MEDICAL COLLEGE OF WISCONSIN SCHOOL OF PHARMACY STUDENT WRITING CLUB:

Advancements in Postpartum Depression Management: A Narrative Review of Brexanolone and Zuranolone

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Abstract

Postpartum depression (PPD) is a serious mood disorder that negatively impacts many new mothers every year. Unfortunately, PPD, which can last weeks to months, may not resolve on its own and can negatively affect how a mother is able to care for herself or her new infant. Since PPD is considered understudied and underdiagnosed compared to other psychiatric disorders, specific PPD treatments have been lacking. Specific selective serotonin reuptake inhibitors (SSRIs), serotonin and norepinephrine reuptake inhibitors (SNRIs), and atypical antidepressants (bupropion and mirtazapine) were previously the only recommended pharmacologic therapies, which can take up to 8 weeks to see full effects. However, two new medications, Zulresso (brexanolone, Sage Therapeutics, Inc.) and Zurzuvae (zuranolone, Biogen Inc.), are now commercially available with FDA approval to treat moderate to severe PPD. Brexanolone and zuranolone exhibit unique mechanisms of action involving Gamma-Aminobutyric Acid (GABA) to treat PPD more quickly. Despite the availability of new therapy options, various patient-specific factors, adverse effects, and cost must be considered for each patient case.

Keywords: Postpartum Depression, Brexanolone, Zuranolone, Allopregnanolone

Postpartum depression (PPD), also known as perinatal or postnatal depression, is a relevant psychiatric disorder that requires increased attention from the medical community.[1] Around 1 in 7 (~15%) mothers develop PPD.[2] This form of depression is likely underdiagnosed, thus resulting in the condition being considered understudied.[1] The American College of Obstetricians and Gynecologists (ACOG) clinical practice guideline defines PPD as "have[ing] intense feelings of sadness, anxiety, or despair that prevent them from being able to do their daily tasks which can occur up to one year after having a baby, but it most commonly starts about one-to-three weeks after childbirth."[3] Postpartum depression, the most common complication of childbirth, significantly affects mothers, with suicide accounting for about 20% of postpartum deaths. As an understudied condition, the full extent of its harmful impact on children and families remains unclear. Studies have shown that PPD can decrease maternal bonding and negatively impact the child's behavioral, emotional, or cognitive development.[1]

Novel PPD Treatment Options

Currently, the 2023 ACOG guideline recommends the use of serotonin reuptake inhibitors (SSRIs) as first-line pharmacotherapy for PPD and serotonin and norepinephrine reuptake inhibitors (SNRIs) as recommended alternatives.[4] However, there are two new treatment options for moderate to severe PPD. The first FDA-approved medication for moderate to severe PPD was Zulresso (brexanolone, Sage Therapeutics, Inc.)

in 2019, administered as an intravenous infusion.[5] The first oral medication, Zurzuvae (zuranolone, Biogen Inc.), was given priority review from the FDA and approved via the fast track designation in August of 2023, providing an option for PPD that was more convenient.[6]

The current ACOG Guidelines for the Treatment and Management of Mental Health Conditions During Pregnancy and Postpartum, released in June 2023, have a strong recommendation with low-quality evidence for the consideration of brexanolone for moderate to severe PPD with onset in the third trimester or within 4 weeks postpartum.[4] In August 2023, ACOG released a Practice Advisory recommending the consideration of zuranolone within the same parameters as brexanolone.[7] The distinction in administration routes adds a layer of choice for patients considering pharmacotherapeutic options, aligning with the potential preferences and needs of individuals seeking treatment for PPD.

Pathophysiological Target

Rapid fluctuations in allopregnanolone post-childbirth, coupled with decreased Gamma-Aminobutyric Acid A ($GABA^A$) receptor expansion during pregnancy, may predispose individuals to PPD.[8] PPD is associated with altered neuroactive steroid levels, including allopregnanolone, GABA, and GABA receptors, contributing to symptoms like stress and anxiety. The precise mechanism of action underlying brexanolone and zuranolone in the treatment of PPD remains unknown. However, it is hypothesized to be associated with their positive allosteric modulation of the $GABA^A$ receptor in adults.[9,10] By enhancing GABA activity through prolonged calcium channel opening, it influences neuronal membrane hyperpolarization. This effect is distinct from benzodiazepines, and it is integral to managing PPD.[8] This differentiation arises from the capacity of neuroactive steroids to engage with both synaptic and extra synaptic receptors. Unlike benzodiazepines, the binding affinity of neuroactive steroids is not contingent upon the presence of a gamma subunit, exclusive to synaptic receptors.[11] This unique binding characteristic contributes to the versatility of neuroactive steroids in modulating $GABA^A$ receptors, allowing for a broader range of receptor interactions and signaling pathways. Synthetic brexanolone, as a therapeutic intervention, facilitates $GABA^A$ modulation, aligning the underlying pathophysiology of PPD. Similarly, zuranolone operates within the realm of neuroactive steroids, contributing to $GABA^A$ receptor modulation and playing a role in addressing the neurochemical imbalances associated with PPD.

