ZAKRZEWSKA, Anna Maria, BOROWSKI, Michał, POPIELARSKA, Kinga, NIWIŃSKA, Klaudia Elżbieta, LEŚNIAK, Natalia Maria, CZAPLIŃSKA-PASZEK, Zofia, PATRZYKĄT, Klaudia Martyna, LEŚNIAK, Julia Aleksandra, MICHALAK, Julia Agnieszka and MIDERA, Aleksander. Zuranolone in Postpartum Depression: A Review of the First Oral Neurosteroid Treatment. Quality in Sport. 2025;48:67350. eISSN 2450-3118.
https://doi.org/10.12775/QS.2025.48.67350
https://apcz.umk.pl/QS/article/view/67350

The journal has been awarded 20 points in the parametric evaluation by the Ministry of Higher Education and Science of Poland. This is according to the Annex to the announcement of the Minister of Higher Education and Science dated 05.01.2024, No. 32553. The journal has a Unique Identifier: 201398. Scientific disciplines assigned: Economics and Finance (Field of Social Sciences); Management and Quality Sciences (Field of Social Sciences).
Punkty Ministerialne z 2019 - aktualny rok 20 punktów. Załącznik do komunikatu Ministra Szkolnictwa Wyższego i Nauki z dnia 05.01.2024 Lp. 32553. Posiada Unikatowy Identyfikator Czasopisma: 201398. Przypisane dyscypliny naukowe: Ekonomia i finanse (Dziedzina nauk społecznych); Nauki o zarządzaniu i jakości (Dziedzina nauk społecznych).
The authors declare that there is no conflict of interest regarding the publication of this paper.
Received: 11.12.2025. Revised: 25.12.2025. Accepted: 25.12.2025. Published: 29.12.2025.

Zuranolone in Postpartum Depression: A Review of the First Oral Neurosteroid Treatment

Anna Maria Zakrzewska, ORCID https://orcid.org/0009-0009-8757-2274

E-mail: lek.annazakrzewska@gmail.com

Central Clinical Hospital of the Medical University of Łódź, Pomorska 251, 92-213 Łódź, Poland

Michał Borowski, ORCID https://orcid.org/0009-0004-7316-2411

E-mail: lek.michalborowski@gmail.com

Independent Public Healthcare Center, Szpitalna 37, 05-300 Mińsk Mazowiecki, Poland

Kinga Popielarska, ORCID https://orcid.org/0009-0009-7797-5301

E-mail: kingapopielarska@gmail.com

Medical University of Gdańsk, Marii Skłodowskiej-Curie 3a, 80-210 Gdańsk, Poland

Klaudia Elżbieta Niwińska, ORCID https://orcid.org/0009-0002-3648-277X

E-mail: klaudia11100210@gmail.com

Independent Public Clinical Hospital named after Prof. W. Orłowski (CMKP), Czerniakowska 231, 00-416 Warszawa, Poland

Natalia Maria Leśniak, ORCID https://orcid.org/0009-0006-0815-6554

E-mail: natalialesniak57@gmail.com

Central Clinical Hospital of the Medical University of Łódź, Pomorska 251, 92-213 Łódź, Poland

Zofia Czaplińska-Paszek, ORCID https://orcid.org/0000-0003-2429-8262

E-mail: czaplinskapaszek@gmail.com

Medical University of Warsaw, Żwirki i Wigury 61, 02-091 Warsaw, Poland

Klaudia Martyna Patrzykąt, ORCID https://orcid.org/0009-0000-9440-5444
E-mail: patrzykat.klaudia@gmail.com
109 Military Hospital with Policlinic in Szczecin, Piotra Skargi 9-11, 70-965 Szczecin, Poland
Julia Aleksandra Leśniak, ORCID https://orcid.org/0009-0005-7375-5951
E-mail: julialesniak577@gmail.com
Central Clinical Hospital of the Medical University of Łódź, Pomorska 251, 92-213 Łódź, Poland
Julia Agnieszka Michalak, ORCID https://orcid.org/0009-0006-2629-7692
E-mail: lekmichalakjulia@gmail.com
Independent Public Healthcare Institution in Kościan, Szpitalna 7, 64-000 Kościan, Poland
Aleksander Midera, ORCID https://orcid.org/0009-0008-5809-427X
E-mail: aleksander.midera@gmail.com
Independent Public Healthcare Center, Tulipanowa 8, 95-060: Brzeziny, Poland

