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REVIEW

Inadequate Evidence for Acupuncture as an Alternative or Adjunct to Antidepressants/ Psychotherapy for Postpartum Depression: A Bayesian Systematic Review and Network Meta-Analysis

Fei-Yi Zhao[1–3,*], Li Li[4,*], Peijie Xu[5,*], Wen-Jing Zhang[3,*], Gerard A Kennedy[2], Zhen Zheng[2], Yan-Mei Wang[3], Li-Ping Yue[1], Yuen-Shan Ho[6], Qiang-Qiang Fu[7], Russell Conduit[2]

[1]Department of Nursing, School of International Medical Technology, Shanghai Sanda University, Shanghai, 201209, People's Republic of China; [2]School of Health and Biomedical Sciences, RMIT University, Bundoora, VIC, 3083, Australia; [3]Shanghai Municipal Hospital of Traditional Chinese Medicine, Shanghai University of Traditional Chinese Medicine, Shanghai, 200071, People's Republic of China; [4]Shanghai Changning Center for Disease Control and Prevention, Shanghai, 200335, People's Republic of China; [5]School of Computing Technologies, RMIT University, Melbourne, VIC, 3000, Australia; [6]School of Nursing, Faculty of Health and Social Sciences, The Hong Kong Polytechnic University, Hong Kong, SAR, People's Republic of China; [7]Yangpu Hospital, School of Medicine, Tongji University, Shanghai, 200090, People's Republic of China

*These authors contributed equally to this work

Correspondence: Yuen-Shan Ho, School of Nursing, Faculty of Health and Social Sciences, The Hong Kong Polytechnic University, Hong Kong, SAR, People's Republic of China, Tel +852 2766-6410, Fax +852 2364-9663, Email janice.ys.ho@polyu.edu.hk; Qiang-Qiang Fu, Yangpu Hospital, School of Medicine, Tongji University, Shanghai, 200090, People's Republic of China, Tel + 86 021-6569 0520, Fax + 86 021-6569 6249, Email qiangqiang.fu@tongji.edu.cn

Background: Acupuncture is popular in the treatment of mental illness. This study determined its feasibility and role in managing postpartum depression (PPD) using a network meta-analysis.

Methods: We systematically searched seven databases up to May 2024 for randomized controlled trials (RCTs) appraising acupuncture's efficacy and safety against waitlist-control, placebo, standard control, or as an add-on treatment. Cochrane criteria were followed.

Results: Thirteen studies encompassing 872 participants underwent analysis. Both pairwise and network meta-analysis indicated that acupuncture, psychotherapy, and antidepressants were comparable in clinical efficacy rate and in reducing Hamilton Depression Scale and Edinburgh Postnatal Depression Scale scores. Acupuncture and psychotherapy also effectively mitigated concurrent anxiety symptoms. Combining acupuncture with antidepressants augmented therapeutic efficacy and reduced reported gastrointestinal adverse effects associated with antidepressant use. Acupuncture combined with psychotherapy offered similar benefits with superior safety profile. However, the quality of evidence ranged from very low to low due to significant risks of bias and limited sample sizes. The efficacy of psychotherapy and the combination of acupuncture and psychotherapy might be underestimated, as most RCTs used supportive therapy or individual counseling as positive controls instead of recommended approaches like interpersonal psychotherapy (IPT) or cognitive behavioral therapy (CBT) per PPD guidelines.

Conclusion: Current evidence precludes strong recommendations of administering acupuncture in PPD. Rigorous RCTs are essential to validate promising outcomes observed in comparisons between acupuncture, antidepressants, and their combined application. It remains inconclusive whether acupuncture's antidepressive effect is specific or non-specific. Given that psychotherapy is a recommended first-line treatment, investigating the potential efficacy enhancement of combining acupuncture with IPT/CBT is paramount to ascertain the preferred therapeutic approach for PPD.

Keywords: postpartum depression, acupuncture, antidepressants, interpersonal psychotherapy, cognitive behavioral therapy, clinical trials

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Background

Postpartum depression (PPD), which involves the onset of depressive episodes after childbirth,[1] is among the most common and disabling complications of childbearing.[2] An estimated 10–20% of women experience a major depressive episode during the postpartum period.[3] However, this figure may be underestimated, as studies indicate that 50–85% of women with PPD go undiagnosed and untreated.[3,4] Over 50% of women with PPD are unwilling to seek or accept treatment. Beyond the lowered motivation to seek help due to PPD symptoms, barriers to treatment include perceived stigma and fear of being labeled as a "bad mother".[5] PPD manifests as extreme sadness, diminished pleasure and interests, low energy, poor appetite, sleep disturbance, feelings of worthlessness and guilt, irritability, and suicidal ideation or behaviour.[4,6] Furthermore, PPD has secondary impacts on the infant through maternal impairment, as puerpera with PPD are more likely to neglect and abuse their children.[7] Children of mothers with PPD usually experience eating and sleeping problems as well as behavioral difficulties, and long-term consequences such as developmental delays and depression.[4]

PPD necessitates psychiatric referral and inpatient psychiatric treatment due to the risk of suicide and infanticide.[7] Antidepressants, such as selective serotonin reuptake inhibitors (SSRIs) and serotonin/norepinephrine reuptake inhibitors (SNRIs), are primary medications for treating PPD.[7,8] However, their use in breastfeeding pose challenges, as both SSRIs and SNRIs pass into breast milk, raising concerns about the newborn's well-being.[1] Most women who intend to exclusively breastfeed are therefore hesitant to take medications, and would also not pursue antidepressants due to concerns regarding infant exposure.[9] In August 2023, the FDA approved zuranolone (Zurzuvae), an oral synthetic allopregnanolone, for the treatment of PPD. Despite its satisfactory short-term efficacy in clinical trials, significant adverse events (AEs) such as dizziness, headache, sedation, and somnolence were reported.[10] Psychotherapy is also a first-line treatment for PPD.[7,8] Although safe and effective, it is costly, time-consuming, and is not readily available in remote and rural areas.[11]

The utilization of Complementary and Alternative Medicine (CAM) therapies is becoming increasingly prevalent among postpartum women. A nationwide survey in the United States revealed that 28% of postpartum women aged 19 to 49 reported using CAM in the past 12 months, with 43.2% of these individuals employing it for anxiety or depression.[12] In Malaysia, 85.5% postpartum mothers engaged in CAM practices to enhance their well-being, including reducing postnatal stress and depression, increasing breast milk production, and/or losing weight.[13] In Taiwan, postnatal women with PPD who underwent Traditional Chinese medicine (TCM) treatment incurred lower overall medical expenditure compared to non-TCM users. Additionally, around 52.7% of PPD patients had the motivation to seek TCM services.[14]

