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Efficacy of esketamine for perinatal depression: a systematic review and meta-analysis*

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Review

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*This article has been updated since it was originally published. A notice detailing this has been published.

Abstract

Objective. Postpartum depression (PPD), now referred to as perinatal depression, is a prevalent and debilitating mood disorder that reduces health-related quality of life (HRQoL) and psychosocial functioning. Esketamine, which is efficacious in adults with treatment-resistant depression and individuals with depression and suicidality, is also analgesic in pain management during childbirth labour. Herein, we investigate the efficacy of prophylactic esketamine in reducing the incidence of PPD.

Methods. We performed a systematic review (i.e., PubMed, Scopus, and Ovid databases; inception to January 22, 2024) of randomized controlled trials that investigated the use of esketamine for PPD. We delimited our search to studies that prespecified the prevention of PPD with esketamine as the primary outcome. A meta-analysis was performed on PPD incidence rates using a random effects model.

Results. Our analysis consisted of seven studies that met our eligibility criteria. We found that esketamine was significantly associated with a decreased incidence of PPD diagnosis within one week of childbirth (OR = 0.30, 95% CI = [0.15, 0.60], p = 0.0047). We also observed that esketamine was significantly associated with a decreased incidence of PPD diagnosis between 4 to 6 weeks post-delivery (OR = 0.33, 95% CI = [0.18, 0.59], p = 0.0034).

Conclusion. Our results indicate that esketamine may have preventive antidepressant effects during the postpartum period. The aforementioned points have both mechanistic and clinically meaningful implications for the treatment of PPD.

Introduction

Perinatal depression, formerly known as postpartum depression (PPD), is a mood disorder defined by the Diagnostic and Statistical Manual of Mental Disorders Fifth Edition Text Revision (DSM-5-TR) as a major depressive episode that occurs either at the start of pregnancy or within 4 weeks of childbirth.[1] Clinically, the onset of PPD is variable, with most cases presenting with symptoms up to one year following childbirth.[2] PPD is reported in approximately 10% of pregnant women, where many of the symptoms overlap with major depressive disorder (MDD).[2] Some of the most commonly reported symptoms include, but are not limited to, depressed mood, anhedonia, insomnia, guilt, and suicidal ideation – all of which can be debilitating and significantly interfere with psychosocial functioning and health-related quality of life (HRQoL).[1] However, many of these symptoms also overlap with "baby blues," which is an emotional condition that lasts for approximately 2 weeks but does not require pharmacotherapy.[3] The frequent occurrence of baby blues and its overlapping symptom presentation with PPD contributes to missed and/or delayed diagnosis of PPD.[4] The aforementioned challenge is further exacerbated by the lack of screening methods and predictive risk factors for PPD.[4,5] The foregoing points pose a question of whether prophylactic pharmacotherapy may be effective in reducing the risk for developing PPD.

Standard of care treatments for PPD consists of selective serotonin reuptake inhibitors (SSRIs) (e.g., sertraline and fluoxetine) and selective norepinephrine reuptake inhibitors (SNRIs) (e.g., venlafaxine).[4] Notably, extant literature has reported conventional oral antidepressants may compromise newborn safety, particularly regarding an increased risk of

congenital heart defects, which supports the impetus to establish new treatment options for PPD.[6] Recently, brexanolone and zuranolone have been FDA-approved as oral antidepressants for PPD, with sustained effects for up to 45 days.[7,8] One of the main advantages of zuranolone is its rapid-acting antidepressant effects that occur within 24 hours of administration.[8] Other promising treatments include neuromodulation, such as repetitive transcranial magnetic stimulation (rTMS).[9] rTMS has been extensively investigated in persons with MDD and has shown promising preliminary efficacy and safety in persons with PPD.[9,10]

Esketamine is currently shown to be effective for treatment-resistant depression (TRD) and depression with imminent risk of suicidality.[11] Additionally, intravenous (IV) esketamine has also been proposed as another prophylactic treatment for PPD. Similarly, sub-anesthetic IV racemic ketamine has been investigated for PPD for its rapid antidepressant and analgesic effects.[12-14] Extant literature reported that IV esketamine not only provides a greater anesthetic effect than racemic ketamine, but has a more favourable safety and tolerability profile.[15] In addition to the replicated evidence that supports esketamine antidepressant therapy for MDD and TRD, esketamine has demonstrated efficacy in both real-world data and in more at-risk populations.[8,16-18] The foregoing point provides the impetus to investigate the efficacy of esketamine for the prevention of PPD. Previous reviews have evaluated the putative preventive effects of esketamine in PPD.[13,19] Those reviews however included studies that did not pre-specify the prevention of PPD as their primary outcome. Hence, we aim to evaluate whether esketamine has preventive effects on PPD, confining our review to those studies that pre-specify the prevention of PPD. Herein, we performed a systematic review and meta-analysis of published clinical trials to synthesize the efficacy of prophylactic esketamine for PPD.

