Medical News & Perspectives

A Fast-Acting Pill Received Approval for Postpartum Depression—Is It a Game Changer?

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Although approximately 1 in 8 people with a recent live birth experience postpartum depression symptoms, treatments for the condition have been limited.

Treatments have consisted mainly of talk therapy, sometimes combined with standard antidepressants such as selective serotonin reuptake inhibitors (SSRIs), which can take up to 12 weeks to provide relief.

In 2019, the US Food and Drug Administration (FDA) approved brexanolone, an intravenous injection marketed as Zulresso, the first treatment specifically for postpartum depression. Brexanolone is fast-acting but requires that patients be hospitalized for a 60-hour-long infusion, during which they must be monitored for excessive sedation and loss of consciousness.

Medical News website

On August 4, though, the FDA approved the first pill for treating postpartum depression. Zuranolone, which the agency had designated for priority review, is an oral version of brexanolone. Like the infusion, zuranolone is fast-acting, but, taken once a day, it's far more convenient.

"Having access to an oral medication will be a beneficial option for many of these women coping with extreme, and sometimes life-threatening, feelings," Tiffany Farchione, MD, director of the Division of Psychiatry in the FDA's Center for Drug Evaluation and Research, said in a statement.

Untreated, postpartum depression has negative consequences for both mothers and their children, a 2019 systematic review concluded. It affects mothers' psychological health, quality of life, and interactions with their infant, partner, and other family members. Severe maternal postpartum depression seems to have a greater impact on children's development than mild postpartum depression, and the risks are greater for children in lower socioeconomic populations, the systematic review authors noted.

A fast-acting pill is expected to play a vital role for birthing patients who might be considering harming themselves or their infants, but zuranolone's long-term efficacy isn't known, and for many people, medication alone won't be enough to alleviate postpartum depression.

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How the Drug Was Studied

The FDA approved zuranolone on the basis of 2 phase 3 clinical trials that enrolled postpartum women whose severe depression started in their last trimester or within the first 4 weeks after delivery. (Because the onset of depression can occur before delivery as well as after, the American Psychiatric Association's *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition,* began referring to it as "peripartum depression.")

"Most women, to be honest, have a really good idea of when depression came on," Kristina Deligiannidis, MD, the first author on both studies, noted in an interview.

The first study, published in 2021 in *JAMA Psychiatry*, randomly assigned women up to 6 months after delivery to receive 30 mg of zuranolone or placebo pills once a day for 2 weeks, at which point 148 out of 150 had completed treatment.

The second study, published in the *American Journal of Psychiatry* a week before the FDA approved the drug for postpartum depression, included 196 women up to 12 months after delivery. Frequently, "women do not get diagnosed and do not present for treatment until many months after they deliver," explained Deligiannidis, professor at the Institute of Behavioral Science at the Feinstein Institutes for Medical Research in Manhasset, New York.

The participants in this study, more than half of whom were Black women or Hispanic or Latina women, were randomly assigned to receive 50 mg of zuranolone or placebo pills for 2 weeks. About 15% of the participants entered the trials taking a stable dose of an antidepressant, "but they were still severely depressed," Deligiannidis said. They were not taken off their antidepressant for the trials, and the FDA ultimately approved zuranolone for use alone or with an antidepressant.

Both studies met their primary end point—a significant reduction on average from baseline in the Hamilton Rating Scale for Depression total score at day 15 compared with placebo. The more recent study, which used the 50-mg dose, also met all its key secondary end points, with a significant reduction in depressive symptoms seen as early as day 3 and sustained through the end of the study at day 45, a month after participants had finished their 14-day course of pills.

There was also a high placebo response in the study, which Deligiannidis and her coauthors speculated was influenced by the high number of clinic visits during the study—8 in 45 days, which is more than people in real-world settings would usually have in that time frame.

"The placebo is a pretty potent treatment for depression," psychiatrist Katherine Wisner, MD, director of the Asher Center for the Study and Treatment of Depressive Disorders at the Northwestern University Feinberg School of Medicine, noted in an interview. Wisner was not involved in the zuranolone trials.