Acupuncture, a modality of CAM therapy, has been extensively used in the treatment of mental illness, including PPD.[15] Depression ranks second among the full spectrum of acupuncture indications.[15] Emerging evidence highlighting the safety and cost-effectiveness of acupuncture has bolstered its popularity for treating depression in the United States and the United Kingdom, where it is particularly favored by women.[16] In Australia, 49.4% of women who gave birth within the past year reported using at least one form of CAM, with 9.5% opting for acupuncture, despite it not being offered within the Australian maternity hospital system.[17] Several systematic reviews and meta-analyses (SR/MAs) have evaluated the effectiveness of acupuncture for PPD; however, their findings are inconsistent, and the credibility of the evidence remains unclear.[16,18,19] Moreover, previous traditional meta-analyses, designed as pairwise comparisons, have only compared acupuncture with placebo or acupuncture with antidepressants/psychotherapy, leaving the comparative efficacy of various therapies unresolved.[16,18,19] Network meta-analysis enables integration of direct and indirect comparison among different interventions and ranks them according to efficacy indicators, identifying the optimal therapy to support clinical decision-making.[20] Currently, no formally published network meta-analysis exists regarding acupuncture for PPD. Our study aimed to address this gap by comparing the efficacy and safety of acupuncture with conventional therapies, elucidating its appropriate role in the treatment regimen for PPD, and providing evidence-based support for clinicians.

Materials and Methods

Study Registration

This review adhered to the *PRISMA Extension Statement for Reporting of Systematic Reviews Incorporating Network Meta-analyses of Health Care Interventions*.[21] A prospective protocol was registered in PROSPERO (No. CRD42023456055).

Eligibility Criteria

The *PICOS* framework was adopted to establish the inclusion criteria and screen eligibles trials.

Participant (P): Postnatal women with a clinical diagnosis of PPD as per standard diagnostic criteria (Appendix 1.1) were included. Trials without a standard diagnostic guideline were excluded, even if they mentioned a PPD diagnosis or provided brief descriptions of puerperal complaints of depressed mood. Studies were also excluded if they included PPD patients with other comorbid psychiatric or physical illnesses.

Intervention (I): Interventions were restricted to traditional needle acupuncture (TNA), including manual acupuncture and electroacupuncture, or TNA combined with standard care for PPD (psychotherapy, antidepressants, and/or other approved drugs for PPD).

Comparator (C): Comparator interventions were restricted to waitlist control, placebo-TNA, standard care, or TNA/placebo-TNA combined with standard care.

Outcome (O): The primary outcome was scores from validated depression scales, such as the Edinburgh Postnatal Depression Scale (EPDS), Postpartum Depression Screening Scale (PDSS), Self-rating Depression Scale (SDS), or Hamilton Depression Scale (HAM-D). There were no restrictions on the HAM-D version for study inclusion. Studies that did not report global scores from any validated depression scale were excluded, even if they reported clinical efficacy rates based on scale scores or partial items of the scale. Secondary outcomes included clinical efficacy rate, sleep/anxiety symptoms, laboratory indicators such as serum hormone levels, and AEs.

Study (S): Only published randomized controlled trials (RCTs) with parallel designs were included.

Search Strategy and Data Extraction

The following three English and four Chinese databases were searched from inception to May 2024: Cochrane Central Register of Controlled Trials (CENTRAL) and MEDLINE (via PubMed), and EMBASE, and Chongqing VIP database (CQVIP), Wanfang database, China biomedical literature service system (SinoMed) and China National Knowledge Infrastructure (CNKI). Only literature in English and Chinese were considered. Appendix 1.2 shows the specific search strategy. Additional trials were also identified from the reference lists of the included papers and existing SR/MAs.

Search results were exported to EndNote 21 for duplicate removal. Titles and abstracts were initially screened to exclude irrelevant papers, with full texts reviewed as needed. Two independent reviewers (YM-W and LP-Y) selected eligible trials, reaching a consensus on inclusion. Data extracted from each eligible RCT included: first author's name, date of publication grouping methods, sample size per group, duration of PPD, diagnostic criteria, participants' TCM syndrome patterns, interventions in the treatment and control groups, acupuncture regimen (acupoints, timing, frequency and dosage), outcome measures, results, follow-up, and AEs.

Evaluation of Risk of Bias in Individual Studies

Two investigators (WJ-Z and FY-Z) independently appraised the included trials, achieving substantial agreement (*Kappa* = 0.79). All discrepancies were solved by discussion and consensus. The methodological quality of the RCTs were assessed using Revised Cochrane Risk-of-Bias Tool for Randomized Trials (RoB 2.0).

Data Analysis

We performed paired and network meta-analyses using the Meta and GeMTC packages respectively, in *R* 4.2.3. Odds ratio (*OR*) and standardized mean difference (*SMD*) with 95% confidence interval (*CI*) were adopted as the preferred effect size for binary and continuous data, respectively.

For paired meta-analysis, continuous variables (ie, depression scales scores and laboratory indicators value) were pooled using the inverse variance method, while dichotomous variables (ie, clinical efficacy rate) were pooled using the Mantel-Haenszel method. Heterogeneity across the RCTs was assessed using the Chi^2 test and was quantified by I^2 statistic. Following the recommendations of Tufanaru et al,[22] the random-effects model was the default, as it generalizes findings beyond the included studies. The fixed-effects model was considered only when heterogeneity was absent ($I^2 = 0$).

Network meta-analysis was conducted using Markov Chain Monte Carlo (MCMC) simulations within a Bayesian framework. Four MCMC chains with different initial values were run, each with 5000 iterations and a 20,000-iteration burn-in period. Convergence was assessed using trace and density plots and the Gelman–Rubin–Brooks method, with a potential scale reduction factor (PSRF) of up to 1. The igraph package in *R* was used to construct the network evidence plot, visualizing interventions for each outcome. The node-splitting method was applied to evaluate the internal inconsistency of network meta-analysis. If no significant inconsistency was detected between direct and indirect comparisons ($p > 0.05$), network meta-analysis was conducted under the consistency model; otherwise, the inconsistency model was considered. Given the GeMTC package defaults to Mean Difference (*MD*) as the effect size, we initially used Stata 17.0 to convert pooled *MD* data from continuous variables into *SMD* data, which was then merged for network meta-analysis using GeMTC. *MD* was used instead of *SMD* only when comparisons among different interventions were derived from the same multi-arm RCT. We created cumulative ranking plots with Surface Under the Cumulative RAnking curve (SUCRA) for each outcome, indicating that an intervention with a higher SUCRA value is more likely to be efficacious.

Using the Netmeta package in *R*, we employed linear regression analysis (*Egger*'s test) with comparison-adjusted funnel plots to detect potential publication bias for outcomes measured in at least ten RCTs.

Confidence Assessment of Network Meta-Analysis Results

The overall quality of evidence obtained from the network meta-synthesis was evaluated using the Confidence-In-Network-Meta-Analysis (CINeMA) framework. The confidence levels of the evidence were classified into four categories, ranging from "High" to "Very low".[23]

Results Analysis

The initial search yielded 135 articles. After removing duplicates and conducting thorough full-text screening, 13 RCTs, comprising a total of 872 participants, met the predefined criteria (Figure 1). A summary of the excluded studies and specific reasons for their exclusion is provided in Appendix 2.

