1. **Introduction**

Postpartum depression (PPD) is a type of major depressive episode (MDE) that is related to childbirth and pregnancy. One of the MDE criteria in the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) Fifth Edition is “peripartum onset,” which recognizes the onset of symptoms that may happen during pregnancy or in the first four weeks after delivery.(1) Regarding the exact time of symptom onset that characterizes PPD, expert opinions differ widely, ranging from the initial postpartum period to 12 months after delivery. (2–5) PPD symptoms have been related to a major decline in bonding between mothers and babies and maternal function, such as breastfeeding and childcare. Women with PPD frequently experience other symptoms or comorbidities in addition to depressive symptoms, that can negatively impact their psychological health and overall well-being. According to DSM-5 criteria, five or more of the following symptoms must be present for the diagnosis of depression: low mood, reduced interest, or pleasure in all (or nearly all) activities, noticeable weight loss or gain, insomnia, psychomotor disturbances or slowing, fatigue or low energy, excessive guilt or feelings of worthlessness, difficulty concentrating or thinking clearly, or persistent thoughts of suicide or death. (1,6–12) As an example, prevalence estimates for anxiety symptoms in PPD patients range as high as 70%.
These symptoms may be evident in female patients. (8,13–15) PPD with anxiety symptoms or sleep disturbance/insomnia symptoms is related to worse mental health status, more severe depression, a longer time to response to treatment, and an increase in ideation of self-harm. (16)

Many studies evaluate rates of PPD based on the presence of essential symptoms since PPD may go undiagnosed due to stigma, barriers to care, and a lack of understanding about the disease (17,18). 9.7% to 23.5% of women in the USA who recently gave birth to a live child experience PPD symptoms. (19) Every year, 5.5% to 13.5% of mothers in eight European nations are estimated to experience symptoms of PPD. (20–27)

2. Pathophysiology of PPD

Various factors may contribute to the development of postpartum depression (PPD). Perturbations in neuroactive steroid (NAS) levels and disruptions in γ-aminobutyric acid (GABA) signaling, leading to an imbalance in excitatory and inhibitory functions within crucial brain networks, are linked to PPD. (28–33)

Neurosteroids, derived from cholesterol in the brain, influence neuronal excitability by interacting with membrane receptors, independent of direct effects on gene expression. Neurosteroids and their counterparts, termed neuroactive steroids, play a vital role in modulating excitability via interactions with membrane receptors and ion channels. GABA receptors, primarily composed of α and β subunits (two of each), in synaptic receptors, or a single γ subunit in synaptic receptors, or a single δ subunit in extrasynaptic receptors, act as ligand-gated anion channels. (34,35)

Female reproductive hormones significantly regulate various neurotransmitters such as serotonin, norepinephrine, dopamine, GABA, and glutamate. They also play a vital role in modulating the HPA (hypothalamic, pituitary, and adrenal) axis and stress responses. Allopregnanolone (ALLO), an endogenous NAS derived from progesterone, is a significant pregnancy hormone and a key regulator of the HPA axis in the reaction to stress, interacting with GABAA receptors. (36,37) During pregnancy, ALLO levels rise, peak in the third trimester, and decline sharply after delivery. Research on mice has demonstrated that administering allopregnanolone exerts anxiolytic and antidepressant effects by enhancing GABAA receptor-mediated tonic inhibition. It acts as a positive allosteric modulator, increasing the frequency and duration of channel opening, thereby augmenting hyperpolarizing GABAergic current. (38,39)

Disruption in neurosteroidogenesis has been related to PPD. Research indicates that cerebrospinal fluid levels of ALLO in depressed patients are lower than those in healthy individuals initially, but they increase and normalize after treatment with selective serotonin reuptake inhibitors (SSRIs) like fluoxetine or fluvoxamine. This suggests that SSRIs may exert antidepressant/anxiolytic effects, at least in part, by promoting neurosteroid synthesis. (40)