Methods

Search string and strategy

This systematic review and meta-analysis was conducted in accordance with the 2020 Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines.[20] A systematic literature search was conducted on PubMed, Scopus, and Ovid (MedLine, Embase, PsychINFO) databases from inception to January 22, 2024. Additional publications were retrieved through manual reference checking. The described databases were searched using the following search string: ("Esketamine" OR "S-ketamine") AND ("Postpartum depression" OR "Post-partum depression" OR "PPD"). No search filters, restrictions, or additional limits were applied to any of the searches within the included databases. The articles were not restricted by publication date, location, or language.

Eligibility criteria

The studies retrieved from the search were included if they met the following inclusion criteria: 1) randomized controlled trial (RCT), 2) must have a pre-specified objective to investigate prophylactic esketamine for postpartum depression, 3) full-text availability, and 4) must be published in English. Studies were excluded if the study met at least one of the exclusion criteria: 1) non-RCT studies, 2) did not investigate an outcome of interest, 3) investigated racemic ketamine, and 4) no full-text availability. The articles were not restricted by publication date, location, or language.

Study selection and data extraction

Using the Covidence platform, two reviewers independently screened and reviewed the retrieved studies against the eligibility criteria (S.W. and G.H.L.). Any conflicts in decisions were resolved through consensus. The search yielded a total of 317 studies. Following the removal of 117 duplicates, 200 studies were screened by their titles and abstracts. Subsequently, 13 studies were assessed for full-text eligibility. One study was manually removed as it reported a duplicate sample population and five studies were removed for not pre-specifying an objective to investigate esketamine treatment for PPD. Therefore, a total of seven studies were included in our meta-analysis ($n = 7$) (Figure 1).

Data were also extracted by two reviewers (S.W. and G.H.L.) independently. The data to be extracted was established a priori and conducted using a piloted data extraction table (Table 1). Relevant data included: 1) sample size, age of participants, treatment groups and respective doses, incidence of PPD of each treatment group, time point at which outcome was measured, and Edinburgh Postnatal Depression Scale (EPDS) scores for each treatment group (if available).

Risk of bias and methodological quality assessment

To assess the included studies for potential risk of bias, two reviewers (S.W. and G.H.L) used the revised Cochrane risk of bias tool for randomized trials (RoB2) tool.[21] In addition, publication bias was assessed using funnel plots. To assess the overall certainty and quality of the body of evidence, a Grades of Recommendation, Assessment, Development and Evaluation Working Group (GRADE) rating was assigned to each included study.

Statistical analysis

All statistical analyses were conducted using RStudio 2023.09.1 +494 "Desert Sunflower" Release. In order to investigate the efficacy of prophylactic esketamine treatment for PPD, we calculated odds ratios (OR) based on the incidence rates of PPD between treatment groups at different time points. Component studies ascertained PPD through administration of the EPDS. ORs were calculated for PPD incidence rates that were measured within 1 week postpartum and between 4 to 6 weeks postpartum. The calculated ORs were pooled using a random effects model and weight using an inverse variance method. ORs and corresponding 95% confidence intervals (95% CIs) were calculated using the 'meta' package.[23] Heterogeneity between the included studies were calculated using Higgins & Thompsons I^2 statistic.[22] The I^2 value is a statistical measure that calculates the variability in effect size estimates that is due to between-study differences rather than sampling error.[19] Forest plots were also constructed on R Studio using the *'meta'* package.[23]

Results

Sample study characteristics

Across the seven studies, a total of 1,448 participants were included in our meta-analysis and sample sizes ranged from 117 to 319 participants (Table 1).[15,24-29] While studies were not restricted by the route of administration for esketamine treatment, only studies investigating the efficacy of intravenous esketamine for PPD were found. Esketamine was used as an adjunctive to standard patient-controlled intravenous analgesia (PCIA) pump, which typically