Description of Studies

Characteristics of each included RCT are presented in Appendix 3. The 13 included studies investigated seven interventions: acupuncture (Acu), placebo-acupuncture (PAcu), antidepressants (Anti), psychotherapy (Psy), acupuncture combined with antidepressants (AcuAnti), acupuncture combined with psychotherapy (AcuPsy), and placebo-acupuncture combined with psychotherapy (PAcuPsy). (*NOTES*: each intervention is abbreviated as shown in parentheses). All RCTs were two-arm trials, except one three-arm trial.[24] In eight RCTs using antidepressants as positive controls, the medications used were fluoxetine (3/8), escitalopram (2/8), sertraline (1/8), venlafaxine (1/8), and maprotiline (1/8). The acupuncture dosage ranged from two sessions per week for four weeks to five sessions per week for eight weeks. Only one RCT[25] included a 4-week follow-up.

All but one RCT[26] employed HAM-D_{17} or HAM-D_{24} to quantify depression severity. The EPDS was used in six RCTs.[25–30] Three trials assessed depression severity with the SDS,[24,26,30] and also included the SAS to evaluate comorbid anxiety symptoms. All RCTs, except one,[31] reported the clinical efficacy rate of acupuncture and control therapies, though grading criteria varied (Appendix 4). Three studies[24,27,32] assessed changes in laboratory indicators, such as serum hormone levels (eg, estradiol, progesterone, thyroid-stimulating hormone, leptin, or orphanin FQ) and neurotransmitter levels (eg, serotonin and dopamine), to explore the biological mechanisms underlying acupuncture's effects on PPD.

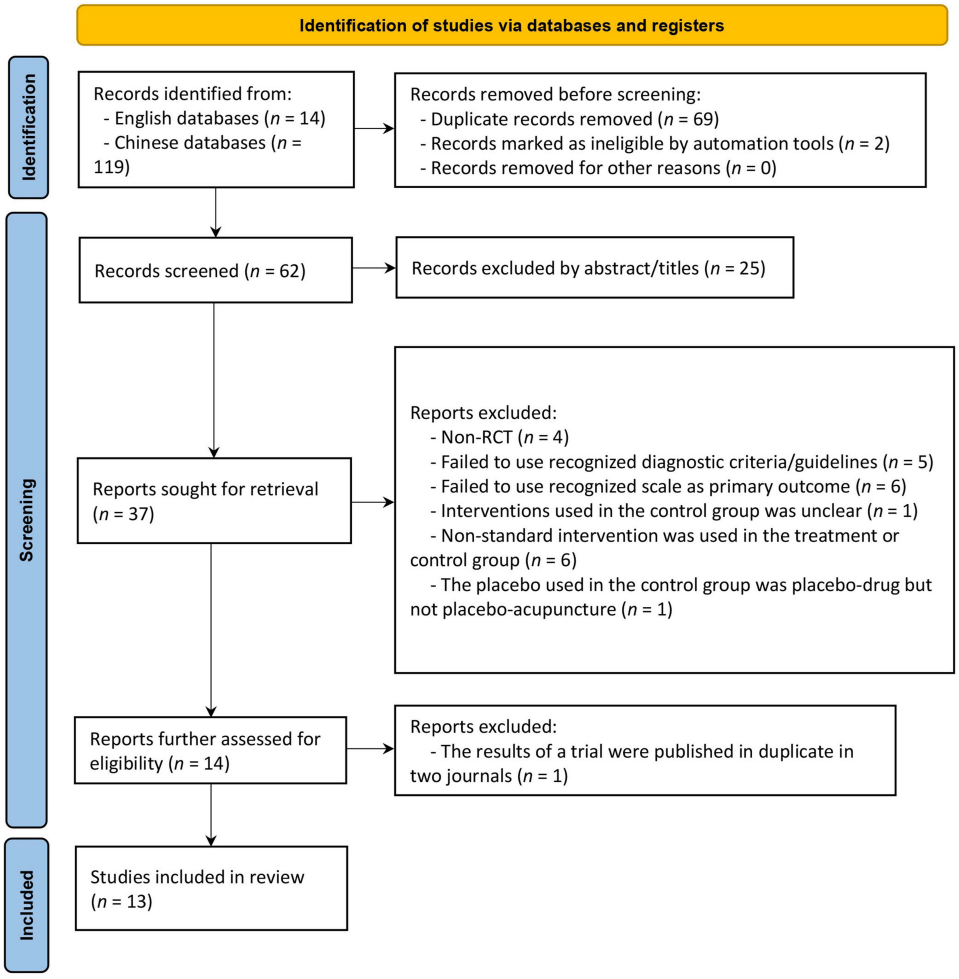

Figure 1 Flow Diagram of the Study Selection.

The HAM-D scores of patients included in the RCTs ranged from eight to 35, or EPDS scores were ≥ 9, indicating variability in the baseline depression severity among the patients. This suggests that the included patients comprised those with mild to moderate PPD as well as potentially severe PPD cases. Three trials did not report whether the patients were from outpatient or inpatient settings; one trial reported patients exclusively from gynecology inpatient cases; five trials reported patients exclusively from psychology, acupuncture or gynecology outpatient clinics; and the remaining trials reported subjects from both outpatient and inpatient settings.

Ten studies reported AEs (Appendix 5). Acupuncture-related AEs included pain and/or hematoma at the needle site (6.1%), dizziness (3.0%), and headache (1.5%). Antidepressant-related AEs included gastrointestinal symptoms such as nausea, vomiting, and loss of appetite (12.1%), dizziness (2.9%), and sleep disturbances (1.3%). When antidepressant was combined with acupuncture, gastrointestinal symptoms (6.5%) was still the most common AE, along with dry mouth (2.8%). No study identified psychotherapy-related AEs. For the combination of acupuncture and psychotherapy, the only AE reported was pain and/or hematoma at the needle site (2.1%).

Evaluation of Risk of Bias in Individual Studies

The allocation sequence was random in all included RCTs, while only three adequately addressed valid allocation concealment using sealed blinding codes.[25,29,30] Hence, these three RCTs were judged as having low risk of bias (RoB) and the others were judged as having some concerns on the "randomization process" item of RoB 2.0 tool. Although acupuncturists cannot be blinded, two RCTs[25,30] blinded the evaluators and patients by incorporating placebo-acupuncture,

resulting in a low RoB in both "deviations from intended interventions" and "bias in measurement of the outcome" items. Insufficient information in other trials led to them being classified as high risk or having some concerns in these two domains. Only one trial[33] directly analyzed data after accounting for drop-out cases, warranting some concerns in the "missing outcome data" item. Studies with no drop-out cases or those employing intention-to-treat analysis were considered to have low RoB in this regard. No RoB in "selection of the reported result" were identified. Overall, two RCTs were rated as having low RoB, while the rest were categorized as having high RoB (Figure 2).

