

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.¹ It is a stage during which women are particularly vulnerable to the onset of depression,²⁻⁴ even without any previous history of depressive disorders.² A large quantity of studies also link both insomnia and vasomotor symptoms (hot flushes and night sweating) to perimenopausal depression (PMD),^{3,5,6} while insomnia is correlated more strongly and consistently with depression than vasomotor symptoms are.⁷⁻⁹ The prevalence of comorbid depression and insomnia in perimenopause is approximately 31.5%.⁹

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.¹⁰ 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.^{11,12} In various insomnia patterns, depression is highly associated with difficulty falling asleep and waking up earlier than desired.¹⁰ Women in the menopausal transition are at increased risk for sleep-disordered breathing, which can also contribute to both depressed mood and poor sleep.³ 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.¹⁰ 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.¹³ Anticipation of symptom self-healing might be futile as untreated PMD can increase medical morbidity after menopause, including risks of endocrine and cardiovascular disease.¹⁴

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.^{4,11} 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.^{4,5} 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.¹⁰

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,^{6,15} 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).⁶ According to NAMS and NNDC, antidepressants and cognitive behavioral therapy (CBT) are the front-line antidepressant treatments for PMD.⁶ 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.^{5,16–18} Similarly, sedatives and hypnotics have side effects that patients may find uncomfortable¹⁹ 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.²⁰ Hormone replacement therapy (HRT) can be an effective treatment for perimenopausal syndrome, while it is not FDA-approved to treat perimenopausal mood disturbance.⁶

Complementary and alternative medicine (CAM) has many proponents and supporters³ and has been sought to treat depression¹⁶ and insomnia¹⁹ 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.^{3,21} Acupuncture has a long tradition of usage for the treatment of various menopause-related symptoms, including PMI and PMD, dating back thousands of years.²² Its clinical efficacy has been investigated for natural menopause and chemical/surgery-induced menopause.²² 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.^{23,24} 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).²⁵ 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.^{19,26,27} 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.²⁸ 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).^{27–30} 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.³¹ Dysfunction or disorder in these cerebral regions has been previously implicated in the development of depression^{32,33} and/or insomnia.^{34,35} 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.²⁹ Furthermore, patterns of usage of MA or EA usually vary by condition treated, stimulus demand, and/or acupuncturist preference.²⁹

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%).^{36,37} No serious AEs requiring hospital visits or resulting in permanent disability or death have been reported from

acupuncture.^{36,37} 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.^{32,38} 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,³⁹ 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.⁴⁰ 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.⁴¹ As of September 2018, there were at least 34 SRs/MAs regarding acupuncture treatment for insomnia.³⁰ 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.^{30,41} 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).³⁰ 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.^{41,42}

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).^{26,28,43} 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.^{26,28,43}

In clinical setting, acupuncture is ubiquitously applied based on the basic theory of TCM, which emphasizes the concept of “syndrome pattern”.⁴⁴ “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.^{44,45} 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.⁴⁶ 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.^{47,48} Based on bibliometric analysis,^{47,48} 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.^{47,49} 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.^{47,49} Smoothing liver (smooths liver and regulates Qi) and nourishing kidney (nourishes kidney

and enriches essence) are regarded as the general principles for perimenopausal disorders.^{47,49}

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^{19,50} 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.^{19,50} 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 PMD

