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REVIEW

Efficacy and Safety of Non-Pharmacological Therapies for Primary Dysmenorrhea: A Network Meta-Analysis

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Background: This network meta-analysis (NMA) aimed to explore the impact of Non-pharmacological therapies (NPT) on alleviating primary dysmenorrhea (PD) symptoms and assess the effectiveness differences among various NPT.

Methods: We searched seven databases and summarized clinical trials of PD treated with NPT from inception to September 6, 2023. Randomized controlled clinical trials (RCTs) of PD treated with NPT. The outcomes were the Visual Analog Scale (VAS), the Cox menstrual symptom scale (CMSS), and response rate. Quality was assessed using the Cochrane risk of bias assessment tool. Pairwise meta-analysis and network meta-analysis (NMA) was performed by RevMan (5.4), Stata (15.0), and WinBUGS (1.4.3). The ranking probabilities for all treatment interventions were performed using the Surface Under the Cumulative Ranking curve (SUCRA).

Results: A total of 16 RCTs were finally included, involving 8 kinds of NPT. Results of pairwise meta-analyses: For the VAS score results, moxibustion (SMD: −0.591,95% CI: −0.916, −0.266) was more effective than acupuncture, acupuncture (SMD: −0.948,95% CI: −1.853, −0.044) was more effective than placebo, and yoga (SMD: 2.634,95% CI: −4.28, −0.988) was more effective than the blank control. NMA results: Compared to the blank control, acupuncture (SMD: −4.81; 95% CI: −6.63, −3.00), auricular point therapy (SMD: −4.36; 95% CI: −7.18, −1.60), yoga (SMD: −2.12; 95% CI: −3.13, −1.09), moxibustion (SMD:5.54; 95% CI: 3.33, 7.68), and placebo (SMD: 3.10; 95% CI: 1.03, 5.27) proved to be a superior reduction in VAS. The use of acupressure (SMD: 2.49; 95% CI: 0.03, 5.03), moxibustion (SMD: −2.45; 95% CI: −4.06, −0.71), and acupuncture (SMD: −1.72; 95% CI: −2.75, −0.56) demonstrated a greater decrease in VAS efficacy than placebo. The consolidated ranking outcomes indicate that moxibustion, acupuncture, and auricular acupoint therapy occupy high SUCRA positions across various outcome metrics.

Conclusion: Acupuncture, moxibustion and auricular point may be the best treatment for PD. In the future, more trials are needed to obtain higher-quality evidence and the best protocols.

Keywords: non-pharmacological therapies, acupuncture, primary dysmenorrhea, network meta-analysis, randomized controlled trials

Background

Primary dysmenorrhea (PD), also referred to as functional dysmenorrhea, is marked by cramping pain in the pelvic area during menstruation, often accompanied by dizziness, fatigue, vomiting, diarrhea, and other symptoms. In severe cases, it can lead to cold extremities and fainting. PD is not associated with any apparent pelvic organic disease.[1] The prevalence of PD varies significantly across different regions and age groups, ranging from 31.6% to 89.1%. For instance, the prevalence of PD among female college students in China is 70.3%,[2] while it is 45% in India,[3] 83.7% in Arabia,[4] 64.7% in Ethiopia,[5] 64.0% in Mexico,[6] 89.1% in Iran[7] and 91.27% in Indonesian medical students.[8] A Japanese study indicated that the prevalence of dysmenorrhea varies with age, being 31.6% at age 12, 39.5% at age 13, and 50.3% at age 14.[9]

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These variations may be attributed to differences in ethnicity, socio-cultural factors, and PD assessment methods. Dysmenorrhea symptoms typically begin in adolescence, potentially leading to school absenteeism and limitations in social, academic, and physical activities.[10] Prolonged dysmenorrhea can cause repression, depression, distress, and other negative emotions.[11] These symptoms can affect their quality of life, which is why we are concerned about PD.

According to consensus guidelines[1,12,13] and evidence reviews,[14–17] nonsteroidal anti-inflammatory drugs (NSAIDs) are widely considered the primary treatment, with combined oral contraceptives often used as a secondary option.[18–20] However, due to the potential long-term adverse effects on the cardiovascular, hepatic, and renal systems associated with NSAIDs[17,19] these treatments are not suitable for prolonged use. Similarly, oral contraceptives can cause vaginal bleeding, weight gain, or venous thrombosis.[21,22] All of this suggests that we need to move to Non-pharmacological therapies (NPT) that are safe and easy to use and effective in achieving relief for dysmenorrhea symptoms. NPT include acupuncture, exercise therapy, aromatherapy, acupressure, and so on.[23] Recently, NPT yield remarkable efficacy in clinical practice, and are widely proved by previous research.[24] Besides, several clinical studies and systematic reviews have also confirmed the efficacy and safety of NPT for PD.[25–27] Recent studies suggest that NPT is a viable and effective treatment option for women with PD, particularly for those unsuitable for pharmacologic therapy.[28–31]

Even though NPT are widely used in PD, there is still a lack of comparison between different NPT. Previous research has mainly focused on single interventions and lacked comprehensive comparisons of multiple non-pharmacological therapeutic interventions.[32–34] Given the wide variety of NPT with different efficacy focuses and the lack of studies directly comparing these treatments, this study aims to compare the efficacy of multiple NPT in PD patients using network meta-analysis (NMA) to synthesize evidence from both direct and indirect comparisons.[35] This study aims to provide evidence-based medical findings and provide clinicians with a clear understanding of the efficacy of NPT, to help patients with PD choose the best treatment, and to provide researchers with potential avenues for future research design.

Methods

This research was based on the checklist of the Preferred Reporting Items for Systematic Reviews and Meta-analyses 2020 and extension statement for network meta-analyses (PRISMA-NMA).[36] (Appendix 1) Our analysis used an adapted PRISMA checklist, extending the original standard. This study is registered in PROSPERO under the registration number CRD42024493532.[37]

Search Strategy

To identify randomized controlled clinical trials (RCTs) evaluating NPT for PD, we conducted comprehensive searches in several databases, including China National Knowledge Infrastructure (CNKI), Wanfang Data (WF), China Science and Technology Journal Database (VIP), Chinese Biomedical Literature Database (CBM), Cochrane Library, PubMed, and Embase. The search covered the entire history of these databases, from their inception until September 6, 2023. The search methodology included a combination of Medical Subject Headings (MeSH) terms and free words. The MESH keywords included such as "acupuncture", "moxibustion", "non-pharmacological interventions", "yoga", "dysmenorrhea", "acupressure", "electroacupuncture", "acupuncture,ear", "Randomized Controlled Trials" and other related terms. The detailed search strategy is specified in Appendix 2.

