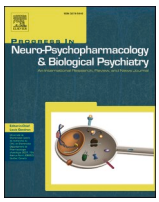
Progress in Neuropsychopharmacology & Biological Psychiatry 132 (2024) 110983

Contents lists available at ScienceDirect

Progress in Neuropsychopharmacology & Biological Psychiatry

journal homepage: www.elsevier.com/locate/pnp



Exploring the clinical potentials of zuranolone in managing postpartum depression: A new therapeutic horizon

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ARTICLE INFO

Keywords:
Postpartum depression
Zuranolone
$GABA_A$
Brexanolone

ABSTRACT

Postpartum depression (PPD) poses a major threat to maternal mental health and wellbeing while also adversely affecting the mother's relationship with her baby, leading to significant repercussions that may hinder the growth and cognitive development of the child. For decades, antidepressants have been the mainstay of treating PPD; however, recent evidence suggests that antidepressants are not as effective as they are believed to be and there is a dire need to explore new treatment options. In 2023, a breakthrough in treating PPD emerged with the recent FDA approval of zuranolone, a gamma-aminobutyric acid ($GABA_A$) receptor selective positive allosteric modulator. The implementation of zuranolone in treating PPD can prove to be revolutionary, considering it is the first oral medication available for PPD. Our review aims to discuss the various clinical trials that have been conducted to validate the efficacy of zuranolone in mitigating the symptoms of PPD, hence, leading to better outcomes for mothers.

1. Introduction

Postpartum depression (PPD) constitutes one of the major complications of childbirth with an alarming incidence of 17% globally (Wang et al., 2021). PPD classically presents as an episode of depression characterized by mood swings, sudden crying episodes, apathy towards the infant and suicidal ideation (Agrawal et al., 2022). The psychiatric disorder not only adversely affects the mother but also has negative effects on the cognitive and emotional development of the infant, leading to lasting consequences (Payne and Maguire, 2019) . Infants born to mothers experiencing depression often exhibit reduced expressive language skills and score lower on cognitive-linguistic functioning assessments later on (*Dev. Psychol.*, 1999; England et al., 2009). Research has established that mothers who suffer from PPD are not able to identify their child's needs compared to healthy mothers and might struggle to bond with the infant (Faisal-Cury et al., 2021). This bonding impairment can deprive the mother from what is considered an essential experience of motherhood.

The severity of PPD and its consequences for the mother cannot be undermined considering that it accounts for a significantly higher rate of suicide in mothers post childbirth (Lee et al., 2022). Women with a history of depression, suffering from low self-esteem and belonging to a low socioeconomic background are more predisposed to developing PPD (Tebeka et al., 2021a). Hence, screening for the disease and early intervention is crucial, especially considering that the period of four to six weeks after delivery is considered a high risk period (Agrawal et al., 2022). All women should receive psychosocial measures to improve self-care, boost practical and emotional social support, and limit the occurrence of stressors once PPD has been diagnosed. However, if PPD is unresponsive to psychological measures, antidepressant medication may be necessary either alone or in conjunction with non-drug therapies (Stewart and Vigod, 2019).

As the search for therapeutic interventions continues, the use of $GABA_A$ receptor selective positive allosteric modulator (PAMs) antidepressants is becoming increasingly popular for the treatment of PPD (Edinoff et al., 2021). One notable agent, Zuranolone has come to light which has demonstrated its efficacy and convenience over traditional therapeutic interventions for PPD by altering the $GABA_A$ receptor (Peitl

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https://doi.org/10.1016/j.pnpbp.2024.110983
Received 20 October 2023; Received in revised form 18 February 2024; Accepted 23 February 2024
Available online 25 February 2024

and Vlahović, 2023). $GABA_A$ is a major inhibitory signaling pathway of the central nervous system and its disruption may contribute to the development of PPD, which is likely multifactorial (Deligiannidis et al., 2021). By modulating the $GABA_A$ receptor, these PAMs provide a promising and efficient approach towards curing PPD.

The $GABA_A$ receptor plays a pivotal role in the inhibitory signaling pathways of the central nervous system, acting as a key regulator of neuronal excitability and mood modulation (Edinoff et al., 2021). Disruptions in GABAergic signaling have been implicated in the etiology of various neuropsychiatric disorders, including PPD (Peitl and Vlahović, 2023). PPD is characterized by a complex interplay of hormonal, genetic, and environmental factors, with emerging evidence suggesting that dysregulation of the GABAergic system may contribute significantly to its development (Peitl and Vlahović, 2023). The decrease in GABAergic tone observed in individuals with PPD may lead to heightened neuronal excitability and mood disturbances, highlighting the therapeutic potential of targeting this pathway (Deligiannidis et al., 2021).