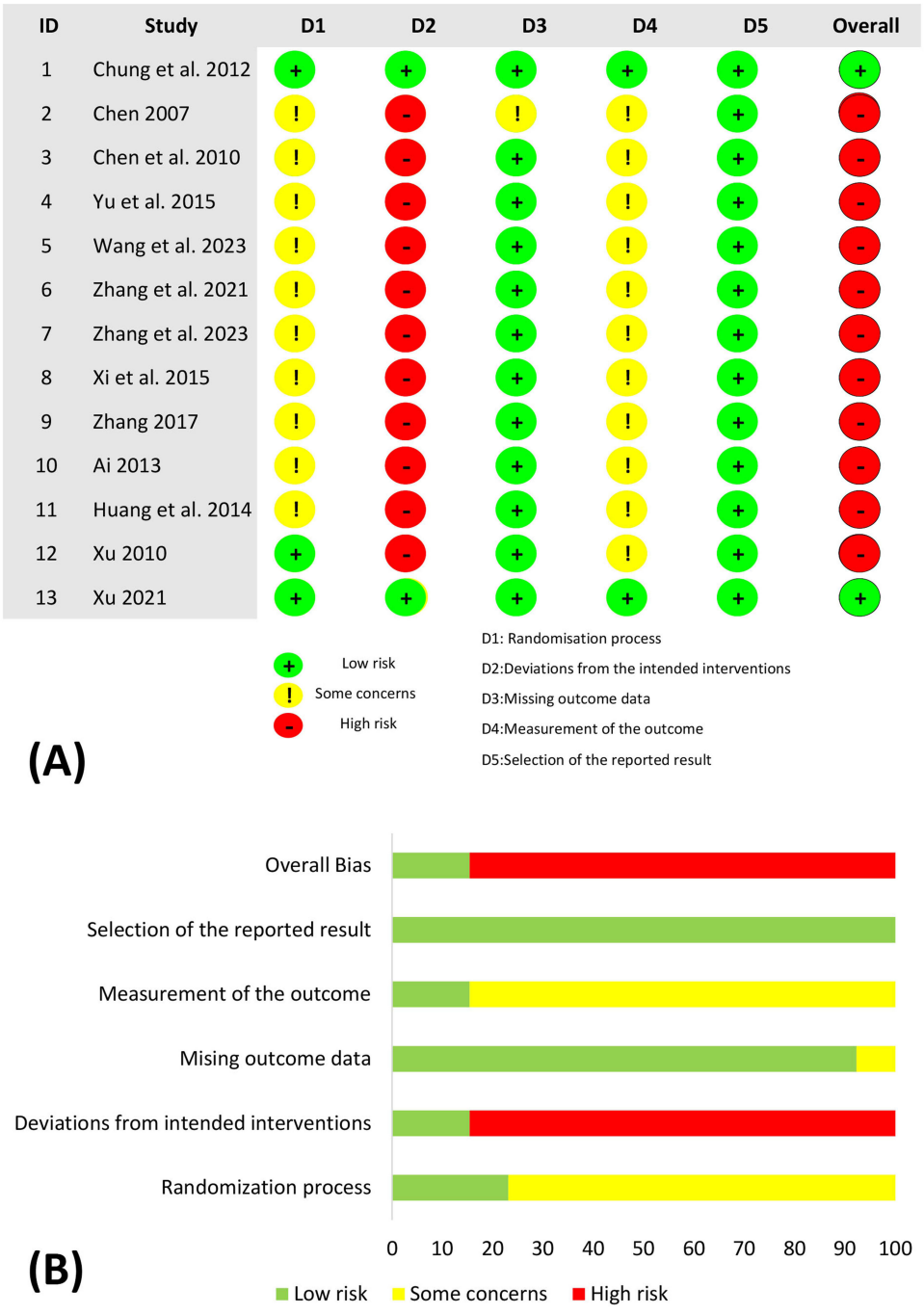

Figure 2 The Risk of Methodological Bias in the Included Studies. (**A**) Risk of Bias summary for RCTs (**B**) Risk of Bias graph for RCTs.

Data Analysis

Pairwise Meta-Analysis Results

The pairwise meta-analysis results demonstrated that Acu yielded comparable results to Anti in reducing HAM-D global scores [*SMD* = −2.08, 95% CI (−4.21, 0.05), $p = 0.06$]. Combining Acu with Anti (AcuAnti) led to a significantly greater reduction in HAM-D scores compared to Anti alone [*SMD* = −2.93, 95% CI (−5.19, −0.67), $p = 0.01$]. Similarly, the clinical efficacy rate was notably higher for AcuAnti or AcuPsy than for Anti alone [*OR* = 4.05, 95% CI (−1.81, 9.07), $p < 0.01$] or Psy alone [*OR* = 2.76, 95% CI (1.16, 6.57), $p = 0.02$] in the treatment of PPD (Appendix 6).

Network Meta-Analysis Results

Convergence Diagnosis

The trace plot indicated that the MCMC chain fluctuations were stable and had good overlap when the number of iterations reached 5000 or more (Appendix 7). The density plot demonstrated that Bandwidth tended to 0 and reached stability when the number of iterations reached 20,000 (Appendix 7). The median and 97.5% values of the PSRF approached 1 and stabilized (Appendix 8). These findings collectively suggest a well-converged model.

Evidence Network Plot

HAM-D global scores and clinical efficacy rates were reported across 12 RCTs, involving 812 and 752 participants, respectively. In the evidence network plot for these outcomes, two three-chain closed-loops emerged: AcuPsy-Anti-Acu and AcuPsy-Psy-Acu. Six studies comprising 342 participants reported EPDS scores but did not form any closed-loops in the evidence network plot. Three trials (with 260 participants) reported both SDS and SAS scores, while an additional three trials comprising 330 participants reported serum levels of estradiol, serotonin, and orphanin FQ. An AcuPsy-Psy-Acu closed-loop was identified in each of these outcomes (Appendix 9).

Evaluation of Inconsistency

For both HAM-D and clinical efficacy rate, no substantial inconsistencies were detected between direct and indirect comparisons for each split node ($p > 0.05$) (Appendix 10). Due to the limited number of involved RCTs, other outcomes were not subjected to local inconsistency tests as they did not meet the a priori conditions for this test model. Consequently, the consistency model was adopted for the network meta-analysis.