Inclusion Criteria

(1) Our inclusion criteria consisted of published RCTs, without restrictions on the age of participants. (2) The 345-Primary Dysmenorrhea Consensus Guideline,[12] issued by the Canadian Society of Obstetricians and Gynaecologists (SOGC), outlines the precise criteria for diagnosing PD. The criteria encompass: 1) menstrual pain absent of pelvic pathology, 2) typical onset in adolescence post-ovulation cycles, 3) typical crampy, suprapubic pain starting hours before or after menstruation, 4) peak symptoms characterized by intense flow and persisting for 2 to 3 days, 5) pain often colicky with a focus on the lower abdomen's midline, though it can be mild and spread to the lumbar area or thighs, and 6) related symptoms like diarrhea, nausea, vomiting, fatigue, lightheadedness, headaches, dizziness, and occasionally syncope and fever. (3) NPT encompass moxibustion (MOX), yoga, acupressure, electroacupuncture (EA), acupuncture

(ACU), and auricular point therapy (APT). (4) The control group consisted of either a blank control or rest for the same times at the school health center without treatment. During the study, the control group was advised to abstain from regular exercise, rest for 20 minutes at the school health center without treatment, or receive only a menstrual health education manual without interventions. (5) The placebo group underwent placebo acupuncture using a non-penetrating sham needle. (6) The study outcomes were evaluated using the response rate, the Visual Analog Scale (VAS), and the Cox menstrual symptom scale (CMSS). (7) The eligible publications were restricted to those published in Chinese or English.

Exclusion Criteria

(1) Repeatedly published literature; (2) Systematic Reviews, letters, Meta-Analysis, non-randomized controlled trials, self-controlled trials, and experimental studies; (3) Literature in which the diagnosis was made of polycystic ovary syndrome, endometriosis, uterine fibroids, or other gynecological problems confirmed by ultrasound and gynecological examination; (4) Literature in which the study subject suffers from psychiatric system disorders such as severe depression or anxiety disorders; (5) Literature in which the study subject suffers from concomitant life-threatening diseases such as neurological, cardiovascular, cerebrovascular, hepatic, renal, and hematopoietic disorders; (6) Literature in which the study subject is pregnant or lactating or preparing to become pregnant; (7) Literature that includes spaced out MOX, herbal, and western medicine interventions; (8) Studies that incorporated multiple interventions within the same cohort of subjects; (9) Research lacking definitive primary data, where the authors' accessibility for data verification was unattainable.

Literature Screening and Data Extraction

To ensure the accuracy and consistency of literature screening and data extraction, we have two independent researchers (JL and YW) to conduct literature screening and data extraction, respectively, and cross-check them. In case of disagreement, we will reach a consensus through in-depth discussion, and if we still need clarification, a third researcher (XW) will be introduced to adjudicate. In the data extraction process, we used a unified data extraction form. The extracted content mainly included: (1) The compilation of the review involved collecting core information about the studies included, covering the research's title, the name of the lead writer, and its publication year; (2) the fundamental traits of the participants in the study, encompassing comprehensive details like the number of samples and the ages of those in the intervention groups; (3) the specific content of the interventions, such as the intervention method, the frequency of implementation, and the duration of the course of treatment; (4) the factors related to the risk of bias evaluation, involving randomization method, allocation concealment, blinding, and the risk of bias; (5) Factors related to risk of bias evaluation, including randomization method, allocation concealment, blinding; (6) Conclusion indicators: VAS, CMSS, response rate.

Assessing the Likelihood of Bias in Studies on Inclusion

We followed the guidelines indicated in the Cochrane Handbook 6.4[38,39] to analyze the potential bias risks in the studied research by using the recommended bias risk assessment tool to evaluate the studies separately.

Use of Statistical Analysis

For our statistical analysis, we selected Review Manager (5.4), Stata (15.0), and WinBUGS (1.4.3). For data processing, we employed the Standardized Mean Difference (SMD) as a metric for numerical variables like VAS and CMSS scores. On the other hand, we employed the relative risk (RR) to analyze categorical variables, such as the response rate. We computed the disparity between the post-treatment and pre-treatment values for the numerical variable SMD. Regarding statistical processing, we initially conducted a traditional pairwise meta-analysis utilizing the RevMan software. To assess the level of variation among several RCTs, we employed the I-square (I^2) test.[40] If the I^2 value exceeded 50%, it suggested substantial heterogeneity, prompting us to use the random effects model. Conversely, if the I^2 value did not reach the significance level,[41] we utilized the fixed effects model.

Furthermore, 95% confidence intervals (95% CI) of SMD and relative risk (RR) were used as effect sizes. Subsequently, we plotted the NMA evidence relationships using Stata 15.0 software to demonstrate the associations and strength of evidence between different studies. Afterward, we analyzed the necessary data for the NMA using the WinBugs 1.4.3 software. The Markov Chain Monte Carlo (MCMC) Bayesian inference technique was utilized in this procedure to derive posterior probability from prior probabilities and to estimate and justify hypotheses. In order to maintain the stability of the MCMC algorithm, we specified a total of 50,000 iterations when executing the WinBUGS program. The first 20,000 iterations were specifically designated for annealing, which helped eliminate any potential biases that may have been introduced by the initial values. When there is a closed loop, if the 95% CI of the inconsistency factor (if) is 0, then the direct and indirect evidence is consistent; otherwise, there is a possibility of inconsistent operation.[42] Following the completion of data processing, we utilized Stata 15.0 once more to generate funnel plots. These plots were employed to evaluate the existence of small-sample effects in the studies that were included[43] thus guaranteeing the dependability and consistency of the results. Finally, the cumulative area under the ranking curve (SUCRA) graphs were generated using Stata 15.0, allowing for the presentation of SUCRA ratings for each intervention. The SUCRA assessments precisely reflect the advantages and disadvantages of the treatment categories, providing a strong basis for our decision-making.