Abstract

Background: Postpartum depression (PPD) is a severe mood disorder affecting 1 in 7 postpartum women. It significantly impacts maternal functioning and infant development. SSRIs are currently the first-line treatment, but require 4-8 weeks to take effect and show variable efficacy. The neurosteroid hypothesis connects PPD symptoms to an abrupt drop in allopregnanolone after childbirth. Zuranolone, a synthetic modulator of the GABA-A receptor, is the first oral neurosteroid specifically indicated for postpartum depression.

Aim: This review analyzes zuranolone's pharmacology, Phase III clinical efficacy, and its practical use for postpartum depression.

Material and methods: We conducted a comprehensive literature review using PubMed. Search terms included „zuranolone", „neurosteroid", and "postpartum depression". We reviewed publications from 2015 to 2025, focusing on Phase III clinical studies, pharmacological analyses, and FDA/EMA regulatory documents.

Results: Zuranolone is administered as 50 mg once daily for 14 days. Two Phase III randomized, placebo-controlled trials (n=150, n=196) evaluated zuranolone for moderate to severe postpartum depression. In the pivotal trial, the least-squares mean difference on the HAM-D was -4.0 versus placebo (95% CI: -6.3 to -1.7; p=0.001). Response rates were 57.0% versus 38.9% (p=0.021), and remission rates were 26.9% versus 16.7%. Effects were seen by day 3 and lasted through day 45.

Conclusions: Zuranolone represents a significant therapeutic advance in the treatment of postpartum depression. It offers immediate symptom relief during the critical early postpartum period. Further research is needed to assess effectiveness and safety in a more heterogeneous population, as well as the long-term effects in mood disorders.

Key words: postpartum depression, zuranolone, neurosteroid, GABA-A receptor, rapid-acting antidepressant, perinatal psychiatry

1. Introduction

Postpartum depression (PPD) affects approximately 1 in 7 women following childbirth [1], representing one of the most common difficulties in the perinatal period. This condition is characterized by persistent depressive symptoms occurring during pregnancy or within four weeks of delivery, though symptoms often persist for months if untreated [2]. PPD significantly impacts maternal well-being, mother-infant bonding, child development, and family functioning [3].

Current treatment for PPD involves a multidisciplinary approach combining psychotherapy with pharmacological interventions in moderate to severe cases [5]. Selective serotonin reuptake inhibitors (SSRIs) such as sertraline are the first-line pharmacological treatment. These antidepressants have significant limitations. Therapeutic onset is delayed, typically requiring 4-6 weeks. Efficacy is variable, and there are concerns regarding infant exposure through breastfeeding. These limitations emphasize the need for rapidly-acting, well-tolerated therapeutic options specific to postpartum women. The neurosteroid hypothesis of PPD has created a new era of PPD medication, with pioneer brexanolone, an intravenous formulation of allopregnanolone, and the newest oral one, zuranolone (Zurzuvae). This synthetic analog

maintains positive allosteric modulation of GABA-A receptors. It demonstrates rapid-onset antidepressant effects within days in Phase III clinical trials, with benefits that last beyond treatment.

Accordingly, this review examines the pharmacology, clinical efficacy, safety profile, and practical implementation aspects of zuranolone in the treatment of postpartum depression. Our work synthesises evidence from pivotal clinical trials and discusses zuranolone's role in addressing unmet needs in perinatal mental health care.

