Original paper

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The efficacy and safety of brexanolone in post-partum depression: A systematic review

S Halder, R Kar, B Gupta, E A Almeida

Abstract

Introduction

Post-partum depression (PPD) affects women in the perinatal period, negatively impacting both maternal and neonatal wellbeing. As it is associated with suicidal tendencies it is important to not only identify this condition but also treat it. Fluctuations/sudden decrease in the levels of allopregnanolone, a neuroactive steroid has been implicated in the pathogenesis of PPD. Brexanolone, an intravenous formulation of allopregnanolone, in phase 1 and phase 2 trials has shown promising results in alleviating the symptoms of PPD. This systematic review is an attempt to evaluate the efficacy and safety of brexanolone in women with PPD.

Methodology

Online database search using key words: brexanolone, postpartum depression, safety, efficacy, clinical trials after establishing inclusion and exclusion criteria yielded 16 studies. Only 5 were selected as rest were review articles. Patients with postpartum depression of ≤ 6 months with baseline HAM-D score ≥20 were included in this systematic review. The CGI, HAMD-A/S, HAM-D (insomnia) scores, dose of brexanolone, time and duration of treatment, evaluation of safety and efficacy and the duration of follow-up were analysed.

Results

HAM D scores showed response to treatment with 50% reduction in score. Some studies showed improvement in CGI, HAMD-A/S, HAM-D (insomnia) scores as well. Very few side effects like headache, dizziness, somnolence, infusion site discomfort were reported.

Conclusion

Other than two serious adverse events seen at higher dose, brexanolone as a treatment option appears safe. It's ability to improve the HAM-D score underlines its potential as a treatment for PPD.

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Introduction

Postpartum depression (PPD) is a common psychiatric condition within the perinatal period. Its prevalence is reported to be approximately 17.2% globally (1) with 40-80% of PPD cases being labelled as moderate to severe (2-5). PPD is associated with substantial psychosocial and functional impairment for mothers, their offspring, and the broader family unit (2, 6). Adverse outcomes linked to PPD include diminished initiation of breastfeeding, impaired maternal-infant attachment, and elevated risk of behavioural, emotional, and cognitive disturbances in infants (6-8). In its severe form, PPD is also associated with suicidal ideation with maternal suicide as a result of PPD contributes to approximately 20% of deaths occurring in the postpartum period (7, 9). According to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5), PPD is classified as a major depressive episode with onset during pregnancy or within four weeks following delivery (10). Timely and effective management of core depressive symptoms is essential, as untreated PPD is linked to unfavourable maternal and neonatal outcomes, as well as compromised maternal functioning (8). Moreover, addressing residual symptoms such as anxiety and insomnia which frequently co-occur with PPD is important for optimizing patients' quality of life (11-13).

Allopregnanolone, an endogenous neuroactive steroid and potent positive allosteric modulator (PAM) of both synaptic and extra synaptic γ-aminobutyric acid type A

(GABAA) receptors, is hypothesized to play a critical role in the pathophysiology of PPD (7, 14, 15). Levels of allopregnanolone, a progesterone derivative have been documented to fluctuate during gestation; its levels rise during pregnancy, peaks in the third trimester, and declining sharply post-delivery. Dysregulation in neurobiological adaptation to these hormonal shifts may contribute to the onset of PPD (16, 17). Functional MRI studies have demonstrated altered resting-state functional connectivity in individuals with PPD. Specifically, increased connectivity between the dorsomedial prefrontal cortex and the default mode network has been observed in PPD patients compared to healthy postpartum controls. These alterations correlated positively with both elevated allopregnanolone levels and increased depressive symptom severity, suggesting a mechanistic link between neurosteroid fluctuations, neural network dynamics, and clinical presentation of PPD (18).

Brexanolone, an intravenous formulation of allopregnanolone, functions as a GABAA receptor PAM (15, 19). It binds directly to GABAA receptors (20) and is postulated to normalize disrupted neural signalling by re-establishing the excitatory-inhibitory balance within the brain (21). Findings from phase 1 and phase 2 clinical trials have indicated that brexanolone administration is associated with significant improvement in depressive symptoms in individuals with PPD, supporting the potential role of GABAA receptor modulation in the treatment of this condition (14). Given the intergenerational impact of maternal mental health, effective PPD treatment with brexanolone may confer benefits extending to both mothers and their children (14).

