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Przemysław Rupiński[1–3], Tadeusz Pietras[3]

New drugs for postpartum depression: brexanolone and zuranolone

Nowe leki przeciw depresji poporodowej: breksanolon i zuranolon

[1] Faculty of Medicine, Lazarski University, Warsaw, Poland
[2] Faculty of Psychology, University of Warsaw, Warsaw, Poland
[3] 2nd Department of Psychiatry, Institute of Psychiatry and Neurology, Warsaw, Poland
Correspondence: Przemysław Rupiński, Faculty of Medicine, Lazarski University, Świeradowska 43, 02-622 Warsaw, Poland, e-mail: rupinskiprzemyslaw@gmail.com

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ORCID iDs
1. Przemysław Rupiński https://orcid.org/0009-0002-3858-3216
2. Tadeusz Pietras https://orcid.org/0000-0003-1771-3819

Abstract

This article presents two novel treatments for postpartum depression – brexanolone and zuranolone – and evaluates their efficacy and safety based on randomised clinical trials. Postpartum depression is a common mental health disorder affecting women after childbirth. Studies indicate that it may affect up to 25% of mothers in the postnatal period. Brexanolone and zuranolone are novel medications that act as modulators of GABA-A receptors, offering the potential for faster and more effective treatment. Randomised clinical trials and subsequent meta-analyses have demonstrated that intravenously administered brexanolone produces a significant reduction in symptoms within 24 hours, with effects lasting for at least 30 days. By contrast, orally administered zuranolone achieved symptom remission in 45% of patients after 15 days of therapy, with benefits persisting for at least 45 days. Brexanolone and zuranolone represent promising therapeutic options for women experiencing postpartum depression, offering both rapid and sustained relief of symptoms. These agents mark a significant advance in the pharmacological management of postpartum depression, addressing the critical need for faster onset of action compared with traditional antidepressants, which often require several weeks to exert an effect. Both drugs are generally well tolerated, although side effects such as drowsiness, headache, and dizziness may occur. Further studies are warranted to fully evaluate the long-term safety and efficacy of these novel treatments.

Keywords: postpartum depression, brexanolone, zuranolone

Streszczenie

W artykule przedstawiono nowe leki na depresję poporodową – breksanolon i zuranolon, a następnie oceniono ich skuteczność oraz bezpieczeństwo na podstawie randomizowanych badań klinicznych. Depresja poporodowa jest powszechnym zaburzeniem psychicznym dotykającym kobiety po porodzie. Badania pokazują, że może dotykać nawet do 25% z nich. Breksanolon i zuranolon to nowe leki modulujące receptory GABA-A, oferujące potencjalnie szybsze i skuteczniejsze leczenie depresji poporodowej. Randomizowane badania kliniczne oraz późniejsze metaanalizy wykazały, że dożylnie podawany breksanolon powoduje istotne zmniejszenie objawów w ciągu 24 godzin, a efekty utrzymują się przez co najmniej 30 dni. Z kolei doustnie podawany zuranolon spowodował remisję objawów u 45% pacjentek po 15 dniach terapii, a efekty utrzymywały się przez co najmniej 45 dni. Breksanolon i zuranolon są obiecującymi opcjami terapeutycznymi dla kobiet cierpiących na depresję poporodową, oferując szybką i trwałą ulgę w objawach. Stosowanie tych leków stanowi znaczący postęp w farmakologicznym leczeniu depresji poporodowej, odpowiadając na krytyczną potrzebę szybkiego działania w porównaniu z tradycyjnymi lekami przeciwdepresyjnymi, które często wykazują efekt po wielu tygodniach przyjmowania. Oba leki są na ogół dobrze tolerowane, choć mogą powodować skutki uboczne, takie jak senność oraz bóle i zawroty głowy. Konieczne są dalsze badania, aby w pełni ocenić ich długoterminowe bezpieczeństwo i skuteczność.

Słowa kluczowe: depresja poporodowa, breksanolon, zuranolon

INTRODUCTION

Postpartum depression (PPD) is a common and serious mental health disorder that causes considerable distress in women during the perinatal period. As early as Hippocrates, mood changes were noted in women in the postpartum period, but PPD was not officially recognised in the DSM classification until 1994 (Miller, 2002). In the DSM-5-TR, PPD is specified as a depressive disorder with peripartum onset.

The condition is estimated to affect 5–25% of women after childbirth, with higher prevalence observed in developing countries. During the COVID-19 pandemic, the proportion of women suffering from PPD was reported to rise to 34% (Chen et al., 2022).