Brexanolone

Brexanolone's pharmacokinetics are characterized by a terminal half-life of approximately 9 hours, with a corresponding total plasma clearance of around 1 L/h/kg.[9] Brexanolone undergoes extensive metabolic transformations orchestrated by non-CYP pathways, predominantly through three principal routes: keto-reduction, glucuronidation, and sulfation. Notably, three primary pharmacologically inactive circulating metabolites have been identified, devoid of any substantial contribution to the overall therapeutic efficacy of brexanolone. As for excretion, radiolabeled brexanolone

TABLE 1. Summary of Brexanolone and Zuranolone Use for Moderate to Severe Postpartum Depression Treatment

Medication	FDA Approval for PPD	MOA	Dosing	Administration	Warnings	Side Effects	Monitoring	Cost
Brexanolone (Zulresso®)	Yes	$GABA^A$ Receptor Positive Modulator	0-4 hours: 30 mcg/kg/hr 4-24 hours: 60 mcg/kg/hr 24-52 hours: 90 mcg/kg/hr (may reduce to 60 mcg/kg/hr based on tolerability) 52-56 hours: 60 mcg/kg/hr 56-60 hours: 30 mcg/kg/hr No dosage adjustments for adolescents ≥ 15	60-hour continuous infusion during inpatient stay	Boxed Warning for excessive sedation and sudden loss of consciousness; interactions with the patient's child(ren) are required to have accompaniment	Presyncope Drowsiness Sedated state Dizziness Vertigo Xerostomia Flushing Loss of consciousness Hot flash Diarrhea	Patients must be monitored for sudden loss of consciousness and excessive sedation. Continuous pulse oximetry monitoring is required	The cost of a single course of treatment with brexanolone is around $34,000 excluding the administration costs at a certified health care facility[13]
Zuranolone (Zurzuvae™)	Yes	$GABA^A$ Receptor Positive Modulator	50 mg by mouth once daily in the evening for 14 days Dosage may be decreased to 40 mg if intolerable. Renal adjustment: eGFR 15-59 mL/min/1.73 m^2: 30 mg every evening for 14 days	Evening Must be taken with a fat-containing food (25%-50%) that is also 400-1000 calories	Boxed Warning for impaired ability to drive or engage in other potentially hazardous activities	Dizziness Drowsiness Diarrhea Memory impairment	Patients are recommended to be monitored for signs of abuse/dependence as well as suicidality	$19,080 for a 14-day course of the therapy. The cost of zuranolone per capsule is approximately 20 mg and 25 mg: $681.43 and 30 mg: $1,362.86

PPD = postpartum depression; $GABA^A$ = Gamma-Aminobutyric Acid A

TABLE 2. Summary of Notable Clinical Trials Examining Brexanolone or Zuranolone in Female Patients with Postpartum Depression

