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Comparative Efficacy of Interventions for Postpartum Depression: A Frequentist Network Meta-analysis

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Abstract: *Objective*: To compare the efficacy of different interventions for postpartum depression and to identify the intervention with the highest probability of benefit. *Methods*: Randomized controlled trials were identified through searches of PubMed, Embase, and Web of Science up to May 2023. The change in depression scores from baseline to post-intervention was extracted and synthesized as standardized mean differences (SMDs) using a frequentist network meta-analysis. Treatments were ranked according to the surface under the cumulative ranking curve (SUCRA). *Results*: Eight randomized controlled trials involving 641 participants were included. According to the SUCRA rankings, cognitive behavioral therapy (CBT) had the highest probability of being the most effective intervention. CBT did not significantly differ from fluoxetine (SMD 0.19, 95% CI -1.14 to 1.51), saffron (SMD 0.30, 95% CI -0.93 to 1.53), or sertraline (SMD 0.61, 95% CI -0.13 to 1.36), but it was superior to brexanolone (SMD 1.60, 95% CI 0.50 to 2.70) and zuranolone (SMD 1.72, 95% CI 0.61 to 2.84). Brexanolone and zuranolone did not significantly differ from each other (SMD 0.12, 95% CI -0.30 to 0.54), although both were superior to placebo. *Conclusion*: With the exception of estradiol, all interventions showed greater efficacy than placebo in reducing depressive symptoms. The ranking results suggest that CBT, fluoxetine, saffron, and sertraline may be among the more effective options for postpartum depression; however, these findings should be interpreted cautiously because of the limited number of studies and the scarcity of direct head-to-head comparisons.

Keywords: Postpartum depression; Network meta-analysis; Cognitive behavioral therapy; Antidepressants; Randomized controlled trials

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1. Introduction

Postpartum depression (PPD) is a common and clinically important psychiatric disorder that can have short- and long-term adverse effects on mothers, infants, and families [1]. In the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5), postpartum depression is generally conceptualized as a major depressive episode

with peripartum onset, with symptoms emerging during pregnancy or within 4 weeks after delivery. Typical manifestations include depressed mood, anhedonia, irritability, appetite or weight changes, sleep disturbance, hopelessness, low self-esteem, fatigue, emotional distress, excessive self-blame or feelings of worthlessness, impaired concentration, indecisiveness, and, in some cases, suicidal ideation. Similar to depression in the general population, PPD can substantially impair emotional functioning and work capacity [1]. Globally, the prevalence of depressive symptoms among postpartum women is estimated to be approximately 20% [1–2]. Although DSM-5 provides a clear diagnostic framework, clinical studies suggest that PPD remains underrecognized and undertreated in routine practice [3–4]. In some women, symptoms remit spontaneously within several weeks, whereas in others they may persist for 1 to 2 years [5]. Available treatments for depression include psychotherapy, selective serotonin reuptake inhibitors (SSRIs), non-SSRI pharmacotherapy, and somatic interventions, and many of these approaches are effective for major depression in general [6]. However, evidence specific to PPD indicates that SSRIs may not perform as consistently in this population [6]. In recent years, several emerging agents have also been evaluated for PPD [7–8]. Nonetheless, the optimal treatment strategy for PPD remains uncertain. Therefore, this study aimed to compare the efficacy of different interventions for PPD using a network meta-analysis of comparative studies.

2. Materials and methods

For continuous outcomes, the change in depression scores from baseline to the study endpoint was used as the primary outcome measure. When the same rating scale was used across studies, the mean difference (MD) from baseline to endpoint was considered; when different scales were used, the standardized mean difference (SMD) was adopted for pooled analysis [9]. For dichotomous outcomes, the risk ratio (RR) was used as the summary effect measure. Data synthesis was performed in Stata 17 using a frequentist framework.

2.1. Search strategy

The research question was developed according to the PICOS framework (participants, interventions, comparisons, outcomes, and study design), and a structured search strategy was designed to compare the efficacy of different interventions for postpartum depression. PubMed, Embase, and Web of Science were searched from database inception to May 2023. Eligible studies were randomized controlled trials comparing any 2 active interventions or comparing an active intervention with a placebo, including SSRIs, non-SSRIs, psychotherapy, estrogen, and traditional Chinese medicine. Both free-text terms and controlled vocabulary were used. The detailed search strategies were as follows:

2.1.1. PubMed search strategy

(Depression, Postpartum OR Postnatal Depression OR Depression, Postnatal OR Post-Partum Depression OR Depression, Post-Partum OR Post Partum Depression OR Postpartum Depression OR Post-Natal Depression OR Depression, Post-Natal OR Post Natal Depression OR Postnatal Dysphoria OR Dysphoria, Postnatal OR Post-Partum Dysphoria OR Dysphoria, Post-Partum OR Post Partum Dysphoria OR Postpartum Dysphoria OR Dysphoria, Postpartum OR Post-Natal Dysphoria OR Dysphoria, Post-Natal OR Post Natal Dysphoria) AND (drug therapy OR Sertraline OR fluoxetine OR Duloxetine OR Escitalopram OR Zuranolone OR Brexanolone OR Zulresso OR saffron OR Cognitive behavioral therapy OR psychotherapy OR estradiol OR estrogen). Filters: Clinical Trial.