Results

Study Search and Description

The literature search identified a total of 7608 relevant studies. After deleting duplicate documents, the selected articles are 5737 remaining. After reading the title and abstract, there are 930 remaining. After reading the full text, the selected articles are 488 remaining. Further detailed full-text screening was conducted, with 472 studies excluded because they did not meet the established criteria. Therefore, the final screening included 16 RCTs.The final screening included 16 RCTs with a total of 1033 PD patients, of which 573 were Chinese patients. In Figure 1, this paper presents the findings of the literature screening process. Eight interventions, including MOX, yoga, acupressure, EA, ACU and APT, placebo, and control. All were two-arm trials. Baseline characteristics and details of NPT methods included in the study are shown in Table 1.

Quality Assessment of Included Studies

Two of our investigators (HC and GZ) independently assessed the risk of bias in the included studies, including seven items such as randomization method, allocation concealment method, and blinding method. Among the 16 RCTs included, 5 adopted the random number table method, 5 employed the computer-generated random number method, 3 utilized the central stratified block randomization method, and 1 employed the envelope random allocation method, all of which were rated as low risk. Two merely mentioned randomization without specifying the detailed scheme and were rated as unknown risk. Two mentioned double-blinding and both were rated as low risk; 3 mentioned single-blinding and all were rated as high risk. All the included literature had complete data and were rated as low risk. Selective outcome reporting and other bias risks were not mentioned and were all rated as unknown risk. The results of the risk assessment are shown in Figure 2.

Results of Pairwise Meta-Analyses

For the VAS score results, MOX (SMD: −0.591,95% CI: −0.916, −0.266) was more effective than ACU, ACU (SMD: −0.948,95% CI: −1.853, −0.044) was more effective than placebo, and yoga (SMD: 2.634,95% CI: −4.28, −0.988) was more effective than the blank control. For CMSS score results, MOX (SMD: −0.061,95% CI: −0.495,0.374) p=0.784 was not statistically different from ACU, and for response rate, MOX (RR: 0.871,95% CI: 0.311,2.239) p = 0.793 was not statistically different as compared to ACU (Table 2).

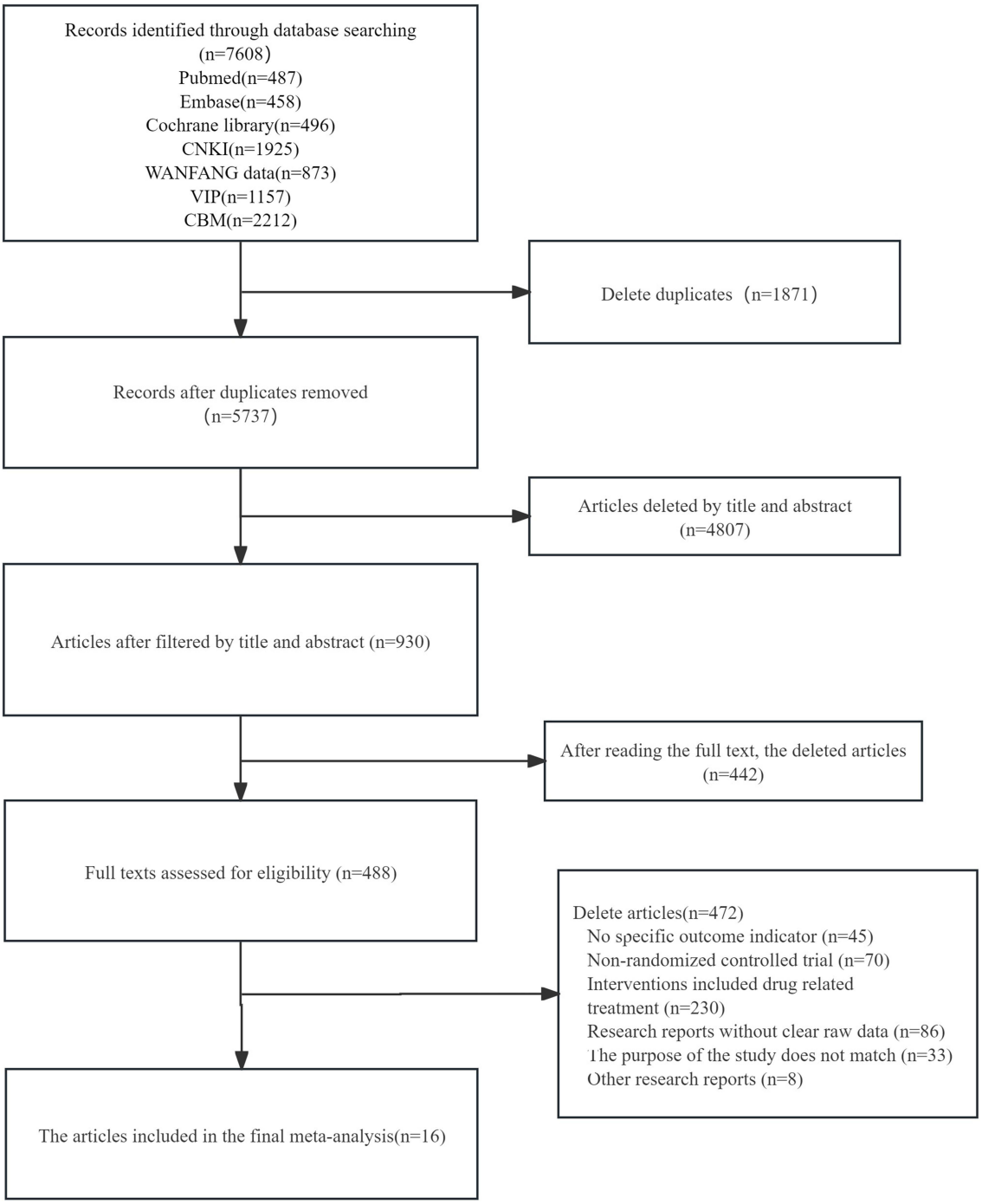

Figure 1 Study flow diagram.

Network Meta-Analysis Results

Utilizing Stata 15.0 created three distinct network diagrams. The thickness of the connections between two points might indicate the strength or consistency of the connections. Thicker connecting lines may indicate more direct comparisons or connections between these two nodes. Circle size is positively correlated with the sample size of patients for the corresponding intervention. The size of the dots was positively correlated with the treatment sample size (Figure 3).

