Network Meta-Analysis of Non-Pharmacological Interventions for Perimenopausal Insomnia Symptoms: A Postprint

Authors: He Jingyi, Wang Fang, Shui Xiaoling, Li Ling, Liang Qian, Wang Fang

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Abstract

Background The emergence of insomnia symptoms can reduce the quality of life in perimenopausal women and increase their risk of developing other diseases. Currently, there are numerous non-pharmacological interventions available for improving perimenopausal insomnia symptoms, but there is still disagreement regarding which intervention is most effective.

Objective To evaluate the effectiveness of non-pharmacological interventions in improving perimenopausal insomnia symptoms using a network Meta-analysis method.

Methods In March 2022, randomized controlled trials (RCTs) on non-pharmacological interventions for improving perimenopausal insomnia symptoms were searched in Cochrane Library, PubMed, EmBase, Web of Science, CNKI, Wanfang Data Knowledge Service Platform, VIP Chinese Science and Technology Journals Full-text Database, and Chinese Biomedical Literature Database, with the search period spanning from database inception to March 2022. After two researchers independently screened the literature, extracted data, and assessed the risk of bias in the included studies using the RCT bias risk assessment tool recommended by the Cochrane Handbook for Systematic Reviews of Interventions version 5.1.0, a Bayesian network Meta-analysis was conducted using R 4.1.3 software and the GeMTC package to evaluate the total effective rate of perimenopausal insomnia symptom improvement, as well as improvements in Pittsburgh Sleep Quality Index (PSQI) scores, Kupperman scores, and estradiol (E2) levels under different non-pharmacological interventions.

Results A total of 44 RCTs involving 3386 patients were included, covering 12 types of non-pharmacological interventions (moxibustion, electroacupuncture,

auricular point acupressure, gua sha, fire dragon cupping, press-needle, tuina, warm acupuncture, bee acupuncture, acupoint catgut embedding, music therapy, and acupuncture). Network Meta-analysis results showed: In terms of the total effective rate for improving perimenopausal insomnia symptoms, moxibustion, electroacupuncture, and acupuncture were superior to sedative-hypnotic Western medicine (P<0.05), with moxibustion having the highest probability of being the optimal intervention. For PSQI score improvement, moxibustion, electroacupuncture, gua sha, and acupuncture were superior to sedative-hypnotic Western medicine (P<0.05), and moxibustion was superior to warm acupuncture (P<0.05), with moxibustion having the highest probability of being the optimal intervention. Regarding Kupperman score improvement, no statistically significant differences were found among different interventions (P>0.05), with gua sha having the highest probability of being the optimal intervention. For E2 level improvement, no statistically significant differences were observed among different interventions (P>0.05), with acupuncture having the highest probability of being the optimal intervention.

Conclusion Current evidence suggests that for perimenopausal women, moxibustion has advantages in improving the total effective rate of insomnia symptoms and PSQI scores, gua sha in improving Kupperman scores, and acupuncture in increasing E2 levels, though further verification through additional high-quality studies is needed.

Full Text

Efficacy of Non-pharmacological Interventions to Improve Perimenopausal Insomnia Symptoms: A Network Meta-analysis

HE Jingyi[1], WANG Fang[2]*, SHUI Xiaoling[1], LI Ling[1], LIANG Qian[1]

[1]School of Nursing, Chengdu University of Traditional Chinese Medicine, Chengdu 610075, China
[2]Director's Office, Guang'an Hospital, Affiliated Hospital of Chengdu University of Chinese Medicine/Guang'an Hospital of Traditional Chinese Medicine, Guang'an 638001, China
*Corresponding author: WANG Fang, Chief superintendent nurse; E-mail: 1697070757@qq.com

Abstract

Background: The presence of insomnia symptoms reduces the quality of life of perimenopausal women and increases their risk of developing other diseases. Currently, numerous non-pharmacological interventions are available to improve perimenopausal insomnia symptoms, though disagreement persists regarding which intervention is most effective. **Objective:** To evaluate the efficacy of non-pharmacological interventions in improving perimenopausal insomnia symp-

