):88–90.
90. Xu HB. Effect of acupuncture on perimenopausal insomnia and its impact on PSQI [article in Chinese]. *Chin Commun Doctors*. 2020;36(31):109–110.
91. Ma WL. Effect of acupuncture combined with medication on perimenopausal insomnia and the impacts on FSH and E2 levels [article in Chinese]. *Acta Chin Med Pharmacol*. 2016;44(2):89–91.
92. Zhu SP, Li PP, Zhu XL. Observation of the effect of Tiaoduan-Anshen acupuncture on perimenopausal insomnia [article in Chinese]. *Mod J Integr Trad Chin West Med*. 2016;25(26):2885–2888.
93. Liu HF, Chen GZ. Effect of acupuncture combined with Sertraline on hormone levels and neurotransmitters in women with perimenopausal depression—clinical data of 40 cases [article in Chinese]. *Jiangsu J Trad Chin Med*. 2019;51(2):70–72.
94. Ning Y. Clinical study on acupuncture treatment of perimenopausal depression [article in Chinese]. *J Sichuan Trad Chin Med*. 2015;33(1):154–155.
95. Ma YB, Guo YM, Li XJ. Therapeutic effect of electroacupuncture combined with paroxetine on 55 cases of perimenopausal depression [article in Chinese]. *Med J Chin Peoples Health*. 2011;23(11):1426–1428.
96. Santoro N, Roeca C, Peters BA, Neal-Perry G. The menopause transition: signs, symptoms, and management options. *J Clin Endocrinol Metab*. 2021;106(1):1–15. doi:10.1210/clinem/dgaa764
97. Ma RJ, Feng SS, He KL, Yang HT. *Clinical Effect of Electroacupuncture on Perimenopausal Insomnia [Article in Chinese]*. *Proceedings of 2017 World Acupuncture Conference/2017 Annual Meeting of the Chinese Acupuncture Society*; 2017:302–303.
98. Wang YH, Zheng CL, Huang C, et al. Systems pharmacology dissecting holistic medicine for treatment of complex diseases: an example using cardiocerebrovascular diseases treated by TCM. *Evid Based Complement Alternat Med*. 2015;980190. doi:10.1155/2015/980190
99. Zhao FY, Fu QQ, Zheng Z, Lao LX, Song HL, Shi Z. Verum-versus sham-acupuncture on Alzheimer's Disease (AD) in animal models: a preclinical systematic review and meta-analysis. *Biomed Res Int*. 2020;2020:5901573.
100. China National Standardization Administration. China International Standardization Administration. *GB/T 30233-2013, Indications of Acupuncture Points*. Beijing: Chinese Standard Press; 2013.
101. van der Watt G, Laugharne J, Janca A. Complementary and alternative medicine in the treatment of anxiety and depression. *Curr Opin Psychiatry*. 2008;21(1):37–42. doi:10.1097/YCO.0b013e3282f2d814
102. van der Sluijs CP, Bensoussan A, Liyanage L, Shah S. Women's health during mid-life survey: the use of complementary and alternative medicine by symptomatic women transitioning through menopause in Sydney. *Menopause*. 2007;14(3 Pt 1):397–403. doi:10.1097/01.gme.0000236937.36078.f4
103. Gentry-Maharaj A, Karpinskyj C, Glazer C, et al. Prevalence and predictors of complementary and alternative medicine/non-pharmacological interventions use for menopausal symptoms within the UK Collaborative Trial of Ovarian Cancer Screening. *Climacteric*. 2017;20(3):240–247. doi:10.1080/13697137.2017.1301919
104. Zhu Y, Yang Y, Li J. Does acupuncture help patients with spasticity? A narrative review. *Ann Phys Rehabil Med*. 2019;62(4):297–301. doi:10.1016/j.rehab.2018.09.010
105. Clayton AH, Ninan PT. Depression or menopause? Presentation and management of major depressive disorder in perimenopausal and postmenopausal women. *Prim Care Companion J Clin Psychiatry*. 2010;12(1):PCC.08r00747.
