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CLINICAL PRACTICE UPDATE

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Zuranolone and Brexanolone for the Treatment of Postpartum Depression

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The Society for Maternal-Fetal Medicine endorses this document.

This Clinical Practice Update provides revised guidance on the use of brexanolone and zuranolone in the postpartum period for depression that has onset in the third trimester or within 4 weeks postpartum. This document is a focused update of related content in Clinical Practice Guideline No. 5, *Treatment and Management of Mental Health Conditions During Pregnancy and Postpartum* (Obstet Gynecol 2023;141:1262–88) and replaces the August 2023 Practice Advisory, *Zuranolone for the Treatment of Postpartum Depression*.

BACKGROUND

Perinatal mental health conditions, manifesting in outcomes such as suicide and overdose or poisoning, are a leading cause of overall and preventable maternal mortality (1, 2). As such, understanding, discussing, and recommending nonpharmacologic therapy, as well as providing pharmacologic treatment when indicated and needed, fall within the scope of the obstetrician–gynecologist's practice (3). Although selective serotonin reuptake inhibitors (SSRIs) and serotonin–norepinephrine reuptake inhibitors (SNRIs) are commonly used medications to treat major depressive disorder including perinatal depression, the only U.S. Food and Drug Administration (FDA)–approved treatments specifically for postpartum depression are two neuroactive steroids that act as positive allosteric modulators of gamma-aminobutyric acid (GABA) A receptors: brexanolone (approved in 2019) and zuranolone (approved in 2023) (4, 5). Brexanolone, administered as an inpatient 60-hour intravenous infusion, is no longer commercially available in the United States as of January 1, 2025 (6, 7). Zuranolone is available; it is administered orally for 14 days.

UPDATED CLINICAL RECOMMENDATION

The American College of Obstetricians & Gynecologists recommends consideration of zuranolone in the postpartum period (ie, within 12 months of delivery) for severe depression that has onset in the third trimester or within 4 weeks postpartum. The decision to use zuranolone should balance the benefits (ie, significantly improved and rapid symptom resolution compared with placebo) alongside challenges specific to initiating and managing this medication that are described in this Clinical Practice Update.

RATIONALE

ACOG recommended consideration of brexanolone administration by intravenous infusion in the postpartum period for moderate-to-severe perinatal depression with onset in the third trimester or within 4 weeks postpartum (3). However, brexanolone is no longer commercially available in the United States as of January 1, 2025. The FDA approval was withdrawn as of April 14, 2025, as requested by the manufacturer given practical treatment limitations associated with complex logistics and high cost, along with strategic realignment toward a new oral therapy (8). The oral agent with a similar mechanism of action, zuranolone, received FDA priority review approval after two phase 3 randomized, double-blind, placebo-controlled, multicenter studies demonstrated efficacy for treatment of severe perinatal depression with third-trimester onset or onset in the first 4 weeks postpartum (9, 10). The primary endpoint of both zuranolone studies was the change in depressive symptoms using

Box 1. Dosing for Zuranolone Therapy

- The daily recommended dose of zuranolone is generally 50 mg. In the case of severe hepatic or moderate-to-severe renal impairment, dosing should be initiated at 30 mg.
- Zuranolone is taken in the evening with a fatty meal (eg, 400–1,000 calories, 25–50% fat), for 14 days.
- If an evening dose is missed, the next dose should be taken at the regular time the next evening; extra doses should not be taken on the same day. Unless there is a reason for early discontinuation, 14 doses of treatment total should be completed, even if more than 14 days is necessary.
- Regular monitoring of CNS-depressant effects is needed. If CNS-depressant effects are mild to moderate (eg, excessive sedation, somnolence, dizziness), hold the dose temporarily and then consider resumption at a decreased dose of 40 mg, assuming a 50-mg starting dose. If CNS-depressant effects are severe (eg, impaired alertness, coordination, or increased fall risk), discontinuation may be the appropriate course, with monitoring until symptom resolution. Use with other CNS depressants should be avoided (alcohol, benzodiazepines, opioids, tricyclic antidepressants, or others). If use with another CNS depressant is unavoidable, consider dose reduction (eg, to 30–40 mg). Dose adjustments also will be needed if patients are taking medications that are strong CYP3A4 *inhibitors.* Concomitant use with CYP3A4 *inducers* should be avoided.*
- Given the FDA boxed warning for increased suicidal thoughts and behaviors, similar to other antidepressants, monitor for suicidal ideation during treatment (see Clinical Practice Guideline No. 4, *Screening and Diagnosis of Mental Health Conditions During Pregnancy and Postpartum* [12]).