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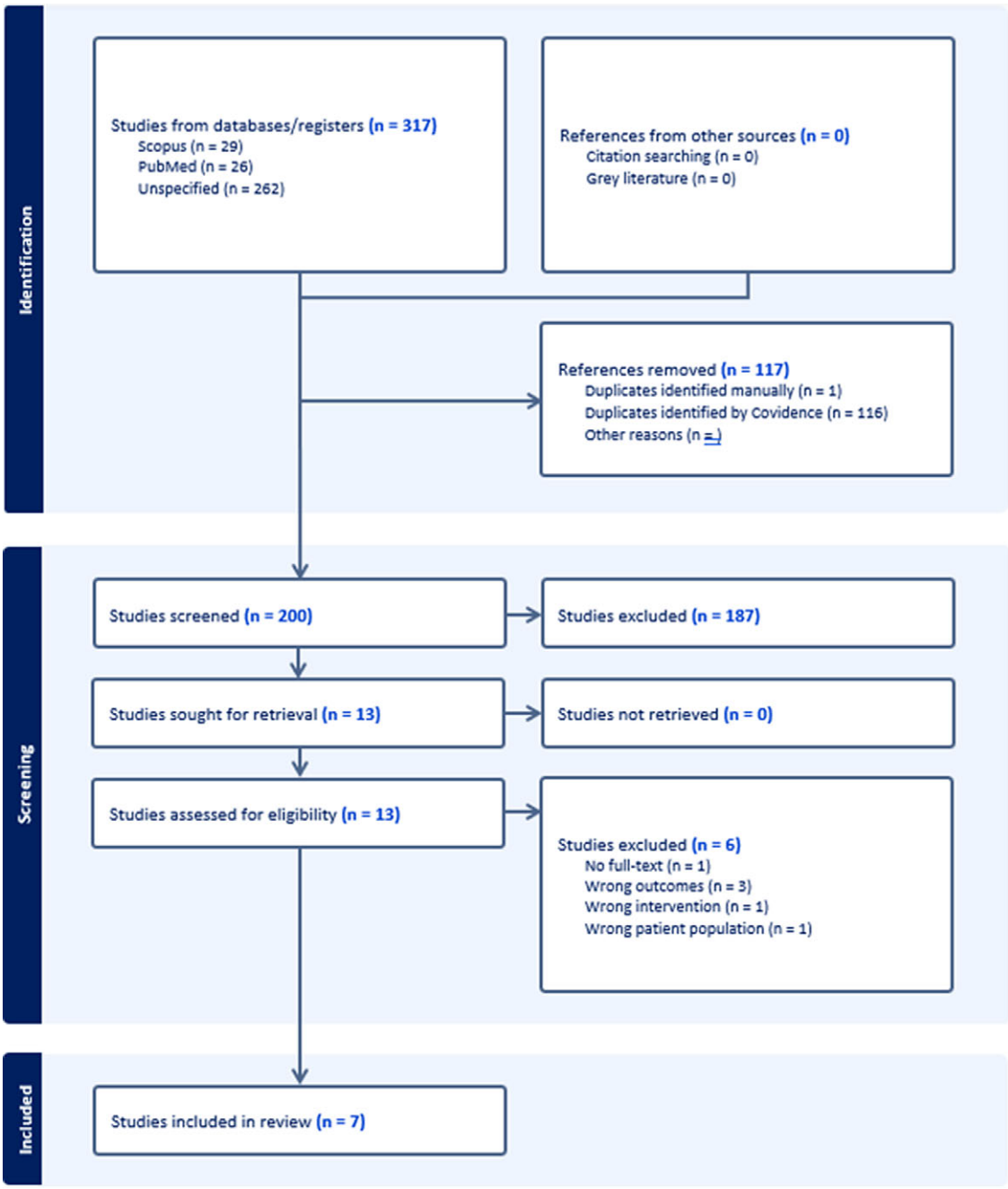

Figure 1. PRISMA Flow Diagram of the Study Selection Process

consists of sufentanil and tropisetron. Esketamine doses ranged between 0.2 to 0.5 mg/kg, except for the study conducted by Liu et al. (2023) and Yang et al. (2023), where esketamine-treated participants were given an initial dose of 0.25 mg/kg of esketamine followed by 1-2 mg/kg esketamine administered through the PCIA.[25,29] Control groups consisted of participants who were given PCIA and volume-matched saline. All of the studies ascertained PPD status through the administration of the EPDS. Studies were not restricted by the scales or metrics utilized; however, the included studies did not assess depressive symptom severity using any other depressive symptom metric or scale. Further details for the individual studies are outlined in Table 1.

