ARTICLE

Brexanolone: A Novel Therapeutic in the Treatment of Postpartum Depression

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Postpartum depression (PPD) is an affective illness characterized by emotional, cognitive, and behavioral disturbances in the postpartum period. Prior to the approval of brexanolone, the standard of care for PPD was psychotherapy or antidepressants, often taking up to 6–8 weeks for efficacy.

Postpartum depression (PPD), or major depressive disorder (MDD) with peripartum onset, is an affective illness associated with childbirth and characterized by emotional, cognitive, and behavioral disturbances in the mother during pregnancy or the postpartum period (defined as the first 4 weeks to 12 months following birth) (1, 2). PPD is arguably the most common complication of childbirth, with prevalence rates ranging from 13% to 19% (3). The exact pathophysiology of PPD is unknown, and it is unclear whether it represents a distinct entity separate from MDD or a variant thereof.

Risk factors for PPD include a personal or family history of depression, low socioeconomic status, and poor social support (4). It is postulated that an interplay between genetic (diathesis) and environmental (stress) factors contributes to the development of PPD, with a heritability cited as high as 40% (5). In addition to this stress-diathesis paradigm, hormonal fluctuations and sleep deprivation during the peripartum period are associated with PPD. Implicated endocrinological changes include variations in estrogen, progesterone, cortisol, oxytocin, and allopregnanolone—a progesterone derivative (6, 7). The presenting symptomatology of PPD includes anhedonia, anergia, low mood, suicidality, and disturbances in sleep, appetite, and concentration (2).

Prior to the approval of allopregnanolone (marketed as brexanolone, brand name Zulresso) by the U.S. Food and Drug Administration (FDA) in March 2019, the standard of care for PPD was psychotherapy, psychotropics, or combination treatment. Nonpharmacologic interventions included peer support, psychodynamic approaches, interpersonal therapy, and cognitive-behavioral therapy. Available medications included selective serotonin/norepinephrine reuptake inhibitors, as well as tricyclic and second-generation antidepressants (8). For severe presentations, there was augmentation with drugs such as second-generation antipsychotics, with ECT as an option for treatment-refractory cases.

THE ROAD TO FDA APPROVAL

Brexanolone became the first drug approved by the FDA specifically intended to treat PPD after a series of three randomized, double-blind, placebo-controlled trials showed remarkable promise (9). The first phase II study enrolled 21 women with severe PPD—defined in the study as a Hamilton Depression Rating Scale (HAM-D) score ≥26—between December 15, 2015 and May 19, 2016, and compared mean score reductions between the 10 subjects receiving brexanolone and 11 controls receiving placebo (10). Kanes et al. (10) found that those receiving brexanolone experienced a mean reduction of 21 points, compared with 8.8 points for those receiving placebo. After 60 hours, seven of the 10 women receiving brexanolone had remission of symptoms. No serious adverse events, discontinuations of the trial, or deaths of participants were reported. Although eight of the 11 women receiving placebo experienced adverse events, only four of the 10 women receiving brexanolone reported the symptoms of dizziness and somnolence (10).

Thereafter, two phase III trials ensued (11). Of the 138 women in one study, 45 were assigned to receive intravenous brexanolone 60 μg/kg/hour, 47 to receive intravenous brexanolone 90 μg/kg/hour, and 46 to receive placebo. After 60 hours, the least-squares mean reductions in the HAM-D score were 19.5 (SE=1.2), 17.7 (SE=1.2), and 14.0 (SE=1.1), respectively (11). The second phase III study enrolled 108 participants randomly assigned to either intravenous brexanolone 90 μg/kg/hour or placebo (11). In contrast to a least-squares mean reduction in the HAM-D score of 12.1 among those receiving placebo, a 14.6 (SE=0.8) decrease was observed among those receiving brexanolone (11).

Headache, dizziness, and somnolence were the most common adverse events observed in the brexanolone groups across both phase III studies (11). Adverse events were found to be unremarkable across arms in both studies, except for one participant in each study (11). In the first study, a patient receiving intravenous brexanolone 60 μg/kg/hour reported suicidal ideation and an intentional overdose attempt; in the second, a patient receiving intravenous brexanolone 90 μg/kg/hour showed altered state of consciousness and syncope (11). Given these results, the drug was approved in March 2019 through a risk evaluation and mitigation strategy (REMS) and is currently available only to patients at certain certified health facilities with active monitoring by health care providers (12).

DRUG PROFILE

Mechanism of Action

Allopregnanolone is an endogenous progesterone metabolite produced by the brain, corpus luteum, as well as placenta during pregnancy (13). It readily crosses the blood-brain barrier and acts as a positive allosteric modulator at the γ-aminobutyric acid type A (GABAA) receptor (13). Plasma concentrations of allopregnanolone increase during pregnancy, reach a peak at the end of pregnancy, and drop precipitously after parturition (13). Fluctuations of allopregnanolone levels have been shown to be associated with symptoms of PPD, likely mediated by changes in neural networks in vulnerable patients (6).