2. Methodology

A comprehensive literature review was conducted in November 2025. We used the PubMed database to identify systematic reviews, clinical trials, and regulatory documents on zuranolone for postpartum depression. Additional sources included FDA and EMA approval documents, prescribing information for zuranolone (Zurzuvae), and Sage Therapeutics publications. Primary search terms included: "zuranolone", "postpartum depression", "GABA-A receptor modulator". Articles were included if they met all of the following criteria: (1) published between 2015 and 2025 to capture recent developments; (2) available in English; (3) study types including randomized controlled trials, Phase II/III clinical trials, systematic reviews, meta-analyses, pharmacokinetic/pharmacodynamic studies, safety analyses, and evidence-based clinical guidelines; (4) full-text availability or abstracts with enough methodological detail and outcome data. Articles were excluded if they: (1) were preclinical or animal studies without human relevance; (2) were case reports; (3) were published before 2015; (4) were in languages other than English; (5) included other mood disorders. After screening, 60 articles were selected for full-text review. Following quality assessment, 36 publications were included in this review.

3. Postpartum depression

3.1. Definition and Characteristics

Motherhood is often regarded as an empowering experience and a primary aspiration for most women. However, childbirth can introduce challenges, including baby blues and postpartum depression (PPD). According to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5), PPD is defined as a major depressive episode with peripartum onset, beginning during pregnancy or within four weeks following delivery, although symptoms may

appear up to several months after childbirth [1, 3, 5, 6]. Diagnosis requires the presence of five or more symptoms, lasting at least two weeks: persistent sadness, anhedonia, diminished interest or pleasure, decreased concentration and appetite, lack of sleep, fatigue or loss of energy, low self-esteem, inappropriate guilt, changes in body weight, recurrent thoughts of death, or suicidal ideation [1-3, 6-7]. Peripartum cases are characterized by manifestations such as difficulties with bonding and feeding, inadequate attachment, social withdrawal, excessive guilt, and inability to care for the baby [1, 3, 4, 8].

Despite its high prevalence and serious consequences, PPD remains underdiagnosed. Only 30.8% of affected women get a formal diagnosis. Just 15.8% receive any treatment, and only 6.3% receive an adequate trial. This gap persists due to stigma, limited mental health service access, and delayed recognition [3].

3.2. Etiology and Pathogenesis

The underlying cause of postpartum depression is unclear. In predisposed individuals, reductions in estrogen and progesterone after birth, combined with psychological stressors, may contribute to the development of PPD. Risk factors include social and psychological challenges, complications during pregnancy, and a family history of psychiatric disorders. Principal risk factors are: a personal history of mood disorders, limited familial support, exposure to domestic violence, high-risk pregnancy, and younger maternal age [3, 9].

The pathogenesis of postpartum depression (PPD) is complex and not fully understood. Some studies suggest that dysregulation of the hormonal system, including an abrupt postpartum decline in progesterone and its neuroactive metabolite allopregnanolone, plays a key role. Allopregnanolone is a positive allosteric modulator of GABA-A receptors. After delivery, rapid withdrawal of this neurosteroid in vulnerable women within 24-48 hours may trigger anxiety, mood changes, and postpartum depression [5, 6, 10].

3.3 Screening and detection

Routine screening for postpartum depression is recommended by major organizations, including the American College of Obstetricians and Gynecologists (ACOG), the American Academy of Pediatrics (AAP), and the American Academy of Family Medicine (AAFP) [5]. Screening should not be limited to pregnancy, but should also be conducted after giving birth. The Edinburgh Postnatal Depression Scale (EPDS) is the most widely validated and utilized

screening instrument. It consists of a 10-item self-report questionnaire that can be completed in about 5 minutes. A score of 9/10 or higher indicates probable depression needing further evaluation. Scores of 12/13 or higher suggest major depression. Item 10, which assesses suicidal ideation, requires immediate clinical attention regardless of the total score [11-14].