Abbreviations: CNS, central nervous system; FDA, U.S. Food and Drug Administration.

* Potent *inhibitors* of CYP3A4 include clarithromycin, erythromycin, diltiazem, itraconazole, ketoconazole, ritonavir, verapamil, goldenseal, and grapefruit. *Inducers* of CYP3A4 include phenobarbital, phenytoin, rifampicin, St. John's wort, and glucocorticoids.

the total score from the HAMD-17 (17-item Hamilton Depression Rating Scale). Change was assessed by difference from baseline to day 15, which corresponded to treatment course completion, between the zuranolone and placebo groups. In both studies, patients in the zuranolone group showed clinically meaningful and statistically significant improvement in their depressive symptoms compared with those in the placebo groups (−15.6 vs −11.6, −4.0 between-group difference [95% CI, −6.3 to −1.4; n=196] [9]; −17.8 vs −13.6, −4.2-between-group difference [95% CI, −6.9 to −1.5; n=153] [10]).

The zuranolone treatment effect was maintained at day 45—4 weeks after the last dose of zuranolone (9, 10). Anxiety symptoms also were reduced in patients who received zuranolone compared with placebo in the original trial (11).

Of note, the FDA approved zuranolone for postpartum depression without a severity qualifier; however, the inclusion criteria for the aforementioned studies included a HAMD-17 score higher than 26, which is consistent with severe disease. The HAMD-17 is used more commonly in research settings; it is anticipated that other validated tools (eg, the EPDS [Edinburgh Postnatal Depression Scale] or the PHQ-9 [Patient Health Questionnaire-9]) will be used in clinical settings (12). In the absence of clinical trial data to support efficacy beyond patients with severe symptoms, many experts suggest limiting zuranolone use to those with severe symptoms (eg, a PHQ-9 score of 20 or higher or an EPDS score of 19 or higher) or shared decision making that considers overall symptomatology along with treatment context and needs. Another important consideration is that existing studies compared zuranolone with placebo rather than with standard treatment for severe postpartum depression, such as SSRIs, psychotherapy, or both, raising questions about its comparative effectiveness relative to established care modalities. Finally, efficacy data were not reported beyond day 45 after treatment completion, leaving ongoing monitoring and management after this time period uncertain.

See Box 1 for zuranolone therapy dosing information. If zuranolone is not effective for an individual patient or if symptoms recur after completing a clinical course of treatment, repeating the medication course is not indicated and other approaches to perinatal depression management should be considered (described in ACOG Clinical Practice Guideline No. 5, *Treatment and Management of Mental Health Conditions During Pregnancy and Postpartum* [3]).

Adverse drug reactions of zuranolone include central nervous system (CNS) depressive effects such as somnolence, dizziness, and confusion; suicidal thoughts and behaviors; potential for nonmedical use or dependence; and embryo–fetal toxicity if inadvertently taken during pregnancy (13, 14). Given the CNS effects, patients should not drive or engage in activities requiring complete mental alertness until at least 12 hours after each dose for the duration of the full treatment course. Patients may not be able to