Analyses of Major Outcome Measures

All seven interventions contributed to clinical efficacy rate, HAM-D, and EPDS. In terms of clinical efficacy rate, the ranking of interventions from highest to lowest was: AcuAnti > AcuPsy > PAcu > Anti > Acu > PAcuPsy > Psy (Figure 3A). However, only four head-to-head comparisons showed significant between-group differences ($p < 0.05$). In summary, AcuAnti had a higher efficacy rate in treating PPD compared to Acu [*OR* = 0.16, 95% CI (0.04, 0.73)], Anti [*OR* = 4.29, 95% CI (1.65, 11.99)], or Psy [*OR* = 8.76, 95% CI (1.76, 46.12)]; AcuPsy was more effective than Psy [*OR* = 2.96, 95% CI (1.02, 9.18)]. There was no significant difference between AcuAnti and AcuPsy [*OR* = 2.95, 95% CI (0.72, 12.85)]. In addition, there was no significant difference between Acu and Anti [*OR* = 0.69, 95% CI (0.22, 2.24)], Acu and Psy [*OR* = 1.41, 95% CI (0.53, 4.2)], or Anti and Psy [*OR* = 2.03, 95% CI (0.55, 7.88)] (Figure 4A). For reducing HAM-D global scores, the ranking of interventions from highest to lowest was: AcuAnti > PAcuPsy > PAcu > AcuPsy > Acu > Psy > Anti (Figure 3B). Among these, between-group difference identified in three head-to-head comparisons ($p < 0.05$). In summary, although AcuAnti more significantly reduced the HAM-D global scores, compared to Acu [*SMD* = 3.7, 95% CI (0.43, 6.59)], Anti [*SMD* = −4.62, 95% CI (−6.85, −2.37)], or Psy [*SMD* = −4.72, 95% CI (−8.5, −0.77)], there was no significant difference between AcuAnti and AcuPsy [*SMD* = −3.07, 95% CI (−6.2, 0.19)]. There was also no significant difference between Acu and Anti [*SMD* = −0.92, 95% CI (−3. 21, 1.03)], Acu and Psy [*SMD* = −1.02, 95% CI (−4.19, 1.92)], or Anti and Psy [*SMD* = −0.1, 95% CI (−3.14, 3.11)] (Figure 4B). For reducing EPDS global scores, the ranking of interventions from highest to lowest was: AcuAnti > PAcuPsy > AcuPsy > Acu > Anti > PAcu > Psy (Figure 3C). No significant difference was found in any head-to-head comparisons (Figure 4C).

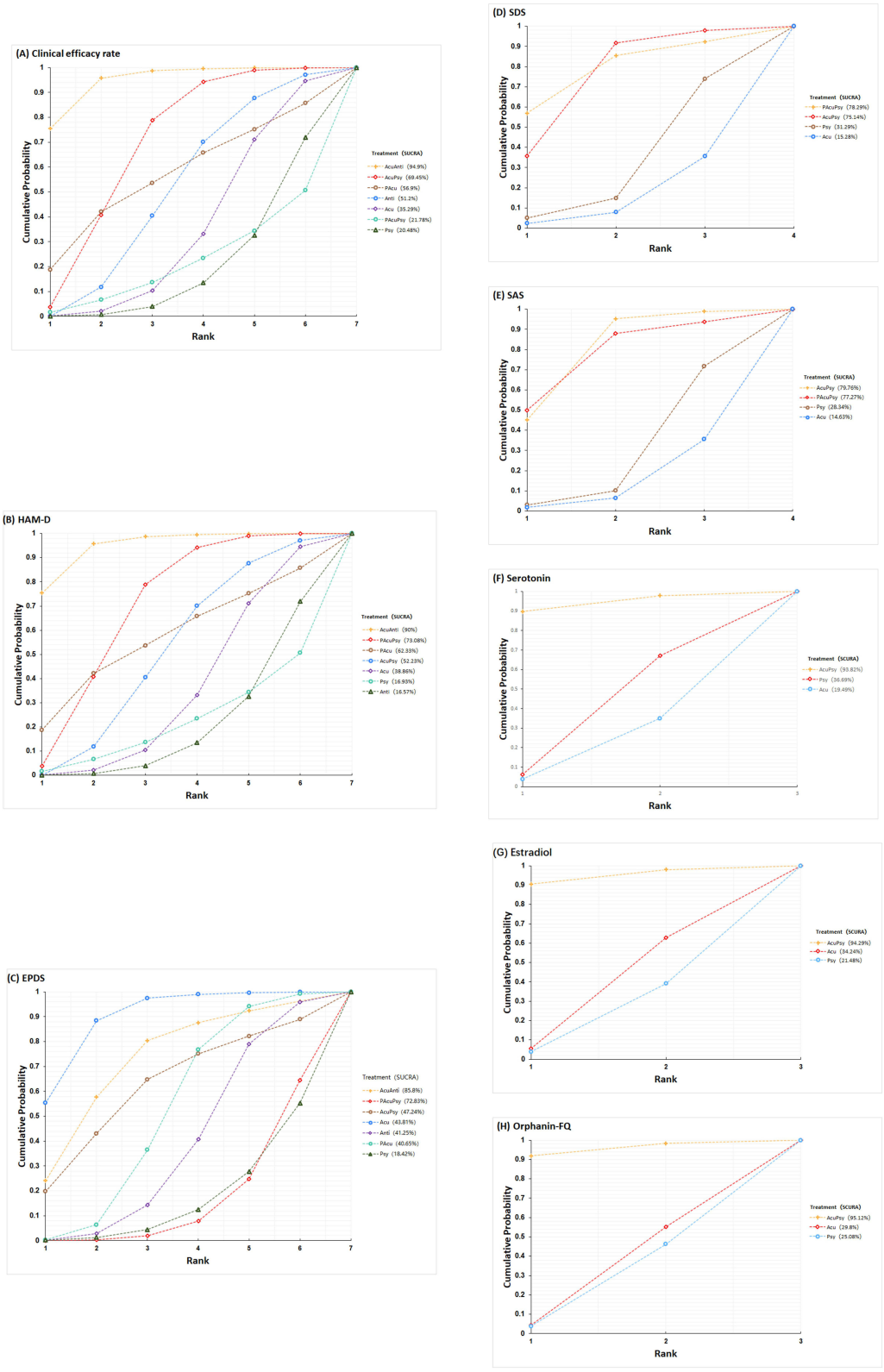

Figure 3 Cumulative Ranking Plots. (**A**) to (**H**) demonstate the primary outcome measures included in the quantitative analysis. (**A**) shows the clinical efficacy rate; (**B**) shows HAM-D scores; (**C**) shows EPDS scores; (**D**) shows SDS scores; (**E**) shows SAS scores; (**F**) shows serum serotonin levels; (**G**) shows serum estradiol levels; (**H**) shows serum orphanin-FQ levels.

Abbreviations: Acu, Acupuncture; Pacu, Placebo-acupuncture; Anti, Antidepressant; Psy, Psychotherapy; AcuAnti, Acupuncture combined with Antidepressant; AcuPsy, Acupuncture combined with Psychotherapy; PAcuPsy, Placebo-acupuncture combined with Psychotherapy. HAM-D, Hamilton Depression Scale; EPDS, Edinburgh Postnatal Depression Scale; SDS, Self-rating Depression Scale; SAS, Self-rating Anxiety Scale.