Alternative screening instruments include the Patient Health Questionnaire-9 (PHQ-9), a 9-item tool assessing DSM-5 depression criteria, and the Postpartum Depression Screening Scale (PDSS), a 35-item instrument specifically designed for postpartum populations [13]. Despite screening recommendations, significant barriers persist, such as a lack of training in mental health assessment, limited availability of follow-up mental health resources, maternal reluctance to disclose symptoms due to shame or fear of child protective services involvement, and normalization of mood symptoms as a typical postpartum experience [3, 14]. Early detection and intervention are critical, as untreated PPD is associated with prolonged symptom duration, increased suicide risk, impaired mother-infant bonding, and adverse effects on child cognitive and socioemotional development [3, 4].

3.4 Differential diagnosis

Accurate diagnosis of PPD requires differentiation from other postpartum mood disturbances and medical conditions presenting with similar symptoms. The most common one is baby blues, affecting 50-75% of postpartum women, and typically manifests shortly after delivery. Its characteristics are: mild mood lability, tearfulness, anxiety, and irritability that should resolve spontaneously within two weeks without intervention. This condition does not affect the ability to care for the baby or everyday functioning. Yet, postpartum baby blues create a risk for perinatal depression [3].

Postpartum psychosis represents a psychiatric emergency occurring in approximately 1-2 per 1,000 deliveries, typically within the first days to the six weeks after birth. Clinical features include paranoia, severe mood lability, disorganized behavior, confusion, hallucinations, and delusions. Substantial risk of infanticide or maternal suicide requires immediate hospitalization [15].

Clinicians should not forget about other medical conditions that may mimic or coexist with PPD. Hyperthyroidism and hypothyroidism, iron deficiency anemia, vitamin D or B12 deficiency, and chronic medical conditions such as autoimmune disorders are only a few

examples to be remembered [3, 5]. A comprehensive evaluation should be conducted to ensure appropriate treatment is targeted at the underlying etiologies.

3.5 Current Treatment Approaches

Recommended treatment for postpartum depression includes both psychotherapeutic and pharmacological interventions, based on symptom severity as well as patient preference. First-line treatment for mild to moderate severity remains a psychotherapeutic approach that encompasses cognitive-behavioral therapy (CBT) and interpersonal therapy (IPT) [16]. In more severe cases, pharmacological treatment is employed. Current evidence-based guidelines recommend selective serotonin reuptake inhibitors that mitigate depressive symptoms by elevating serotonin levels. Sertraline and escitalopram are the first-choice treatments, while paroxetine should be avoided during pregnancy [3, 8, 16]. SSRIs are generally effective and safe, but the 4-8 week delay before therapeutic benefits emerge can feel impossibly long for a mother struggling with severe depressive symptoms [17]. Other treatments, such as SNRIs (serotonin-norepinephrine reuptake inhibitors) and TCAs (tricyclic antidepressants), are considered when SSRIs are not well tolerated or ineffective [5, 18]. TCAs (e.g., nortriptyline) should be used cautiously, due to their higher transfer to breastmilk and increased risk of overdose [5].

Non-pharmacological therapies, which are transcranial magnetic stimulation and electroconvulsive therapy (ECT), are reserved for patients who do not respond to psychotherapy or pharmacotherapy [3, 5, 18].

A new promising pharmacological approach is currently being developed and evaluated. Brexanolone and zuranolone are neuroactive steroids that modulate GABAa receptors, which might become alternatives in PPD treatment [5-6, 19].

To conclude, currently, there is no ideal way of treating PPD. Pharmacological limitations, such as delayed onset, variable efficacy, adverse effects, and concerns about infant exposure, highlight the need for a rapidly-acting, well-tolerated therapeutic alternative with finite treatment courses specifically designed for the postpartum population.