	Brexanolone			*Zuranolone*	
Clinical Trial	***HUMMINGBIRD-1***		***HUMMINGBIRD-2***	***ROBIN***[17]	***SKYLARK***[18]
Objective	Reduce depressive symptoms in female patients with severe PPD[24]		Reduce depressive symptoms in female patients with moderate PPD[25]	Safety and efficacy of zuranolone 30 mg in female patients with PPD	Safety and efficacy of zuranolone 50 mg in female patients with PPD
Main Inclusion Criteria	Between the ages of 18 and 45, have had postpartum depression for at least six months at the time of screening, and have a qualifying score on the HAM-D (score of ≥26)[14]		Between the ages of 18 and 45, have had postpartum depression for at least six months at the time of screening, and have a qualifying score on the HAM-D (score of 20–25)[14]	Female patients (ages 18-45) ≤6 months postpartum while experiencing a major depressive episode without psychosis; baseline HAM-D score of ≥26; negative pregnancy test on day 1 and must have used 1 highly effective contraceptive method during the study and for 30 days after treatment	Female patients (ages 18-45), ≤6 months postpartum while experiencing a major depressive episode without psychosis; baseline HAM-D score of ≥26; negative pregnancy test on day 1 and must have used 1 highly effective contraceptive method during the study and for 30 days after treatment
Comparator	(1:1:1) to receive a single intravenous injection of either BRX90, BRX60, or matching placebo for 60 hours[14]		Placebo (1:1) BRX90 or matching placebo for 60 hours[14]	Placebo (1:1)	Placebo (1:1) in a stratified manner based on antidepressant use
Primary Endpoint	Change from baseline (score of ≥26) in HAM-D total score at 60 hours[24]		Change from baseline (score of 20-25) in HAM-D total score at 60 hours[25]	Change from baseline (score of ≥26) in HAM-D total score at day 15	Change from baseline (score of ≥26) in HAM-D score at day 15
Key Secondary Endpoint(s)	Change from baseline (score of ≥26) in HAM-D total score at 30 days[24]		Change from baseline (score of 20-25) in HAM-D total score at 30 days[25]	Change from baseline (score of ≥26) in HAM-D total score at all times points except day 15 HAM-D response (≥50% reduction from baseline HAM-D total score) HAM-D remission (HAM-D total score ≤7)	Change from baseline (score of ≥26) in HAM-D total score at days 3, 28, and 45 Change from baseline in CGI-S score at day 15
Primary Results	**BRX60**[24] –5.5 [95% CI –8.8 to –2.2], p=0.0013	**BRX90**[25] –3.7 [95% CI –6.9 to –0.5], p=0.0252	–2.5 [95% CI –4.5 to –0.5], p=0.0160	LSM –17.8 vs -13.6 [95% CI –6.9 to –1.5] p=0.003	LSM -15.6 vs. -11.6 [95% CI –6.3 to -1.7] p=0.001
Secondary Results	**BRX60**[24] -5.63 [95% CI –9.46 to –1.79], p= 0.0044	**BRX90**[25] –3.79 [95% CI –7.56 to –0.03], p= 0.0481	0.54 [95% CI –1.98 to 3.07], p= 0.6710	**Day 3:** LSM difference –2.7 [95% CI -5.1 to –0.3] p=0.03 **Day 45:** LSM difference –4.1 [95% CI -6.7 to –1.4] p=0.003 **Response:** 72% vs. 48%; OR, 2.6; [95% CI 1.3 to 5.2] p =0.005 **Remission:** 45% vs. 23%; OR, 2.5; [95% CI 1.2-5.2] p=0.01	**Day 3:** LSM difference –3.4 [95% CI –5.4 to –1.4] p=0.001 **Day 28:** LSM difference –2.9 [95% CI –5.4 to –0.5] p=0.02 **Day 45:** LSM difference –3.5 [95% CI –6.0 to –1.0] p=0.007
Safety Profile	Common Adverse Effects: headache, dizziness, somnolence[14] Serious Adverse Effects reported with one patient: suicidal ideation and an attempt of an overdose[14]		Common Adverse Effects: headache, dizziness, somnolence[14] Serious Adverse Effects with one patient: altered state of consciousness and syncope[14]	**Somnolence:** 15% (12/78) vs. 11% (8/73) Headache: 9% (7/78) vs. 12% (9/73) **Dizziness:** 8% (6/78) vs. 6% (4/73) **URTI:** 8% (6/78) vs. 1% (1/73) **Diarrhea:** 6% (5/78) vs. 3% (2/73)	**Adverse Effect leading to dosage reduction:** 16.3% (16/98) vs. 1% (1/98) **Somnolence:** 26.5% (26/98) vs. 5.1% (5/98) **Dizziness:** 13.3% (13/98) vs. 10.2% (10/98) **Sedation:** 11.2% (11/98) vs. 1% (1/98)

PPD = postpartum depression; HAM-D = Hamilton Depression Rating Scale; BRX90 = brexanolone 90 µg/kg/hr; BRX60 = brexanolone 60 µg/kg/hr; CGI-S = Clinical Global Impressions severity score; LSM = least squares mean

administration yielded 47% recovery in feces, primarily in the form of metabolites, and 42% in urine, where less than 1% existed as unchanged brexanolone.[9]

Regarding breastfeeding considerations, brexanolone is transferred to breast milk in nursing mothers, as indicated by data from a clinical lactation study in 12 patients.[9,12] The relative infant dose (RID) for brexanolone ranges from 1-2%, indicating levels below 10 ng/mL in over 95% of women. This is well within the generally acceptable RID of 10%. Available data does not indicate a significant risk of adverse reactions in breastfed infants from exposure to brexanolone. The developmental and health benefits of breastfeeding should be weighed against the mother's clinical need for brexanolone and any potential adverse effects on the breastfeeding child, considering the low RID and concentrations in breast milk.