Brexanolone is structurally identical to allopregnanolone (12). GABAA receptors, which are ligand-gated chloride ion channels, mediate inhibitory neurotransmission in the CNS via phasic and tonic inhibition (13). Brexanolone increases phasic and tonic inhibitory tone at synaptic and extrasynaptic GABAA receptors, respectively (12). Although its exact mechanism of action is not known, brexanolone is thought to exert its therapeutic effects on patients with PPD through modulation of disrupted GABAergic activity in the CNS (13). This restoration of dysregulated neural activity may have downstream effects and subsequently ameliorate symptoms of depression. The formulated compound that was used for the randomized-controlled clinical trials is comprised of an isotonic solution of allopregnanolone in citrate-buffered sulfobutylether-β-cyclodextrin (SBECD), diluted with sterile water (12). Given the rapid clearance of brexanolone in the blood, it is intended for continuous intravenous infusion over a 60-hour period in order to maintain steady-state therapeutic plasma concentration (11). Brexanolone is administered postpartum with weight-based dosing, with a recommended maximal dose of 90 μg/kg/hour, titrated as follows: 30 μg/kg/hour × 4 hours, 60 μg/kg/hour × 20 hours, 90 μg/kg/hour × 28 hours, 60 μg/kg/hour × 4 hours, and 30 μg/kg/hour × 4 hours (12).

Side-Effect Profile and Drug-Drug Interactions

As noted above, headache, dizziness, and somnolence were the most common adverse events observed in both phase III studies (11). Brexanolone is extensively metabolized by many pathways and thus unlikely to have significant drug-drug interactions (11). CYP2C9 is the only cytochrome P450 enzyme that has shown to be inhibited by brexanolone in in vitro studies. A clinical interaction study failed to show any alterations in pharmacokinetics when brexanolone was coadministered with phenytoin, a CYP2C9 substrate (11). Abuse potential has also been demonstrated to be low, as evidenced by no differences in subjective reports compared with placebo (12). In terms of the impact of hepatic and renal impairment on pharmacokinetics, there were no changes in tolerability in patients with moderate to severe liver disease, and no dose adjustments were necessary for severe kidney disease (12). However, the solubilizing agent SBECD may accumulate in patients with severe renal impairment (14), and thus brexanolone should not be given to patients with end-stage renal disease.

CLINICAL APPLICATIONS

Many were enthused by brexanolone's approval, not only as an innovation in maternal-child health but also as a sign of promise that more targeted pharmacotherapies are under way. With regard to its clinical applications, some have expressed concerns about brexanolone's accessibility, notably its approval status contingent upon the REMS program, which limits its delivery to certain certified health care facilities and requires a patient to be hospitalized for 60 hours. Another concern is its cost, which comes to about $34,000, depending on the patient's weight and excluding costs of hospitalization (15). Elucidating the salience of these concerns, a study examining attitudes regarding treatment for PPD among well-educated, high-income women found that only 35% of those surveyed indicated that they would opt to take medication if their clinician recommended pharmacotherapy (16). Among the factors preventing treatment, 65% of women reported lack of time, 43% stigma, and 33% issues with childcare (16). These issues come into conversation with recently announced findings from SAGE Therapeutics' Phase III ROBIN study, in which a sister formulation of brexanolone with oral bioavailability demonstrated efficacy in reducing symptoms of PPD after 2 weeks of outpatient administration (17).

Nevertheless, over half of women with PPD remain undiagnosed, 85% go untreated, and over 90% are inadequately treated (18). Moreover, some researchers have theorized that incidence rates of PPD may be higher among women of color or of lower socioeconomic status (19). Furthermore, black postpartum mothers have been found to be less likely than their Caucasian counterparts to accept both psychotherapy and pharmacotherapy (20). Given these findings in the setting of this exciting psychopharmacologic breakthrough, more translational and implementation research is needed

Key Points/Clinical Pearls

- Brexanolone is the first therapeutic option approved by the Food and Drug Administration specifically for the treatment of postpartum depression.
- Recent trials of brexanolone demonstrated its efficacy, with a limited side-effect profile and minimal drug-drug interactions. Headache, dizziness, and somnolence were the most commonly reported side effects.
- Rare instances of suicidal ideation, altered consciousness, and syncope warrant the administration of brexanolone under medical supervision.
- Postpartum depression is a highly prevalent, underdiagnosed, and undertreated mental illness. Further research is needed to mitigate gaps in access to evolving standards of care.

to understand how this innovation affects individual- and structural-level factors that have historically limited access to new standards of care.

CONCLUSIONS

PPD is a highly prevalent, underdiagnosed, and undertreated mental illness. Brexanolone, approved by the FDA under a REMS in March 2019, offers promise as a targeted pharmacotherapeutic intervention for PPD, with limited side effects and drug-drug interactions. More research is needed to understand the etiology of postpartum depression, expand therapeutic options, and translate findings to meaningful patient care.

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