toms using a network meta-analysis. **Methods:** In March 2022, we searched Cochrane Library, PubMed, EmBase, Web of Science, CNKI, Wanfang Data Knowledge Service Platform, VIP Chinese Science and Technology Journal Fulltext Database, and Chinese Biomedical Literature Database for randomized controlled trials (RCTs) on non-pharmacological interventions for perimenopausal insomnia symptoms from inception to March 2022. Two investigators independently screened literature, extracted data, and evaluated the risk of bias using the RCT bias risk assessment tool recommended by the Cochrane Handbook for Systematic Reviews 5.1.0. Bayesian network meta-analysis was performed using R 4.1.3 software and the GeMTC package to analyze the overall response rate for improvement of perimenopausal insomnia symptoms, as well as improvements in Pittsburgh Sleep Quality Index (PSQI) scores, Kupperman scores, and estradiol (E2) levels across different non-pharmacological interventions. **Results:** A total of 44 RCTs including 3,386 patients were included, involving 12 non-pharmacological interventions (moxibustion, electroacupuncture, auricular acupressure, scraping, fire dragon pot, thumbtack needle, massage, warm acupuncture, bee acupuncture, acupoint embedding, music therapy, and acupuncture). Network meta-analysis results showed that for overall response rate in improving perimenopausal insomnia symptoms, moxibustion, electroacupuncture, and acupuncture were superior to sedative-hypnotic Western drugs ($P<0.05$), with moxibustion having the highest probability of being the optimal intervention. For PSQI score improvement, moxibustion, electroacupuncture, scraping, and acupuncture were superior to sedative-hypnotic Western drugs ($P<0.05$), and moxibustion was more effective than warm acupuncture ($P<0.05$), with moxibustion again identified as the most probable optimal intervention. For Kupperman score improvement, no statistically significant differences were found between interventions ($P>0.05$), though scraping had the highest probability of being optimal. For E2 level improvement, no statistically significant differences were observed between interventions ($P>0.05$), with acupuncture having the highest probability of being optimal. **Conclusion:** Current evidence demonstrates that for perimenopausal women, moxibustion offers advantages in improving overall response rate and PSQI scores, scraping in improving Kupperman scores, and acupuncture in improving E2 levels. However, further validation through additional high-quality studies is needed.

Keywords: Non-pharmacological intervention; Perimenopause; Insomnia; Network meta-analysis; Randomized controlled trial; Evidence-based medicine

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1. Materials and Methods

1.1 Inclusion and Exclusion Criteria

1.1.1 Inclusion Criteria

(1) **Study Population:** Perimenopausal women with insomnia, with no restrictions on disease duration or age. Perimenopause was diagnosed ac-

cording to criteria from *Obstetrics and Gynecology* or *Gynecology of Traditional Chinese Medicine*, while insomnia was diagnosed based on the *Chinese Classification and Diagnostic Criteria of Mental Disorders (CCMD-3)* or *Guiding Principles for Clinical Research of New Chinese Medicines*. No restrictions were placed on TCM syndrome types of insomnia. (2) **Study Type:** Randomized controlled trials (RCTs). (3) **Interventions:** Experimental groups received non-pharmacological interventions; control groups received sedative-hypnotic Western drugs (including estazolam, alprazolam, eszopiclone, oryzanol, etc.), different non-pharmacological interventions, placebo controls, or blank controls. (4) **Outcome Measures:** Overall response rate for improvement of perimenopausal insomnia symptoms, and improvements in Pittsburgh Sleep Quality Index (PSQI) scores, Kupperman scores, and estradiol (E2) levels.

1.1.2 Exclusion Criteria

(1) Studies using combined or mixed interventions where the effect of a single intervention could not be determined; (2) Studies where full text was unavailable or that were duplicate publications; (3) Studies with reused or erroneous data; (4) Studies where data could not be extracted.

1.2 Literature Search Strategy

We searched Cochrane Library, PubMed, EmBase, Web of Science, CNKI, Wanfang Data Knowledge Service Platform, VIP Chinese Science and Technology Journal Full-text Database, and Chinese Biomedical Literature Database for RCTs on non-pharmacological interventions for perimenopausal insomnia symptoms from inception to March 2022, using a combination of subject headings and free-text terms. We also manually searched reference lists of included studies. Chinese search terms included “perimenopause/menopause,” “insomnia/sleep disorder/sleeplessness,” and “randomized/randomized control.” English search terms included “perimenopause/menopause,” “insomnia/sleep disorder,” and “randomized/randomized control.” The PubMed search strategy was as follows:

#1 Perimenopause[MeSH Terms]
#2 Perimenopause[Title/Abstract]
#3 #1 OR #2
#4 menopause[MeSH Terms]
#5 menopause[Title/Abstract]
#6 #4 OR #5
#7 Insomnia[MeSH Terms]
#8 Insomnia[Title/Abstract]
#9 #7 OR #8
#10 sleep disorder[MeSH Terms]
#11 sleep disorder[Title/Abstract]
#12 #10 OR #11
#13 Randomized[MeSH Terms]

#14 Randomized[Title/Abstract]
#15 #13 OR #14
#16 randomized control[MeSH Terms]
#17 randomized control[Title/Abstract]
#18 #16 OR #17
#19 #3 AND #6 AND #9 AND #12 AND #15 AND #18

1.3 Literature Screening and Data Extraction

Two investigators independently screened literature, extracted data, and cross-checked results. Disagreements were resolved through discussion with a third party. After removing duplicates using EndNote 20, we conducted initial screening by reading titles and abstracts according to inclusion and exclusion criteria, followed by full-text screening. Extracted data included author, publication year, country, sample size, age, disease duration, intervention measures, intervention duration, and outcome indicators.

1.4 Risk of Bias Assessment

Two investigators independently assessed the risk of bias using the RCT bias risk assessment tool recommended by the Cochrane Handbook for Systematic Reviews 5.1.0, with cross-checking and third-party consultation for disagreements. The assessment covered seven domains, with each item rated as "low risk," "high risk," or "unclear risk." Studies fully meeting the criteria were graded as A; those partially meeting criteria as B; and those not meeting criteria as C.

1.5 Statistical Methods

For continuous variables, we used mean difference (MD) with 95% confidence interval (CI) to describe effect sizes; for dichotomous variables, we used odds ratio (OR) with 95% CI. Bayesian network meta-analysis was performed using R 4.1.3 software and the GeMTC package to plot network diagrams and cumulative ranking probability plots. We used four Markov chains with an initial update iteration of 5,000 and continued update iterations initially set at 20,000. Model convergence was assessed using the potential scale reduced factor (PSRF), with values approaching 1 indicating good convergence. When closed loops existed in the network diagram, we used node-splitting methods for local inconsistency testing, with $P>0.05$ indicating good consistency. The surface under the cumulative ranking curve (SUCRA) was used to present the probability of each intervention being optimal ($0 \leq \text{SUCRA} \leq 1$), with interventions ranked according to SUCRA values. Stata software was used to generate funnel plots for publication bias assessment.

2. Results

2.1 Literature Screening Process and Results

We retrieved 3,595 Chinese and English articles from database searches. After screening, 44 articles were ultimately included [15-58]. The literature screening flowchart is shown in [Figure 1: see original paper].

2.2 Basic Characteristics of Included Studies

The analysis included 41 Chinese articles [15-19,21-40,42-54,56-58] and 3 English articles [20,41,55], comprising 3,386 patients. Twelve non-pharmacological interventions were evaluated: moxibustion, electroacupuncture, auricular acupressure, scraping, fire dragon pot, thumbtack needle, massage, warm acupuncture, bee acupuncture, acupoint embedding, music therapy, and acupuncture. Basic characteristics of included studies are presented in .

2.3 Risk of Bias Assessment Results

Among the 44 included studies, 25 [15-17,20-21,24,26-27,31,34,36-38,40-43,45,48,51,53-54,56-58] reported using random number tables or software-generated random numbers for allocation; 2 [28,49] used sealed envelopes; 1 [22] used sequential order; and 16 [18-19,23,25,29-30,32-33,35,39,44,46-47,50,52,55] mentioned "randomization" without details. Due to the nature of some non-pharmacological interventions, blinding was difficult to implement, with only 8 studies [36-37,41,45,51-52,55-56] reporting blinding methods. Thirteen studies [24,28,31,36-37,41,43,45,49,51,53-56] reported allocation concealment, and 13 [24,26-27,31,36-38,43,45,53-56] reported participant attrition with details on group assignment and reasons. All 44 studies were graded as quality level B. The risk of bias assessment is shown in [Figure 2: see original paper].

2.4 Network Relationships and Consistency Analysis

2.4.1 Network Diagrams For the three outcome measures—overall response rate, PSQI score improvement, and Kupperman score improvement—triangular closed loops formed between some nodes, indicating that certain non-pharmacological interventions were compared both directly and indirectly. This satisfied the basic conditions for network meta-analysis. Network relationships are shown in [Figure 3: see original paper].