106. Tian SL. *Effect of Pre-Acupuncture on Guanyuan and Sanyinjiao on HPO Axis of Ovariectomized Rats and Its Antioxidant Effect [Article in Chinese]* [Master thesis]. Beijing University of Chinese Medicine; 2007.
107. Zhang H, Zhang LF, Li XH, et al. Pre-acupuncture at Guanyuan acupoint in the regulation of superoxide dismutase and nitric oxide synthase activities in the natural aging rat model [article in Chinese]. *J Clin Rehabil Tis Eng Res*. 2005;9(31):147–149.
108. Li XH, Wang HB, Xu LL, et al. Effect of pre-acupuncture at Guanyuan on the expression of HSP 70 and HSP 70 mRNA in spleen and the contents of serum IL-2, TNF- $\alpha$  in perimenopausal model rat [article in Chinese]. *Acupunct Res*. 2009;34(2):83–88.
109. Li YJ, Mo YP, Deng XF, et al. Expression of 5-HT, 5-HTT in hippocampus of chronic unpredictable mild stress-induced depressive rats treated by electroacupuncture pretreatment [article in Chinese]. *J Clin Acupunct Moxib*. 2014;30(7):57–60.

110. Ciano C, King TS, Wright RR, Perlis M, Sawyer AM. Longitudinal study of insomnia symptoms among women during perimenopause. *J Obstet Gynecol Neonatal Nurs*. 2017;46(6):804–813. doi:10.1016/j.jogn.2017.07.011
111. Woods NF, Mitchell ES. Sleep symptoms during the menopausal transition and early postmenopause: observations from the Seattle Midlife Women's Health Study. *Sleep*. 2010;33(4):539–549. doi:10.1093/sleep/33.4.539
112. Freeman EW, Sammel MD, Lin H, Nelson DB. Associations of hormones and menopausal status with depressed mood in women with no history of depression. *Arch Gen Psychiatry*. 2006;63(4):375–382. doi:10.1001/archpsyc.63.4.375
113. de Zambotti M, Colrain IM, Baker FC. Interaction between reproductive hormones and physiological sleep in women. *J Clin Endocrinol Metab*. 2015;100(4):1426–1433. doi:10.1210/jc.2014-3892
114. Douma SL, Husband C, O'Donnell ME, Barwin BN, Woodend AK. Estrogen-related mood disorders: reproductive life cycle factors. *ANS Adv Nurs Sci*. 2005;28(4):364–375. doi:10.1097/00012272-200510000-00008
115. Freeman EW, Sammel MD, Liu L, Gracia CR, Nelson DB, Hollander L. Hormones and menopausal status as predictors of depression in women in transition to menopause. *Arch Gen Psychiatry*. 2004;61(1):62–70. doi:10.1001/archpsyc.61.1.62
116. Xie C. *Experimental Study of Electroacupuncture Intervening Rat's Sleep-Wake During Perimenopause by Adjusting VLPO and TMN* [Article in Chinese] [Master thesis]. Shanghai University of Traditional Chinese Medicine; 2013.
117. Yu XT. *Experimental Study of Electroacupuncture for Sleep-Wake Regulation on Rats with Insomnia During Perimenopause* [Article in Chinese] [Master thesis]. Shanghai University of Traditional Chinese Medicine; 2012.
118. Sun Y. *Experimental Study on the Mechanism of Electroacupuncture in the Treatment of Perimenopausal Depression* [Article in Chinese] [Master thesis]. Liaoning University of Traditional Chinese Medicine; 2009.
119. Song L, Li WC, Li HF, et al. Effects of acupuncture with YangXueRouGan technique on estrogen level in perimenopausal depression mice [article in Chinese]. *Occup Health*. 2021;37(7):902–904.
