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Column Editor: Patricia Anne O'Malley, PhD, APRN-CNS

ZURZUVAE—The First Oral Treatment Approved for Postpartum Depression

Patricia Anne O'Malley, PhD, APRN-CNS

Postpartum depression (PPD) rates range from 5.5% to 23.5% of all live births across Europe and the United States. Underdiagnosed and untreated, PPD is associated with problems in maternal health and mother-infant attachment and results in significant negative emotional and cognitive effects on child development.[1–4] Lack of an efficacious treatment for PPD has resulted in use of interventions adapted from major depression pharmacotherapies prescribed outside the peripartum period. Until now, the lack of an evidence-based treatment for PPD has been the function of limited randomized clinical trials, underpowered samples, and lack of long-term follow-up, as well as a lack of knowledge regarding PPD pathophysiology. Added to this chasm in care is the implicit stigma that surrounds women seeking help for PPD and the lack of care providers with education and training in perinatal mental health particularly in poorer settings where mental health is low on the priority list.[2]

PATHOPHYSIOLOGY OF PPD

The precise pathophysiology of PPD remains hidden. What is known is that variance in neurosteroid hormone levels appears to induce physiological plasticity in the expression γ-aminobutyric acid A (GABA-A) receptors during pregnancy and postpartum.[1] Neurosteroids produced from cholesterol in the brain alter neuronal excitability through membrane receptors. The downregulation of neurosteroidogenesis, large neurosteroid level fluctuations, and deficits in GABA-A receptor plasticity may be the root cause of biological vulnerability to depression.[1,5,6]

Author Affiliation: Nurse Scientist, Center of Nursing Excellence, Premier Health–Miami Valley Hospital is in Dayton, Ohio.

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Correspondence: Patricia Anne O'Malley, PhD, APRN-CNS, Premier Health–Miami Valley Hospital, 1 Wyoming Street Dayton, Ohio 45409 (pomalley@premierhealth.com; pomalley5@woh.rr.com).

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In acute stress, elevation of the neuroactive steroid allopregnanolone appears to be neuroprotective. However, in chronic stress, allopregnanolone levels fall, altering GABA and glutamate transmission.[5,7–9] Support for this theory is evidenced by the reduced levels of allopregnanolone in blood or cerebrospinal fluid with major depression, anxiety, premenstrual dysphoric disorder, negative symptoms in schizophrenia, and impulsive aggression. Allopregnanolone appears to also support neurogenesis, myelination, and neuroprotection, as well as regulation of the hypothalamic-pituitary-adrenocortical axis.[5,7–9]

In pregnancy, the placenta synthesizes a significant amount of progesterone hormone beginning late in the first trimester and through the second and third trimesters. The rapid decrease of progesterone postdelivery results in a decrease of allopregnanolone neuroactive steroid throughout the central nervous system (CNS).[10] Therefore, mood, anxiety, and other depressive symptoms in PPD appear to be strongly correlated with variance in expression of allopregnanolone and other neurosteroids.[6,10]

PPD PRESENTATION

Women with PPD can present reporting constant sadness, regret, agitation, low attention span, sleep disturbances, and changes in eating. Risk of self-harm and child abuse are associated with severe PPD, with maternal suicide a leading cause of mortality in the first postpartum year. Additional risk factors for PPD include young age, low income, limited social support, stressful life experiences during pregnancy, African American race, previous PPD, and intimate-partner abuse. When depression begins during pregnancy, there are significant risks for substance abuse, preterm delivery, low birth weight, and impaired mother-infant bonding.[2]

EMERGING PHARMACOLOGICAL INTERVENTIONS

In light of the risks of untreated PPD, allopregnanolone agonists have emerged as having a place in the treatment of PPD. Controlled clinical trials to date have assessed the efficacy of pharmacological treatments for PPD, including

estradiol, selective serotonin reuptake inhibitors, brexanolone (an intravenous formulation of allopregnanolone), and a neuroactive steroid and GABA-A–positive allosteric modulator, zuranolone.[1]

Brexanolone (Zulresso; no generic option) was the first therapeutic approved for PPD in 2019 (Sage Therapeutics, Cambridge Massachusetts).[11] Zulresso is a solubilized preparation of the progesterone metabolite synthetic allopregnanolone, a neuroactive steroid, which provides rapid and effective relief of PPD.[2] Delivered via an intravenous infusion over a 60-hour period requires hospital admission and constant medical supervision related to risks for deep sedation, loss of consciousness, hypnosis, and respiratory arrest. Dosing of brexanolone is intended to achieve plasma allopregnanolone concentrations equivalent to those present during the third trimester of pregnancy. Brexanolone is subject to control under the Federal Controlled Substances Act of 1970 as a Schedule IV (C-IV) drug, and distribution of brexanolone is restricted. The long hours required for administration coupled with a cost of nearly US $35,000 make access for women with PPD problematic.[6,10] The quick onset of action and requirement for only one treatment in PPD suggested that this therapy could become a bridge intervention to maintenance therapy with selective serotonin reuptake inhibitors in PPD.[9]