Risk of bias results

From the seven studies, all of the studies obtained a low risk of bias result (Table 2). Therefore, all of the studies were included in this meta-analysis. Notably, all of the studies had some concerns for a potential risk of bias regarding the second domain, performance bias. As the studies used saline as the control, participants may be functionally unblinded by potential dissociative effects. While the concern for potential bias was consistent across all of the studies, it should be noted that the esketamine-treated participants may have been functionally unblinded by potential dissociative effects as the control group only received saline.

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Table 1. Characteristics of Studies Obtained from Search

Authors	Sample Size (Per protocol)	Sample Age, years (sd)	Intervention(s)	Aim(s) and Objective(s)	PPD Incidence Rates*	PPD Symptom Severity*
Han et al. (2022)	275 total participants 122 esketamine-treated participants 153 placebo treated participants	Esketamine: 31.64 (3.93) Control: 31.85 (4.16)	Treatment: sufentanil 2μg/kg + tropisetron 10mg + esketamine 0.5 mg/kg Control: sufentanil 2μg/kg + tropisetron 10mg	Investigating the efficacy of analgesia and esketamine adjuvant therapy to prevent PPD in women that underwent cesarean section.	Day 3– 17.6% in the control group vs 8.2% in the esketamine group Day 14 – 24.2% in the control group and 9.8% in the esketamine group	Baseline - average score was 6.54 (2.35) in the esketamine group and 6.72 (2.25) in the control group. Day 3 - average score was 7.65 (3.14) in the esketamine group and 6.00 (2.47) in the control group. Day 14 - average score was 7.62 (3.14) in the esketamine group and 6.38 (2.67) in the control group.
Ling et al. (2023)	117 total participants 58 esketamine-treated participants 59 placebo-treated participants	Esketamine: 28.2 (4.8) Placebo: 27.8 (4.4)	Treatment: Esketamine, 0.2 mg/kg Control: Placebo (saline)	Investigating the efficacy of intravenous esketamine after analgesia for PPD in women that delivered vaginally.	1 week – 3.4% in the esketamine-treated group vs 15.3% in the placebo-treated group 6 weeks – 5.2% in the esketamine-treated group vs 18.6% in the placebo-treated group	N/A
Liu et al. (2023)	123 total participants 62 esketamine-treated participants 61 placebo-treated participants	Esketamine: 30.3 (4.1) Placebo: 29.8 (4.2)	Treatment: Esketamine, 0.25 mg/kg followed by 1.25 mg/kg of esketamine in PCIA Control: Placebo (saline) with PCIA	Investigating the efficacy of perioperative esketamine for prophylactic prevention of PPD in women that underwent cesarean section.	3 days – 6.5% in the esketamine-treated group vs 9.8% in the placebo-treated group 42 days – 8.1% in the esketamine-treated group vs 13.1% in the placebo-treated group 3 months – 10.0% in the esketamine-treated group vs 11.9% in the placebo-treated group 6 months – 7.0% in the esketamine-treated group vs 10.5% in the placebo-treated group	Baseline: Esketamine – 7.0 (95% CI = [4.0, 10.0]); placebo – 6.0 (95% CI = [3.0, 9.0]), p = 0.508 3 days: Esketamine – 6.0 (95% CI = [2.0, 8.0]); placebo – 6.0 (95% CI = [3.0, 9.0]), p = 0.724 42 days: Esketamine – 5.0 (95% CI = [2.0, 8.0]); placebo – 5.5 (95% CI = [3.0, 8.0]), p = 0.825 3 months: Esketamine – 5.0 (95% CI = [1.5, 8.0]); placebo – 5.0 (95% CI = [2.0, 9.0]), p = 0.654 6 months: Esketamine – 4.0 (95% CI = [0.0, 8.0]); placebo – 5.5 (95% CI = [2.0, 9.0]), p = 0.224
Shen et al. (2023)	202 total participants 102 esketamine-treated participants 100 placebo-treated participants	Esketamine: 28.9 (3.9) Placebo: 29.6 (3.9)	Treatment: Esketamine, 0.25 mg/kg Control: Placebo (saline)	Investigating the efficacy of single-dosed IV esketamine for PPD following cesarean section.	Pre-partum: Esketamine – 26 (25.5); placebo – 31 (31.0%) 1 week: Esketamine – 4 (3.9%); placebo – 2 (2.0%) 2 weeks: Esketamine – 2 (2.0%); placebo – 1 (1.0%)	N/A