Box 2. Considerations for Zuranolone Therapy

- Individuals with bipolar disorder, psychotic disorders, history of suicide attempt, or active suicidal ideation or risk were excluded from zuranolone trials and, thus, should not be prescribed zuranolone.
- Zuranolone can be used alone or as an adjunct to other stable doses of oral antidepressant therapy such as SSRIs and SNRIs. Current treatment with oral antidepressants should not be empirically stopped when zuranolone is initiated.
- The most common side effects include dizziness, fatigue, drowsiness, diarrhea, common cold–like symptoms, and urinary tract infections.
- For at least 12 hours after each dose, patients should avoid driving, operating heavy machinery, engaging in potentially dangerous activities, and, importantly, caring for their infant alone (including feeding, changing, or bathing).
- Patients may not be able to accurately assess their own degree of impairment during the treatment cycle.
- Patients should use effective contraception during the 14-day treatment course and for 1 week after the final dose. Based on animal data, zuranolone may cause embryo or fetal harm and is not approved for use during pregnancy (5). If pregnancy does occur, there is a registry.*
- The patient's clinical need for zuranolone and the developmental and health benefits of human milk feeding should be balanced through a shared decision-making process. Pumping and discarding human milk through 1 week past treatment completion given the absence of direct infant data is a consideration and should be contrasted with possible continuation, given a simulated RID of 50 mg, which is below the 10% threshold generally considered compatible with human milk feeding.
- Understanding the context in which perinatal depression develops or is exacerbated, and the associated social and structural determinants of health, necessitates treatment approaches that extend beyond pharmacotherapy.

SSRIs, selective serotonin reuptake inhibitors; SNRIs, serotonin–norepinephrine reuptake inhibitors; RID, relative infant dose.

* National Pregnancy Registry for Antidepressants (1-844-405-6185 and https://womensmentalhealth.org/research/pregnancyregistry/antidepressants/).

accurately assess their own degree of impairment during the treatment cycle. Other CNS-depressant substances should be avoided when taking zuranolone. The FDA reported that zuranolone had some reinforcing effects similar to benzodiazepines, some dose-dependent euphoric effects that raise concerns for nonmedical use or dependence, and evidence to support a biochemical similarity to barbiturates (15); hence, it is in schedule IV of the Controlled Substances Act (16). Animal studies suggest that zuranolone produces harmful effects on the embryo and fetus; thus, pregnancy should be avoided for 1 week after therapeutic course completion (see Box 2 for additional considerations). A contraceptive plan should be clearly documented before zuranolone initiation. A phase 1 open-label study was performed to assess zuranolone transfer into human milk (17). Fifteen healthy, nonpregnant, lactating adults participated, and 14 completed the study; each received a daily dose of 30 mg zuranolone from day 1 through day 5. The day 5 relative infant dose (RID) of 30 mg was 0.357% and the subsequent simulated RID of 50 mg was estimated to be less than 1%, which is below the less than 10% threshold that is generally considered compatible with human milk feeding. There are no data on direct effects of zuranolone on human milk feeding on infants, and there are limited data on milk production. Pumping and discarding human milk through 1 week past treatment completion may be considered due to the absence of direct clinical safety data; however, this option should be weighed against the option of continued breastfeeding through shared decision making given that the RID is generally considered compatible with human milk feeding.

The limitations of the evidence supporting zuranolone's FDA approval alongside its side effect profile need to be balanced against its demonstrated efficacy compared with placebo and rapid symptom resolution, particularly given the significant negative consequences of untreated depression for the postpartum person and infant. Informed consent and shared decision making remain paramount as a standard.

IMPLEMENTATION CONSIDERATIONS

Please see Box 1 and Box 2 for dosing information and other considerations for zuranolone therapy.

Use of Language

The American College of Obstetricians & Gynecologists recognizes and supports the gender diversity of all

patients who seek obstetric and gynecologic care. In original portions of this document, authors seek to use gender-inclusive language or gender-neutral language. When describing research findings, this document uses gender terminology reported by investigators. To review ACOG's policy on inclusive language, see https://www.acog.org/clinical-information/policy-and-position-statements/statements-of-policy/2022/inclusive-language.