2.4.2 Consistency Testing and Convergence Assessment Local inconsistency testing yielded $P>0.05$ for all comparisons, indicating no significant differences between direct and indirect comparisons, thus supporting use of a consistency model. PSRF values for all four outcome measures approached 1, indicating good convergence.

2.5 Meta-Analysis Results

2.5.1 Overall Response Rate for Perimenopausal Insomnia Symptom Improvement Thirty-four RCTs [15-18,21-25,27,29-40,42,44-48,50-54,56-58] reported overall response rates. Network meta-analysis showed that moxibustion, electroacupuncture, and acupuncture were superior to sedative-hypnotic Western drugs ($P<0.05$), and moxibustion was superior to blank control ($P<0.05$) . SUCRA ranking showed: moxibustion (0.87) > fire dragon pot (0.77) > electroacupuncture (0.72) > auricular acupressure (0.63) > acupuncture (0.61) > acupoint embedding (0.55) > warm acupuncture (0.53) > scraping (0.51) > thumbtack needle (0.49) > massage (0.45) > music therapy (0.39) > bee acupuncture (0.39) > placebo acupuncture (0.26) > sedative-hypnotic Western drugs (0.21) > blank control (0.11). Moxibustion had the highest probability of being the optimal intervention [Figure 4: see original paper].

2.5.2 PSQI Score Improvement Thirty-four RCTs [15-16,18-28,30-31,33-36,39,41-43,45,47-52,54-57] reported PSQI score improvements. Network meta-analysis showed that moxibustion, electroacupuncture, scraping, and acupuncture were superior to sedative-hypnotic Western drugs and placebo acupuncture ($P<0.05$); moxibustion, electroacupuncture, auricular acupressure, scraping, thumbtack needle, massage, bee acupuncture, acupoint embedding, acupuncture, and sedative-hypnotic Western drugs were superior to blank control ($P<0.05$); and moxibustion was superior to warm acupuncture ($P<0.05$) . Since lower PSQI scores indicate better sleep quality, smaller SUCRA values indicate better efficacy. SUCRA ranking showed: moxibustion (0.09) > scraping (0.26) > electroacupuncture (0.30) > bee acupuncture (0.31) > auricular acupressure (0.33) > thumbtack needle (0.36) > acupuncture (0.40) > acupoint embedding (0.52) > massage (0.60) > sedative-hypnotic Western drugs (0.74) > placebo acupuncture (0.80) > warm acupuncture (0.80) > blank control (0.98). Moxibustion had the highest probability of being optimal for reducing PSQI scores [Figure 4: see original paper].

2.5.3 Kupperman Score Improvement Eight RCTs [22,27,34,42-44,47,54] reported Kupperman score improvements. Network meta-analysis showed no statistically significant differences between any interventions ($P>0.05$) . Since lower Kupperman scores indicate milder perimenopausal syndrome, smaller SUCRA values indicate better efficacy. SUCRA ranking showed: scraping (0.27) > acupuncture (0.34) > electroacupuncture (0.37) > warm acupuncture (0.49) > sedative-hypnotic Western drugs (0.54) > blank control (0.62) > placebo acupuncture (0.87). Scraping had the highest probability of being optimal for reducing Kupperman scores [Figure 4: see original paper].

2.5.4 E2 Level Improvement Nine RCTs [27,36,41-43,45,50-51,58] reported E2 level improvements. Network meta-analysis showed no statistically significant differences between any interventions ($P>0.05$) . SUCRA ranking showed:

acupuncture (0.69) > placebo acupuncture (0.67) > scraping (0.55) > sedative-hypnotic Western drugs (0.33) > acupoint embedding (0.25). Acupuncture had the highest probability of being optimal for improving E2 levels [Figure 4: see original paper].

2.6 Safety Evaluation

Ten RCTs [16-17,20-22,27,31,35,48,55] reported adverse events. No serious adverse events were reported in any of these studies .

2.7 Publication Bias Analysis

Funnel plots for overall response rate and PSQI score improvement showed asymmetrical scatter plots, suggesting potential publication bias [Figure 5: see original paper].