120. Zhou XD, Yang XJ, Zheng Y, et al. Jie-Yu Pill, a proprietary herbal medicine, ameliorates mood disorder-like behavior and cognitive impairment in estrogen-deprived mice exposed to chronic unpredictable mild stress: implication for a potential therapy of menopause syndrome. *Front Psychiatry*. 2020;11:579995. doi:10.3389/fpsy.2020.579995
121. Yang WJ. *Study on the Neuroendocrine Mechanism of Acupuncture in the Treatment of Perimenopausal Insomnia Based on Estrogen and Its Receptor* [Article in Chinese] [Doctorate thesis]. Shanghai University of Traditional Chinese Medicine; 2017.
122. Natari RB, Clavarino AM, McGuire TM, Dingle KD, Hollingworth SA. The bidirectional relationship between vasomotor symptoms and depression across the menopausal transition: a systematic review of longitudinal studies. *Menopause*. 2018;25(1):109–120. doi:10.1097/GME.0000000000000949
123. Han X, Gao Y, Yin X, et al. The mechanism of electroacupuncture for depression on basic research: a systematic review. *Chin Med*. 2021;16(1):10. doi:10.1186/s13020-020-00421-y
124. Jiang XR. *Study on the Correlation Between HPO Axis-and HPA-Axis in Perimenopausal Depression Model Rats Treated by Electroacupuncture* [Article in Chinese] [Master thesis]. Liaoning University of Traditional Chinese Medicine; 2017.
125. Liu C, Zheng S, Wu W, et al. Effects of acupuncture on the hypothalamus-pituitary-adrenal axis in chronic insomnia patients: a study protocol for a randomized controlled trial. *Trials*. 2019;20(1):810. doi:10.1186/s13063-019-3964-5
126. Xi HQ, Wu WZ, Liu CY, et al. Effect of Tongdu-Tiaoshen acupuncture in treatment of chronic insomnia by regulating the hypothalamus-pituitary-adrenal axis [article in Chinese]. *Acupunct Res*. 2020;45(7):552–556.
127. Jiang XR, Ren L, Li CR. Effect of electroacupuncture on HPO axis in rats with perimenopausal depression [article in Chinese]. *Acupunct Res*. 2017;42(1):45–49.
128. Zhang JB. *Effect of Electroacupuncture on the Behavior and Brain  $\beta$ -Endorphin and Other Indices of Rats with Perimenopausal Depression* [Article in Chinese] [Master thesis]. Liaoning University of Traditional Chinese Medicine; 2009.
129. Huangfu WL. *Effect of Electroacupuncture on Hippocampus and Internal Environment of Perimenopausal Depression Model Rats* [Article in Chinese] [Master thesis]. Liaoning University of Traditional Chinese Medicine; 2018.
130. Hartmann J, Bajaj T, Klengel C, et al. Mineralocorticoid receptors dampen glucocorticoid receptor sensitivity to stress via regulation of FKBP5. *Cell Rep*. 2021;35(9):109185. doi:10.1016/j.celrep.2021.109185
131. Oh J, Petersen C, Walsh CM, Bittencourt JC, Neylan TC, Grinberg LT. The role of co-neurotransmitters in sleep and wake regulation. *Mol Psychiatry*. 2019;24(9):1284–1295. doi:10.1038/s41380-018-0291-2
132. Eichling PS, Sahni J. Menopause related sleep disorders. *J Clin Sleep Med*. 2005;1(3):291–300. doi:10.5664/jcsm.26347
133. Schweizer-Schubert S, Gordon JL, Eisenlohr-Moul TA, et al. Steroid hormone sensitivity in reproductive mood disorders: on the role of the GABA<sub>A</sub> receptor complex and stress during hormonal transitions. *Front Med (Lausanne)*. 2021;7:479646. doi:10.3389/fmed.2020.479646
134. Riemann D, Nissen C, Palagini L, Otte A, Perlis ML, Spiegelhalter K. The neurobiology, investigation, and treatment of chronic insomnia. *Lancet Neurol*. 2015;14(5):547–558. doi:10.1016/S1474-4422(15)00021-6
135. Saito YC, Maejima T, Nishitani M, et al. Monoamines inhibit GABAergic neurons in ventrolateral preoptic area that make direct synaptic connections to hypothalamic arousal neurons. *J Neurosci*. 2018;38(28):6366–6378. doi:10.1523/JNEUROSCI.2835-17.2018
136. Cao H, Feng MG, Hou S, Wei KX. Effects of electroacupuncture at HT7 and EX-HN1 on sleep phases and PGD2 system of CSF in ovariectomized rats [article in Chinese]. *JCAM*. 2020;36(05):71–75.