2.1.2. Embase search strategy

#1 = 'baby blues' OR 'depression, postpartum' OR 'depression, puerperium' OR 'maternal depression' OR 'maternity blues' OR 'post partum depression' OR 'post-natal depression' OR 'postnatal blues' OR 'postpartum depression' OR 'puerperal depression' OR 'puerperium depression' OR 'third day blues' OR 'postnatal depression'

#2 = 'drug therapy' OR 'Sertraline' OR 'fluoxetine' OR 'Duloxetine' OR 'Escitalopram' OR 'Zuranolone' OR 'Brexanolone' OR 'Zulresso' OR 'saffron' OR 'Cognitive behavioral therapy' OR 'psychotherapy' OR 'estradiol' OR 'estrogen'

#1 AND #2 AND 'clinical trial'/de

2.1.3. Web of Science search strategy

(TS=(Depression, Postpartum OR Postnatal Depression OR Depression, Postnatal OR Post-Partum Depression OR Depression, Post-Partum OR Post Partum Depression OR Postpartum Depression OR Post-Natal Depression OR Post Natal Depression OR Postnatal Dysphoria OR Dysphoria, Postnatal OR Post-Partum Dysphoria OR Post Partum Dysphoria OR Postpartum Dysphoria OR Dysphoria, Postpartum OR Post-Natal Dysphoria OR Dysphoria, Post-Natal OR Post Natal Dysphoria)) AND TS=(drug therapy OR Sertraline OR fluoxetine OR Duloxetine OR Escitalopram OR Zuranolone OR Brexanolone OR Zulresso OR saffron OR Cognitive behavioral therapy OR psychotherapy OR estradiol OR estrogen) AND clinical trials.

2.2. Inclusion criteria

(1) Original studies were randomized controlled trials comparing one drug with a placebo, psychotherapy, or another pharmacological treatment.

(2) Participants met DSM-5 diagnostic criteria for postpartum depression.

(3) Studies reported mean depression scores before and after treatment, or the mean change in depression scores from baseline to the endpoint within each group.

2.3. Exclusion criteria

(1) Participants had other major physical illnesses.

(2) Participants had other psychiatric disorders meeting DSM-5 diagnostic criteria.

(3) Studies with a dropout rate greater than 50% at outcome assessment were excluded [10].

(4) Conference abstracts, editorials, reviews, guidelines, and letters were excluded.

(5) Full-text articles were unavailable.

2.4. Data extraction and quality assessment

Two investigators independently screened the literature according to the predefined criteria, evaluated study quality, and extracted data from the included studies. Disagreements were resolved through discussion with additional investigators. Extracted data included publication year, study region, authors, study design, intervention, baseline mean depression score, and post-intervention mean depression score. Study quality was assessed using the Cochrane risk-of-bias tool for randomized controlled trials, which includes the following domains: (1) random sequence generation; (2) allocation concealment; (3) blinding of study personnel; (4) blinding of outcome assessment; (5) completeness of outcome data; (6) selective reporting; and (7) other potential sources of bias [11].

2.5. Data synthesis and analysis

A frequentist network meta-analysis model was used to compare the efficacy of all interventions. Changes in depression scores from baseline to post-intervention were converted to standardized mean differences (SMDs) using Cohen's d method. Study weights were calculated using the inverse-variance method, and studies with the same comparisons were pooled accordingly. Because both direct and indirect evidence were incorporated, inconsistency was assessed using the inconsistency assumption and a global inconsistency test when the network structure permitted. Interventions were ranked according to SUCRA values: a larger SUCRA value indicated a higher probability that the intervention was the most effective, whereas a smaller value indicated a lower probability of being the best option. Heterogeneity across the included randomized controlled trials was assessed using Cochran's Q test and the I^2 statistic, with 0%–40% indicating low heterogeneity, 30%–60% moderate heterogeneity, 50%–90% substantial heterogeneity, and 75%.