4. Zuranolone

4.1 Pharmacology and mechanism

Zuranolone (developmental name SAGE-217) is a synthetic neuroactive steroid structurally related to allopregnanolone, incorporating strategic modifications that enable oral administration while maintaining positive allosteric modulation of GABA-A receptors [19-21]. Developed by Sage Therapeutics Inc. and Biogen Inc., it was approved by the FDA in August 2023 under the name "ZURZUVAE" for the treatment of postnatal depression in adult women. In the European Union, the Committee for Medicinal Products for Human Use (CHMP) adopted a positive opinion in July 2025 and authorized it in September 2025 [22]. The wholesale acquisition cost in the USA for a 14-day treatment course is priced at $15,900 USD [23]. In the EU, there is no fixed price for zuranolone yet.

The recommended dosage of zuranolone is 50 mg taken orally once daily in the evening for 14 days [24]. Following oral administration, it demonstrates adequate gastrointestinal absorption. Administration with a fatty meal (approximately 400 to 1,000 calories, 25% to 50% fat) is essential, as food substantially increases bioavailability. The peak of zuranolone concentration is achieved approximately 5-6 hours after dosing. The elimination half-life ranges from 19.7 to 24.6 hours, supporting once-daily dosing. Zuranolone undergoes hepatic metabolism primarily via cytochrome CYP3A4 [19, 24, 25]. Concomitant use of strong CYP3A4 inhibitors (e.g., clarithromycin, fluoxetine, grapefruit juice) may require a reduction in dosage to avoid adverse effects, whereas CYP3A4 inducers (e.g., rifampin, carbamazepine) may decrease the efficacy of zuranolone, and thus should be avoided during treatment.

During clinical trials, the drug was generally well-tolerated. The most common adverse effect was somnolence, which, in a few cases, led to a dosage reduction or discontinuation of treatment. Other reported reactions were dizziness, diarrhea, fatigue, and urinary tract infection [21, 24, 26]. Yet, the severity was mild to modest [27].

The first neuroactive steroid that was approved by the FDA in 2019 for the treatment of PPD was Brexanolone. It was administered as a continuous intravenous infusion over 60 hours under medical supervision [21, 28]. A recent study by Wilson CA et al., published in 2025, demonstrates that brexanolone may have little or no effect on symptoms (response and remission) in PPD compared with placebo [29]. Regardless, the FDA withdrew the drug's approval in April 2025 [30, 31]. The company Sage Therapeutics Inc.'s strategic plan is to focus on the commercialization of zuranolone for the treatment of women with PPD [32]

4.2. Clinical Trials and Efficacy

Initial phase III evaluation of zuranolone in women with postpartum depression was conducted by Deligiannidis et al. (2021) in a double-blind, randomized, placebo-controlled trial with 150 participants with postpartum depression. Inclusion criteria were: age between 18 and 45 years, within 6 months postpartum, with PPD (major depressive episode beginning peripartum in the third trimester or within 4 weeks postdelivery), and baseline 17-item Hamilton Rating Scale for Depression (HAMD-17) score of 26 or higher. Participants received zuranolone 30 mg for 2 weeks. The study demonstrated a substantial reduction in depressive symptoms compared with placebo at day 15, as evidenced by a change from baseline on the HAMD-17 (least-squares mean, −17.8 points vs placebo, −13.6 points; 95% CI, −6.9 to −1.5; P = .003; effect size, 0.53). By day 3, improvements became apparent and remained at all measured time points through day 45 (day 3: least-squares means difference, −2.7; 95% CI, −5.1 to −0.3; P = .03; day 45: least-squares means difference, −4.1; 95% CI, −6.7 to −1.4; P = .003). Patients receiving zuranolone achieved higher response and remission rates compared to placebo (response: 72% vs 48% and remission: 45% vs 23%). An improvement from baseline was also observed on the Montgomery-Åsberg Depression Rating Scale (MADRS), the Hamilton Anxiety Rating Scale (HAM-A), the Clinical Global Impression - Improvement Scale (CGI-I), and the Barkin Index of Maternal Functioning (BIMF). The medicine was well tolerated, with adverse events generally mild to moderate. Findings from this trial indicate that zuranolone not only has a great and fast-acting antidepressant effect, but also improves maternal functioning and reduces anxiety. These findings were later confirmed in upcoming studies [27].

