

# Can a novel, rapid-acting oral treatment effectively manage PPD?

**Although it may be considered in specific cases, no, zuranolone (a GABA<sub>A</sub> receptor modulator) should not yet be offered routinely to all patients for the treatment of postpartum depression (PPD).** While a double-blind, randomized

trial of zuranolone versus placebo in 170 patients with PPD showed promising results at all time points studied, the study was relatively small and included a limited patient population. Further studies should be completed to determine the lowest effective dose of zuranolone and long-term outcomes.

*Deligiannidis KM, Meltzer-Brody S, Maximos B, et al. Zuranolone for the treatment of postpartum depression. Am J Psychiatry. 2023;180:668-675. doi:10.1176/appi.ajp.20220785.*

## EXPERT COMMENTARY

**Jaimey M. Pauli, MD**, is Professor, Department of Obstetrics and Gynecology; Chief, Division of Maternal-Fetal Medicine, Pennsylvania State College of Medicine, Milton S. Hershey Medical Center, Hershey, Pennsylvania. She serves on the OBG MANAGEMENT Board of Editors.

**Kendall Cunningham, MD**, is Maternal-Fetal Medicine Fellow, Penn State Health Milton S. Hershey Medical Center, Hershey.

**P**ostpartum depression affects approximately 17.2% of patients in the peripartum period.<sup>1</sup> Typical pharmacologic treatment of PPD includes selective serotonin reuptake inhibitors (SSRIs), which may take up to 12 weeks to take effect. Postpartum depression is thought to be secondary

to maladaptation to hormonal fluctuations in the peripartum period, including allo-pregnanolone, a positive allosteric modulator of GABA<sub>A</sub> (γ-aminobutyric acid type A) receptors and a metabolite of progesterone, levels of which increase in pregnancy and abruptly decrease following delivery.<sup>1</sup> In 2019, the GABA<sub>A</sub> receptor modulator brexanolone was approved by the US Food and Drug Administration (FDA) to treat PPD through continuous intravenous infusion over 60 hours in the hospital setting.

Zuranolone, an allosteric modulator of GABA<sub>A</sub> receptors, also has been studied as an investigational medication for rapid treatment of PPD. Prior studies demonstrated the efficacy of oral zuranolone 30 mg daily for the treatment of PPD<sup>2</sup> and 50 mg for the treatment of major depression in nonpregnant patients.<sup>3</sup> Deligiannidis and colleagues conducted a trial to investigate the 50-mg dose of zuranolone for the treatment of PPD. (Notably, in August 2023, the FDA approved oral zuranolone once daily for 14 days for the treatment of PPD.) Following the FDA

## FAST TRACK

*Postpartum depression affects approximately 17.2% of patients in the peripartum period*

*The authors report no financial relationships relevant to this article.*

doi: 10.12788/obgm.0310

approval, the American College of Obstetricians and Gynecologists (ACOG) released a Practice Advisory recommending consideration of zuranolone for PPD that takes into account balancing the benefits and risks, including known sedative effects, potential need for decreasing the dose due to adverse effects, lack of safety data in lactation, and unknown long-term efficacy.<sup>4</sup>

### Details of the study

This randomized, double-blind, placebo-controlled study included 196 patients with an episode of major depression, characterized as a baseline score of 26 or greater on the Hamilton Depression Rating Scale (HAM-D) beginning in the third trimester or within the first 4 weeks postpartum. Patients were randomly assigned in a 1:1 ratio to receive zuranolone 50 mg daily or placebo, with stratification by stable concurrent antidepressant use. Treatment duration was for 14 days, with follow-up through day 45.

The study's primary outcome was a change in the baseline HAM-D score at day 15. Changes in HAM-D score also were recorded at days 3, 28, and 45.

The 2 study groups were well balanced by demographic and baseline characteristics. In both groups, the majority of patients experienced the onset of their major depressive episodes within the first 4 weeks postpartum. Completion rates of the 14-day treatment course and 45-day follow-up were high and similar in both groups; 170 patients completed the study. The rate of concurrent psychiatric medications taken, most of

which were SSRIs, was similar between the 2 groups at approximately 15% of patients.

**Results.** A statistically significant improvement in the primary outcome (the change in HAM-D score) at day 15 occurred in patients who received zuranolone versus placebo ( $P = .001$ ). Additionally, there were statistically significant improvements in the secondary outcomes HAM-D scores at days 3, 28, and 45. Initial response, as measured by changes in HAM-D scores, occurred at a median duration of 9 days in the zuranolone group and 43 days in the placebo group. More patients in the zuranolone group achieved a reduction in HAM-D score at 15 days (57.0% vs 38.9%;  $P = .02$ ). Zuranolone was associated with a higher rate of HAM-D remission at day 45 (44.0% vs 29.4%;  $P = .02$ ).

With regard to safety, 16.3% of patients (17) in the zuranolone group (vs 1% in the placebo group) experienced an adverse event, most commonly somnolence, dizziness, and sedation, which led to a dose reduction. However, 15 of these 17 patients still completed the study, and there were no serious adverse events.

### Study strengths and limitations

This study's strengths include the double-blinded design that was continued throughout the duration of the follow-up. Additionally, the study population was heterogeneous and reflective of patients from diverse racial and ethnic backgrounds. Lastly, only minor and moderate adverse events were reported and, despite this, nearly all patients who experienced adverse events completed the study.

Limitations of the study include the lack of generalizability, as patients with bipolar disorder and mild or moderate PPD were excluded. Additionally, the majority of patients had depressive episodes within the first 4 weeks postpartum, thereby excluding patients with depressive episodes at other time points in the peripartum period. Further, as breastfeeding was prohibited, safety in lactating patients using zuranolone is unknown. Lastly, the study follow-up period was 45 days; therefore, the long-term efficacy of zuranolone treatment is unclear. ●

### WHAT THIS EVIDENCE MEANS FOR PRACTICE

Zuranolone, a GABA<sub>A</sub> allosteric modulator, shows promise as an alternative to existing pharmacologic treatments for severe PPD that is orally administered and rapidly acting. While it is reasonable to consider its use in the specific patient population that benefited in this study, further studies are needed to determine its efficacy in other populations, the lowest effective dose for clinical improvement, and its interaction with other medications and breastfeeding. Additionally, the long-term remission rates of depressive symptoms in patients treated with zuranolone are unknown and warrant further study.

JAIMEY M. PAULI, MD; KENDALL CUNNINGHAM, MD

---

## References

1. Deligiannidis KM, Meltzer-Brody S, Maximos B, et al. Zuranolone for the treatment of postpartum depression. *Am J Psychiatry*. 2023;180:668-675. doi:10.1176/appi.ajp.20220785
2. Deligiannidis KM, Meltzer-Brody S, Gunduz-Bruce H, et al. Effect of zuranolone vs placebo in postpartum depression: a randomized clinical trial. *JAMA Psychiatry*. 2021;78:951-959. doi:10.1001/jamapsychiatry.2021.1559
3. Clayton AH, Lasser R, Parikh SV, et al. Zuranolone for the treatment of adults with major depressive disorder: a randomized, placebo-controlled phase 3 trial. *Am J Psychiatry*. 2023;180:676-684. doi:10.1176/appi.ajp.20220459
4. Zuranolone for the treatment of postpartum depression. Practice Advisory. American College of Obstetricians and Gynecologists. August 2023. Accessed September 18, 2023. <https://www.acog.org/clinical/clinical-guidance/practice-advisory/articles/2023/08/zuranolone-for-the-treatment-of-postpartum-depression>