The administration of brexanolone involves a continuous intravenous infusion over the course of 60 hours (Table 1).[12] Brexanolone dosing is weight-based and varies over five specific time intervals over the 60 hours. The side effects of brexanolone are signs of xerostomia, drowsiness, dizziness, flushing, diarrhea, and dyspepsia. A boxed warning for brexanolone emphasizes the risk of excessive sedation or sudden loss of consciousness during treatment, requiring continuous monitoring and accompaniment during interactions with their children due to the potential for serious harm. This requirement is part of a restricted drug monitoring (REMS) program designed to mitigate these risks. The cost of brexanolone per treatment would be about $34,000 (for one infusion).[13] Patients of reproductive potential should prioritize the use of effective contraception throughout their therapy and for 30 days following their infusion of brexanolone to avoid fetal harm.[12]

A clinical trial called HUMMINGBIRD contributed to the approval of brexanolone.[14] The HUMMINGBIRD trial consisted of HUMMINGBIRD-1 and HUMMINGBIRD-2. HUMMINGBIRD was a double-blind, randomized, placebo-controlled, and phase 3 trial.[14] The eligibility of participants is outlined in Table 2. The women who met the eligibility criteria in HUMMINGBIRD-1 were randomly assigned to receive a single intravenous injection of either brexanolone 90 µg/kg/hr (BRX90), brexanolone 60 µg/kg/hr (BRX60), or matching placebo for 60 hours (Table 2).[14] The women who met the eligibility criteria in HUMMINGBIRD-2 were randomly assigned to receive a single intravenous injection of either BRX90 or matching placebo for 60 hours. The primary endpoint, change in Hamilton Depression Rating Scale (HAM-D) score compared from baseline score of ≥26 (HUMMINGBIRD-1) and baseline score of 20-25 (HUMMINGBIRD-2), showed a statistically significant reduction when comparing BRX90 to placebo for both HUMMINGBIRD-1 and HUMMINGBIRD-2 and BRX60 to placebo in HUMMINGBIRD-1. A clinically meaningful difference was defined as a decrease of ≥50% from the baseline HAM-D total score in both the HUMMINGBIRD-1 and HUMMINGBIRD-2 trials. The HAM-D rating scale is an observer-rated 17-item assessment with a maximum score of 52. Items are scored on either a scale of 0 to 2 points or 0 to 4 points and require a skilled interviewer to evaluate correctly. In general, a higher total score suggests more severe depression with scores 8-16 suggesting mild depression, 17-23 moderate depression, and scores above 24 indicating severe depression.[15]

Zuranolone

Zuranolone's absorption profile reveals that peak concentrations are achieved at 5 to 6 hours postoral administration (T_{max}), but the absolute bioavailability of zuranolone remains unevaluated.[10] Zuranolone exhibits a terminal half-life ranging from approximately 20 to 25 hours within the adult population, with a mean apparent clearance of 33 L/h. Zuranolone experiences substantial metabolic transformations, primarily mediated by the enzymatic activity of CYP3A4. Notably, no human metabolites exceeding 10% of the total drug-related materials were detected in circulation, and none were deemed contributory to the therapeutic effects of zuranolone. Upon oral administration of radiolabeled zuranolone, 45% of the administered dose manifested in urine as metabolites, with negligible levels of unchanged zuranolone. Additionally, 41% appeared in feces as metabolites, with less than 2% detected as unchanged zuranolone.[10]

Regarding breastfeeding considerations, zuranolone is transferred to breast milk in nursing mothers, as indicated by data from a clinical lactation study in 14 patients.[10,16] The RID of zuranolone is calculated to be less than 1% at a steady state, indicating minimal exposure for breastfed infants. Daily infant doses were also found to be low, reflecting a mean RID of 0.357% compared to the maternal dose. Concentrations of zuranolone in breast milk were below the level of quantification limit by four to six days after the last dose.[10,16] The developmental and health benefits of breastfeeding should be weighed against the mother's clinical need for zuranolone and any potential adverse effects on the breastfeeding child, considering the low RID and concentrations in breast milk.