Research has identified a wide range of biological and psychosocial risk factors for PPD. Important aspects include previous episodes of depression (during pregnancy or otherwise), a family history of PPD, anxiety disorders in pregnancy, young maternal age, low socioeconomic status, a history of antenatal depression, and the use of antidepressants before pregnancy. The risk is also increased by obstetric complications such as gestational diabetes, pre-eclampsia, hospitalisation during pregnancy, emergency caesarean section, or epidural anaesthesia during labour. In addition, the sex of the child may be a predisposing factor, with some studies suggesting a higher risk of PPD among mothers of boys. Stressful life events, traumatic experiences prior to pregnancy, premature rupture of membranes, as well as difficulties with lactation and sleep disturbances in the postpartum period, are other significant contributors. Insufficient social support, particularly a lack of support from a partner, further increases the risk of developing PPD. Conversely, protective factors – such as strong social support, emotional stability, physical activity, and good sleep quality – may reduce the risk of developing this disorder (Klein et al., 2024).

An increasing body of evidence points to an association between PPD and the bipolar spectrum. Studies conducted in a population of Polish patients demonstrated that women with a positive score on the Edinburgh Postnatal Depression Scale (EPDS) were significantly more likely also to obtain a positive score on the Mood Disorder Questionnaire (MDQ), suggesting that in some patients PPD may represent the first manifest episode of bipolar disorder (Dudek et al., 2014).

Insufficient support from a partner, single motherhood, smoking during pregnancy, and previous treatment for infertility have all been associated with an increased risk of developing the condition.

Beyond the burden of the illness itself, PPD may also have negative consequences for the child. Maternal mood disturbances weaken the ability to establish a healthy emotional bond, which may affect the child's development in terms of emotional regulation and adaptive capacities. Research indicates that children of mothers suffering from PPD may experience difficulties in initiating and maintaining social interactions and may be more vulnerable to emotional problems, including an increased risk of anxiety disorders later in life (Jaeschke et al., 2012; Liu et al., 2022). A systematic review of 14 studies involving 6,406,245 women during pregnancy and the postpartum period found that the average global incidence of suicide attempts was 680 per 100,000 (95% confidence interval, 0.10–4.69%) during pregnancy and 210 per 100,000 (95% confidence interval, 0.01–3.21%) in the first year after delivery. Although suicide attempts and suicides are relatively rare in the perinatal period, experts emphasise the need to implement effective preventive strategies (Rao et al., 2021). It is also noteworthy that suicide accounts for as many as 20% of deaths in the postpartum period, highlighting the importance of early diagnosis and effective treatment of PPD (Lindahl et al., 2005).

In the pharmacological treatment of PPD, selective serotonin reuptake inhibitors (SSRIs) are most commonly used as first-line therapy. Examples include sertraline, paroxetine, citalopram, escitalopram, and fluoxetine. Most of these agents, particularly sertraline and paroxetine, are characterised by low levels of transfer into breast milk, making them preferred options for women who are breastfeeding. Sertraline (categorised as L2 in Hale's classification) is among the most frequently prescribed medications during lactation, as its concentration in breast milk is low and the risk of adverse effects in infants is minimal (Den Besten-Bertholee et al., 2024; Drugs and Lactation Database: Sertraline, 2025).

Paroxetine (classified as L2) also shows low levels of transfer into breast milk, although in rare cases infants may experience mild adverse effects such as irritability or feeding difficulties (Drugs and Lactation Database: Paroxetine, 2025).

Citalopram and escitalopram (classified as L2) pass into breast milk, but their concentrations are relatively low and the risk of adverse effects in infants is small. Infants breastfed by mothers taking these medications rarely exhibit noticeable effects such as excessive sleepiness or irritability, and no serious developmental adverse effects have been observed (Drugs and Lactation Database: Citalopram, 2025; Escitalopram, 2025).

Fluoxetine (classified as L2) is also considered a safe choice during lactation; however, its long half-life and the presence of an active metabolite (norfluoxetine) may lead to higher concentrations in infants' blood. For this reason, some experts recommend caution, particularly in infants during the first months of life. Although fluoxetine is classified as L2, it may be less preferred than other SSRIs owing to the risk of drug accumulation in infants (Drugs and Lactation Database: Fluoxetine, 2025).

Nortriptyline (L2), a tricyclic antidepressant, is considered one of the preferred agents during lactation. It is characterised by low levels of transfer into breast milk, with minimal risk of adverse effects. It is regarded as one of the safest drugs in this group and is relatively frequently chosen in the treatment of PPD in breastfeeding women (Drugs and Lactation Database: Nortriptyline, 2025).