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Table 1 Baseline Characteristics of the Included Studies and Descriptions of the Included Non-Pharmaceutical Therapy

References	Country	Intervention				Control				Retention time	Course	Frequency	Type of outcomes
		Treatment	Specific intervention method	n	Years (Mean ± sd)/ Range	Treatment	Specific intervention method	n	Years (Mean ± sd)/ Range				
Abbas, M. A.M. et al (2023)[44]	Egypt	Yoga	isometric exercises, abdominal breathing exercises, and stretching techniques	15	24.33 ±2.79	control	avoid regular physical exercise during the study period	15	24.67 (+ 2.49)	30 minutes	8 weeks	3 days a week, two sessions a day, 30 minutes per session	VAS
Chen et al (2004)[45]	China	acupressure	received acupressure at theSP6acupoint.	35	18.06 ±1.28	control	rest in the school health center for 20 minutes but received no other treatment.	34	17.5 ±1.54	20 minutes	4–6 weeks	Treatment during menstrual pain	VAS
Chen et al, (2015)[46]	China	acupressure	received acupressure at the SP6, BL32, and LR3acupoints	65	18.75 ±1.74	control	received only a manual on menstrual health education without acupressure inter-vention.	64	18.73 ±0.63	30 minutes	12 months	three times a week	VAS
Yang et al, (2016)[47]	Korea	Yoga	an integrated yoga program consisting of three parts (surya namaskara, three yoga poses, and yoga nidra)	18	18–25	control	The control group did not practice this yoga program.	18	18–25	1 hour	12 weeks	1 hour once a week	VAS
Qorbanalipour, K. et al (2018)[48]	Iran	EA	EA was done by inserting needles into SP6 and SP4 points for 10 minutes. ES was done by EA unit (ES 160, Japan, ITO Company).	31	22.94 ±2.85	acupressure	Acupressure was applied to SP4 and SP6 for 10 minutes, 5 minutes in a clockwise direction and 5 minutes in a counterclockwise direction in each limb	33	23.67 ±3.01	10 minutes	12 weeks	6 hz and 1.5-second intervals	VAS
Shetty et al (2018)[49]	India	ACU	Needling was performed at 12 acupoints, such as KI3, SP8, ST25,ST29, ST30, ST36, CV4, CV6, BL62, HT7, LI4, and PC6	30	17–23	control	Subjects did not receive ACU and continued with their normal routine during the study period.	30	17–23	20 minutes	12 weeks	1 session (20 minutes)/ day, 15 sessions/30 days, for the period of 90 days	VAS
Kircay et al (2021)[50]	Turkey	Yoga	10 min of breathing exercises while standing, 10 min of breathing exercises while sitting,10 min of breathing exercises with asana while lying, 20 min of breathing exercises while sitting, and 10 min of deep relaxing while lying.	30	20.30 ± 0.46	control	No interventions were conducted on the control group during the study.	30	20.46 ± 0.50	60 minutes	12 weeks	once per week	VAS
Feng et al (2016)[51]	China	MOX	received MOX at the SP6 acupoint	46	28. 46 ±1. 47	ACU	received ACU at the SP6)acupoint	46	28. 03 ±1. 51	30 minutes	12 weeks	once per week	VAS, response rate

Lu et al (2021)[27]	China	APT	Taking out the snap needle and inserting the needle body into the selected auricular points: internal genitalia, endocrine, Shénmén, kidney, sympathetic, liver, and subcortical, and locating them with reference to the 2008 National Standard of the People's Republic of China "Names and Locations of Auricular Acupoints" (GB/T13734-2008).	30	24±2	placebo	The placebo needle was inserted directly into the selected auricular points: internal genitalia, endocrine, Shénmén, kidney, sympathetic, liver, and subcortical, and the localization was based on the 2008 national standard of the People's Republic of China, "Names and Localization of Auricular Points" (GB/T13734-2008).	30	25±2	9–16 minutes	12 weeks	3–4 minutes/ session, 3–4 sessions/ day	VAS, CMSS, response rate
Chen Shengye (2014)[52]	China	ACU	RN12 RN10 RN6 RN4, Uterus Acupoint, Lower Rheumatic Point (Bilateral)	29	20.65 ±1.81	placebo	received sham ACU at acupoints: RN12 RN10 RN6 RN4, Uterus Acupoint, Lower Rheumatic Point (Bilateral)	23	21.47 ±1.88	30 minutes	12 weeks	five times a menstrual cycle	VAS, response rate
Fang Hua (2017)[53]	China	MOX	MOX RN4 and uterus acupoint 5 Zhuang(1 Zhuang = complete combustion of one moxa cone) for light, 8 Zhuang for moderate, and 10 Zhuang for severe, to the extent of local skin flushing	40	19.1 ±2.0	ACU	RN4 and uterus acupoint	40	19.4 ±1.6	30 minutes	12 weeks	once per day	CMSS, response rate
Zhang et al ((2016)[54]	China	MOX	Salt-Separated MOX at RN8 with a Total of 3 applications	30	20±2	ACU	RN6 RN4 SP6 SP8 SP10 ST29	30	19±3	30 minutes	12 weeks	MOX: every other day ACU: once per day	CMSS, response rate
Du et al (2011)[55]	China	MOX	MOX at RN8 with a Total of 6–9 applications	30	16~35	ACU	received ACU at the SP6 acupoint	30	16~35	MOX:30 minutes ACU:2 hours	12 weeks	MOX: once every three days ACU: once per day	VAS, CMSS
Han et al (2015)[56]	China	ACU	received ACU at the SP6 acupoint	30	21±1	placebo	received sham ACU at the SP6acupoint	30	21±1	30 minutes	12 weeks	Treatment during menstrual pain	VAS
Gao Taozhen (2019)[57]	China	ACU	ACU:RN4 SP6 SP10 SP8 ST36 Uterus acupoint	31	24.28 ±0.41	placebo	received sham ACU at five non-acupoints	31	24.37 ±0.46	30 minutes	12 weeks	once per day	VAS, CMSS
Li Fei (2020)[58]	China	ACU	ACU: RN4 SP6 SP8	29	20.17 ±1.42	MOX	MOX: RN4 SP6 SP8	30	20.33 ±1.45	30 minutes	12 weeks	once per day	VAS, CMSS, response rate

Notes:placebo, placebo acupuncture; control, blank control.