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 ⁵¹	- 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, Arl, NI%, N2%, N3%, REM%)	(i) Lower PSQI and ISI in MA group (ii) Shorter SOL and WASO, longer TST, higher SE, lower Arl, 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 ⁵²	- 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 ⁵³	- 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 ⁵⁴	- EA/n=42 - placebo-EA/n=42	PMI (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 (I); mild pain (I)] - placebo-EA/n=1 (mild pain)
Wang et al 2015 ⁵⁵	- 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 ⁵⁶	- 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, LH4, 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 ⁹⁷	- EA/n=37 - Progynova + Medroxyprogesterone acetate/n=36	PM1 (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 Progynova 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)] - Progynova + Medroxyprogesterone acetate/n=4 [breast tenderness (2); mild headache (1); colporrhagia (1)]
Chen et al 2013 ⁵⁷	- EA/n=38 - Alprazolam/n=32	PM1 (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 ⁵⁸	- MA/n=30 - Estazolam/n=30	PM1 (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 ⁵⁹	- EA/n=41 - Estazolam/n=41	PM1 (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 ⁶⁰	- 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 ⁶¹	- 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 ⁶²	- 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 ⁶³	- 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 ⁴⁹	- 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 ⁶⁴	- EA/n=45 - Estazolam/n=45	PM1 (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 GBI4)	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 ⁶⁵	- MA/n=34 - Estazolam/n=33	PM1 (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, MSMS (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 ⁶⁶	- MA/n=81 - Estazolam/n=81	PM1 (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 ⁶⁷	- MA/n=31 - Estazolam/n=30	PM1 (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 ⁶⁸	- MA/n=42 - Estazolam/n=43	PM1 (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 2018 ⁶⁹	- 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 ⁷⁰	- MA/n=30 - Fluoxetine/n=30	PMD (CCMD-3)	NR	30 min/day for 4 weeks	EX-HN1, EX-HN3, GV20, KI3, LR3, LR14, 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 ⁷¹	- 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); breast dreadiness (6); breast distending pain (5)]
Dong 2015 ⁸⁵	- 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 ⁷²	- MA/n=32 - Fluoxetine/n=32	PMD (CCMD-3)	Liver stagnation and kidney deficiency	30 min/day, 6 days/week for 12 weeks	BLI5, BLI8, 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 ⁷³	- 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 ⁷⁴	- MA/n=41 - Fluoxetine/n=41	PMD (CCMD-3)	Stagnation of liver Qi	30 min/day, 5 days/week for 6 weeks	BLI3, BLI5, BLI7, BLI8, 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 ⁷⁵	- MA/n=33 - Fluoxetine/n=30	PMD (CCMD-3)	NR	25 min/day, 5 days/week for 6 weeks	BLI3, BLI5, BLI7, BLI8, 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 ⁷⁶	- MA/n=30 - Fluoxetine/n=30	PMD (CCMD-3)	NR	25 min/day, 5 days/week for 6 weeks	BLI5, BLI8, 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 ⁷⁷	- 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 ⁷⁸	- 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 ⁷⁹	- 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 ⁸⁶	- EA/n=44 - Nilotriol+ 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	Nilotriol 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) - Nilotriol+ Fluoxetine/n=23 [dry mouth and halitosis (5); nausea (6); dysphoria (2); constipation (6); dreaminess (2); breast distending pain (2)]
Zhang 2013 ⁸⁷	- 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 ⁸⁸	- 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); leukorrhea (2); spasmus (1)]
Ding et al 2007 ⁸⁰	- 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 ⁸¹	- 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 ⁸²	- 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 ⁸³	- 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 ⁸⁴	- 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 ⁸⁹	- 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 ⁹⁰	- 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 ⁹¹	- 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 ⁹²	- 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 ⁹⁵	- 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 ⁹³	- 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 ⁹⁴	- 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 Depression Scale; WHOQOL-BREF, World Health Organization's quality of life scale-brief form questionnaire; TESS, Treatment Emergent Symptom Scale; PSG, polysomnography; MSMS, 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; disturbance of liver due to phlegm heat; Yin deficiency leading to excessive fire; Heart and Spleen deficiency; Heart and Gallbladder Qi deficiency]; BL8, Luoque; BL13, Feishu; BL15, Xinshu; 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, Annian; EX-B2, Jiaji; EX-CA1, Zigong; EX-HN1, Sishencong; EX-HN3, Yintang; GB13, Benshen; GB14, Yangbai; GB15, Toulunqi; 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, Wailing; 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 = 21); 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^{51–54} as well as depressed mood,^{55,56} when compared with waitlist or placebo controls. Thirteen RCTs compared the effects between acupuncture and various hypnotics including Estazolam, Alprazolam, and Eszopiclone.^{49,57–68} 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^{58,61} 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,^{56,69–84} or the effects between acupuncture and antidepressants combined with HRT.^{85–88} 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^{89–92} 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^{93,94} indicated that acupuncture combined with antidepressants produced lower HAMD scores than antidepressants alone. Although another RCT⁹⁵ 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,^{36,37} 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.^{19,50} 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.^{13,96} 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 RCT⁹⁷ 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.^{43,44,98} "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.^{26,28,43} 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.^{43,44} 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).^{43,44,98} 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.²³ 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 study⁹⁵ 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.¹⁹ 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.⁹⁹ 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),¹⁰⁰ 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.¹⁰⁰ 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.^{23,101} 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;¹⁰² In the UK, 6.4% climacteric women utilize aromatherapy, reflexology, or acupuncture to reduce symptoms.¹⁰³ 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.¹⁰⁴ 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 depression¹⁰⁵ or experiencing stressful

events⁶ 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.¹⁰ 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.⁴⁴ 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,^{106,107} inhibit the hyperactivity of hypothalamic-pituitary-ovary (HPO) axis,¹⁰⁶ as well as regulate the inflammatory response and disorders of the immune system¹⁰⁸ 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).¹⁰⁹