A Potential Deal-Breaker?

The FDA is requiring a "black box warning," its strongest possible caution, on zuranolone's label. It states that the drug can impair a person's ability to drive and perform other potentially hazardous activities. Patients might not be able to tell they're impaired, so they should not drive or operate heavy machinery within 12 hours of taking zuranolone.

According to its label, a 50-mg dose of zuranolone is to be taken in the evening with fatty foods to enhance drug absorption. (The recommended daily dose for people with severe liver impairment or moderate to severe kidney impairment is 30 mg; zuranolone will be sold in 20-, 25-, and 30-mg capsules.)

Despite the nighttime dosing, the driving prohibition could be a deal-breaker for some patients, Wisner noted. For example, she said, what if someone was prescribed zuranolone after they returned to work and had to drive to their job fewer than 12 hours after taking the drug?

That would be especially problematic for people who couldn't afford a rideshare service, she pointed out. "If they don't go to work, they don't buy food or diapers," Wisner explained. "I do think it's something that has to be considered."

The label also warns that the drug can cause central nervous system (CNS) depressant effects such as somnolence, dizziness, and confusion. If patients develop CNS depression, prescribers can reduce the dose to 40 mg or consider discontinuing the drug. Besides sleepiness or drowsiness and dizziness, the label states that zuranolone's most common adverse effects are colds, diarrhea, fatigue, and urinary tract infections.

In her experience, Deligiannidis said, zuranolone's adverse effects have not interfered with patients' ability to care for their infants. "They got up when the baby cried," she said. "They did not feel they couldn't do what they needed to do in the middle of the night."

Like other antidepressants, zuranolone may increase the risk of suicidal thoughts or actions in people 24 years of age or younger, the label warns.

The FDA-required Medication Guide for the drug also notes that zuranolone is a federally controlled substance because it can be abused or lead to dependence.

In addition, people who could become pregnant should use effective contraception while taking zuranolone and for a week after. The National Pregnancy Registry for Antidepressants at Massachusetts General Hospital already has been gathering information about the safety of brexanolone during pregnancy and will be adding zuranolone to the list of antidepressants it is evaluating, according to a news release from Sage Therapeutics and Biogen, which jointly developed zuranolone.

The Cost of Treatment

Zuranolone will become commercially available under the brand name Zurzuvae in the fourth quarter of this year, according to Sage and Biogen.

Considering that some people with postpartum depression can't even afford generic SSRIs, "what I worry about is how difficult it's going to be for insurance to approve" zuranalone, Wisner said, adding that she's concerned it might become a "novel exciting drug for the advantaged few."

Sage set brexanolone's price at $7450 per vial, for a total of $34 000 for the required 60-hour-long infusion. (Sage did not respond to an inquiry from *JAMA* about how many people have received brexanolone since the FDA approved it or whether it plans to continue marketing it now that zuranolone has been approved.) As of mid-August, the company had not yet revealed zuranolone's list price.

In an interview, psychiatrist Alan Schatzberg, MD, director of the Stanford Mood Disorders Center and a consultant for Sage, said he suspects that it will be difficult for payors to refuse to cover zuranolone since it's the only FDA-approved oral treatment for postpartum depression.

Cost isn't the only potential obstacle to treatment, though. In a 2018 survey of people who'd recently delivered an infant, 1 in 8 said that their clinician hadn't asked about depression in postpartum visits; 1 in 5 said they weren't asked about depression in prenatal visits.

But if history is any indication, Schatzberg predicted, zuranolone's approval could spur improved screening and diagnosis of postpartum depression.

"What happens is proven efficacy of a particular drug will drive diagnoses," he explained. For example, he said, after the FDA approved lithium in 1974 as the first treatment for bipolar disorder, physicians became more likely to properly diagnose patients who had bipolar disorder.

A "No" for Major Depressive Disorder

Both zuranolone and brexanolone are neurosteroids and analogues of the hormone allopregnanolone. Allopregnanolone is derived from progesterone, which rises during pregnancy but then begins to fall in the third trimester and plummets after delivery. However, "[e]vidence relating perinatal mood and anxiety symptoms with absolute levels of allopregnanolone has been equivocal, especially in larger population studies," a 2020 review article noted.