Table 1. *Continued*

Authors	Sample Size (Per protocol)	Sample Age, years (sd)	Intervention(s)	Aim(s) and Objective(s)	PPD Incidence Rates*	PPD Symptom Severity*
					4 weeks: Esketamine – 2 (2.0%); placebo – 1 (1.0%)	
Wang et al. (2024)	117 total participants 59 esketamine-treated participants 58 placebo-treated participants	Esketamine: 27.6 (4.3) Placebo: 28.1 (3.9)	Treatment: Esketamine, 0.2 mg/kg Control: Placebo (saline)	Investigating the efficacy of esketamine after analgesia on PPD incidence in women that delivered vaginally.	1 week: Esketamine – 2 (3.4%); placebo – 10 (17.2%) 6 weeks: Esketamine – 3 (5.1%); placebo – 12 (20.7%)	N/A
Xu et al. (2024)	319 total participants 159 esketamine-treated participants 160 placebo-treated participants	Esketamine: 30.3 (3.8) Control: 30.9 (3.8)	Treatment: Esketamine, 0.2 mg/kg Control: Placebo (saline)	Investigating the efficacy of pre-treatment of esketamine on PPD incidence rates following cesarean section.	4 days: Esketamine – 13.8%; placebo – 23.1% 42 days: Esketamine – 17%; placebo – 25%	N/A
Yang et al. (2023)	295 total participants 99 2 mg/kg esketamine-treated participants 99 1 mg/kg esketamine-treated participants 97 placebo-treated participants	2 mg/kg esketamine: 31.9 (3.9) 1 mg/kg esketamine: 31.7 (3.8) Placebo: 32.2 (4.2)	Treatment: Initial 0.25 mg/kg infusion followed by 2 mg/kg esketamine or 1 mg/kg esketamine in PCIA Control: Placebo (saline)	Investigating the efficacy of different doses of esketamine for PPD following cesarean section.	7 days: 2 mg/kg esketamine – 7 (7.1%); 1 mg/kg esketamine – 11 (11.1%); placebo – 29 (29.9%) 42 days: 2 mg/kg esketamine – 9 (9.1%); 1 mg/kg esketamine – 14 (14.1%); placebo – 27 (27.8%)	Baseline (median): 2 mg/kg esketamine – 11.0 (95% CI = [10.0, 13.0]); 1 mg/kg esketamine – 12.0 (95% CI = [10.0, 13.0]); placebo – 12.0 (95% CI = [11.0, 13.0]), p > 0.05 7 days (median): 2 mg/kg esketamine – 4.0 (95% CI = [1.0, 7.0]); 1 mg/kg esketamine – 5.0 (95% CI = [2.0, 7.0]); placebo – 7.0 (95% CI = [4.0, 10.0]) 42 days (median): 2 mg/kg esketamine – 3.0 (95% CI = [1.0, 7.0]); 1 mg/kg esketamine – 5.0 (95% CI = [2.0, 8.0]); placebo – 6.0 (95% CI = [3.0, 10.0]), p > 0.05

Abbreviation: CI - Confidence interval; EPDS - Edinburgh Perinatal Depression Scale; N/A - not applicable; PCIA - Patient-controlled intravenous analgesia; PPD - Postpartum depression; SD - Standard deviation.
*Ascertained using the Edinburgh Perinatal Depression Scale.

Table 2. Risk of Bias Assessment Using the Revised Cochrane Risk of Bias Tool for Randomized Trials (RoB2)

	Domain						
Study	1	2	3	4	5	Risk of Bias Judgement	GRADE Quality Assessment
Han et al. (2022)	Low	Some concerns	Some concerns	Low	Low	Low	Moderate
Ling et al. (2023)	Low	Some concerns	Low	Low	Low	Low	Moderate
Liu et al. (2023)	Low	Some concerns	Some concerns	Low	Low	Low	Moderate
Shen et al. (2023)	Low	Some concerns	Some concerns	Low	Low	Low	Moderate
Wang et al. (2024)	Low	Some concerns	Low	Low	Low	Low	Moderate
Xu et al. (2024)	Low	Some concerns	Low	Low	Low	Low	Moderate
Yang et al. (2023)	Low	Some concerns	Low	Low	Low	Low	Moderate

Domains: 1 - Selection bias; 2 - Performance bias; 3 - Detection bias; 4 - Attrition bias; 5 - Reporting bias.