Building on the positive results of the 30 mg dose study, the pivotal Phase III trial by Deligiannidis et al. evaluated the higher 50 mg dose in women with severe postpartum depression. The study, published in 2023, was a randomized, double-blind, placebo-controlled study evaluating zuranolone in PPD. 196 women, in a 1:1 ratio, received 50 mg/day of zuranolone or placebo for 14 days, and were monitored through day 45 post-treatment. Participants included had a baseline score ≥ 26 on the 17-item Hamilton Depression Rating Scale (HAMD-17) and experienced a major depressive episode with peripartum onset (occurring during the third trimester or within 4 weeks postpartum) and presented within 12 months postpartum. At day 15, the primary outcome was met. The mean change in HAMD-17 score from baseline was -15.6 points in the zuranolone group compared to -11.6 points in the placebo group, representing a least squares mean difference of -4.0 points (95% CI: -6.3 to -1.7, p=0.001, Cohen's d=0.52). This 4-point difference exceeded most accepted thresholds for

clinical significance in depression research, suggesting real-world benefits for patients. At day 15, response rates (≥50% reduction in HAMD-17) were 57.0% for zuranolone versus 38.9% for placebo (p=0.021), indicating that significantly more women achieved substantial symptom improvement with active treatment. Remission rates (HAM-D ≤7) were 26.9% for zuranolone versus 16.7% for placebo (p=0.111). Significant separation from placebo was observed as early as day 3 of treatment, with the advantage maintained and increasing through day 15. The rapid onset of therapeutic effects represents a notable advantage over traditional antidepressants, which typically require 4-6 weeks for initial response [33].

A 2024 phase I open-label study (Deligiannidis et al.) evaluated zuranolone transfer into breast milk in 15 lactating women receiving 30 mg daily for 5 days. The mean relative infant dose (RID; weight-adjusted proportion of the maternal dose in breast milk over 24 hours) was 0.357% for the 30 mg dose. The estimated mean RID for 50 mg zuranolone was 0.98%, suggesting low transfer into breast milk. Further studies with larger samples and the FDA-approved 50 mg dose are needed to fully characterize the risk of infant exposure [34].

4.3. Limitations

Despite promising Phase III clinical trial findings, several important limitations should be considered. The first limitation concerns the follow-up duration in pivotal studies, which extended only to 45 days. It was insufficient to assess the long-term durability of response or relapse rates. Longer-term studies are needed to evaluate sustained efficacy, identify factors predicting relapse, and determine optimal strategies for women experiencing symptom recurrence after initial treatment response. Trial populations also were relatively homogeneous, with limited representation of diverse ethnic, racial, and socioeconomic groups. Future studies should include a more diverse range of participants to identify potential variations in treatment response. Additionally, the absence of direct head-to-head comparisons with standard treatments, including SSRIs and evidence-based psychotherapy, limits the ability to determine zuranolone's comparative effectiveness and optimal positioning within treatment algorithms. An important limitation is the exclusion of women with bipolar disorder or psychotic features - populations we frequently encounter in clinical practice. Thus, studies with more heterogeneous groups, including patients with a history of psychiatric diseases and those with diverse PPD onset timing, are needed [26, 33, 35, 36].