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.^{19,50} As reported, poor-quality acupuncture studies usually show a higher proportion of positive results than high-quality studies.¹⁰⁴ 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.^{2-4,13,110} The endocrine system is regarded as one of the principal intrinsic factors affecting women's sleep and mood during their reproductive life span.^{1,14,96} 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.⁴ 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.¹¹¹ 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.¹¹² Some longitudinal analyses have suggested the correlation between reproductive hormones [eg, estradiol (E2), follicle-stimulating hormone (FSH), luteinizing hormone (LH), etc] levels and sleep disturbances¹ or depressive symptoms¹¹² 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.¹ 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).¹⁰

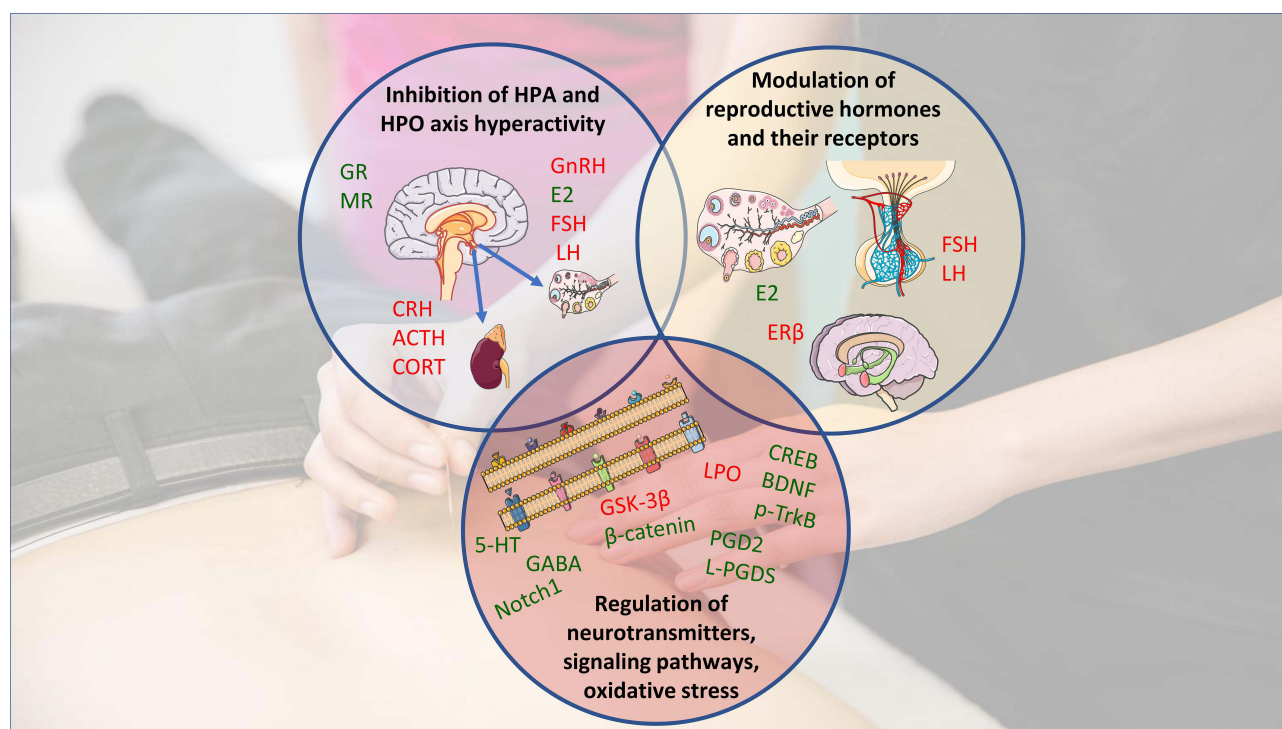


Figure 1 Potential mechanisms by which acupuncture may improve perimenopausal depression and insomnia. Manual- and/or electro-acupuncture may alter hypothalamic-pituitary-adrenal and -ovarian hyperactivity; modulate reproductive hormones and their receptors, or regulate neurotransmitters, signaling pathways, 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, adrenocorticotrophic hormone; CORT, cortisol; ERβ, 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; PGD2, prostaglandin D2; L-PGDS, lipocalin-type prostaglandin D synthase; LPO, lipid peroxidation; GSK-3β, 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.^{13,110} The latter two alterations can reduce women's ability to tolerate nocturnal hot flashes and subsequently cause sleep disruption.¹¹⁰ 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.¹⁰ Among women with PMI, Fu et al also observed that acupuncture induced reductions in both wake after sleep onset (WASO) and arousal index (ArI),⁵¹ which were negatively correlated with E2 levels but positively correlated with FSH.¹¹³ Estrogen is a mood-elevator as well, and its effect on emotional functions is partly mediated by the amygdala and hypothalamus.¹¹⁴ New onset of PMD was strikingly associated

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

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.^{116–119}

The estrogen receptors (ERα and ERβ) are closely related to the pathophysiology of climacteric-related neurological and psychiatric illness,¹²⁰ 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 ¹⁵²	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 ¹³⁶	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-HN1, 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 ¹⁸⁹	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 ¹⁹⁰	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 ¹¹⁶	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 ¹¹⁷	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 ¹²¹	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-α mRNA, ER-β 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 ERβmRNA; no significant change in ERαmRNA
Jing et al 2020 ¹⁷⁴	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-3β mRNA, β-catenin mRNA in hippocampus (iv) β-Catenin protein, p-β-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-3β mRNA and increased β-catenin mRNA expression (iii) EA increased β-catenin protein and decreased p-β-catenin protein expression