Zuranolone represents a different therapeutic approach by selectively modulating the $GABA_A$ receptors (Nashwan et al., 2024). Unlike traditional antidepressants that may act through multiple neurotransmitter systems and have a delayed onset of action, zuranolone's mechanism of action is more direct and may offer a faster therapeutic effect (Nashwan et al., 2024). By enhancing the inhibitory action of GABA through positive allosteric modulation of $GABA_A$ receptors, zuranolone can help to restore the balance in neuronal excitability and mood regulation (Peitl and Vlahović, 2023). This targeted modulation not only underscores the drug's efficacy but also its convenience as an oral medication, offering a significant advantage over other treatment modalities that may require more invasive administration methods or have less favorable side effect profiles (Peitl and Vlahović, 2023).

Furthermore, the exploration of $GABA_A$ receptor PAMs like zuranolone illuminates the critical role of the GABAergic system in the pathophysiology of PPD and offers a promising avenue for the development of targeted, efficient, and potentially faster-acting therapeutic interventions (Cutler et al., 2023). This focus aligns with the ongoing search for more effective and patient-friendly treatments for PPD, emphasizing the need for a deeper understanding of molecular mechanisms to inform drug development and clinical practice (Cutler et al., 2023). In this review, we aim to discuss the impact of zuranolone as a treatment option of PPD as demonstrated by multiple clinical trials and its implications in the clinical world.

2. Current treatment options For PPD

A multidisciplinary approach is preferred to tackle PPD with the therapeutic options ranging from psychosocial strategies to pharmacological interventions, depending on the severity of the disease. Results from a study show that individual interpersonal therapy, cognitive-behavior therapy, and psychodynamic therapy may all be efficient psychological treatments for PPD (Pearlstein et al., 2009). For disease resistant to psychological treatment, pharmacological drugs are advised with antidepressants being the major treatment modality (Stewart and Vigod, 2019). Selective serotonin reuptake inhibitors (SSRIs) are a popular drug of choice; however, antidepressants are associated with higher remission rates in mothers (Lee et al., 2022). Moreover, SSRIs seldom achieve response rates above 50% and take several weeks to produce any pharmacological effects (Pinna et al., 2022). In the context of PPD, additional psychotropic drugs may be used to treat comorbid anxiety and insomnia (hypnotics, benzodiazepines) or to boost the effectiveness of antidepressants (Stewart and Vigod, 2019). The conventional treatment options used to treat PPD have been summarized in Table 1.

Currently, there is a paucity of clinical trials investigating pharmacological therapies that target PPD meaning that the landscape of therapeutic options is not as broad as one might hope. This probes more research into PPD-specific treatments that address the particular physiological and psychological complexities that characterize this condition.

Table 1
Summary of the available conventional treatment options for PPD.

Treatment option	Intervention description/ Mechanism of action	Therapeutic outcomes	Adverse effects/ major drawbacks (main)
Interpersonal therapy (IPT)	Patients and therapists collaborate on issues like role transition, dispute, grief, or deficits through a problem-solving approach over a 12–20 week period.	• Reduced Symptoms of Depression. • Improved Maternal-Infant Bonding. • Increased Coping Skills. • Enhanced Social Support. • Better Interpersonal Relationships . • Improved Self-esteem and Confidence.	• Social stigma. • Childcare needs. • The cost of therapy.
Cognitive Behavioral therapy (CBT)	Helps in reducing distress, promotes positive behavioral changes and coping mechanisms.		• Lack of availability of trained professionals. • Time commitment.
Psycho-Social Treatment	Address interpersonal issues, enhancing mental health through behavioral and emotional support mechanisms.		• Emotional Discomfort. • Increased Anxiety. • Over-dependence on Therapy. • Stress Related to Time Commitment. • Social Stigma.
Selective Serotonin Reuptake Inhibitors (SSRIs)	Inhibits the reuptake of serotonin, increasing its availability in the brain.		• Gastrointestinal Issues. • Sexual Dysfunction. • Insomnia or Drowsiness. • Weight Changes. • Increased Anxiety or Agitation. • Dry Mouth. • Headaches.