This systematic review aims to evaluate the clinical efficacy and safety profile of brexanolone in the management of postpartum depression.

Methods

This systematic review adheres to the guidelines outlined in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.

Eligibility Criteria and Search Strategy

A comprehensive systematic search was conducted across the following electronic databases from their inception through April 30, 2025: EPOC, SCOPUS, ERIC, CINAHL, Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, Web of Science, NYAM Library, ClinicalTrials.gov, and African Journals Online (AJOL).

The search strategy was limited to studies conducted on human subjects and published in English. An initial broad search identified literature related to the efficacy and safety of brexanolone in the treatment of PPD. This was followed by a refined search using Medical Subject Headings (MeSH) and relevant keywords: brexanolone, postpartum depression, safety, efficacy, clinical trials. Studies from Phase I, II, and III clinical trials that evaluated the pharmacological profile, safety, and efficacy of brexanolone in PPD were included. Additionally, reference lists of selected articles were screened to identify other potentially eligible studies. One study evaluating zuranolone, an oral allopregnanolone analogue, was also included for its relevance in safety and efficacy assessment.

Study Selection

Two reviewers independently screened all retrieved records, including titles, abstracts, and full texts. Discrepancies in study selection were resolved through consensus discussions with the broader review team. Eligibility criteria were pre-specified. **Included studies** were required to meet the following criteria:

Participants: Women aged 18-45 years diagnosed with postpartum depression within six months postpartum.

Clinical severity: Baseline Hamilton Depression Rating Scale (HAM-D) score of ≥ 20. Where available, Clinical Global Impression (CGI) scores, HAM-A/S, and HAM-D (insomnia subscale) scores were also extracted.

Exclusion criteria comprised: End-stage renal disease requiring dialysis; Fulminant hepatic failure; Anaemia (haemoglobin <10 g/dL); Known hypersensitivity to allopregnanolone or progesterone; Active psychosis symptoms as assessed by investigators; Diagnosed schizophrenia, bipolar disorder, or schizoaffective disorder; History of suicide attempt during the current depressive episode; History of substance use disorder (alcohol or drug abuse) within the previous 12 months; Prior participation in studies involving brexanolone or exposure to other investigational medications within 30 days before screening.

Only randomized controlled trials and clinical trials with full-text availability were considered eligible for inclusion.

Data Extraction

Two reviewers independently extracted data from the included studies using a standardized form. Extracted variables included: Year of publication; Country of study; Sample size; Intervention type (e.g., brexanolone dosage); Summary of key findings and overall conclusion. Baseline comparability between treatment and control groups was evaluated in terms of major prognostic and potential confounding variables.

Quality Assessment

Study quality and risk of bias were evaluated using the Cochrane Risk of Bias Tool. Selection bias was assessed

through randomization and allocation concealment, while performance and detection biases were evaluated based on blinding procedures. Risk of bias was assessed independently by two reviewers. Discrepancies were resolved through discussion, and if needed, consultation with a third reviewer. A detailed summary of the risk of bias assessment is presented in Supplementary Figure 1.

Results

Search Results

Total 16 articles were found using the key words. 11 of these were review articles so were excluded. Only 5 articles were based on clinical trials and were included.