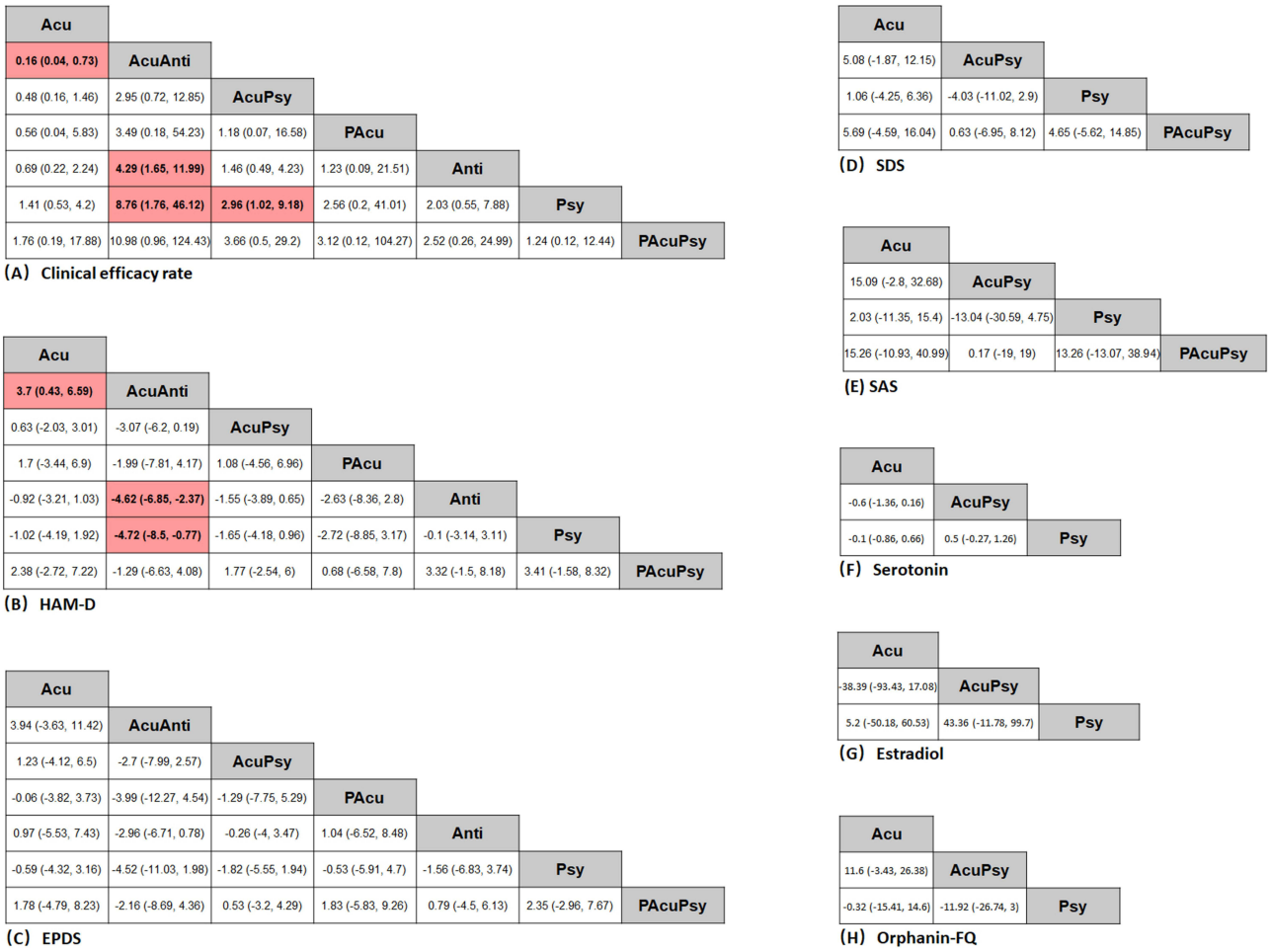

Figure 4 League Table. (**A**) to (**H**) demonstate the primary outcome measures included in the quantitative analysis. (**A**) shows the clinical efficacy rate; (**B**) shows HAM-D scores; (**C**) shows EPDS scores; (**D**) shows SDS scores; (**E**) shows SAS scores; (**F**) shows serum serotonin levels; (**G**) shows serum estradiol levels; (**H**) shows serum orphanin-FQ levels. **Abbreviations**: Acu, Acupuncture; Pacu, Placebo-acupuncture; Anti, Antidepressant; Psy, Psychotherapy; AcuAnti, Acupuncture combined with Antidepressant; AcuPsy, Acupuncture combined with Psychotherapy; PAcuPsy, Placebo-acupuncture combined with Psychotherapy. HAM-D, Hamilton Depression Scale; EPDS, Edinburgh Postnatal Depression Scale; SDS, Self-rating Depression Scale; SAS, Self-rating Anxiety Scale.

Four interventions contributed to SDS and SAS. In terms of reducing SDS and SAS scores, the rankings from highest to lowest were PAcuPsy > AcuPsy > Psy > Acu (Figure 3D) and AcuPsy > PAcuPsy > Psy > Acu (Figure 3E), respectively. Three interventions contributed to laboratory indicators. For increasing serum serotonin, the ranking was AcuPsy > Psy > Acu (Figure 3F); for increasing serum estradiol (Figure 3G) and reducing serum orphanin-FQ (Figure 3H), the ranking was AcuPsy > Acu > Psy. However, the league table did not identify significant difference in any head-to-head comparisons within these outcomes (Figure 4D–H).

The *R* GeMTC package only presented heterogeneity results for four outcomes. This is because the number of RCTs involved in other outcomes was limited to analyze inter-study heterogeneity. In terms of clinical efficacy rate, only the Acu Vs Psy comparison exhibited acceptable heterogeneity (I^2 = 30.5%), while comparisons among other interventions showed no heterogeneity, indicating the stability of the results. For HAM-D, the AcuAnti Vs Anti comparison displayed acceptable heterogeneity (I^2 = 19.3%), whereas all other comparisons exhibited significant heterogeneity (I^2 from 78.9% to 98.5%). Regarding the SDS and SAS, significant heterogeneity was observed in the Acu Vs Psy comparison (I^2 = 98.7% for SDS, and I^2 = 99.4%, SAS) (Appendix 11).

Publication Bias Test

The publication bias test was carried out based on clinical efficacy rate and HAM-D scores, revealing no statistically significant effect (p = 0.30 for clinical efficacy rate; and p = 0.32 for HAM-D) (Appendix 12).

Certainty and Quality of Evidence

The confidence in the results of network meta-analyses were delineated in Appendix 13. In pursuance of the CINeMA system, the certainty and quality of evidence ranged between "Very low" and "Low". The predominant factor contributing to degradation was the substantial RoB across the trials and limited sample size of original RCTs.