Serotonin–norepinephrine reuptake inhibitors (SNRIs), such as venlafaxine (L2) and duloxetine (L3), are also used in the treatment of PPD, but caution is advised, particularly in preterm infants or those showing signs of excessive sleepiness. Venlafaxine and duloxetine pass into breast milk, and their metabolites are detectable in infants, which necessitates monitoring (Drugs and Lactation Database: Venlafaxine, 2025). Mirtazapine (L3) is considered relatively safe during lactation, although data on its use remain limited. Consequently, as with other medications, monitoring infants for potential adverse effects is important (Hale and Krutsch, 2022; Ostenfeld et al., 2025).

The pathophysiology of PPD is complex and not yet fully understood. However, evidence suggests that biological factors such as hormones, genetics, and immune system functioning may play a significant role in the development of the condition. Particular attention has been paid to reproductive hormones, which are considered important in the aetiology of PPD due to their influence on emotional processes, arousal, cognitive functions, and motivation (Schiller et al., 2015).

Numerous studies have shown that changes in the levels of allopregnanolone, the principal metabolite of progesterone, may have a substantial impact on the development of PPD. Allopregnanolone acts as a modulator of γ-aminobutyric acid (GABA) receptors, which are implicated in both anxiety and depression. Recent studies suggest that the sharp decline in allopregnanolone levels after childbirth may be a triggering factor for PPD through mechanisms related to GABA receptors (Epperson et al., 2006). In 2019, the U.S. Food and Drug Administration approved intravenous allopregnanolone as a therapy for PPD (Sage Therapeutics, 2019; U.S. Food and Drug Administration, 2019), and in 2023 it also authorised oral zuranolone (U.S. Food and Drug Administration, 2023). The following sections outline both drugs and the research conducted on them.

METHODOLOGY

The review involved a literature search in medical databases such as PubMed, using the terms "brexanolone" and "zuranolone". Only randomised controlled trials (RCTs) investigating psychiatric applications were considered; studies focused on non-psychiatric uses were excluded. After removing duplicates and harmonising records referring to the same clinical trials, the methodology, study populations, interventions, outcomes, and reported adverse effects were analysed. Findings were summarised narratively, with emphasis on key results, differences between studies, and potential clinical implications.

Brexanolone

Brexanolone (formerly SAGE-547) is an aqueous formulation of allopregnanolone based on β-cyclodextrin, which can be administered intravenously, allowing stable serum levels to be achieved. It is chemically identical to naturally produced allopregnanolone, a neurosteroid that plays an important role in mood regulation, particularly in the postpartum period. Allopregnanolone has poor oral bioavailability and is rapidly metabolised, which makes intravenous administration capable of achieving a therapeutic effect within a short time, effectively compensating for the decline in neurosteroid levels after childbirth.

The mechanism of action of brexanolone in the treatment of PPD is not yet fully understood, but it is believed to be associated with GABA-A receptor activity. Unlike benzodiazepines, brexanolone acts on both subtypes of GABA-A receptors (synaptic and extrasynaptic), affecting different aspects of GABAergic activity, both phasic (synaptic) and tonic (extrasynaptic). This difference in mechanism of action may explain the faster and more sustained antidepressant effect of brexanolone in the treatment of PPD compared with drugs acting mainly on synaptic receptors, such as benzodiazepines, which are primarily used in the treatment of anxiety disorders but have limited influence on tonic GABAergic activity (Chuang and Reddy, 2018).

In the treatment of PPD, brexanolone could potentially compensate for the sharp decline in allopregnanolone levels after childbirth, providing doses comparable to endogenous concentrations of this neurosteroid in the third trimester of pregnancy (Kanes et al., 2017a).

Three RCTs on brexanolone have been published, two of which focused on severe PPD and one on moderate PPD (Tab. 1).

In all three RCTs, a titration regimen of gradual dose escalation followed by tapering was employed: 30 μg/kg/h – 60 μg/kg/h – 30 μg/kg/h or 30 μg/kg/h – 60 μg/kg/h – 90 μg/kg/h – 60 μg/kg/h – 30 μg/kg/h.

Remission was defined as a 50% reduction in the score on the Hamilton Depression Rating Scale (HAM-D).