Regarding assessment for potential publication bias, funnel plots were generated (Supplementary Figures 1 and 2). For the odds ratios for PPD incidence rates within 1 week of delivery, there is noticeable asymmetry in the plot, which may be caused by publication bias (Supplementary Figure 1). For Liu et al. (2023) and Shen et al. (2023), both report insignificant effect sizes ($p > 0.05$), with relatively large standard error.[25,26] While Wang et al. (2023) and Ling et al. (2023) also have relatively large standard errors, their effect sizes were determined to be statistically significant ($p < 0.05$).[24,27] For the ORs for PPD incidence rates between 4-6 weeks following delivery, there is also some asymmetry to the plot that could be caused by potential publication bias (Supplementary Figure 2). Again, Liu et al. (2023) and Shen et al. (2023) obtained insignificant effect sizes ($p > 0.05$); however, the OR for Liu et al. (2023) does lay closer to the average effect size with similar standard error to the studies that did have significant effect sizes.[25,26] Based on the GRADE approach, all of the studies were determined to have 'moderate' certainty and quality of evidence. Specifically, while all of the evidence is derived from RCTs, the quality of the evidence was downgraded as risk of PPD was not predetermined in the samples and there were differences in the directionality and magnitude of esketamine's efficacy on PPD prevention. Notwithstanding the foregoing points, the quality of the component study results support the observed effects may be attributable to esketamine treatment.

The efficacy of esketamine for postpartum depression

The efficacy of prophylactic esketamine for PPD was analyzed for incidence rates that were measured within 1-week postpartum and between 4- to 6-weeks postpartum. Beginning with 1-week postpartum, the pooled OR indicates that treatment with esketamine is associated with a statistically significant decrease in the odds of developing PPD within 1 week (OR = 0.30, 95% CI = [0.15, 0.60], p = 0.0047) (Figure 2). There was significant between-study heterogeneity (I^2 = 53%, p = 0.04).

Regarding the studies individually, five out of the seven studies reported a similar trend with significant ORs ranging between 0.11 to 0.44.[15,24,27-29] Contrastingly, Liu et al. (2023) and Shen et al. (2023) did not report statistically significant ORs (OR = 0.60, 95% CI = [0.16, 2.27]; OR = 2.04, 95% CI = [0.37, 11.42], respectively).[25,26]

At the 4- to 6-week timepoint, the pooled OR also indicates that prophylactic esketamine treatment may be associated with decreased odds of developing PPD (OR = 0.33, 95% CI = [0.18, 0.59], p = 0.0034) (Figure 3). Notably, the between-study heterogeneity was not statistically significant (I^2 = 33%, p = 0.18). With respect to individual studies, five out of the seven studies reported statistically significant ORs that ranged from 0.16 to 0.54.[15,24,27-29] Consistently, the two studies that did not report statistically significant ORs of developing PPD using prophylactic esketamine within 4-6 weeks postpartum were Liu et al. (2023) and Shen et al. (2023).[25,26] The Liu et al. (2023) study obtained an OR of 0.54 (95% CI = [0.17, 1.77]) and the Shen et al. (2023) study obtained an OR of 2.00 (95% CI = [0.18, 22.42]).[25,26]

Safety and tolerability of esketamine

The most commonly reported (>5%) treatment-emergent adverse events (TEAEs) across the included studies include nausea,