137. Pan Y, Luo J, Zhang HL. Study on the effect of acupuncture at Sishencong and Baihui on the serum amino acids neurotransmitters of insomnia patients. *WJAM*. 2017;27(1):23–27.
138. Xi HQ, Wu WZ, Liu CY, et al. Effect of acupuncture at Tiaoshen acupoints on hyperarousal state in chronic insomnia [article in Chinese]. *Chin Acup Moxib*. 2021;41(3):263–267.
139. Wang D, Wang X, Luo MT, Wang H, Li YH. Gamma-aminobutyric acid levels in the anterior cingulate cortex of perimenopausal women with depression: a magnetic resonance spectroscopy study. *Front Neurosci*. 2019;13:785. doi:10.3389/fnins.2019.00785
140. Duan DM, Tu Y, Liu P, Jiao S. Antidepressant effect of electroacupuncture regulates signal targeting in the brain and increases brain-derived neurotrophic factor levels. *Neural Regen Res*. 2016;11(10):1595–1602. doi:10.4103/1673-5374.193238
141. Liu HJ, He XF, Chen XH. Effects of acupuncture on behavior and hippocampal amino-acid neurotransmitters in rats with depression [article in Chinese]. *J Med Res*. 2010;39(3):79–81.
142. Schneider-Matyka D, Grochans E, Lubkowska A, Panczyk M, Szkup M. The effect of tryptophan and serotonin levels on the severity of depressive and climacteric symptoms in perimenopausal women. *Eur Rev Med Pharmacol Sci*. 2021;25(9):3425–3431.

143. Gonzales GF, Carrillo C. Blood serotonin levels in postmenopausal women: effects of age and serum oestradiol levels. *Maturitas*. 1993;17(1):23–29. doi:10.1016/0378-5122(93)90120-7
144. Albertazzi P. A review of non-hormonal options for the relief of menopausal symptoms. *Treat Endocrinol*. 2006;5(2):101–113. doi:10.2165/00024677-200605020-00004
145. Guo X, Pan F, Wang B, Li W, Xia C, Ju Z. Effect of electroacupuncture on mice model of perimenopausal depression. *Saudi J Biol Sci*. 2019;26(8):2030–2036. doi:10.1016/j.sjbs.2019.08.007
146. Zhou SH, Sun FJ, Chen Z, Kong NN. Regulation of acupuncture with Kidney-tonifying method on monoamine neurotransmitter in perimenopausal depression model rats [article in Chinese]. *Lishizhen Med Materia Medica Res*. 2015;26(9):2299–2301.
147. Shi MQ, Han K. Mechanism study of Kidney-Tonifying-and-Liver-Soothing therapy in regulating estradiol and 5-HT levels in ovariectomized rats [article in Chinese]. *J Liaoning Univ TCM*. 2012;14(2):185–188.
148. Wu GF. *Study on the Effect and Mechanism of Electroacupuncture on Animal Model of Perimenopausal Depression with Liver-Stagnation Syndrome Pattern [Article in Chinese]* [Master thesis]. Liaoning University of Traditional Chinese Medicine; 2012.
149. Zhao SZ, Ren L. Effect of electroacupuncture on high-density lipoprotein in rat model of perimenopausal depression [article in Chinese]. *Heilongjiang Med J*. 2011;24(3):395–397.