3. Results

3.1. Literature search results

A total of 1,433 records were identified from Web of Science, PubMed, and Embase. After duplicate removal, 1,020 articles remained. Most records were excluded after title and abstract screening, primarily because they were not randomized controlled trials, leaving 25 articles for full-text review. Of these, 7 were excluded because the full text could not be obtained, leaving 18 studies for full-text assessment. Among these 18 studies, 1 was excluded because the dropout rate at outcome assessment exceeded 50%, and 9 were excluded because the required baseline or outcome data were unavailable. Ultimately, 8 studies reporting complete baseline and outcome depression scores, or changes in depression scores from baseline to outcome, were included. The detailed study-selection process is shown in **Figure 1**.

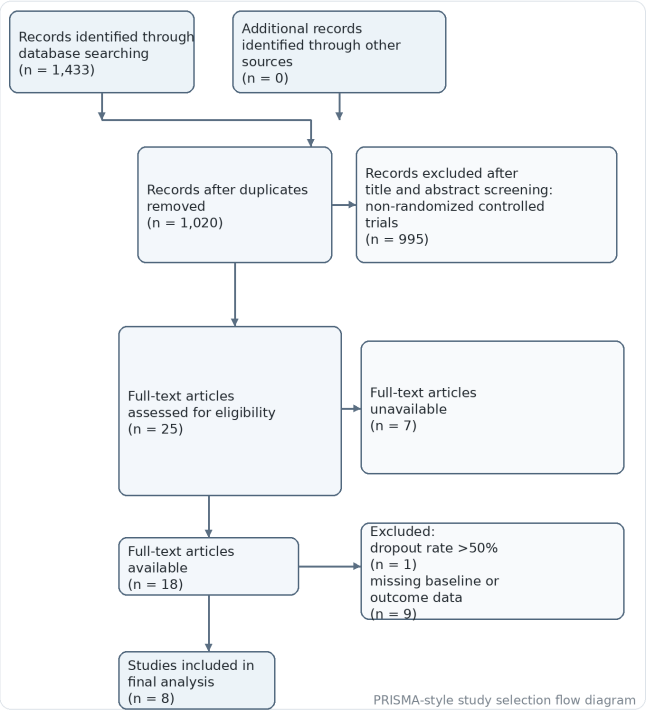

Figure 1. Flow chart of study selection

3.2. Quality assessment of included studies

Figure 2 presents the quality assessment of the included studies. Of the 8 studies included in the network meta-analysis, 7 were judged to have a low risk of bias, whereas 1 study was judged to have a moderate risk of bias because its allocation-concealment strategy was not clearly described [7–8, 12–17]. **Figure 3** shows the assessment of publication bias. The funnel plot did not show obvious asymmetry, suggesting no apparent publication bias among the included studies.