4.4. Zuranolone in real life

Real-world evidence for zuranolone in clinical practice settings remains narrow, given its recent approval. Several practical considerations have emerged from early clinical experience. The requirement for administration with a high-fat meal might pose adherence challenges. Postpartum women commonly have irregular eating habits due to infant care demands, sleep deprivation, and appetite changes. Whether suboptimal meal requirements affect therapeutic response in real-world settings remains to be investigated. The sleepiness profile of zuranolone necessitates careful patient counseling regarding driving, operating machinery, and caring for the infant. Women living alone or lacking adequate social support may face particular challenges in everyday life. Clinical experience suggests that careful patient selection optimizes outcomes. Zuranolone may be less suitable for women with a limited support environment, those who must maintain full caregiving responsibilities, or patients with comorbid conditions requiring medication regimens that may interact with CYP3A4 metabolism. Safety and efficacy data are lacking for women with bipolar disorder or psychotic features, those with PPD onset beyond 12 months postpartum, adolescent mothers under age 18, and those with significant medical comorbidities. Real-world registries and observational studies will be essential to characterize outcomes in these understudied populations. While pharmacokinetic data suggest a low relative infant dose, during the decision-making process, clinicians must weigh the benefits of rapid maternal symptom improvement against theoretical risks of infant exposure.

Key unanswered questions include: What proportion of responders maintain remission beyond 6 months? What are the relapse rates after treatment discontinuation? Is zuranolone effective for women excluded from the initial clinical trials? How do real-world outcomes compare to SSRI therapy? Systematic post-marketing surveillance and patient registries will be critical for addressing these gaps and refining evidence-based prescribing guidelines.

4.5. Summary

In summary, Phase III clinical trials have established zuranolone as an effective and innovative treatment for postpartum depression. Both the 30 mg and 50 mg dose studies demonstrated statistically significant improvements in depressive symptoms compared to placebo. The rapid onset of action, with therapeutic effects emerging by day 3, offers potential relief during the critical early postpartum period when maternal functioning and infant bonding are paramount. The finite 14-day treatment course may appeal to women hesitant about long-term medication

use. These findings suggest that zuranolone addresses a gap in PPD management. It provides rapid symptom alleviation with sustained efficacy. Nevertheless, longer-term follow-up studies and real-world effectiveness data are needed to fully characterize the durability of response and identify optimal patient selection criteria for this novel neurosteroid therapy.

5. Conclusion

Zuranolone is a significant advancement in postpartum depression treatment as the first orally administered neurosteroid antidepressant approved for this indication. Phase III clinical trials demonstrated rapid onset of therapeutic effects within 3 days, sustained benefits extending 4 weeks beyond the 14-day treatment period, and clinically meaningful improvements in depressive symptoms, maternal functioning, and anxiety compared to placebo. This medication provides quick symptom relief during the vulnerable early postpartum period. While zuranolone represents an important therapeutic progress, limitations, including high cost, little long-term follow-up data, and absence of comparative effectiveness studies with standard treatments, need acknowledgement. As real-world clinical experience accumulates and ongoing research further clarifies patient selection, treatment positioning, and long-term outcomes, zuranolone has the full potential to meaningfully improve maternal mental health and infant development. This neurosteroid-based approach represents a shift in perinatal psychiatry. It validates the neurobiological hypothesis of PPD and offers hope for women requiring rapid symptom relief during the postpartum critical period.

Disclosure:

Author Contributions

Conceptualization: Anna Maria Zakrzewska, Julia Aleksandra Leśniak, Julia Agnieszka Michalak, Michał Borowski

Methodology: Kinga Popielarska, Zofia Czaplińska-Paszek, Klaudia Martyna Patrzykąt

Formalanalysis: Julia Agnieszka Michalak, Aleksander Midera, Klaudia Martyna Patrzykąt

Writing-Rough Preparation: Anna Maria Zakrzewska, Klaudia Elżbieta Niwińska, Natalia Maria Leśniak, Aleksander Midera,

Writing - Review and Editing: Anna Maria Zakrzewska, Michał Borowski, Kinga Popielarska, Julia Aleksandra Leśniak,

Project administration: Anna Maria Zakrzewska, Klaudia Elżbieta Niwińska, Natalia Maria Leśniak, Zofia Czaplińska-Paszek

All Authors have read and agreed with the published version of the manuscript.

Funding Statement:

The Authors did not receive special funding

Institutional Review Board Statement

Not applicable

Informed Consent Statement

Not applicable

Data Availability Statement

Not applicable

Conflicts of Interest Statement

The authors declare no conflicts of interest

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