Discussion

Summary of Findings

Our review encapsulated the current knowledge state regarding managing PPD with acupuncture. The outcomes from both pairwise and network meta-analyses aligned consistently. Acupuncture, alongside antidepressants and psychotherapy, exhibited comparable efficacy in reducing EPDS and HAM-D global scores. The augmentation of acupuncture to antidepressants led to a notable decline in HAM-D scores by 2.93–4.62 points, which was clinically significant.[34] The clinical efficacy rate observed with combined acupuncture and antidepressants paralleled that of combined acupuncture and psychotherapy. Moreover, both acupuncture and psychotherapy demonstrated significant reductions in SAS scores among PPD patients, with similar efficacy. However, the amalgamation of these two therapies did not amplify this efficacy. The impact of acupuncture combined with antidepressants on SAS scores remained uncertain. Unfortunately, the evidence supporting the aforementioned positive results exhibited very-low-to-low quality, primarily due to insufficient blinding and limited number of RCTs with small sample size. Acupuncture was well-tolerated, with the most frequent AEs being pain and/or hematoma at the needling sites (6.1%). Furthermore, it has been proposed that such subjective sensations should not be categorized as AEs, given that skin penetration is inherent in acupuncture treatment.[35] Conversely, nausea, vomiting, and/or loss of appetite were frequently associated with antidepressants but not observed in acupuncture-only recipients. Furthermore, the addition of acupuncture to antidepressants was associated with reduced incidence of such reported gastrointestinal AEs from 12.1% to 6.5%. No AEs related to psychotherapy were identified. Notably, 92.3% of the reviewed RCTs lacked follow-up, thus obscuring the intermediate-to-long term effects of acupuncture.

Overall, acupuncture emerges as a potential safe and efficacious alternative to conventional treatments for PPD, at least for short-term relief. To optimize efficacy while ensuring safety, combining acupuncture with psychotherapy is advocated as the primary treatment strategy, followed by the combination of acupuncture with antidepressants.

Strengths, Limitations, and Comparison with Previous Systematic Reviews

We came across seven English and four Chinese available SR/MAs that shared a similar thematic focus. However, these SR/MAs included inappropriate original trials. Specifically, three SR/MAs[19,36,37] included a trial focusing on antenatal depression rather than postpartum depression.[38] Ten SR/MAs[6,18,19,36,37,39–43] included trials that estimated the efficacy of acupuncture by comparing it with non-standard controls such as Tuina, herbal medicine, placebo-herbal medicine, moxibustion, auricular acupressure, or acupuncture with another technique. Five SR/MAs[37,39,41–43] included trials that did not use recognized guidelines to diagnose PPD. Including inappropriate original trials in meta-syntheses introduced extra variability, making it challenging to interpret the results. Additionally, seven out of the 11 existing SR/MAs were conducted over five years ago,[6,16,18,19,37,40,42] potentially indicating outdated information.

Our review, with updated retrieval and stricter selection criteria, included a greater number of relevant trials and reduced variability. Other strengths included: (1) utilizing the network meta-analysis paradigm, we first quantified the differences between multiple intervention modes, including acupuncture, conventional therapy, and their combined use; and (2) the CINeMA system, employed in our review, was not used in any prior works to assess the quality of evidence.

However, limitations exist. First, certain outcomes, notably SDS and SAS, had a very limited number of included RCTs (< 3), precluding meta-synthesis and comprehensive analysis. This dearth of RCTs also hindered subgroup and sensitivity analyses aimed at detecting sources of heterogeneity in these outcomes. Second, the poor methodological quality of included RCTs seriously undermined evidence reliability. Lastly, all trials were conducted in China, indicating a potential geographic and ethnic bias. A survey in Australia revealed substantial acupuncture utilization among childbearing-aged women (approximately 68%),[17] highlighting a potential demand and acceptance of acupuncture in

perinatal care. Consequently, validating such findings among postnatal women in diverse regions and ethnicities becomes imperative.

Interpretation of Findings

At least ten international Clinical practice guidelines recommend psychotherapy as the first clinical option or alternative to antidepressants for peripartum depression, including PPD.[44] Analyzing six RCTs involving psychotherapy, our review determined that the combined use of psychotherapy and acupuncture matches the efficacy of combining antidepressants with acupuncture. However, it is possible that psychotherapy's true efficacy might be undervalued. This is due to the inclusion of individual counseling[24,29,45] or supportive psychotherapy[28,30] as positive controls in five RCTs, instead of guideline-recommended approaches like Interpersonal Psychotherapy (IPT) or Cognitive Behavioral Therapy (CBT).[44] Although no studies were found on combining acupuncture with IPT, combining acupuncture with CBT is a common strategy for various mental disorders, including insomnia,[46] anxiety,[47] and depression.[48] This combination offers potential additive effects and lower early withdrawal rates compared to CBT alone,[46] highlighting its advantages. In terms of safety, psychotherapy significantly outperforms antidepressants (Appendix 5). Consequently, it is reasonable to speculate that the combined use of acupuncture and psychotherapy presents a more preferable option than acupuncture and antidepressants, showing promise as the favored treatment for PPD. This, however, warrants further investigation into the feasibility and potential benefits of combining acupuncture with IPT/CBT in well-designed RCTs.

Beyond efficacy, considerations such as patient preferences and cost-effectiveness should guide treatment selection. This network meta-analysis revealed that acupuncture, psychotherapy, and antidepressants exhibited equal effectiveness in reducing depressive symptoms in PPD patients. Additionally, both acupuncture and psychotherapy alleviated comorbid anxiety symptoms in PPD patients. It has been demonstrated amongst patients with depression that acupuncture is more cost-effective compared to receiving counseling or usual care alone.[49] Acupuncture also improves PPD-related somatic symptoms like sleep disturbances and pain, with its direct effect being considered superior to psychotherapy.[15] As such, it is advisable for PPD patients experiencing comorbid anxiety symptoms, sleep disorders, and/or pain and a preference for CAM therapies to initially consider acupuncture, with the option to add psychotherapy like CBT if initial results are unsatisfactory.

In the reviewed RCTs that included serum indicators, both antidepressant and psychotherapy was observed to significantly increase the levels of serotonin,[24,27,32] dopamine,[32] progesterone,[27] and estradiol,[24,27,32] reduce the levels of orphanin-FQ,[24,27,32] in addition to lowering HAM-D scores. The addition of acupuncture led to more pronounced alterations in HAM-D scores and these serum biomarkers. These results hold substantial implications for elucidating the mechanisms underlying acupuncture against PPD. Hormonal imbalance, such as the sharp decline in progesterone and estradiol after childbirth, have been identified as contributing factors to PPD.[1] The dopaminergic,[50] serotonergic[51] and nociceptin/orphanin-FQ receptor[52] system are also implicated in the pathophysiology of PPD. The mesolimbic dopamine system function is significantly attenuated in women with PPD, interfering with reward-related processes necessary for motivated maternal behaviors.[50] Women with PPD often exhibit lower serotonin[53] and higher nociceptin/orphanin-FQ[52] levels compared to nondepressed counterparts. Furthermore, estrogen has regulatory effects on serotonin receptor's expression and activity,[51,53] with increased estradiol levels potentially enhancing serotonin synthesis or reducing its reuptake, thereby alleviating depressive symptoms.[1] Hence, the efficacy of acupuncture in improving PPD might be attributed to its modulation of these neurotransmitters or estrogen expression. Nonetheless, this hypothesis also necessitates more rigorous validation through high-quality RCTs, given the current limitations in trial quantity and quality.