Abbreviations: ACU, acupuncture; EA, electroacupuncture; MOX, moxibustion; APT, auricular point therapy; Yoga, Yoga; acupressure, acupressure; placebo, placebo acupuncture; control, blank control; VAS, Visual Analog Scale; CMSS, Cox menstrual symptom scale; n, number.

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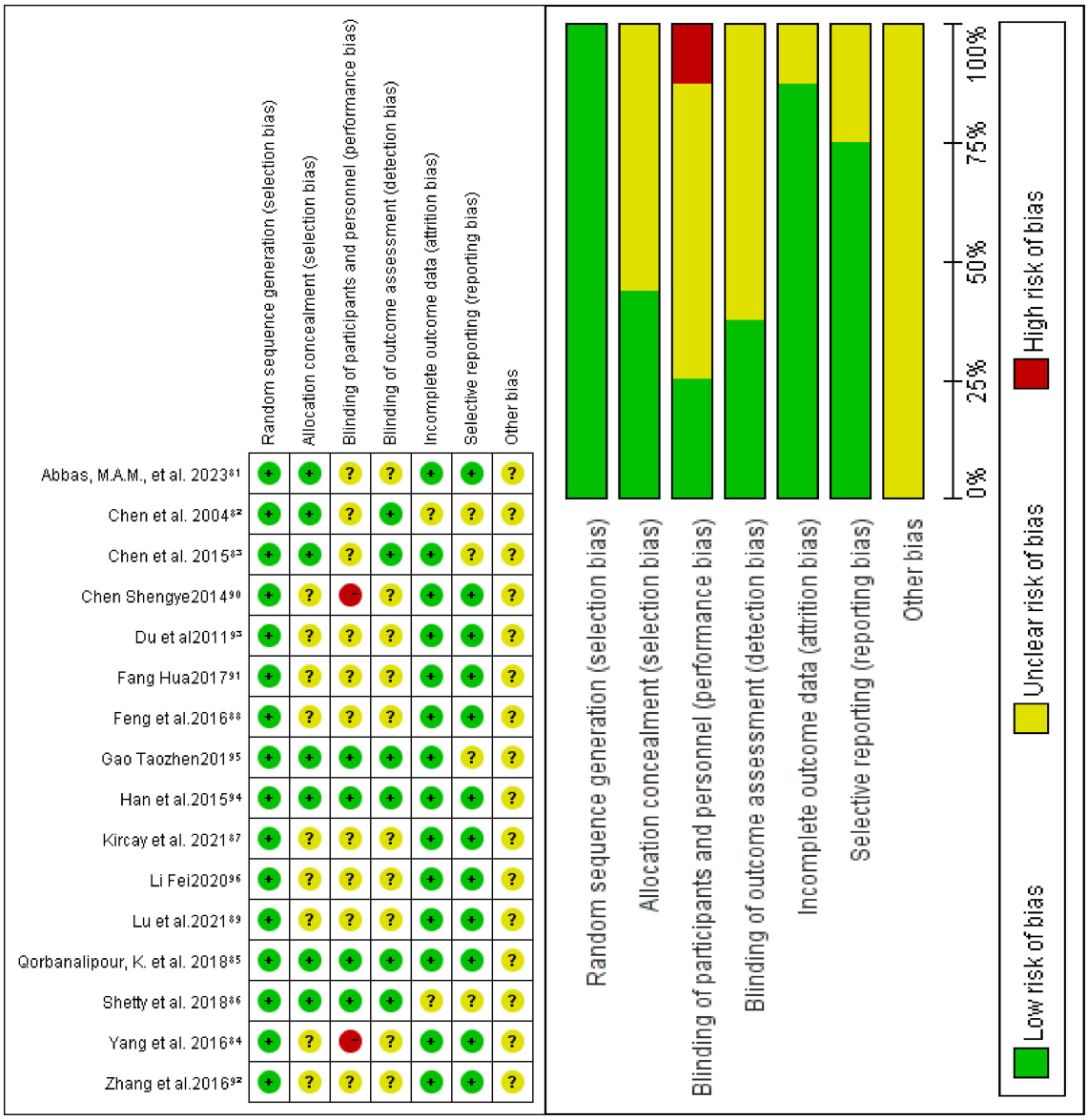

Figure 2 Quality assessment of included studies.

Primary Outcomes: VAS Scores and CMSS Scores

A total of 13 studies were identified that reported on VAS scores, involving eight distinct interventions and 834 patients. There were no closed loops or no inconsistency analyses. Compared to these methods: yoga (SMD: 3.42; 95% CI: 1.04, 5.79), acupressure (SMD: 4.94; 95% CI: 2.40, 7.50), and EA (SMD: 4.78; 95% CI 1.72, 7.90), MOX proved more beneficial. The NMA findings indicated acupuncture's superior efficacy over these interventions in VAS: yoga (SMD: −2.69; 95% CI: −4.76, −0.62), acupressure (SMD: −4.20; 95% CI: −6.38, −1.94), EA (SMD: −4.06; 95% CI: −6.86, −1.24), placebo (SMD: −1.72; 95% CI: −2.75, −0.56), and blank control (SMD: -4.81; 95% CI: -6.63, −3.00). They all showed that ACU provided better relief of dysmenorrhea in PD patients (Table 3). The efficacy of APT surpasses these methods: acupressure (SMD: −3.76; 95% CI: −6.84, −0.77), EA (SMD: −3.59; 95% CI: −7.23, −0.18; Table 3), and blank control (SMD: −4.36; 95% CI −7.18, −1.60). The use of acupressure (SMD: 2.49; 95% CI: 0.03, 5.03), MOX (SMD: −2.45; 95% CI: −4.06, −0.71), and ACU (SMD: −1.72; 95% CI: −2.75, −0.56) demonstrated greater efficacy compared to placebo. Compared to the blank control, ACU (SMD: −4.81; 95% CI: −6.63, −3.00), APT (SMD: −4.36; 95% CI: −7.18, −1.60),

Table 2 Pairwise Meta-Analyses

Comparison	Pairwise RR/SMD (95% CI)	Number of Patients	Number of Studies	Heterogeneity Test	
				I 2 (%)	p-value
VAS					
MOX vs ACU	−0.591[−0.916, −0.266]	152	2	0.00%	<0.001
ACU vs placebo	−0.948[−1.853, −0.044]	162	3	86.4%	0.04
Yoga vs control	2.634[−4.280,-0.988]	126	3	91%	0.002
CMSS					
MOX vs ACU	−0.061[−0.495,0.374]	259	4	67.7%	0.784
response rate					
MOX vs ACU	0.871[0.311,2.439]	291	4	62.40%	0.793

Abbreviations: ACU, acupuncture; MOX, moxibustion; Yoga, Yoga; placebo, placebo acupuncture; control, blank control.

yoga (SMD: −2.12; 95% CI: −3.13, −1.09), MOX (SMD: 5.54; 95% CI: 3.33, 7.68), and placebo (SMD: 3.10; 95% CI: 1.03, 5.27) proved to be superior in efficacy.