3. $GABA_A$ receptors in modulating PPD

γ-Aminobutyric acid (GABA) acts as an integral inhibitory neurotransmitter in the central nervous system and plays a major role in regulating brain activity (Ghit et al., 2021). $GABA_A$ receptor signaling leads to tonic and phasic inhibition and any disturbance in this inhibitory pathway may result in neurological or psychiatric diseases (Ghit et al., 2021). The role of GABAergic deficits is implicated in depressive disorders and is supported by the diminished GABA levels seen in the plasma, CSF, and cortical tissue of depressed patients (Luscher et al., 2011).

Allopregnanolone, a neurosteroid, is an endogenous positive allosteric regulator which extends the decay time of GABA-gated ion channels, hence increasing the inhibitory potential of neurons (Chen et al., 2021). By positively modulating the $GABA_A$ receptor, Allopregnanolone provides a potential therapeutic pathway for the treatment of PPD (Chen et al., 2021).

4. Brexanolone as a first line drug in PPD

Brexanolone, an allopregnanolone analogue, is the first drug approved by the FDA to treat PPD. Brexanolone mimics a progesterone

metabolite that is naturally created and fluctuates during pregnancy and postpartum and enhances the inhibitory effects of $GABA_A$ while also restoring malfunctioning $GABA_A$ transmembrane channels (Edinoff et al., 2021). While revolutionary in the treatment of PPD, brexanolone is limited by its intravenous mode of administration which requires dosing for a total of 60 hours (Edinoff et al., 2021). Hence, the patient needs to be admitted and carefully monitored in the hospital while on brexanolone infusion. Brexanolone's use is also hindered by its adverse effects, namely sedation, disturbed mental status and loss of consciousness. The drug is also contraindicated in patients with end stage renal disease and can further damage the kidneys (Edinoff et al., 2021). The safety profile of brexanolone, its inconvenient mode of administration and continuous monitoring probed further research into alternative treatment options for PPD. Furthermore, the cost of brexanolone treatment in the US ranges significantly, from $15,000 to $34,000 per vial (Eldar-Lissai et al., 2020), presenting a potential barrier to accessing this PPD treatment.

5. Zuranolone for the treatment of PDD

The drawbacks posed by brexanolone therapy were successfully overcome with the FDA approval of the drug zuranolone for treating PPD on 4th August 2023 (Nashwan et al., 2024). Zuranolone, a neuroactive steroid, is a positive allosteric regulator of the $GABA_A$ receptor and has the potential to ameliorate depressive symptoms more than traditional medications (Peitl and Vlahović, 2023).

Clinical trials have also demonstrated the antidepressant efficacy of zuranolone as it brought significant changes in maternal functioning and anxiety when compared to placebo (Edinoff et al., 2021). Oral administration of zuranolone also led to positive outcomes in women with PPD suffering from insomnia. Overall, a once daily dosing for 14 days led to the improvement of depressive symptoms and functional health of mothers (Deligiannidis et al., 2023). Zuranolone's efficacy is further corroborated by its safety profile with the most common adverse effects being somnolence, dizziness, and sedation. There were no threatening events observed like loss of consciousness or suicidal ideation (Clayton et al., 2023).

The significance of zuranolone therapy lies in its convenient mode of administration as its excellent pharmacokinetic profile supports daily oral dosing (Deligiannidis et al., 2023). This is a major improvement compared to brexanolone's laborious 60-h continuous intravenous infusion. Since zuranolone is taken orally once daily, it does not require hospital admission like brexanolone, making it the more patient-friendly efficacious drug for the treatment of PPD.

6. Clinical trials

A Phase 3 randomized controlled trial (RCT) was conducted to assess the efficacy of zuranolone. The study enrolled a total of 153 participants, with 77 individuals assigned to the zuranolone 30 mg group and 76 individuals allocated to the placebo group. The primary outcome measure was the evaluation of efficacy using the Hamilton Depression Rating Scale with 17 items (HAMD-17), and assessments were conducted at three time points: day 3, day 15, and day 45. The results revealed a statistically significant improvement in HAMD-17 scores among patients administered zuranolone 30 mg compared to those in the placebo group at day 3 (mean difference, −2.7; 95% confidence interval [CI], −5.1 to −0.3; $p = 0.03$), day 15 (mean difference, −4.2; 95% CI, −6.9 to −1.5; $P = 0.003$), and day 45 (mean difference, −4.1; 95% CI, −6.7 to −1.4; $p = 0.003$). In total two adverse events were noted, one case of confusional state in the zuranolone group and one case of pancreatitis in the placebo group (Deligiannidis et al., 2021).