While acupuncture shows promise as an alternative or adjunct treatment for PPD, caution is warranted in interpreting current favorable findings due to several reliability concerns. First, a prior systematic review noted that the dropout rate in acupuncture RCTs was approximately 12%.[54] However, our SR/MA found no dropouts in 10 trials (76.9%), which recruited patients from outpatient or combined outpatient and inpatient settings. The absence of dropouts in outpatient cases is unusual and may be linked to the fact that all trials were conducted in China, involving only local women. Previous research has shown that in acupuncture RCTs, participants' confidence in and expectations of acupuncture enhance their adherence to the trial.[55] Influenced by traditional Chinese culture, the local population holds a strong belief in TCM, which in China is not commonly

regarded as CAM but rather as a parallel system to modern biomedicine.[56] This may account for the lower dropout rates compared to RCTs conducted elsewhere. Second, an intriguing observation was made: there was no significant difference between Acu and PAcu in reducing EPDS and HAM-D scores. Similarly, AcuPsy did not significantly differ from PAcuPsy in reducing scores on these scales. Cumulative ranking plots indicated that PAcuPsy was ranked higher than AcuPsy. However, these results were based on two RCTs with very small sample sizes (one with 20 participants and the other with 42), thus lacking robustness. This issue however is noteworthy as a previous RCT from our team also showed no significant difference between acupuncture and placebo-acupuncture in reducing HAM-D scores in women with perimenopausal depression.[57] Hence, well-designed RCTs with larger samples are necessary to determine whether acupuncture's antidepressant effect is simply a nonspecific (placebo) response. Third, in the reviewed RCTs, the baseline severity of depression among patients varied considerably, which impedes determining the efficacy of acupuncture for different levels of PPD. Hence, it is recommended that future trials standardize the severity of depression among recruited participants to ensure more consistent and comparable results. Such design would also help to more clearly delineate the specific applicability of acupuncture in PPD patients. Fourth, most included RCTs had methodological limitations, leading to potential ROB. To enhance evidence quality, optimizing RCT designs is essential. Defining inclusion criteria based on both conventional and traditional TCM diagnostic standards can ensure group homogeneity, thereby improving internal and model validity. Standardizing diagnostic parameters and therapeutic approaches addresses practitioner variability while allowing for treatment flexibility, thus enhancing both internal and external validity. The use of placebo controls, blinding, and allocation concealment further mitigates bias. Adhering to STRICTA guidelines will standardize study protocols and reporting, including ensuring clear descriptions of acupuncture techniques.[58] Finally, six RCTs reviewed used HAM-D as the sole tool for screening and quantifying depression.[31–33,45,59,60] While, the committee opinion on screening for depression during and after pregnancy developed by the American Congress of Obstetricians and Gynecologists (ACOG) lists seven different scales/questionnaires,[61] which do not include HAM-D. This discrepancy raises concerns about potential bias in the results of these six RCTs due to the tool's limited sensitivity. Although other reviewed RCTs employed EPDS and/or SDS, these tools are also suboptimal choices. Among the ACOG-listed tools, PDSS demonstrates superior sensitivity (91–94%) and specificity (72–98%).[61] Future acupuncture studies on PPD should consider using PDSS as the primary outcome measure.

Conclusions

This study, employing network meta-analysis, is the first to quantify and rank the efficacy of acupuncture, conventional PPD treatments, and their combined use. By addressing this gap in the literature, it provides valuable insights for guiding future research and clinical decision-making. The results indicate that acupuncture is comparably effective to antidepressants or psychotherapy in ameliorating PPD. Additionally, both acupuncture and psychotherapy demonstrate concurrent improvements in patients' comorbid anxiety symptoms. When acupuncture is combined with antidepressants, it not only enhances therapeutic efficacy but also mitigates AEs, particularly gastrointestinal discomforts. Likewise, the amalgamation of acupuncture with psychotherapy amplifies treatment outcomes, with efficacy on par with acupuncture combined with antidepressants, yet notably safer. Although the rankings indicate that acupuncture combined with psychotherapy presents as a promising and preferable approach for PPD, the credibility of this evidence is significantly weakened by the limited number and poor quality of the trials included. Furthermore, the determination of whether acupuncture's antidepressive effect is merely a placebo response is inconclusive. To delve deeper into the current findings and improve the quality of evidence, rigorously-designed RCTs are imperative, involving larger sample sizes, effective allocation concealment, blinding of participants and assessors, and the adoption of a more sensitive measurement tool, such as the PDSS recommended by ACOG. These steps will also help determine whether acupuncture's effects are specific or non-specific. This study only addresses the short-term effects of acupuncture, highlighting the need for extended follow-up to evaluate its medium- and long-term efficacy. The disparity in efficacy between acupuncture and IPT or CBT, as well as their combined effects, remains ambiguous. Given the safety advantages of psychotherapy, exploring the combination of acupuncture with IPT or CBT may reduce antidepressant overuse and offer an alternative for patients intolerant to these medications. However, the existing evidence is not strong enough to conclusively support the use of acupuncture as an alternative or adjunct to conventional treatment for managing PPD.

Abbreviations

ACOG, The American Congress of Obstetricians and Gynecologists; AE(s), Adverse Event(s); CAM, Complementary and Alternative Medicine; *CI*, Confidence Interval; CINeMA, Confidence-In-Network-Meta-Analysis; EPDS, Edinburgh Postnatal Depression Scale; HAM-$D_{17/24}$, 17/24-item Hamilton Depression Scale; MCMC, Markov Chain Monte Carlo; *MD*, Mean Difference; *OR*, Odds Ratio; PPD, Postpartum Depression; PDSS, Postpartum Depression Screening Scale; PSRF, Potential Scale Reduction Factor; RCT(s), Randomized Controlled Trials; RoB, Risk of Bias; RoB 2.0 tool, Revised Cochrane Risk-of-Bias Tool for Randomized Trials; SAS, Self-rating Anxiety Scale; SDS, Self-rating Depression Scale; *SMD*, Standardized Mean Difference; SNRIs, Serotonin/Norepinephrine Reuptake Inhibitors; SSRIs, Selective Serotonin Reuptake Inhibitors; SR/MA(s), Systematic Review and Meta-Analysis; SUCRA, Surface Under the Cumulative RAnking curve; TCM, Traditional Chinese Medicine; TNA, Traditional Needle Acupuncture; Acu, Acupuncture; PAcu, Placebo-acupuncture; Anti, Antidepressant; Psy, Psychotherapy; AcuAnti, Acupuncture combined with Antidepressant; AcuPsy, Acupuncture combined with Psychotherapy; PAcuPsy, Placebo-acupuncture combined with Psychotherapy.

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Disclosure

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