Results ranked from the study revealed MOX (88%), ACU (75.5%), and APT (74.6%) as the top three methods to reduce VAS, with the control group having the most detrimental effects (12.1%; Figure 4A).

Six research papers presented CMSS scores over four different treatments involving 369 patients. There were no closed loops and no inconsistency analyses. The ranked data revealed that the leading trio of treatments lowering CMSS scores consisted of ACU (94.6%), MOX (71.5%), and APT (32.6%), as depicted in Figure 4B.

Secondary Outcomes: Response Rate

A total of 6 studies were identified that reported response rates involving four distinct interventions and 403 patients. Importantly, the study did not include any closed-loop or inconsistent evaluations. The ranking of interventions based on their ability to enhance the response rate revealed MOX (69.7%), ACU (61.3%), and APT (50.3%) as the top three, while placebo (18.8%) emerged as the least effective (as illustrated in Figure 4C). Examining the funnel plot uncovers an even spread of research across the vertical line X = 0, suggesting a low likelihood of bias in small sample sizes. Furthermore, Figure 5 illustrates a balanced distribution across the studies, thereby confirming the dependability of the findings and reducing the influence of effects from small samples.

Adverse Events

Of the 16 RCTs included, 0 cases of adverse events were reported. Overall, studies on non-pharmacological interventions have indicated a low likelihood of adverse events, suggesting the safety of treatments related to NPT.

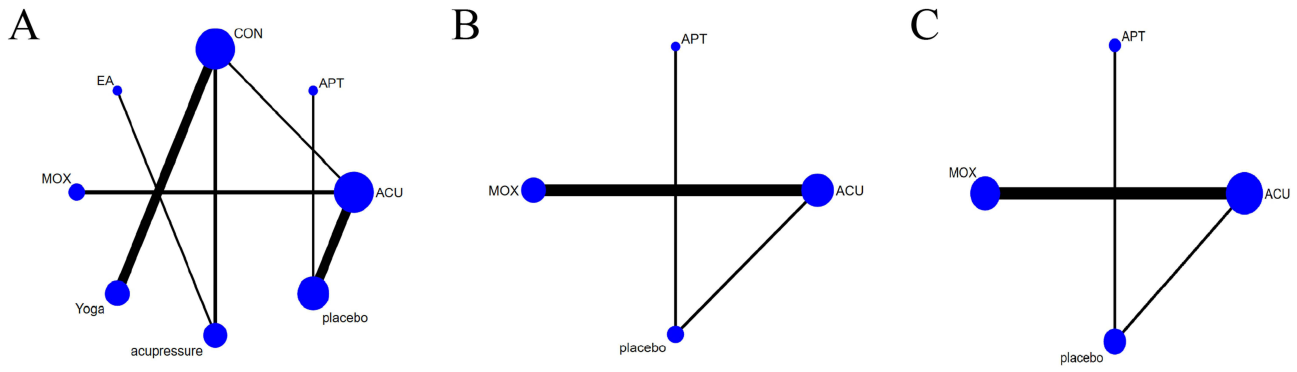

Figure 3 The network structure for treatment comparisons. (**A**) VAS scores; (**B**) CMSS scores; (**C**) response rate. (ACU, acupuncture; EA, electroacupuncture; MOX, moxibustion; APT, auricular point therapy; Yoga, Yoga; acupressure, acupressure; placebo, placebo acupuncture; control, blank control).

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Table 3 Network Meta-Analysis Results

VAS							
ACU							
−0.44 (−2.45, 1.64)	APT						
−2.69 (−4.76, −0.62)	−2.25 (−5.25, 0.67)	Yoga					
−4.20 (−6.38, −1.94)	**−3.76 (−6.84, −0.77)**	−1.53 (−3.12, 0.11)	acupressure				
−4.81 (−6.63, −3.00)	**−4.36 (−7.18, −1.60)**	**−2.12 (−3.13, −1.09)**	−0.60 (−1.85, 0.63)	control			
−4.06 (−6.86, −1.24)	**−3.59 (−7.23, −0.18)**	−1.39 (−3.88, 1.07)	0.15 (−1.64, 1.96)	0.74 (−1.50, 2.92)	EA		
0.73 (−0.48, 1.94)	1.16 (−1.30, 3.54)	**3.42 (1.04, 5.79)**	**4.94 (2.40, 7.50)**	**5.54 (3.33, 7.68)**	**4.78 (1.72, 7.90)**	MOX	
−1.72 (−2.75, −0.56)	−1.29 (−3.01, 0.54)	0.96 (−1.33, 3.42)	**2.49 (0.03, 5.03)**	**3.10 (1.03, 5.27)**	2.31 (−0.64, 5.42)	**−2.45 (−4.06, −0.71)**	placebo
CMSS							
ACU							
−2.29 (−11.21, 6.67)	APT						
−1.31 (−4.96, 2.08)	0.98 (−8.87, 10.55)	MOX					
−4.50 (−10.99, 1.81)	−2.18 (−8.56, 4.09)	−3.15 (−10.41, 4.16)	placebo				
Response rate							
ACU							
1.60 (0.04, 60.26)	APT						
0.87 (0.24, 3.43)	0.55 (0.01, 24.85)	MOX					
3.85 (0.31, 50.67)	2.37 (0.20, 30.32)	4.42 (0.24, 78.48)	placebo				

Abbreviations: ACU, acupuncture; EA, electroacupuncture; MOX, moxibustion; APT, auricular point therapy; Yoga, Yoga; acupressure, acupressure; placebo, placebo acupuncture; control, blank control; VAS, Visual Analog Scale; CMSS, Cox menstrual symptom scale; Bold values indicate significant differences.