AN ORAL ALTERNATIVE

Zuranolone (SAGE-217 or trade name Zurzuvae; no generic option) has been developed as an oral allopregnanolone (brexanolone) with high bioavailability and a half-life appropriate for once-daily administration.[6,10] Approved on August 4, 2023, Zurzuvae (Sage Therapeutics) is the first oral medication indicated for treatment of PPD and should be commercially available in the fourth quarter of 2023 pending scheduling by the US Drug Enforcement Administration.[12]

The path to approval of Zurzuvae was expedited by the Food and Drug Administration granting *priority review* and *fast track* designation for the drug application. Priority review moves forward evaluation of a drug that may offer significant improvements for serious conditions compared with standard drug applications (https://www.fda.gov/patients/fast-track-breakthrough-therapy-accelerated-approval-priority-review/priority-review, accessed September 18, 2023). Fast track designation is a process designed to expedite drugs for review that treat serious conditions and move these agents to patients earlier (https://www.fda.gov/patients/fast-track-breakthrough-therapy-accelerated-approval-priority-review/fast-track, accessed September 18, 2023).

Results from 2 randomized, double-blind, placebo-controlled, multicenter studies of women with PPD (Robin & Skylark studies; https://investor.sagerx.com/news-releases/news-release-details/fda-approves-zurzuvaetm-zuranolone-first-and-only-oral-treatment) supported Food and Drug Administration approval. Subjects included those with the diagnostic criteria for a major depressive episode with symptoms beginning in the third trimester or within 4 weeks of delivery. The primary end point of both studies was the change in total score from the 17-item Hamilton Depression Rating Scale. After the 2-week treatment course, patients in the Zurzuvae groups had significant improvement in symptoms compared with the placebo groups, and improvement was sustained at day 42 or 4 weeks after the last dose of Zurzuvae.[12]

PRESCRIBING CONSIDERATIONS

Zurzuvae contains zuranolone, a neuroactive steroid GABA-A receptor–positive modulator. The terminal half-life of Zurzuvae is approximately 19.7 to 24.6 hours.[13]

REPORTED ADVERSE EFFECTS AND MONITORING

Commonly reported adverse effects include drowsiness, dizziness, diarrhea, fatigue, nasopharyngitis, and urinary tract infection. Monitoring the patient during therapy is important because Zurzuvae may cause suicidal thoughts or fetal harm. This once-a-day therapy is taken once a day in the evening with a fatty meal.[12,13]

DRUG-DRUG INTERACTIONS

There are significant risks for drug-drug interactions with Zurzuvae. Concomitant use with CNS depressants can result in impaired psychomotor activity or CNS depressant effects. If use with another CNS depressant is unavoidable, consider dosage reduction.[6] Concomitant use with strong CYP3A4 inhibitors increases risk of Zurzuvae-associated adverse reactions and may require dose reduction. Concomitant use with CYP3A4 inducers can decrease the efficacy of Zurzuvae. Therefore, concomitant use should be avoided.[13]

PREGNANCY AND LACTATION

Women should use effective contraception during the 2 weeks of Zurzuvae therapy and for 1 week after therapy. Advise patients that there is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to Zurzuvae during pregnancy.[12]

Available data regarding lactation from 14 women revealed that zuranolone is present in low levels in human milk. There are no data regarding the effects of zuranolone on a breastfed infant or regarding the effects on milk production. The developmental and health benefits of breastfeeding should be weighed with the mother's clinical need for Zurzuvae with all potential adverse effects on the breastfed child.[13]

IMPAIRMENT AND POTENTIAL FOR ABUSE

Patients must be warned that Zurzuvae can negatively impact one's ability to drive and perform potentially hazardous activities. Furthermore, the patient may not be able to grasp their degree of impairment. This is why Zurzuvae carries a Box Warning. To reduce the risk of harm, patients should

be advised not to drive or operate heavy machinery for at least 12 hours after taking Zurzuvae.[12]

In evaluation of potential human abuse, Zurzuvae is associated with dose-dependent, abuse-related adverse responses, including euphoric mood, feeling drunk, and somnolence. This abuse potential was found to be comparable to alprazolam and demonstrated a higher abuse potential than placebo on positive subjective measures of "drug liking," "overall drug liking," "take drug again," "high," and "good drug effects." In addition, there may be a risk of developing physical dependence and withdrawal syndrome with abrupt Zurzuvae discontinuation for individuals who take a higher than recommended dosage and/or use Zurzuvae for a longer duration than the recommended 2 weeks. Adverse reactions reported upon discontinuation of zuranolone in healthy subjects receiving 50 mg of zuranolone for 5 to 7 days included insomnia, palpitations, decreased appetite, nightmare, nausea, hyperhidrosis, and paranoia. These adverse reactions were mild to moderate in severity.[13]

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