Additionally, in another RCT involving a larger sample size of 581 patients, 194 received zuranolone 20 mg, 194 received zuranolone 30 mg, and 193 were assigned to the placebo group. The primary outcome measure was assessed on day 15 using the least squares mean (LSM) change in the HDRS-17. On day 15, the HDRS-17 LSM change was −12.5 in the zuranolone 30 mg group and − 11.1 in the placebo group ($p = 0.116$). Statistically significant improvements were observed at days 3, 8, and 12 ($p < 0.05$) in the zuranolone 30 mg group, while no significant improvements were reported in patients receiving zuranolone 20 mg. During the 15-day treatment period, similar adverse events were observed in 54.7% of patients in the zuranolone 30 mg group and 48.9% of patients in the placebo group, which included headache, dizziness, sedation, nausea, diarrhea, somnolence, and fatigue (Clayton et al., 2023).

A very recent phase 3 CORAL Study by Parikh et al. demonstrated that zuranolone, when combined with standard-of-care antidepressants (ADT), significantly improved depressive symptoms by Day 3 compared to placebo+ADT, with the majority of side effects being mild or moderate, including somnolence, dizziness, headache, and nausea (Parikh et al., 2024). This suggests zuranolone+ADT could offer quicker symptom relief in MDD with a manageable safety profile.

These clinical trials collectively provide strong support for the potential of zuranolone as an effective treatment option for postpartum depression, with consistent findings across various measures of symptom improvement and overall well-being.

7. Discussion

PPD presents substantial challenges for both mothers and infants, necessitating the development of effective pharmaceutical interventions to mitigate the associated anxiety and stress. Zuranolone, a positive allosteric modulator (PAM) of the gamma-aminobutyric acid type A receptor, represents a targeted approach to addressing this challenge (Peitl and Vlahović, 2023). Zuranolone has demonstrated a broad spectrum of advantages compared to traditional treatment options, such as SSRIs and tricyclic antidepressants (TCAs). Notably, it offers a more rapid onset of action, providing swift relief in contrast to the delayed response observed with traditional therapies. Furthermore, zuranolone exhibits sustained effects for up to two weeks after discontinuation, surpassing the transient benefits of conventional treatments. Additionally, zuranolone has exhibited significantly higher rates of remission in patients when compared to traditional therapies (Deligiannidis et al., 2021).

Zuranolone demonstrates superiority over brexanolone, as brexanolone requires continuous intravenous (IV) infusion for either 60 or 90 h, while zuranolone can be administered orally on a daily basis (Parikh et al., 2024). Given that postpartum depression remains relatively under-recognized in many parts of the world due to limited awareness and the stigma surrounding depression, zuranolone emerges as a practical option for mothers, sparing them the need for prolonged hospitalization that may also have adverse effects on the infant's well-being. Brexanolone therapy may hinder patient adherence due to its demanding administration regimen, whereas zuranolone offers ease of drug administration, greater flexibility, and enhanced feasibility for patients.

Nonetheless, certain limitations pertain to zuranolone, including the relatively small sample sizes used in clinical trials and the limited duration of patient exposure, typically 45 days. Moreover, many trials involved the cessation of breastfeeding, leaving the relationship between breastfeeding and zuranolone efficacy unexplored. Consequently, large-scale clinical trials are imperative to comprehensively evaluate the effectiveness of zuranolone and secure its status as an FDA-approved treatment option. Moreover, it is crucial to distinguish between early and late-onset PPD and their unique associated factors (Tebeka et al., 2021b). This distinction indeed suggests the possibility of tailored treatment approaches for different PPD timelines and potentially guiding more personalized treatment strategies.

8. Conclusion

Zuranolone has demonstrated promising efficacy in the treatment of postpartum depression among women. Its use has led to the cessation of depressive and anxiety symptoms in patients, ultimately achieving remission. There is a pressing need for further exploration of zuranolone treatments through large-scale clinical trials to validate and expand upon these promising results.

Funding

No external funding has been received for this paper.

CRediT authorship contribution statement

Abdulqadir J. Nashwan: Conceptualization, Writing – original draft, Writing – review & editing. **Syeda Tayyaba Rehan:** Conceptualization, Writing – original draft, Writing – review & editing. **Laiba Imran:** Writing – original draft, Writing – review & editing. **Samina Ghulam Abbas:** Writing – original draft, Writing – review & editing. **Sara Fahim Khan:** Writing – original draft, Writing – review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

Open Access funding provided by the Qatar National Library.

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