Results of the RCTs

1. **Kanes et al. (2017b):**
   - This study produced a statistically significant reduction in the severity of symptoms of severe PPD with

Publication	Study sample (brexanolone vs. placebo)	Indication	Dose	Trial duration	Trial
Kanes et al. (2017b)	10/11	Severe postpartum depression	30–90 μg/kg/h	Up to 30 days	NCT02614547
Meltzer-Brody-1 (2018)	54/54	Moderate postpartum depression	30–90 μg/kg/h	Up to 30 days	NCT02942017
Meltzer-Brody-2 (2018)	46/92	Severe postpartum depression	30–60, 30–90 μg/kg/h	Up to 30 days	NCT02942004

Tab. 1. RCTs on brexanolone

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brexanolone at a maximum dose of 90 μg/kg/h compared with placebo after 24 hours. The effect was maintained during the 30-day follow-up.

2. **Meltzer-Brody et al. (2018):**
   - This study included patients with severe PPD who received infusions at maximum doses of 60 μg/kg/h and 90 μg/kg/h, as well as patients with moderate PPD who received an infusion at a maximum dose of 90 μg/kg/h;
   - Only patients with severe PPD, receiving brexanolone at a maximum dose of 60 μg/kg/h, showed a comparable response to that reported in Kanes et al. (2017b);
   - In both groups receiving brexanolone at a maximum dose of 90 μg/kg/h, a statistically significant difference compared with placebo was observed after completion of the 60-hour infusion. This effect was sustained during the 30-day follow-up only in the severe PPD group;
   - In the moderate PPD group, the severity of depression measured by the HAM-D did not show a statistically significant difference compared with the control group, although an effect was observed between the second and seventh day after initiation of brexanolone treatment.

Meta-analyses

1. **Zheng et al. (2019):**
   - It was demonstrated that the statistically significant advantage of brexanolone began within 24 hours, peaked at 36 hours, and persisted for 7 days. Short-term remission began after 24 hours, reached its peak at 60 hours, and lasted up to 72 hours. This effect was compared with the antidepressant action of a single ketamine infusion (Kishimoto et al., 2016).
2. **Gerbasi et al. (2021):**
   - Researchers involved in the three previously mentioned RCTs conducted a meta-analysis showing that the antidepressant effect of brexanolone persists for at least 30 days. They also found that the effect of brexanolone lasts longer than that of a single ketamine infusion.

Adverse effects of brexanolone

In the case of brexanolone, both adverse effects and serious adverse events have been documented. In clinical trials, the most commonly reported adverse effects included drowsiness, headache, dry mouth, and sedation. Other reactions comprised suicidal ideation, dizziness, syncope, tachycardia, and hot flushes. In one patient, severe drowsiness resulted in a brief episode of apnoea lasting less than one minute during drug administration (Reddy et al., 2023).

Zuranolone

Zuranolone (formerly SAGE-217) is a synthetic positive allosteric modulator of the GABA-A receptor, selective for this receptor. Unlike benzodiazepines, which act mainly on synaptic GABA-A receptors, zuranolone influences both synaptic and extrasynaptic GABA-A receptors, thereby exerting a broader effect on GABAergic activity. Zuranolone enhances the activation of both synaptic receptors containing the γ subunit and extrasynaptic receptors containing the σ subunit, providing more comprehensive modulation of GABAergic activity (both phasic and tonic).

Additionally, zuranolone exhibits non-competitive synergistic activity with diazepam. Thanks to its improved pharmacokinetic properties, zuranolone can be administered orally, which enhances its therapeutic availability compared with other neurosteroids such as allopregnanolone, which has poor oral bioavailability and is rapidly metabolised (Althaus et al., 2020; Marecki et al., 2023).

Eight RCTs on zuranolone have been published. Two studies focused on PPD, five on the treatment of general depressive episodes, and one on insomnia (Tab. 2). In addition, one open longitudinal study was conducted. In these trials, zuranolone was administered orally at doses of 20–50 mg per day.

The ROBIN and SKYLARK studies, both examining PPD, confirmed the efficacy of zuranolone relative to placebo. In the ROBIN study, remission was achieved in 45% of patients after 15 days of treatment with zuranolone at a daily dose of 30 mg, compared with 23% in the control group. After 45 days, remission was observed in 52% of patients in the treatment group and 30% in the control group. In the SKYLARK study, in which patients received 50 mg of zuranolone daily, 27% achieved remission after 15 days and 44% after 45 days, compared with 17% and 29% respectively in the placebo group. Remission was defined as a 50% reduction in the HAM-D score.

A meta-analysis conducted by Li et al. (2024) confirmed the efficacy of zuranolone in the treatment of PPD, as demonstrated in the ROBIN and SKYLARK studies.

Zuranolone has also been investigated in relation to major depressive episodes. Studies showed that its antidepressant effect was observed as early as the third day of treatment, and these effects persisted for at least two weeks. However, no statistically significant difference compared with placebo was observed on days 42/43.