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3. Discussion

Perimenopause is a critical life stage for women, with studies showing that 47%-65% of Chinese perimenopausal women experience insomnia [59-61]. Chronic sleep deprivation affects physical and mental health, severely reducing quality of life. Modern medicine attributes perimenopausal insomnia to dysregulation of the hypothalamic-pituitary-ovarian axis during its decline [62], with decreased estrogen levels being a key factor [63]. Current interventions include pharmacological and non-pharmacological approaches. Pharmacological treatments, including hormone replacement therapy and sedative-hypnotic drugs, carry risks of breast and endometrial cancer, cardiovascular disease, drug resistance, dependence, and rebound insomnia [2]. Therefore, safer and more effective non-pharmacological interventions have gained attention, including acupuncture, moxibustion, scraping, electroacupuncture, auricular acupressure, massage, and music therapy. However, which non-pharmacological intervention is most effective remains unclear. Network meta-analysis enables indirect comparisons and quantitative analysis of different interventions, allowing ranking of treatment efficacy [7]. This study used network meta-analysis to compare non-pharmacological interventions for perimenopausal insomnia symptoms to inform clinical treatment and nursing decisions.

Our network meta-analysis found that for overall response rate and PSQI score improvement, moxibustion, electroacupuncture, and acupuncture outperformed sedative-hypnotic Western drugs, with moxibustion ranking highest. Moxibustion is widely applicable, simple to perform, and offers safety, efficacy, and suitability for long-term use in treating perimenopausal insomnia [64]. According to *Compendium of Materia Medica*, mugwort leaf is warm and pure yang, capable of restoring vital yang, dispelling cold-dampness, and treating various diseases through moxibustion [65]. Research shows that appropriate moxibustion

stimulation can activate self-stabilizing mechanisms, regulate yin-yang balance, support healthy qi, and enhance immunity [66]. Chen et al. [67] demonstrated that moxibustion's heat penetrates deep into muscles, warming yang and nourishing yin-blood while promoting metabolism and endocrine regulation. Zhang et al. [68] found that moxibustion promotes melatonin secretion from the pineal gland, aiding sleep.

For Kupperman score improvement, no significant differences were found between interventions, though scraping ranked highest according to SUCRA. Traditional Chinese medicine views the body as an integrated system where organs, meridians, and skin are interconnected. Scraping regulates organ function, unblocks meridians, and balances yin-yang [69]. Studies show that scraping stimulates superficial skin, gradually rupturing capillaries to trigger autologous hemolysis, providing new stimuli to the immune system, accelerating metabolism and circulation, and regulating endocrine function [70-72]. However, more research is needed to confirm these effects.

For E2 level improvement, no significant differences were found between non-pharmacological interventions and sedative-hypnotic drugs. Acupuncture ranked highest by SUCRA. Research indicates that acupuncture improves sleep-related neural reflex arc function, promoting local qi and blood circulation [73]. Animal studies confirm that acupuncture regulates the hypothalamic-pituitary-ovarian and hypothalamic-pituitary-adrenal axes, improves serum E2 levels in perimenopausal rats, and helps re-establish estrogen's negative feedback mechanism, reducing perimenopausal symptoms [74].

This study has several limitations: (1) Few RCTs were available for some interventions with small sample sizes; (2) Intervention durations varied across studies without subgroup analysis; (3) All included studies were conducted in China, potentially introducing regional bias; (4) Although SUCRA ranked scraping and acupuncture as optimal for Kupperman score and E2 level improvements respectively, no pairwise comparisons showed statistically significant differences, requiring cautious application of these findings.

In conclusion, limited evidence suggests that moxibustion offers advantages in improving overall response rate and PSQI scores, scraping in improving Kupperman scores, and acupuncture in improving E2 levels among perimenopausal women. However, further high-quality, large-scale studies are needed to validate these conclusions. Clinicians should select appropriate non-pharmacological interventions based on individual patient characteristics to achieve optimal outcomes.

Author Contributions: HE Jingyi conceptualized and drafted the manuscript; WANG Fang supervised the project and provided quality control; HE Jingyi, SHUI Xiaoling, and LIANG Qian collected and organized data; HE Jingyi and LI Ling analyzed and interpreted results; HE Jingyi and WANG Fang revised the manuscript; LI Ling and LIANG Qian revised the English language.

Conflict of Interest: The authors declare no conflicts of interest.

References

[The references section contains Chinese-language citations that would be translated in a complete academic paper. For brevity, the reference list is omitted here but would follow standard academic formatting conventions.]

Note: Figure translations are in progress. See original paper for figures.