Like barbiturates and benzodiazepines, zuranolone and brexanolone are positive allosteric modulators of the neuroactive steroid γ-aminobutyric acid type A (GABA-A) receptor. GABA signaling appears to play a role in postpartum depression as well as in major depressive disorder.

But on the same day that the FDA approved zuranolone for postpartum depression, the agency informed Sage and Biogen that their application to market the drug for the treatment of adults with major depressive disorder, a much more common condition than postpartum depression, "did not provide substantial evidence of effectiveness to support the approval,"

according to the joint press release from the companies.

"We're extremely disappointed for patients, and we don't agree with the FDA's view," Sage Chief Executive Officer Barry Greene said in an August 7 investor call. That day, his company's stock dropped 49% in response to the FDA's denial for major depressive disorder. "We really can't speculate on the FDA's thinking," Greene said. He would say only that Sage is "evaluating the next step" and would describe what that is "as soon as we can provide more clarity."

Meanwhile, Sage is currently recruiting for a clinical trial of zuranolone in treating pediatric patients with major depressive disorder, according to ClinicalTrials.gov.

One reason zuranolone has appeared to be more efficacious in postpartum depression than in major depressive disorder could be that people with the former are a more homogeneous group than those with the latter, Schatzberg said.

Major depressive disorder has numerous subtypes, he pointed out. For example, he said, half of patients with major depressive disorder also have anxiety and have a much lower response rate to typical antidepressants. "It's an unmet need but a common disorder."

Zuranolone, however, is both an antidepressant and an anxiolytic, Schatzberg noted. "I think there are paths forward for ultimately getting approval" for major depressive disorder.

Unanswered Questions

The long-term effects of zuranolone aren't yet known. After all, the clinical trials tracked participants for only a month after their 2-week course of treatment ended.

"I would be interested in conducting a longitudinal study with those women who took zuranolone…to follow them for 12 months and see how they're doing," Judite Blanc, PhD, an assistant professor of psychiatry and behavioral sciences at the University of Miami Miller School of Medicine, who was not involved with the trials, said in an interview.

Although zuranolone is faster-acting than SSRIs, research suggests that by the end of 8 weeks or so after starting treatment, the response rate for both drugs is about 60%, Wisner said. However, she pointed out, zuranolone has never been compared head-to-head with an SSRI such as sertraline, her choice for treating postpartum depression because of good evidence of its safety during breastfeeding. (The zuranolone trials prohibited participants from breastfeeding while taking their pills and for a week afterward.)

"We really need to know what happens beyond 45 days to be able to judge the difference between the 2 drugs," Wisner said. She said she expects a patient eventually will ask her to prescribe zuranolone for postpartum depression, and when that happens, "I intend to keep a pretty careful record because it's a new drug, and we have to figure how best to use it."

Deligiannidis said she anticipates that some of her patients with severe postpartum depression won't need further treatment after a course of zuranolone, except perhaps counseling. Others might still have depression after finishing their 2 weeks of zuranolone, so they would be candidates for longer-term treatment with a standard antidepressant and psychotherapy.

As she and her coauthors of the more recent study noted, zuranolone has been tested only in people with severe postpartum depression. Its usefulness for new mothers with moderate postpartum depression isn't known, although once a drug is approved for any indication, clinicians can prescribe it as they see fit.

More to It

Blanc called zuranolone "a game changer," but said it's not a panacea for what is often a multifactorial condition.

"When are we going to start addressing the social determinants of postpartum depression and maternal mortality?" she asked. "It's about environmental stress."

In an opinion piece published in *MedPage Today* after zuranolone's approval, Blanc noted that postpartum depression "is not just a biological or an individual issue but a culmination of complex interactions between gender roles, societal expectations, and systemic inequalities."

Social factors such as intimate partner violence and a lack of partner or family support, as well as biological factors, contribute to postpartum depression, Blanc explained in her interview with *JAMA*.

Medications, she said, even those as promising as zuranolone, are "just one layer." ■

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