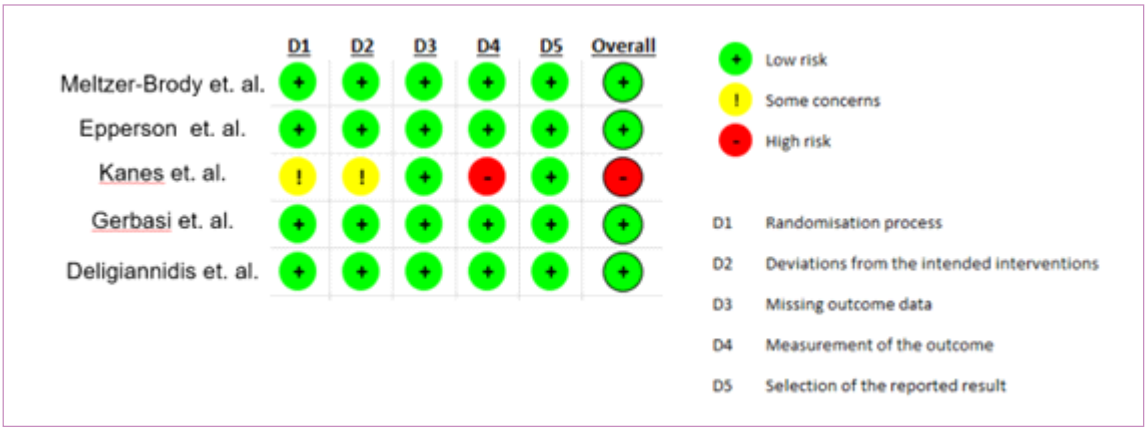

Figure 1.

Table 1. The response observed after brenoxolone treatment in terms of HAMD scores and % patients showing 50% reduction in HAMD scores after treatment

SL. no	Article	Research study	Baseline HAMD Scores	Response after treatment with brexanolone		% patients showing 50% reduction in HAMD Scores	Duration of treatment
1	Meltzer-Brody et al. 2018	Study 1	BRX60 BRX90 Placebo	29.1±2.7 28.4±2.5 28.6±2.5	BRX60: 60% reduction BRX90: 70% reduction Placebo: 50% reduction		30 days
		Study 2	BRX90 Placebo	22.6±1.6 22.7±1.6	BRX90: 70% reduction Placebo: 50% reduction		
2	Deligiannidis et al. 2023		Zuranolone (50mg/kg) 24.4±6.0 Placebo: 24.7± 6.0		Zuranolone: 62% reduction Placebo 41% reduction		28 days
3	Epperson et al. 2023	Study A	BRX90 Placebo	25.5 ± 3.5 25.7 ± 3.6	BRX90: (50% reduction) Placebo: (50% reduction)	88.2% 75.7%	30 days
4	Gerbasi et al. 2021		BRX60	25.43 ± 3.56	BRX60 (50% reduction)	58.2%	30 days
5	Kanes et al. 2017		BRX60	26.5 ± 4.1	BRX60 (81% reduction)		84 hrs

BRX60: group receiving 60 µg/kg brenoxolone; BRX90: group receiving 90 µg/kg brenoxolone.

Included Studies

A total sample size of 911 patients were evaluated. The average baseline score in the placebo group and treatment groups was ≥ 20. Patients were treated with brexanolone 60, 90 µg/kg and placebo. Patients were given 60 hr infusion and additional 12 hr for completion of assessments. They were observed for treatment response and safety assessment after 7 days and 30 days of brexanolone treatment. The total follow-up period was 30 days.

Efficacy of Brexanolone

A significant response to brexanolone (i.e. ≥50% reduction of HAM-D score) was observed on day 3 and day 30 in treatment group as depicted in Table 1. Few studies also showed additional improvement in CGI, HAMD-A/S and HAM-D (insomnia) scores.

Adverse drug reactions

Both minor and major adverse drug reactions were noted in the study participants and are described in Table 2. Minor side effects included headache, dizziness and somnolence while major reactions included suicide ideations and overdose attempts.

Table 2. Adverse drug reactions as reported in the studies

SL. no	Adverse Drug Reactions (ADRs)					
	Articles	Headache	Dizziness	Somnolence	Others	Serious A
1	Meltzer-Brody et al. 2018	Study 1: BRX60=7 BRX90=6 Placebo=1 Study 2: BRX90=9 Placebo=6	Study 1: BRX60=6 BRX90=6 Placebo=1 Study 2: BRX90=5 Placebo=4	Study 1: BRX60=7 BRX90=2 Placebo=3 Study 2: BRX90=4 Placebo=2		Study 1: BRX60=1 (2 ADRs – suicidal ideation and intentional overdose attempt) Study 2: BRX90:1 (2ADRs – (altered state of consciousness and syncope).
2	Deligiannidis et al. 2023	9.2%	13.3%	26.5%	11.2%	No loss of consciousness, withdrawal symptoms, or increased suicidal ideation or behaviour were observed.
3	Epperson et al. 2023			Not studied		
4	Gerbasi et al. 2021			Not studied		
5	Kanes et al. 2017	AEs were reported by all four patients (14 total; 10 considered treatment related).			Sedation 50% infusion site discomfort, infusion site erythema, infusion site pain, rash, thyroid stimulating hormone increase, dizziness, flushing, and oropharyngeal pain)	All ADRs were of mild or moderate severity and self-limited. No serious AEs reported