150. Duan D, Tu Y, Yang X, Liu P. Electroacupuncture restores 5-HT system deficit in chronic mild stress-induced depressed rats. *Evid Based Complement Alternat Med*. 2016;2016:7950635. doi:10.1155/2016/7950635
151. Cespuglio R. Serotonin: its place today in sleep preparation, triggering or maintenance. *Sleep Med*. 2018;49:31–39. doi:10.1016/j.sleep.2018.05.034
152. Cao H, Feng MG, Hou S, Teng JY. Effects and mechanism of electroacupuncture at SP6 on sleep phase in rats with perimenopausal insomnia [article in Chinese]. *JCAM*. 2019;35(08):80–83.
153. Rybaczyk LA, Bashaw MJ, Pathak DR, Moody SM, Gilders RM, Holzschu DL. An overlooked connection: serotonergic mediation of estrogen-related physiology and pathology. *BMC Womens Health*. 2005;5:12. doi:10.1186/1472-6874-5-12
154. Palagini L, Geoffroy PA, Miniati M, et al. Insomnia, sleep loss, and circadian sleep disturbances in mood disorders: a pathway toward neurodegeneration and neuroprogression? A theoretical review. *CNS Spectr*. 2021;1–11. doi:10.1017/S1092852921000018
155. Gulec M, Ozkol H, Selvi Y, et al. Oxidative stress in patients with primary insomnia. *Prog Neuropsychopharmacol Biol Psychiatry*. 2012;37(2):247–251. doi:10.1016/j.pnpb.2012.02.011
156. Doshi SB, Agarwal A. The role of oxidative stress in menopause. *J Midlife Health*. 2013;4(3):140–146.
157. Sánchez-Rodríguez MA, Zacarias-Flores M, Arronte-Rosales A, Correa-Muñoz E, Mendoza-Núñez VM. Menopause as risk factor for oxidative stress. *Menopause*. 2012;19(3):361–367. doi:10.1097/gme.0b013e318229977d
158. Agarwal A, Aponte-Mellado A, Premkumar BJ, Shaman A, Gupta S. The effects of oxidative stress on female reproduction: a review. *Reprod Biol Endocrinol*. 2012;10:49. doi:10.1186/1477-7827-10-49
159. Hachul de Campos H, Brandão LC, D'Almeida V, et al. Sleep disturbances, oxidative stress and cardiovascular risk parameters in postmenopausal women complaining of insomnia. *Climacteric*. 2006;9(4):312–319. doi:10.1080/13697130600871947
160. Kolesnikova LL, Semenova NV, Solodova EI, Madaeva LM. Oxidative stress in women with insomnia in different stages of menopause [article in Russian]. *Ter Arkh*. 2017;89(8):50–56.
161. Kolesnikova LL, Madaeva LM, Semenova NV, Solodova EI, Grebenkina LA, Darenskaya MA. Evaluation of lipid peroxidation - antioxidant protection in perimenopausal women with sleep disorders [article in Russian]. *Vestn Ross Akad Med Nauk*. 2014;69(11–12):11–16. doi:10.15690/vramn.v69i11-12.1177
162. Lin YF, Liu ZD, Ma W, Shen WD. Hazards of insomnia and the effects of acupuncture treatment on insomnia. *J Integr Med*. 2016;14(3):174–186. doi:10.1016/S2095-4964(16)60248-0
163. Wu BF. *An Experimental Study on the Mechanism of Electroacupuncture on Sleep Deprivation and Its Induced Oxidative Stress in Rats [Article in Chinese]* [Doctorate thesis]. Heilongjiang University of Chinese Medicine; 2008.