REFERENCES

1. Trost SL, Beauregard JL, Smoots AN, Ko JY, Haight SC, Moore Simas TA, et al. Preventing pregnancy-related mental health deaths: insights from 14 US maternal mortality review committees, 2008-17. Health Aff (Millwood) 2021;40:1551–9. doi: 10.1377/hlthaff.2021.00615
2. Centers for Disease Control and Prevention. Pregnancy-related deaths: data from maternal mortality review committees. Accessed August 15, 2025. https://www.cdc.gov/maternal-mortality/php/data-research/mmrc/?CDC_AAref_Val=https://www.cdc.gov/maternal-mortality/php/data-research/mmrc-2017-2019.html
3. Treatment and management of mental health conditions during pregnancy and postpartum. ACOG Clinical Practice Guideline No. 5. American College of Obstetricians and Gynecologists. Obstet Gynecol 2023;141:1262–88. doi: 10.1097/AOG.0000000000005202
4. U.S. Food and Drug Administration. CY 2019 CDER drug and biologic calendar year priority approvals. Accessed August 21, 2025. https://www.fda.gov/media/147412/download
5. U.S. Food and Drug Administration. Drug approval package: Zurzuvae. Accessed August 21, 2025. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2023/217369Orig2s000TOC.cfm
6. Azhar Y, Din AU. Brexanolone. In: StatPearls [Internet]. Accessed August 21, 2025. https://www.ncbi.nlm.nih.gov/books/NBK541054/
7. U.S. Food and Drug Administration. Prescription and over-the-counter drug product list: additions/deletions for prescription drug product list. In: Approved drug products with therapeutic equivalence evaluations. 45th ed. Accessed August 21, 2025. https://www.fda.gov/media/185455/download
8. Sage Therapeutics, Inc.; withdrawal of approval of a new drug application for Zulresso (brexanolone) solution, 100 milligrams/20 milliliters. Accessed August 15, 2025. https://www.federalregister.gov/documents/2025/03/14/2025-04101/sage-therapeutics-inc-withdrawal-of-approval-of-a-new-drug-application-for-zulresso-brexanolone
9. Deligiannidis KM, Meltzer-Brody S, Maximos B, Peeper EQ, Freeman M, Lasser R, et al. Zuranolone for the treatment of postpartum depression [published erratum appears in Am J Psychiatry 2025;182:311]. Am J Psychiatry 2023;180:668–75. doi: 10.1176/appi.ajp.20220785
10. Deligiannidis KM, Meltzer-Brody S, Gunduz-Bruce H, Doherty J, Jonas J, Li S, et al. Effect of zuranolone vs placebo in postpartum depression: a randomized clinical trial [published errata appear in JAMA Psychiatry 2022;79:740; JAMA Psychiatry 2023;80:191]. JAMA Psychiatry 2021;78:951–9. doi: 10.1001/jamapsychiatry.2021.1559
11. Deligiannidis KM, Citrome L, Huang M, Acaster S, Fridman M, Bonthapally V, et al. Effect of zuranolone on concurrent anxiety and insomnia symptoms in women with postpartum depression. J Clin Psychiatry 2023;84:22m14475. doi: 10.4088/JCP.22m14475.
12. Screening and diagnosis of mental health conditions during pregnancy and postpartum. Clinical practice guideline no. 4. American College of Obstetricians and Gynecologists. Obstet Gynecol 2023;141:1232–61. doi: 10.1097/AOG.0000000000005200
13. Sharma R, Bansal P, Saini L, Sharma N, Dhingra R. Zuranolone, a neuroactive drug, used in the treatment of postpartum depression by modulation of GABA(A) receptors. Pharmacol Biochem Behav 2024;238:173734. doi: 10.1016/j.pbb.2024.173734
14. Dunbar J, Morelli G, Jain R, Vaudreuil C, Nandy I, Ona V, et al. Effects of zuranolone on next-day simulated driving in healthy adults. Psychopharmacology (Berl) 2025;242:389–400. doi: 10.1007/s00213-024-06687-6
15. Center for Drug Evaluation and Research. Zurzuvae (zuranolone). Integrated review. Accessed August 15, 2025. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2023/217369Orig2s000IntegratedR.pdf
16. Schedules of controlled substances: placement of zuranolone in schedule IV. Drug Enforcement Administration, Department of Justice. Accessed August 15, 2025. https://www.federalregister.gov/documents/2023/10/31/2023-23982/schedules-of-controlled-substances-placement-of-zuranolone-in-schedule-iv
17. Deligiannidis KM, Bullock A, Nandy I, Dunbar J, Lasser R, Witte M, et al. Zuranolone concentrations in the breast milk of healthy, lactating individuals: results from a phase 1 open-label study. J Clin Psychopharmacol 2024;44:337–44. doi: 10.1097/JCP.0000000000001873

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