Guo et al 2019 ¹⁴⁵	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 ¹⁷⁰	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 ¹⁸⁵	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, Norch I, Jagged I, Hes I in hippocampus (iii) MAP-2 mRNA, Norch I mRNA, Jagged I mRNA, Hes I mRNA in hippocampus	(i) EA improved rats' depression-like behavior in behavioral tests (ii) EA increased MAP-2 protein and Notch I protein levels, and decreased Jagged I protein and Hes I protein levels (iii) EA increased MAP-2 mRNA and Notch I mRNA expression, and decreased Jagged I mRNA and Hes I mRNA expression
Deng 2017 ¹⁷⁷	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-3 β , β -catenin in hippocampus (iii) β -catenin protein, p- β -catenin protein in hippocampus (iv) GSK-3 β mRNA, β - catenin mRNA in hippocampus	(i) EA improved rats' depression-like behavior in behavioral tests (ii) EA decreased GSK-3 β 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-3 β mRNA and increased β -catenin mRNA expression

Huangfu 2018 ¹²⁹	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 ¹²⁴	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, β -EP	(i) EA improved rats' depression-like behavior in behavioral tests (ii) EA increased E2 and β -EP, and decreased FSH, LH, GnRH, CORT, ACTH and CRH levels
Jiang et al 2017 ¹²⁷	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, β -EP	(i) EA improved rats' depression-like behavior in behavioral test (ii) EA increased E2 and β -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 ⁷⁸	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 ¹⁴⁶	SD rats, 220–260g	PMD	(i) OVX (ii) CUMS	- MA/n= 9 - Model-1/n= 9 - Model-2/n= 8 - Sham-surgery/n= 6 - Nilotriol + Fluoxetine/n= 9	- MA/OVX + CUMS + MA - Model-1/OVX + CUMS - Model-2/OVX - Sham-surgery/ sham-OVX - Nilotriol + Fluoxetine/OVX + CUMS + Nilotriol + 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 ¹⁴⁷	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 ¹¹⁸	(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 ¹⁷¹	SD rats, 220–260g, 17 weeks	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 ¹⁴⁸	(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 ¹²⁸	(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) β -EP in hippocampus	(i) EA improved rats' depression-like behavior in behavioral test (ii) EA increased E2 level (ii) EA increased β -EP level
Zhao et al 2011 ¹⁴⁹	(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 ¹¹⁹	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, SPI0, 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 synthase; GABA, gamma-aminobutyric acid; 5-HT, 5-hydroxytryptamine; 5-HIAA, 5-hydroxyindole acetic acid; NE, norepinephrine; DA, dopamine; ER- α , Estrogen receptor- α ; ER- β , Estrogen receptor- β ; GnRH, gonadotropin-releasing hormone; GSK-3 β , glycogen synthase kinase-3 β ; p- β -catenin, phosphorylated β -catenin; BDNF, brain-derived neurotrophic factor; NPY, neuropeptide Y; MAP-2, microtubule-associated protein-2; CRH, corticotropin-releasing hormone; ACTH, adrenocorticotrophic hormone; CORT, cortisol; β -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, Shihengcong; GV20, Baihui; HT7, Shenmen; KI3, Taixi; KI15, Zhongzhu; LI4, Hegu; LR3, Taichong; PC6, Neiguan; SP6, Sanyinjiao; SPI0, Xuehai; ST36, Zusanli.