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Discussion

The findings of the five studies included in this systematic review consistently indicate that brexanolone is an effective therapeutic agent for the treatment of PPD, with a favourable safety profile and generally mild adverse effects.

In two double-blind, randomized, placebo-controlled, phase 3 clinical trials conducted at 30 clinical centres including psychiatric clinics across the United States, Meltzer-Brody et al. demonstrated that intravenous brexanolone significantly and rapidly reduced depressive symptoms in women with PPD, as measured by the Hamilton Rating Scale for Depression (HAM-D) total score at 60 hours, compared to placebo. The therapeutic effects were not only rapid in onset but also durable over the duration of the study (22). These results support the utility of brexanolone as a novel pharmacological intervention for PPD.

Epperson et al. assessed brexanolone within the HUMMINGBIRD clinical program, demonstrating that treatment resulted in rapid reductions in depressive symptoms, as well as improvements in comorbid anxiety and insomnia, compared to placebo. However, the study was not sufficiently powered to statistically validate exploratory outcomes (23).

In another study, Gerbasi et al. investigated the impact of PPD on health-related quality of life (HRQoL). Their findings indicated that brexanolone facilitated a rapid clinical response by day 7, which persisted through day 30 post-treatment. This sustained improvement was associated with significant gains in HRQoL, underscoring the importance of early identification and intervention in PPD (24).

An open-label study by Kanes et al. found that brexanolone was well tolerated and demonstrated clinical efficacy in women with severe PPD. However, the authors emphasized the need for larger, placebo-controlled trials to further substantiate these preliminary findings (14).

In a separate trial, Deligiannidis et al. evaluated zuranolone, an investigational oral neuroactive steroid and PAM of both synaptic and extrasynaptic GABAA receptors. Their findings revealed significant improvement in depressive symptoms, and the compound was generally well tolerated. Zuranolone's oral administration and rapid antidepressant effects make it a promising candidate for further development as a treatment for PPD (25).

Across all studies, brexanolone treatment at both 60 mg/kg and 90 mg/kg doses resulted in significant reductions in HAM-D scores compared to placebo, with symptom improvement maintained for up to 28 days post-infusion. Adverse events were predominantly mild in nature, including headache, dizziness, somnolence, and sedation (14, 22, 25). Notably, Meltzer-Brody et al. reported two serious adverse events (altered state of consciousness and syncope) in a single patient receiving the 90 mg/kg dose, which were attributed to the treatment (22).

Overall, brexanolone appears to be a safe and effective option for managing postpartum depression, with the potential to produce rapid and sustained clinical improvement. While the safety profile is generally acceptable, further investigation is warranted to better understand the risk of serious adverse events at higher doses. Taken together, the evidence positions brexanolone as a promising treatment that may significantly improve the quality of life for women affected by PPD.

Key points

- Although a maternal illness, postpartum depression is associated with adverse neonatal outcomes as well.
- Brexanolone is a promising drug in the treatment of postpartum depression.
- Further research is required to help develop the proper dosing and list of adverse effects.

S Halder, Department of Pharmacology, University College of Medical Sciences and GTB Hospital, University of Delhi, Delhi, India

R Kar, Department of Biochemistry, University College of Medical Sciences and GTB Hospital, University of Delhi, Delhi, India

B Gupta, Department of Obstetrics and Gynaecology, University College of Medical Sciences and GTB Hospital, University of Delhi, Delhi, India.

E A Almeida, Department of Biochemistry, University College of Medical Sciences and GTB Hospital, University of Delhi, Delhi, India

Corresponding author: E A Almeida

E-mail: dreducms@gmail.com

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