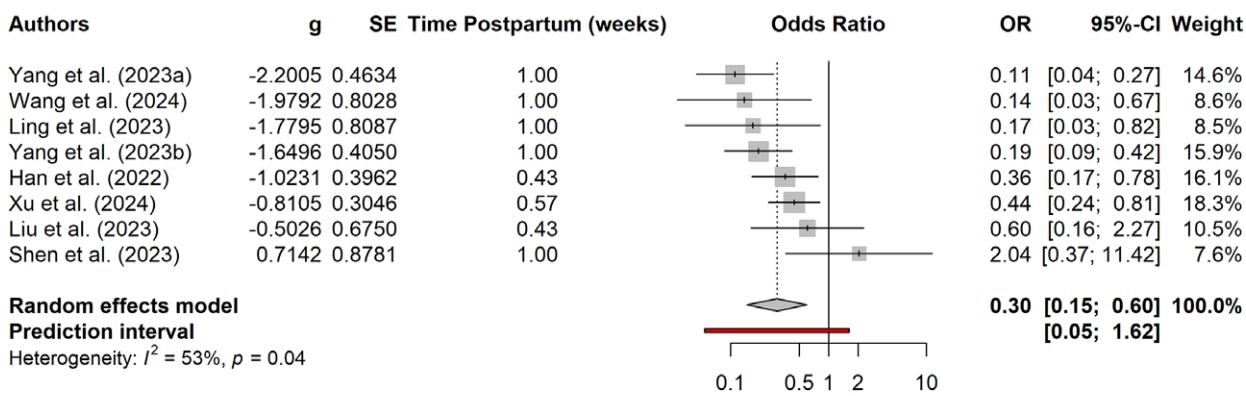

Figure 2. Pooled Odds Ratios of Postpartum Depression Within 1 Week of Delivery. Incidence rates of postpartum depression within 1 week following delivery were compared between the esketamine-treated groups and the placebo groups.

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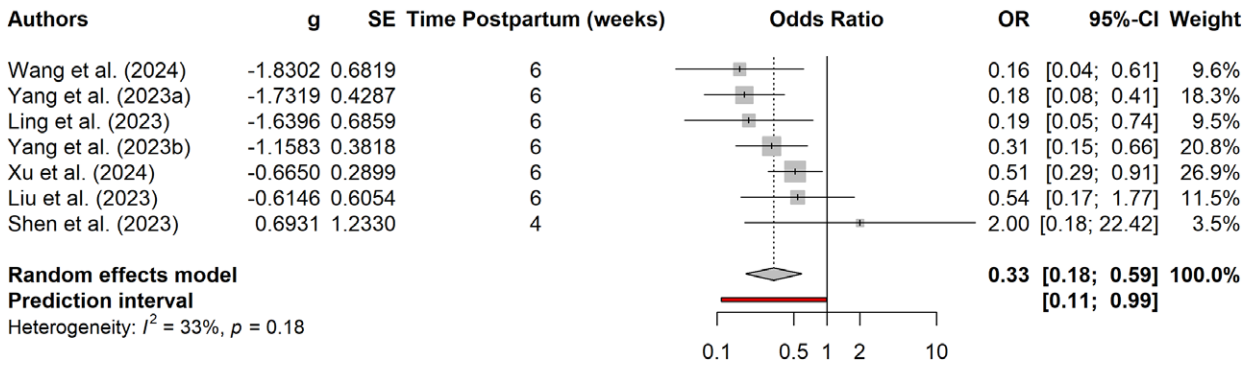

Figure 3. Pooled Odds Ratios of Postpartum Depression Between 4-6 Weeks Following Delivery. Incidence rates of postpartum depression between 4 to 6 weeks following delivery were compared between the esketamine-treated groups and the placebo groups.

vomiting, dizziness, drowsiness and blurred vision.[15,24-29] In addition, TEAEs that were reported to be significantly greater in the esketamine-treated group compared to the placebo group included dizziness, blurred vision, drowsiness and hallucinations, which are known to be associated with ketamine and esketamine treatment.[25,26,28] Moreover, TEAEs were transient and none of the included studies reported severe adverse events.[15,24-29] The foregoing points suggest that esketamine may be a safe and tolerable prophylactic treatment for PPD.

In terms of the safety of esketamine on the newborn, safety measures were inconsistently reported. Four of the included studies administered treatment following delivery, including the study conducted by Yang et al. (2023), which was the only study to report on newborn safety. Specifically, neonatal intensive care unit hospitalization rates did not significantly differ between esketamine (high-dose: 24.2% and low-dose: 30.3%) and placebo treated groups (35.1%); however, any changes in vital signs were not reported.[29] The studies that administered esketamine pre- and intra-operatively did not report on any potential side effects on the newborn.[25,27,28]

Discussion

Our results indicate that esketamine may be an effective treatment in the prevention of PPD. Specifically, there was a disproportionate reporting of decreased PPD incidence rates in favour of the esketamine-treated group compared to the placebo group.[15,24,27-29] The foregoing observation was also consistent regardless of the esketamine dose and the mode of child delivery. Notwithstanding the foregoing trends, the studies conducted by Shen et al. (2023) and Liu et al. (2023) failed to observe significant differences in PPD incidence rates between treatments. Differences in efficacy may be attributable to the fact that the included studies did not evaluate participants' risk for PPD prior to treatment. Moreover, there were differences in the timing of drug administration and the analgesic treatments utilized. Therefore, the optimization of the esketamine treatment for PPD prevention requires further replication within large-scale clinical trials with clearly defined sample populations and treatment protocols.