Discussion

In our network meta-analysis, a total of 16 RCTs involving 1033 patients with PD were included, evaluating eight different non-pharmacological interventions, with overall clinical effectiveness, VAS pain scores, and dysmenorrhea symptom scores as outcome indicators. The results of our study showed that: 1. the most commonly used intervention, except for control, was ACU, followed by MOX, and the least was APT; 2. the results of two-by-two meta-analysis showed that MOX was superior to ACU, ACU was superior to placebo, and Yoga was superior to control in improving VAS scores in patients with PD; however, the results of the NMA showed that MOX, ACU, and APT were all were superior to the blank control. Typically, MOX, APT, and ACU showed greater efficacy; 3. The ranking results revealed that MOX, ACU, and APT achieved higher SUCRA scores in different outcome metrics, suggesting their effectiveness in reducing dysmenorrheal pain in PD patients; 4. The findings on adverse events revealed no adverse events linked to NPT in the study's literature, thereby further undermining the safety of such treatments.

PD is recognized as one of the most common functional disorders for gynecological counseling and one of the most common reasons for short-term absenteeism from school or work in both young and adult women.[21] Despite extensive research, the pathological mechanisms of dysmenorrhea are not fully understood. Previous studies have shown that PD is a complex process that may depend on many factors[14,59,60] Among them, the level of prostaglandin and uterine contractile activity are one of the factors leading to dysmenorrhea. PD is primarily treated to relieve pain and other related symptoms (such as back and leg pain, anxiety, stress, and other symptoms that affect quality of life).[61,62] At present, pain VAS as a subjective way of assessing pain has been widely used to evaluate various pain disorders. Woodforde and Merskey first reported use of the VAS pain scale in patients presenting with a range of pain conditions.[63] Therefore, we use the VAS as the primary outcome measure of NPT for PD. CMSS is developed by Daniel J. Cox in 1978, including 18 items, a more comprehensive summary of dysmenorrhea-related symptoms. For patients with PD, in addition to improving uterine pain, other clinically relevant symptoms are also more important. In the

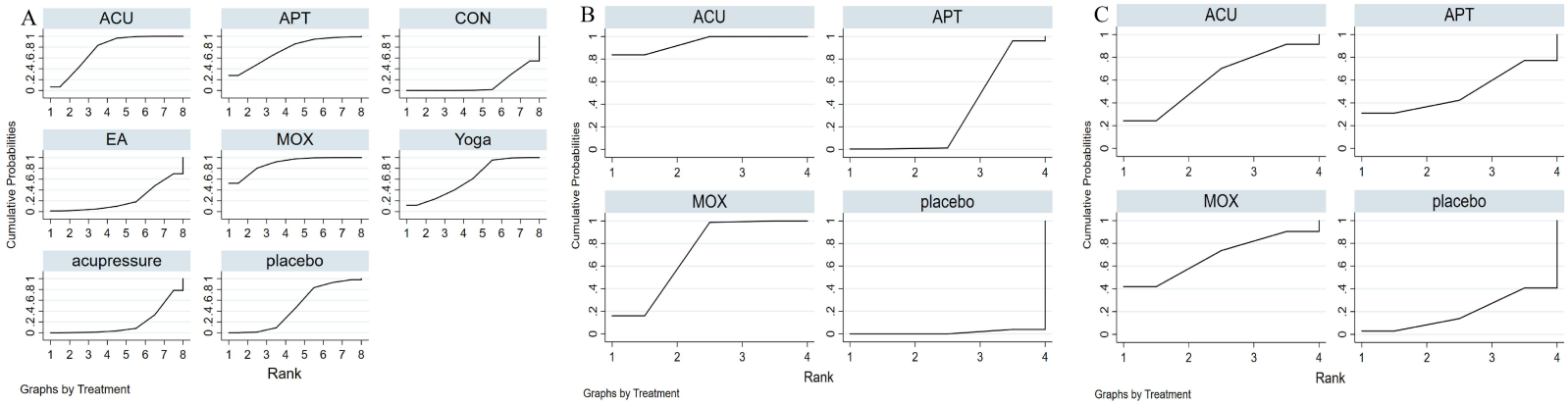

Figure 4 Surface under the cumulative ranking curves. (**A**) VAS scores; (**B**) CMSS scores; (**C**) response rate; (ACU, acupuncture; EA, electroacupuncture; MOX, moxibustion; APT, auricular point therapy; Yoga, Yoga; acupressure, acupressure; placebo, placebo acupuncture; control, blank control).

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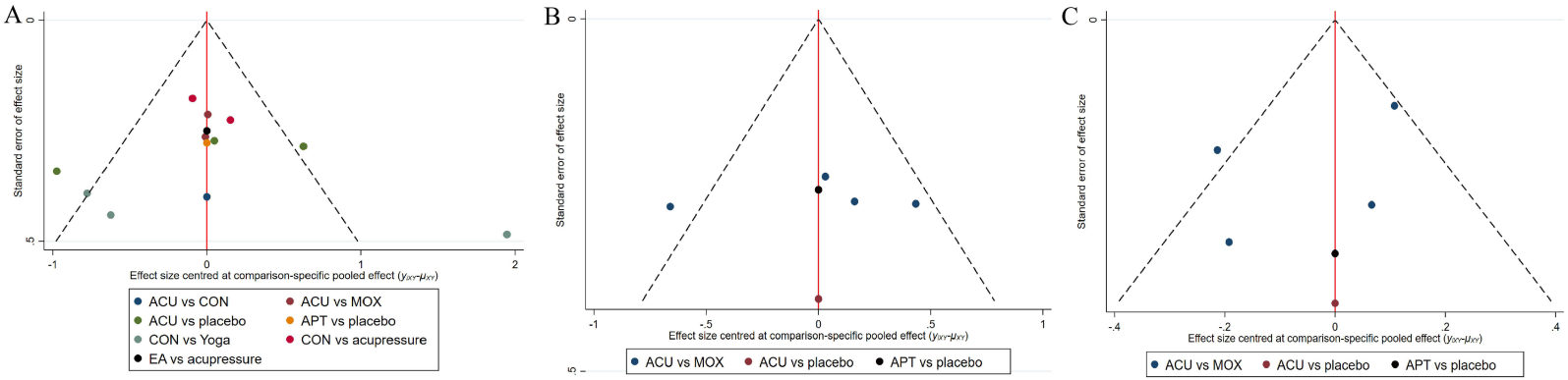