expression has been linked to a variety of cancers, particularly breast and ovarian cancers.¹²⁰ Yang reported that successful PMI modeling resulted in an increased expression of ER β in the hypothalamus, which was prevented by acupuncture.¹²¹ 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.¹²⁰ 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.¹²² 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.¹²³ This hypothesis was tested in a PMD model by Jiang et al.¹²⁴ 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.¹²⁴ The response of HPA axis can be modulated by estrogen.¹²² 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.¹²⁵ Xi et al reported significant symptom-relief in chronic insomniacs who underwent acupuncture, accompanied by downregulation in serum CRH, ACTH and CORT expression.¹²⁶ A reciprocal relationship has been established between the HPO and HPA axes.¹²² Acupuncture appears to suppress these two axes synchronously. In three animal studies,^{124,127,128} 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.¹¹³ 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.¹¹³

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).¹²⁹ Disruption of GR signaling is proposed to underlie HPA axis dysregulation observed in stress-related psychiatric illness.¹³⁰ 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.¹²⁹

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.¹³¹ For instance, the positive regulation of estrogen in sleep and mood disorders associated with menopause-^{114,132} 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.¹³²

It is well known that GABA is the dominant inhibitory transmitter.¹³³ Decreased GABAergic activity links to a weakening of the sleep-promotion system or a strengthening of the arousal system.¹³⁴ 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_A 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.¹³⁴ 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.¹³⁵ 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.¹³⁶ 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.^{137,138} Estrogen receptors are found throughout the brain, so estrogen shows modulatory effects on the neurotransmitter systems.⁵ 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.^{8,14} Dysregulation of the GABA balance between GABA_A and GABA_B due to hormone fluctuations also contributes to the increased vulnerability to depression during perimenopause.⁹⁶ 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.¹³⁹ 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.¹³³ The effect of acupuncture in reinstating reduced hippocampal GABA content in rats with depression has been widely investigated and confirmed.^{140,141} 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.¹³³ 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.^{133,142} The available evidence suggests there are lower serum 5-HT levels in postmenopausal women than in regularly menstruating women;¹⁴³ and in comparison to the natural menopause in humans, the decline of 5-HT levels following ovariectomy is more drastic.¹⁴³ Selective serotonin reuptake inhibitors are one of the most frequently utilized non-hormonal substitutes for menopausal symptoms,¹⁴⁴ 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.¹⁴² Both human clinical^{71,84,93} and animal studies^{145–149} 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.^{123,150} 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.¹²³ 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.¹⁵¹ In both serum and hippocampus of PMI rats,^{121,152} 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.¹¹ 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.^{114,153} E2, for instance, is able to

stimulate the production of neurotransmitters such as serotonin and to enhance serotonergic function in depression and its treatment.¹¹⁴ 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.¹⁵⁴ Compared with good sleepers, insomniacs generally have much higher oxidative stress parameters.¹⁵⁵ Meanwhile, oxidative stress is a pivotal factor in ageing.¹⁵⁶ Menopause is an aging process, in which oxidative stress plays a crucial role in developing a diversity of symptoms.¹⁵⁶ The decline of estrogen during menopause results in the massive release of reactive oxygen species (ROS) and creates a pro-oxidant state,^{157,158} 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.^{13,159} Recent study identified an evident imbalance between lipid peroxidation (LPO) and the antioxidant defense system among the menopausal insomniacs,¹⁶⁰ providing a pathogenic rationale for including drugs that inhibit LPO activation in the synthetical therapy of these patients.¹⁶¹ A cross-sectional study involving 187 perimenopausal women also suggested that there was a positive correlation between insomnia score, menopause rating score, and LPO.¹⁵⁷ 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.^{162,163} 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.¹⁶⁴ 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.¹⁶⁵ 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.¹⁶⁴ 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.¹⁰⁶ A recent RCT revealed that EA significantly decreased level of lipid hydroperoxides, a byproduct of oxidative stress, among insomniacs.¹⁶⁶ 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.¹⁰⁷ 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.¹⁶² 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,^{167,168} a potential contributor of PMI¹⁶⁹ and PMD⁵ 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.¹⁶⁸ 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.¹²³ 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,¹⁷⁰ and it may be linked with the development of depression by cAMP-response element-binding protein (CREB) and its upstream pathways.¹⁴⁰ Many conventional antidepressive agents mediate antidepressant-like effects via increasing synthesis and signal transduction of cerebral BDNF expression.^{123,170} 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.^{170,171} 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 β /CREB/BDNF/TrkB signaling pathway.¹⁷²