3. Current treatment landscape and limitations

The primary pharmacological approach for treating postpartum depression (PPD) has traditionally involved using antidepressants typically prescribed for major depressive disorder, notably SSRIs. However, these medications, including SSRIs and other antidepressants, often do not provide swift relief or specifically target PPD. Additionally, many women do not experience adequate improvement in symptoms or achieve complete remission with these treatments. Therefore, there is a significant need for new therapies designed specifically for PPD that address its underlying physiological mechanisms. There is also a pressing demand for antidepressant medications that act rapidly to alleviate the distress associated with a depressive episode as quickly as possible. (41–43)

Brexanolone, an innovative drug developed by Sage Therapeutics, holds a specific indication for treating postpartum depression (PPD) in adult women.
Administered intravenously for over 60 hours, this medication showcased a reduction in depressive symptoms across three double-blind, randomized, placebo-controlled trials. It marked a significant milestone by becoming the first treatment for PPD approved by the US Food and Drug Administration (FDA), demonstrating both rapid and sustained improvements in PPD symptoms (44). This drug is an aqueous, chemically similar formulation of endogenous allopregnanolone, a neuroactive steroid that modulates GABA (gamma-aminobutyric acid) A receptors. Brexanolone, mimicking the actions of the neurosteroid allopregnanolone, was identified for its impact on GABAA receptors. Augmented activity of GABAA receptors is recognized for its potent antidepressant and anxiolytic actions. (45,46) Allopregnanolone binds to GABAA receptors at a distinct site from benzodiazepines (47). Its varied actions potentially manifest as an antidepressant through neuroprotective mechanisms and by reducing the inflammatory response. However, Several limitations on using this drug include the need for hospitalization and intravenous administration and the associated risks of sedation or loss of consciousness, along with possible side effects such as dry mouth, skin flushing, and its relatively high cost. (48)

5. Pre-clinical study of zuranolone
In vitro, zuranolone displayed the capacity to amplify GABAA receptor current across nine distinct human recombinant receptor subtypes. These subtypes encompassed receptors characteristic of both synaptic (containing the γ subunit) and extrasynaptic (containing the δ subunit) configurations. When tested on a representative synaptic subunit configuration (α1β2γ2), zuranolone demonstrated an increase in GABA currents in synergy with the benzodiazepine diazepam. This observation aligns with the non-competitive nature of both compounds and their specific binding sites at synaptic receptors. In vivo experiments, zuranolone exhibited robust activity, represents its capacity to modify GABAA receptors in the central nervous system (CNS) after oral administration. This was evident as it offered protection against chemo-convulsant seizures in a mouse model and enhanced electroencephalogram β-frequency power in rats. Collectively, these findings demonstrate that zuranolone is a powerful and efficient neuroactive steroid that positively regulates the GABAA receptor, possessing drug-like properties and CNS exposure in preclinical models.(57)

6. Clinical trials and research studies involving zuranolone
A phase 1 study conducted by Sonoyama T et al. in 2023 aimed to evaluate zuranolone's pharmacokinetics, safety, and tolerance in White and Japanese healthy adults as well as elderly Japanese individuals. This single-center study comprised three parts. In Part A,
which was randomized and double-blind, the safety, tolerance, and pharmacokinetics of a single and consecutive 7-day multiple doses of zuranolone (10, 20, and 30 mg, as well as a placebo, were investigated in 12 elderly Japanese participants, aged between 65 and 75, and 26 Japanese adults and 24 White adults. Part B, a randomized and open-label crossover section, focused on investigating the effect of eating a meal on the safety and pharmacokinetics of a single 30 mg dose of zuranolone in 12 Japanese adults. Part C, a randomized and double-blind crossover part, aimed to assess the effects of single doses of zuranolone at 10 and 30 mg, as well as placebo, on electroencephalography parameters in 8 Japanese adults. Results revealed that Zuranolone was administered in single and multiple dosages and was well-tolerated across all subjects. Linear pharmacokinetics were noted within the investigated dosage range. The time taken to achieve a steady-state plasma concentration was under 72 h for Japanese and White adults. Similar pharmacokinetic profiles were observed among Japanese and White adults, as well as between Japanese adults and elderly participants. Plasma exposure to zuranolone was higher in individuals in the fed state compared to those in a fasted state. Furthermore, Single-dose zuranolone administration at 30 mg resulted in an increase in low-beta electroencephalography power. This outcome aligns with the activation of GABA A receptor by zuranolone. In summary, in healthy Japanese subjects, zuranolone demonstrated good tolerance, unaffected pharmacokinetic profiles by ethnicity or age, and higher plasma exposure in the fed state. The 30-mg dose's observed elevation of low-beta electroencephalography power is consistent with zuranolone's activation of GABA A receptor. (58)