Figure 5 Funnel diagram. (**A**) VAS scores; (**B**) CMSS scores; (**C**) response rate; (ACU, acupuncture; EA, electroacupuncture; MOX, moxibustion; APT, auricular point therapy; Yoga, Yoga; acupressure, acupressure;placebo, placebo acupuncture; control, blank control).

treatment of PD, CMSS can monitor the treatment effect very well.[64] As the treatment progresses, the symptoms of dysmenorrhea in patients will change, and CMSS can capture these changes in a timely and sensitive manner. By the decrease of the total score of CMSS, it can be inferred that the treatment may be effective, and by analyzing the changes in the subitems, further understanding can be gained as to whether the degree of pain has decreased or whether accompanying symptoms have improved.[65] A number of studies have shown[66] that NPT are effective in improving related symptoms caused by PD.

MOX is an external therapeutic method originating from traditional Chinese medicine (TCM), which is based on TCM theories and usually uses burning moxa to stimulate acupuncture points. MOX has a history of more than 2,500 years with the advantages of simple operation and high cost-effectiveness.[67] Studies have shown that qi stagnation, cold condensation, and blood stasis are prevalent in PD.[68] The warm stimulation of moxibustion warms the meridians, activates the collateral branches, maintains the smooth flow of qi and blood, and relieves pain symptoms.[69] MOX can regulate immune functions, endocrine hormones, and neural factors, and enhance uterine microcirculation to alleviate the symptoms of dysmenorrhea.[70] MOX also alleviates menstrual pain in patients with PD in various ways,[71–76] and a large number of studies confirm its efficacy and effectiveness. The results of this study show that MOX is superior to other NPTs in improving VAS scores in patients with PD, which further confirms the clinical guideline of "moxibustion in case of cold" in Chinese medicine theory.

ACU, a fundamental component of Chinese medicinal practices, boasts an extensive background in addressing gynecological issues. ACU, in contrast to medication, presents fewer adverse effects. ACU works by stimulating acupuncture points in specific parts of the body to unblock meridians and promote circulation of qi and blood.[77,78] The Food and Drug Act has approved it. Modern studies have shown that acupuncture treatment for PD may be associated with improving uterine circulation disorders,[79,80] regulating endocrine function,[81] and affecting neurotransmitters.[82–84] PD, as a common visceral pain condition, is also closely related to inflammatory factors. ACU could reduce the release of PGs and downstream inflammatory cytokines by regulating nuclear factor-κB (NF-κB) signaling pathway, further relieving the inflammatory environment of uterus and uterine ischemia and hypoxia to alleviate menstrual pain.[85] Clinical studies have shown that ACU is more effective than NSAIDs in reducing the pain of PD.[86] ACU is widely recognized as one of the best NPT for the treatment of PD. The results of this study showed that ACU was the most commonly used therapy among the eight NPT and was also more advantageous in improving VAS, CMSS, and overall clinical effectiveness of PD.

APT is a Chinese medicine method that regulates the body's physiological and pathological states by stimulating specific acupoints on the auricle to treat disease or promote health.[87–89] These auricular points are believed to be connected to various organs and parts of the body and can influence the function of the entire body through the reflex zones of the ear. APT originated in ancient Chinese medicine and has been documented in ancient texts such as the Yellow Emperor's Classic of Internal Medicine. Over time, APT has evolved into an independent treatment system widely used and recognized. Modern medical research has also confirmed that APT can alleviate PD pain symptoms by activating and regulating the flow of qi and blood and reducing uterine tension and contraction.[90] As reported previously, it can relieve pain and neuronal excitability through regulating proinflammatory cytokines, such as IL-1b, IL-6, and TNF.[91] The results of the present study showed that APT ranked first in improving CMSS scores in treating PD.

Compared with previous studies,[90,92–95] our study reaffirmed the advantages of ACU in improving the symptoms of primary dysmenorrheal pain, and that NPT, such as ACU, have a better safety profile compared with pharmacological therapies. However, we also found some discrepancies. For example, studies by Ukachukwu Okoroafor et al,[96] Mike Armour et al,[97] and Remedios López-Liria et al,[34] found advantages of acupressure, self-care, and physical therapy (yoga) in relieving the symptoms of PD through meta-analysis, which may be at variance with the results of our study. In addition, a meta-analysis has shown that physical therapy and warm bath therapy are more effective at alleviating gynecological problems.[98] These differences may be because all of these studies used the traditional two-by-two controlled meta-analysis method, which only allowed comparison of the two interventions included. In contrast, our study used a reticulated meta-analysis approach that allowed for simultaneous comparison of multiple treatments and allowed for indirect comparisons. Such an analytic approach made it possible to estimate the relative effect between treatments without direct comparison data. Additionally, NMA can provide an ordering of the best probabilities for the included interventions, thus providing a prioritization for medical decision-making. In summary, the use of NMA in this study to assess the effectiveness and ranking of all known NPT for treating PD may be more clinically recommendable than the conclusions drawn from previous studies.

However, this study still has some limitations: (1) the quality of the included studies was low, which may pose a risk of bias; the sample sizes of some of the interventions were small, and the statistical efficacy may be insufficient; (2) the methodological quality of all the RCTs was moderate, which may have stemmed from the difficulties of randomization and blinding. Due to the unique nature of NPT, it is difficult to practice double blindness in clinic; (3) the total clinical effectiveness was not used as the primary outcome indicator, which may have led to a biased result; (4) the majority of the included RCTs were conducted in China, which may reduce the generalizability of the findings; (5) In this study, the results did not form a closed loop, and the effect estimation was mainly based on indirect comparison, which may affect the robustness of the results to some extent.

Conclusion

In summary, this study's evidence suggests that compared to placebo and no treatment, non-pharmacological therapy can reduce the severity of primary dysmenorrhea in patients. Among them, acupuncture, moxibustion, and auricular point therapy may be the best treatments for improving symptoms associated with primary dysmenorrhea. Indeed, future large, well-designed randomized controlled trials, extensive follow-up and better methodological quality are needed in the future to summarize and update the results of this analysis.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors state that they have no known competing financial interests or personal relationships that could influence the work reported in this article.

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