Esketamine was associated with mild and transient adverse events including nausea, vomiting, dizziness, drowsiness and blurred vision. Notwithstanding the foregoing observations, the overall safety profile of esketamine appears to be safe and tolerable. Notably, the potential risks of esketamine on newborn safety are insufficiently reported. While four of the seven studies administered esketamine post-childbirth, the studies that investigated esketamine pre- and intra-operatively did not report safety measures of the newborn. Together, our results presented herein support the preliminary safety and efficacy of intravenous esketamine as a post-operative, preventative treatment for PPD. However, a comprehensive exposure and risk assessment of the potential harms of esketamine on newborns should be conducted prior to the implementation of esketamine as an adjunctive treatment to intraoperative analgesia.

In efforts to prevent the introduction of reporting bias, we delimited our search to RCTs that pre-specified an objective to analyze esketamine for the prevention of PPD. Notably, our results align with Li et al. (2024), which is a previously published meta-analysis that included post-hoc analyses and primary studies that did not have a pre-specified objective.[13] Specifically, Li et al. (2024) also observed a significantly smaller PPD incidence rate in the esketamine groups within 1-week postpartum and after 4-weeks postpartum.[13] Furthermore, Li et al. (2024) also noted that at these time points, EPDS scores were statistically significantly lower in the esketamine-treated participants compared to the placebo group.[13] However, their analysis consisted of studies that investigated racemic ketamine and esketamine, which introduced greater between-group heterogeneity. Thus, the effects of esketamine on PPD incidence rates cannot be directly extrapolated from these results.

There are methodological limitations that affect the inferences and interpretations of our analysis. First, as the use of esketamine for PPD is still a relatively novel topic and the majority of the published studies have been conducted in China, the analyzed results are preliminary and may not accurately represent the efficacy of esketamine for PPD in the general population or for ethnic populations in other geographic locations. Second, the component studies investigated varying doses of esketamine. As such, dose-dependent effects cannot be determined. As there are no esketamine dosing recommendations for PPD prevention, there may have been non-response in some participants if a high enough dose was not given. Therefore, PPD incidence rates in response to esketamine and the duration of response can only be estimated. As the majority of the studies only measured PPD incidence rates for up to 6-weeks postpartum, we cannot evaluate the efficacy of maintenance esketamine on PPD incidence rates or PPD depressive symptom severity.

Finally, by delimiting our search results to RCTs with a pre-specified outcome of esketamine as preventive treatment for PPD, there was an insufficient number of studies to perform further statistical analyses such as calculating between-group differences in EPDS scores at multiple time points. Therefore, we are unable to determine the degree to which esketamine reduces PPD depressive

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symptom severity. Fourth, the effect of esketamine on breastfeeding is unknown. Preliminary results have reported the potential for esketamine to be secreted into breast milk; however, the effects of esketamine on the baby are under investigated, which warrants further research.[30]

Conclusion

Taking into consideration our methodological limitations, results from our meta-analysis suggest that esketamine may have preventative effects for PPD. The administration of treatment at the time of parturition as a single administration has the advantage of reduced neonatal toxicity. Future research will need to replicate the findings of the component studies herein in larger samples recruiting mixed demographic populations with careful characterization of safety and tolerability. Separately, whether IV racemic ketamine exerts differential effects relative to esketamine in the context of PPD would also be informative. In the interim, the data published to date are promising and suggest that glutamatergic signaling may be relevant not only in the treatment but prevention of depressive syndromes. Specifically, our results may serve as preliminary support for the investigation of esketamine as a prophylactic treatment for other mood and/or depressive disorders.

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Competing interest

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Clinical implications

- Perinatal depression incidence rates were significantly lower in esketamine-treated participants at 1-week following childbirth
- The incidence rates for perinatal depression were also significantly lower in esketamine-treated participants at the 4-6 week time point
- Esketamine may be an effective prophylactic antidepressant for the prevention of perinatal depression

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