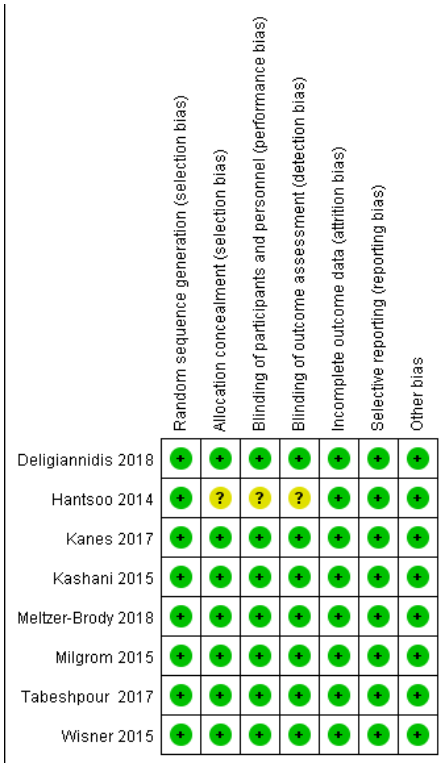

Figure 2. Risk-of-bias assessment of the included studies

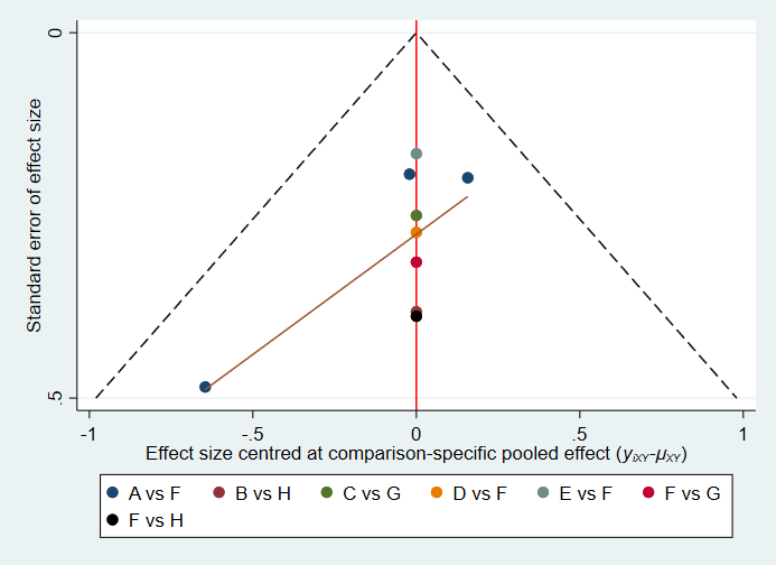

Figure 3. Publication bias of the included studies

3.3. Characteristics of included studies

The demographic and clinical characteristics of the included studies are summarized in **Figure 4**. Sample sizes ranged from 21 to 150 participants, with a total sample of 641, including 259 participants in the placebo group. Across all studies, there were 15 participants in the CBT group, 26 in the estradiol group, 76 in the zuranolone group, 62 in the saffron group, 32 in the fluoxetine group, 31 in the sertraline group, and 140 in the brexanolone group. Across the 8 studies, the mean age of participants ranged from 26.2 to 29.5 years. Six studies were conducted in the United States, 1 in Iran, and 1 in Australia. Five studies used the 17-item Hamilton Depression Rating Scale (HAMD-17) to assess depressive symptoms, 2 used the Beck Depression Inventory-II (BDI-II), and 1 used the Structured Interview Guide for the Hamilton Depression Rating Scale, Atypical Depression Symptoms Version (SIGH-ADS). Intervention duration ranged from 60 hours to 12 weeks.

Study	Year	Country	Intervention	N	Scale	Baseline depression score	Duration	Mean age
Deligiannidis	2018	USA	zuranolone vs placebo	76/74	HAMD-17	28.4 ± 2.0 vs 28.8 ± 2.0	15 d	29.3 ± 5.4 vs 27.4 ± 5.3
Wisner	2015	USA	TE vs placebo	26/29	SIGH-ADS	23.3 ± 4.9 vs 25.1 ± 4.9	8 w	26.2 ± 6.0 vs 27.3 ± 5.4
Kashani	2015	Iran	saffron vs fluoxetine	32/32	HAMD-17	16.53 ± 1.48 vs 16.65 ± 1.12	6 w	29.2 ± 7.7 vs 32.1 ± 5.0
Tabeshpour	2017	Iran	saffron vs placebo	30/30	BDI-II	20.0 ± 5.7 vs 19.7 ± 5.3	8 w	28.1 ± 5.3 vs 28.0 ± 7.4
Hantsoo	2014	USA	sertraline vs placebo	17/19	HAMD-17	20.6 ± 2.8 vs 23.2 ± 3.9	6 w	29.6 ± 4.0 vs 31.7 ± 3.7
Kanes	2017	USA	brexanolone vs placebo	10/11	HAMD-17	28.1 ± 1.53 vs 28.8 ± 4.17	60 h	27.4 ± 5.3 vs 28.8 ± 4.6
Meltzer-Brody	2018	USA	brexanolone vs placebo	79/43	HAMD-17	28.75 ± 2.6 vs 28.6 ± 2.5	60 h	27.5 ± 6.0 vs 27.0 ± 6.0
Meltzer-Brody	2018	USA	brexanolone vs placebo	51/53	HAMD-17	22.6 ± 1.6 vs 22.7 ± 1.6	60 h	28.4 ± 6.1 vs 27.4 ± 5.9
Milgrom	2015	Australia	sertraline vs CBT	14/15	BDI-II	29.21 ± 7.07 vs 27.53 ± 9.75	12 w	NR

Figure 4. Baseline characteristics of the included studies and participants

3.4. Comparison of efficacy among different interventions

Using the within-group change in mean depression scores from baseline to post-intervention as the primary outcome, a network plot was generated (**Figure 5**). The network consisted of 8 nodes. Most studies used a placebo as the control group; therefore, direct comparisons between active interventions were limited, and the overall network did not form a closed loop. Consequently, inconsistency testing for the entire network structure could not be performed. The SUCRA values are shown in **Figure 6**. CBT had the highest probability of being the most effective intervention for postpartum depression, whereas estradiol had the lowest probability of being the best treatment. A league table was used to present the network meta-analysis results. All interventions except estradiol were statistically superior to placebo. The SMDs ranged from 0.46 (95% CI 0.13 to 0.78) to 2.18 (95% CI 1.11 to 3.25). Estradiol did not significantly differ from placebo (SMD 0.42, 95% CI -0.12 to 0.95). There were also no statistically significant differences between CBT and fluoxetine (SMD 0.19, 95% CI -1.14 to 1.51), saffron (SMD 0.30, 95% CI -0.93 to 1.53), or sertraline (SMD 0.61, 95% CI -0.13 to 1.36).