In 2024, Parikh et al. published a study comparing zuranolone administered alongside traditional antidepressant therapies (ADT) with placebo plus ADT. The study demonstrated that the combination of zuranolone with ADT was more effective than placebo with ADT during the first two weeks of treatment (Parikh et al., 2024).

Bullock et al. (2022) focused on the aspect of insomnia. It has been shown that zuranolone at doses of 30 mg and 45 mg significantly improved sleep quality compared with placebo. The median sleep efficiency was 84.6% and 87.6% for zuranolone, compared with 72.9% for placebo. Wake time decreased to 55.0 minutes (30 mg) and 42.5 minutes (45 mg), compared with 113.0 minutes for placebo. Total sleep time increased to 406.3 minutes (30 mg) and 420.3 minutes (45 mg), compared with 350.0 minutes for placebo.

Publication	Study sample (zuranolone vs. placebo)	Duration of therapy	Indication	Dose	Location	Clinical trial
Gunduz-Bruce et al. (2019); Suthoff et al. (2022)	45/45	Up to day 42	Depression	30 mg/day	USA	201B (NCT03000530)
Werneburg et al. (2020)	380/190	Up to day 182	Depression	20, 30 mg/day	USA	MOUNTAIN (NCT03672175)
Cutler et al. (2023)*	924	Up to one year	Depression	30, 50 mg/day	USA	SHORELINE (NCT03864614)
Deligiannidis et al. (2021)	77/76	Up to day 45	Postpartum depression	30 mg/day	USA	ROBIN (NCT02978326)
Bullock et al. (2022)	86/41	After 7 days	Insomnia	30–45 mg/day	USA	NCT03284931
Deligiannidis et al. (2023a); Deligiannidis et al. (2023b)	98/98	Up to day 45	Postpartum depression	50 mg/day	USA, UK, Spain	SKYLARK (NCT04442503)
Clayton et al. (2023)	266/268	Up to day 42	Depression	50 mg/day	USA	WATERFALL (NCT04442490)
Kato et al. (2023)	167/83	Up to day 99	Depression	20, 30 mg/day	Japan	JapicCTI-205276
Parikh et al. (2024)	212/218	Up to day 42	Depression	50 mg/day + antidepressants	USA	CORAL (NCT04476030)
* Open-label study.						

Tab. 2. RCTs on zuranolone

Comparison of costs and effectiveness of treating PPD with zuranolone and SSRIs

In the context of PPD treatment, O'Callaghan et al. (2024) compared zuranolone with traditional SSRIs in terms of cost-effectiveness in the United States. Although zuranolone was associated with higher direct treatment costs (USD 15,902 for a 14-day course), it proved more cost-effective for the long-term management of PPD. The study found that, owing to its faster onset of action, zuranolone was linked to lower overall healthcare costs, including fewer hospitalisations and reduced losses from absenteeism and decreased work productivity. Zuranolone also demonstrated more favourable outcomes in terms of quality of life (quality-adjusted life year, QALY), suggesting that rapid improvement in patients' health may reduce the long-term social and healthcare costs associated with PPD. Zuranolone provides a more balanced cost-to-quality-of-life ratio compared with SSRIs, making it a preferable option, particularly in the context of faster recovery and reduced treatment-related expenditure.

Adverse effects of zuranolone

Across all included studies, adverse events were reported during the administration of either zuranolone or placebo. In particular, somnolence, dizziness, and sedation occurred more frequently in the zuranolone group than in the placebo group. However, there was no significant difference in the incidence of serious adverse events between the two groups. In addition, the frequency of infections, headache, nausea, diarrhoea, and fatigue did not differ significantly between participants receiving zuranolone and those receiving placebo (Li et al., 2024).

CONCLUSIONS

Brexanolone and zuranolone are innovative treatments for PPD that act by modulating GABA-A receptors. Clinical studies have confirmed their effectiveness in rapidly reducing depressive symptoms, with brexanolone administered intravenously and zuranolone taken orally. Both medications are generally well tolerated, although adverse effects may occur. Their introduction offers new therapeutic options for women with PPD; however, further research is needed to fully evaluate their long-term benefits and risks.

Conflict of interest

The authors do not declare any financial or personal links with other persons or organisations that might adversely affect the content of the publication or claim any right to the publication.

Author contribution

Original concept of study; collection, recording and/or compilation of data; analysis and interpretation of data; writing of manuscript: PR. Critical review of manuscript; final approval of manuscript: TP.

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