Activation of the Wnt/ β -catenin signaling pathway has moderation effect on multiple aspects of hippocampal neurogenesis, which has been linked to depressive symptoms.¹⁷³ Glycogen synthase kinase-3 β (GSK-3 β) and β -catenin are key proteins of Wnt signaling, which comprise a degradation complex to phosphorylated (p)- β -catenin to be ubiquitinated.¹⁷⁴ These critical regulatory molecules particularly GSK-3 β and β -catenin are suggested to be targets and/or action modifiers of antidepressants such as lithium¹⁷⁵ and fluoxetine.¹⁷⁶ Interestingly, regulation of these proteins was also observed in two studies in which acupuncture improved depressive-like symptoms in PMD rats.^{174,177} As reported, hippocampal mRNA and protein expression of GSK-3 β were decreased, while mRNA and protein expression of β -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.¹⁷⁸ As an endogenous inhibitor, DKK1 binds to LRP 5/6 and results in the inhibition of canonical Wnt signaling pathway.¹⁷⁹ These findings suggest that activation of the Wnt/ β -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/ β -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.¹⁸⁰

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

the depression-like performance in mid-aged female rats undergoing chronic restraint stress.¹⁸² 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.¹⁸⁵ 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.¹⁶⁹ Some longitudinal investigations and SRs/MAs of perimenopause have also indicated the positive correlation between vasomotor complaints and poor sleep and/or depressive symptoms.^{1,2} In comparison with those without vasomotor symptoms, women suffering from more night sweats weekly are with more likelihood to report sleep difficulties.¹ Translated, women with vasomotor symptoms are more at risk for insomnia.¹⁸⁶ However, there is a theory that vasomotor symptoms are not a necessary prerequisite for PMD,¹³ while perimenopausal women with hot flushes are indeed at higher risk of developing depression.⁵ Moreover, women with PMD have a higher likelihood of being irritable from vasomotor symptoms and report greater severity of their hot flushes. They are also most likely to seek help from primary health care services.⁵ Some recent evidence reveals a bidirectional relationship between PMD and vasomotor complaints.^{8,122} It is thought that this relationship may not be simply explained by the mediating effect of sleep disruption,^{8,122} whereas PMD and perimenopausal anxiety due to vasomotor symptoms do contribute to the impaired sleep.¹¹⁰ Attenuation of vasomotor symptoms by acupuncture thereby partially explains why it promotes the PMI relief.¹⁸⁶ Plenty of clinical data cited in our review have shown that acupuncture significantly lowered the Kupperman Index global scores (Table 2). Hot flushes and sweating are the critical and most weighted items of the Kupperman Index scale.¹⁸⁷ Although the frequency of hot flushes and night sweats were not directly assessed in our included clinical papers, acupuncture is sure to be promising to mitigate menopausal-associated vasomotor symptoms.¹⁸⁸ 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.¹⁸⁸ Additionally, two included animal studies^{189,190} 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.¹⁹¹ These benefits of acupuncture were validated again in PMD rats and were accompanied by a significant reduction in depression-like behavior.^{124,127,128} Interestingly, serotonin regulates thermoregulation and peripheral vasculature.¹⁵³ 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,¹⁹² another network meta-analysis exhibited opposite conclusion.¹⁹³ In comparison with no treatment, however, the benefits of acupuncture or placebo-acupuncture are clear, according to both papers.^{192,193} 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.^{6,13,15} 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^{54,64,65,67} 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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None of the authors have any conflicts of interest to declare in this study.

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