164. Hirose A, Terauchi M, Akiyoshi M, Owa Y, Kato K, Kubota T. Depressive symptoms are associated with oxidative stress in middle-aged women: a cross-sectional study. *Biopsychosoc Med*. 2016;10:12. doi:10.1186/s13030-016-0066-4
165. Liu CZ, Shi GX, Huang YL, Zhu H, Wang LP. Effect of acupuncture on urinary biomarkers of oxidative stress in vascular dementia patients [article in Chinese]. *Chin J Inf Tradit Chin Med*. 2011;18(7):18–20.
166. Yeung WF, Yu BYM, Yuen JWM, et al. Semi-individualized acupuncture for insomnia disorder and oxidative stress: a randomized, double-Blind, sham-controlled trial. *Nat Sci Sleep*. 2021;13:1195–1207. doi:10.2147/NSS.S318874
167. Sánchez-Rodríguez MA, Zacarias-Flores M, Arronte-Rosales A, Mendoza-Núñez VM. Association between hot flashes severity and oxidative stress among Mexican postmenopausal women: a cross-sectional study. *PLoS One*. 2019;14(9):e0214264. doi:10.1371/journal.pone.0214264
168. Miquel J, Ramírez-Bosca JV, Ramírez-Bosca JV, Alperi JD. Menopause: a review on the role of oxygen stress and favorable effects of dietary antioxidants. *Arch Gerontol Geriatr*. 2006;42(3):289–306. doi:10.1016/j.archger.2005.08.005
169. Krystal AD, Edinger J, Wohlgenuth W, Marsh GR. Sleep in perimenopausal and post-menopausal women. *Sleep Med Rev*. 1998;2(4):243–253. doi:10.1016/S1087-0792(98)90011-9
170. Seo SY, Moon JY, Kang SY, et al. An estradiol-independent BDNF-NPY cascade is involved in the antidepressant effect of mechanical acupuncture instruments in ovariectomized rats. *Sci Rep*. 2018;8(1):5849. doi:10.1038/s41598-018-23824-2
171. Wang G, Ren L. Effect of electroacupuncture on hippocampal BDNF and CREB in rats with perimenopausal depression [article in Chinese]. *Liaoning J TCM*. 2016;43(4):858–860.
172. Liu YZ. *Comparative Effects Between Electroacupuncture at Single Acupoint and at Group of Acupoints on Learning and Memory Ability of Sleep-Deprived Rats [Article in Chinese]* [Master thesis]. Changchun University of Chinese Medicine; 2019.
173. Xiao Z, Cao Z, Yang J, et al. Baicalin promotes hippocampal neurogenesis via the Wnt/β-catenin pathway in a chronic unpredictable mild stress-induced mouse model of depression. *Biochem Pharmacol*. 2021;190:114594. doi:10.1016/j.bcp.2021.114594
174. Jing Q, Ren L, Deng X, et al. Electroacupuncture promotes neural proliferation in hippocampus of perimenopausal depression rats via Wnt/β-Catenin signaling pathway. *J Acupunct Meridian Stud*. 2020;13(3):94–103. doi:10.1016/j.jams.2020.03.065
175. Wexler EM, Geschwind DH, Palmer TD. Lithium regulates adult hippocampal progenitor development through canonical Wnt pathway activation. *Mol Psychiatry*. 2008;13(3):285–292. doi:10.1038/sj.mp.4002093
176. Dai J, Pan JY, Liao N, et al. Influence of miR-155 on behaviors of depression mice through regulating Wnt/β-catenin signaling pathway. *Eur Rev Med Pharmacol Sci*. 2020;24(3):1398–1407.
177. Deng X. *Effect of Electroacupuncture on the Proliferation and Differentiation of Hippocampal Neural Stem Cells and Wnt Pathway in a Rat Model of Perimenopausal Depression [Article in Chinese]* [Doctorate thesis]. Liaoning University of Traditional Chinese Medicine; 2017.
178. Jing Q, Lin H, Ren L. Effect of electroacupuncture on Wnt/β-Catenin signaling pathway in hippocampus of perimenopausal depression rats model [article in Chinese]. *Chin Archiv TCM*. 2018;36(6):1347–1350.