The studies conducted by Deligiannidis KM et al. in 2021 and 2023 focused on assessing zuranolone's effectiveness in treating PPD in women between the ages of 18 and 45 years, within six months postpartum, with a baseline 17-item Hamilton Rating Scale for Depression (HAMD-17) score of 26 or higher. Both were phase 3, double-blind, randomized, placebo-controlled trials carried out from January 2017 to December 2018. The study involved women aged 18 to 45 years, within six months postpartum, experiencing PPD, marked by the onset of a major episode of depression during the third trimester or within four weeks post-delivery, with a baseline HAMD-17 score of 26 or higher. (54, 59) In the initial study (2021), Randomization was done at a 1:1 ratio to either placebo or oral administration of zuranolone at a dose of 30 mg every evening for two weeks. The primary outcome was the alteration in HAMD-17 score from baseline for zuranolone in comparison with a placebo on day 15. Secondary outcome encompassed changes in HAMD-17 total scores at different time points, HAMD-17 response rates (indicating a 50% reduction in score), rates of remission (with a score of 7 or lower), Montgomery-Åsberg Depression Rating Scale score, and Hamilton Rating Scale for Anxiety score. Safety was evaluated through monitoring adverse events and clinical assessments. Of the 153 patients randomized, 150 comprised the efficacy set, with 148 successfully completing the treatment. Among these, 76 were categorised into the placebo group, while 77 received zuranolone at 30 mg. Zuranolone displayed notable improvements in HAMD-17 scores compared to placebo, with significant enhancements observed from day 15 (p = .003). Consistent improvements favoring zuranolone were seen from day 3 (p = .03) to day 45 (p = .003). Additionally, persisting variations that favour zuranolone were noted in HAMD-17 response (p = .005) and HAMD-17 score remission (p = .01) at day 15. In terms of safety, one patient experienced a major adverse event (pancreatitis in the group receiving a placebo and a condition of confusion in the group receiving zuranolone). Among the zuranolone group, one patient discontinued treatment due to an adverse event, but nobody in the placebo group did. The clinical trial concluded that zuranolone effectively ameliorated core depression symptoms, as evidenced by improved women with PPD's HAMD-17 scores, and it was generally well tolerated. These findings support further exploration of zuranolone's potential in treating PPD. (54)

The subsequent study conducted in 2023, Women were separated into two groups at random, 1:1, to receive either oral zuranolone at a dosage of 30 mg once daily (n=77) or a placebo (n=76) for a duration of 14 days, and follow-up assessments were conducted through day 45. The evaluation focused on simultaneous resolution of anxiety and depression symptoms, improvement in insomnia symptoms, patient-perceived functional health, and treatment effect sizes as determined by the NNT (number needed to treat). It's important to note that the analyses conducted were exploratory, and the reported P values are nominal. The findings indicated
higher frequencies of simultaneous remission of anxiety and depression symptoms among individuals administered zuranolone compared to the placebo group (P < .05) at days 3, 15, and 45. Moreover, the rate of continuous concurrent remission, defined as remission on days 15 and 45, was also notably higher in the zuranolone group (P < .05). Anxiety symptoms, assessed by the HDRS-17 anxiety/somatization subscale and Edinburgh Postnatal Depression Scale anxiety subscale, exhibited improvement with zuranolone versus placebo (P < .05) from the third to the 45 day. Furthermore, there were observed advantages for improving symptoms of insomnia and the patient's perception of their functional health. The calculated NNT at day 15 indicated a value of 5 for both HDRS-17 response and remission, indicating the effectiveness of zuranolone in achieving these outcomes. Overall, zuranolone demonstrated concurrent enhancements in both anxiety and depression symptoms, along with positive impacts on symptoms of insomnia and the perception of functional health in patients among adults experiencing postpartum depression (PPD). (59)