Zuranolone should be taken with fat-containing foods (400-1000 calories, 25% to 50% fat) in the evening for 14 days (Table 1).[16] The noted side effects of zuranolone are dizziness, sedation, dry mouth, or flushing. The boxed warning for zuranolone highlights its potential to impair driving and other hazardous activities for at least 12 hours after administration due to its central nervous system depressant effects. The cost of zuranolone per treatment would be about $19,080 (for two 25 mg capsules nightly for 14 days).[16] Patients of reproductive potential should prioritize the use of effective contraception throughout their therapy and for an additional week following the final dose of zuranolone to avoid fetal harm.[16]

The safety and efficacy of zuranolone in patients with PPD were studied in two notable clinical trials, which are known as the ROBIN and SKYLARK trials.[17,18] Between these two trials, two different zuranolone doses were evaluated as a stand-alone or add-on therapy with other psychotropic medications, like SSRIs, for PPD.[17,18] Both clinical trials were phase 3, randomized, double-blind, placebo-controlled trials; however, the SKYLARK was a parallel group clinical trial.[17,18] In each trial, patients self-administered zuranolone or placebo orally once in the evening with fat-containing food for 14 days.[17,18] The HAM-D scores were recorded until day 45.[17,18] Patients in the experimental treatment arm of the ROBIN trial received

zuranolone 30 mg while patients in the SKYLARK trial received zuranolone 50 mg.[17,18] Both of the studies showed statistically significant change from baseline score of ≥26 in HAM-D total score at day 15 versus placebo (Table 2).[17,18] In both the ROBIN and SKYLARK trials, zuranolone demonstrated a significant percentage of HAM-D response (≥ 50% reduction in score from baseline) in patients achieving response and remission at day 45 compared to placebo (Table 2).[17,18] Safety analyses were conducted in both trials in which somnolence, dizziness, and sedation were the most common adverse effects, were more prevalent in the SKYLARK trial due to the higher dosage.[17,18] Due to the extensive list of inclusion and exclusion criteria, there are some possible limitations of the ROBIN and SKYLARK trials, such as the exclusion of patients with other psychiatric disorders (e.g. bipolar disorder), patients with a HAM-D score less than 26, patients who had a miscarriage, a birth that resulted in death, or terminated parental rights.[18] In addition, the long-term efficacy of zuranolone is unknown beyond day 45 as well as its utility in women with a major depressive episode greater than four weeks postpartum. Also, because more participants in the experimental group experienced somnolence compared to the placebo group in the SKYLARK trial, blinding may have been impacted.[18] Despite these possible limitations, the results of both the ROBIN and SKYLARK trials demonstrate that zuranolone is a well-tolerated drug that may have a place in PPD treatment in the future.

Future Directions

Although brexanolone and zuranolone were originally developed for the treatment of PPD, recent research suggests that steroids are involved in aging, neurodegenerative disorders, HIV-associated dementia, neoplasm, and other psychological disorders.[19] In addition to PPD, zuranolone has been investigated for the treatment of bipolar disorder, insomnia, major depression, and Parkinson's tremor.[19,20] Because these are novel drugs, more clinical data is necessary to establish safety and dosing for the treatment of other conditions.[19,21] Other potential areas for future research for brexanolone and zuranolone include long-term remission rates, abuse potential, and impact on PPD suicide rates. Additionally, future research needs to address the burden of PPD on marginalized populations and families in addition to broader long-term outcomes for mothers and their infants.[19,22]

The high cost of the drugs limits patient access, and the use of brexanolone and zuranolone may need to be reserved for patients who have failed other antidepressant therapy or require results quickly.[23] However, as more clinical data on long-term outcomes and real-world treatment effectiveness becomes available, the cost-effectiveness should be re-evaluated. In the future, brexanolone and zuranolone may become a more cost-effective therapy for PPD than SSRIs given faster relief for patients and require a shorter treatment duration, shortening the window for possible adverse effects.[21,22] Furthermore, more head-to-head data between the most commonly prescribed SSRIs for PPD, like sertraline, and these two novel agents is necessary to provide insight.

Conclusion

PPD poses a significant psychiatric challenge, often going undiagnosed and impacting both maternal and child well-being. Brexanolone and zuranolone stand as newly developed treatment options, with brexanolone being the first FDA-approved intravenous medication for moderate to severe PPD, and zuranolone offering a convenient oral alternative. The ACOG endorses both medications, acknowledging their distinctive administration routes, and emphasizing their adaptability in tailored PPD management. The value of brexanolone and zuranolone lies in their potential to fill a critical gap in PPD therapy by providing rapid relief, shorter treatment durations, and potentially reducing adverse effects, positioning them as valuable additions to the arsenal of psychiatric care for PPD.

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