179. Park BM, Kim EJ, Nam HJ, et al. Cyclized oligopeptide targeting LRP5/6-DKK1 interaction reduces the growth of tumor burden in a multiple myeloma mouse model. *Yonsei Med J.* 2017;58(3):505–513. doi:10.3349/ymj.2017.58.3.505
180. Qu DJ, Huan Y, Zhao YY, et al. Involvement of Wnt/ $\beta$ -catenin signaling mediated hippocampal neurogenesis in sleep-deprivation induced memory impairment in mice [article in Chinese]. *Chin J Neuroanat.* 2019;35(02):134–140.
181. Ables JL, Breunig JJ, Eisch AJ, Rakic P. Not(ch) just development: notch signalling in the adult brain. *Nat Rev Neurosci.* 2011;12(5):269–283. doi:10.1038/nrn3024
182. Shen J, Lin L, Liao L, et al. The involvement of Notch1 signaling pathway in mid-aged female rats under chronic restraint stress. *Neurosci Lett.* 2020;738:135313. doi:10.1016/j.neulet.2020.135313
183. Tian H, Li X, Tang Q, et al. Yi-nao-jie-yu prescription exerts a positive effect on neurogenesis by regulating Notch signals in the hippocampus of post-stroke depression rats. *Front Psychiatry.* 2018;9:483. doi:10.3389/fpsy.2018.00483
184. Jalali A, Bassuk AG, Kan L, et al. HeyL promotes neuronal differentiation of neural progenitor cells. *J Neurosci Res.* 2011;89(3):299–309. doi:10.1002/jnr.22562
185. Deng X, Ren L. Effect of electroacupuncture on expression of hippocampal Notch signaling pathway in rats with perimenopausal depression [article in Chinese]. *Liaoning J TCM.* 2017;44(3):595–601.
186. Mathews SB, Epperson CN. Clinical management of menopause-related sleep disturbance. In: Pal L, Sayegh R, editors. *Essentials of Menopause Management.* Cham: Springer; 2017:105–127.
187. Davis SR. The Kupperman Index undressed. *Maturitas.* 2019;126:90–91. doi:10.1016/j.maturitas.2019.04.219
188. Befus D, Coeytaux RR, Goldstein KM, et al. Management of menopause symptoms with acupuncture: an umbrella systematic review and meta-analysis. *J Altern Complement Med.* 2018;24(4):314–323. doi:10.1089/acm.2016.0408
189. Jin YB, Yang ZY, Jin HF, Mi HQ. Discussion of the effect on ethology of perimenopausal syndrome rats by electroacupuncture in different periods [article in Chinese]. *CJTCMP.* 2010;25(10):1689–1693.
190. Jin YB, Mi HQ, Jin HF. Discussion of the best intervention time for electroacupuncture in treating rats with perimenopausal syndrome. *J Acupunct Tuina Sci.* 2011;9(5):273–277. doi:10.1007/s11726-011-0530-4
191. Ebrahimi A, Tayebi N, Fatemeh A, Akbarzadeh M. Investigation of the role of herbal medicine, acupressure, and acupuncture in the menopausal symptoms: an evidence-based systematic review study. *J Fam Med Prim Care.* 2020;9(6):2638–2649. doi:10.4103/jfmpc.jfmpc\_1094\_19
192. Ee C, French SD, Xue CC, Pirotta M, Teede H. Acupuncture for menopausal hot flashes: clinical evidence update and its relevance to decision making. *Menopause.* 2017;24(8):980–987. doi:10.1097/GME.0000000000000850
193. Kim TH, Lee MS, Alraek T, Birch S. Acupuncture in sham device controlled trials may not be as effective as acupuncture in the real world: a preliminary network meta-analysis of studies of acupuncture for hot flashes in menopausal women. *Acupunct Med.* 2020;38(1):37–44. doi:10.1136/acupmed-2018-011671

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