In the double-blind phase 3 trial conducted by Deligiannidis KM et al. in 2023, women diagnosed with severe PPD were chosen at random allocated in a 1:1 ratio to receive either zuranolone at a dosage of 50 mg/day or a placebo for a period of 14 days. The primary focus was on the alteration from baseline in the total score on the 17-item Hamilton Depression Rating Scale (HAM-D) at day 15, while secondary endpoints encompassed changes in HAM-D score at days 3, 28, and 45, as well as the modification in Clinical Global Impressions severity (CGI-S) score at day 15. Adverse events were carefully observed during the entire study. Of the 196 patients who undergo randomization (98 for placebo and 98 with zuranolone, a total of 170 individuals (86.7%) successfully completed the 45-day study duration. The analysis revealed that treatment with zuranolone, in comparison to placebo, led to statistically substantial reductions in depressed symptoms at day 15 (measured by the HAM-D score's least squares mean [LSM] change from baseline. Similarly, significant enhancements in depressive symptoms were observed at days 3, 28, and 45. The CGI-S score on day 15 also notably enhanced by zuranolone compared to the placebo. Regarding adverse events, the most frequently reported ones (≥10%) associated with zuranolone included somnolence, dizziness, and sedation. Importantly, there were no instances of loss of consciousness, withdrawal symptoms, or increased suicidal ideation or behavior observed during the trial. In summary, the trial findings demonstrated that zuranolone exhibited notable reductions in depression symptoms and was well-tolerated overall. These results offer encouraging evidence that zuranolone may be developed into a novel, quick-acting oral therapy for PPD. (60)

7. Conclusion
In recent years, there has been significant progress in understanding and addressing postpartum depression (PPD), a condition that significantly affects mothers following childbirth. PPD manifest during the postpartum phase and extends beyond, impacting maternal well-being and the critical mother-infant bond. Symptoms of PPD encompass depressive signs, anxiety, and sleep disturbances, often leading to challenges in diagnosis and treatment, thereby contributing to underrecognition and undertreatment. The pathophysiology of PPD involves multifaceted factors, including altered neuroactive steroid levels, disrupted GABA signaling, and hormonal fluctuations post-delivery. Neurosteroids, particularly allopregnanolone (ALLO), play an essential role in modulating brain excitability through GABA receptors and are linked to stress response regulation. PPD has been linked to dysregulation in the neurosteroidogenesis process, with studies indicating lower ALLO levels in depressed individuals and subsequent normalization post-SSRI treatment. This connection highlights the potential role of SSRIs in promoting neurosteroid synthesis, contributing to their antidepressant effects. The treatment landscape for PPD has predominantly relied on antidepressants, specifically SSRIs, which lack specificity for PPD and have delayed response times. This unmet need for more effective, rapid-acting, and PPD-specific treatments led to the development of brexanolone, the first drug approved by the FDA for PPD. Brexanolone, mimicking the neurosteroid ALLO, demonstrated efficacy in reducing depressive symptoms, albeit with limitations such as the need for intravenous administration, hospitalization, and potential side effects. Recent advancements brought zuranolone into focus—a synthetic neuroactive steroid GABAA receptor modulator. Differentiating itself from brexanolone and benzodiazepines, zuranolone's oral bioavailability and dose once per day set a promising path for treating PPD. Preclinical studies demonstrated its potency in
modulating GABAA receptors, presenting a novel treatment avenue. Clinical trials on zuranolone showed its safety, tolerability, and efficacy in improving depressive symptoms among women with PPD. Zuranolone showed favorable effects on anxiety symptoms, insomnia, and patient-perceived functional health, suggesting a holistic benefit beyond targeting depressive symptoms. Overall, zuranolone emerges as a potential breakthrough in the landscape of PPD treatment, offering a rapid-acting, orally administered option with promising results in ameliorating not only depressive symptoms but also associated anxiety and functional impairments. These findings underscore the need for continued research and development to enhance the options available for mothers experiencing PPD, emphasizing the importance of tailored, effective interventions in promoting mental health and well-being of mothers after giving birth.

References


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