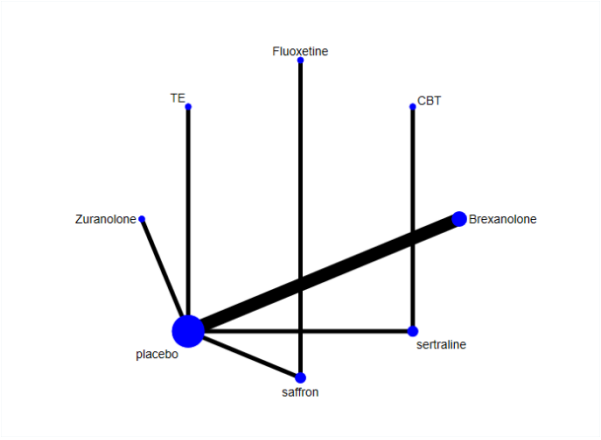

Figure 5. Network plot of changes in depression scores across studies

Node size represents the number of participants receiving each intervention; larger nodes indicate more participants. The thickness of the line between two nodes represents the number of studies directly comparing the two interventions; thicker lines indicate more studies. CBT, cognitive behavioral therapy; brexanolone; sertraline; saffron; placebo; zuranolone; TE, estradiol; fluoxetine.

Treatment	SUCRA	PrBest	MeanRank
Brexanolone	38.9	0.0	5.3
CBT	89.0	57.2	1.8
Fluoxetine	83.6	31.5	2.1
TE	0.9	0.0	7.9
Zuranolone	32.7	0.0	5.7
placebo	13.4	0.0	7.1
saffron	77.0	10.3	2.6
sertraline	64.5	1.0	3.5

Figure 6. Surface under the cumulative ranking curve (SUCRA) values calculated after pooling the included studies

A larger value indicates a higher probability that the intervention is the best treatment.

4. Discussion

This study is the first to compare the efficacy of a range of different interventions for postpartum depression. By comparing changes in depression scores from baseline to outcome among patients with postpartum depression, and because the included studies used different measurement scales, the study pooled the findings using standardized mean differences as the effect size. The final results showed that all interventions except estradiol were superior to placebo, with statistically significant differences. In terms of reducing depression scores before and after intervention, CBT did not differ significantly from fluoxetine, saffron, or sertraline; however, according to the SUCRA ranking, CBT was the intervention most likely to be superior to the others. Previous meta-analyses of CBT for postpartum depression have also suggested that CBT has good efficacy in reducing postpartum depression compared with placebo, which is consistent with the findings [18–19].

Among previously used treatment strategies for postpartum depression, psychosocial treatment delivered by mental health professionals has been recommended for mild postpartum depression, whereas standardized psychotherapy has been recommended for patients with moderate to severe depressive disorder [20–21]. In the present study, CBT appeared to have a better effect than pharmacological interventions. This may be because the baseline severity of depression differed across the included studies during the analytical process.

This study also has several limitations. First, during the network meta-analysis, direct comparisons between many interventions were lacking; therefore, the findings were based primarily on indirect comparisons. Second, the sample sizes for some intervention comparisons were small, which may have influenced the results. Third, intervention duration varied across studies, ranging from 48 hours to 12 weeks, which may also have affected the final assessment of efficacy.

5. Conclusion

This study systematically compared the effects of different interventions for postpartum depression using a network meta-analysis approach. Compared with placebo, all interventions except estradiol improved depressive

symptoms in patients with postpartum depression to varying degrees, among which cognitive behavioral therapy, fluoxetine, saffron, and sertraline showed relatively favorable effects. Although the differences between cognitive behavioral therapy and fluoxetine, saffron, and sertraline did not reach statistical significance, the SUCRA rankings indicated that cognitive behavioral therapy had a relatively high probability of being the optimal intervention, suggesting that it may be a preferred option for the treatment of postpartum depression. Nevertheless, the conclusions of this study should be interpreted with caution because of the small sample sizes of the included studies and the limited direct comparative evidence between some interventions. Further large-sample, multicenter, high-quality randomized controlled trials are still needed to verify the differences in efficacy among interventions and their applicable populations, thereby providing stronger evidence for the clinical management and decision-making of postpartum depression.

Disclosure statement

The authors declare no conflict of interest.

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