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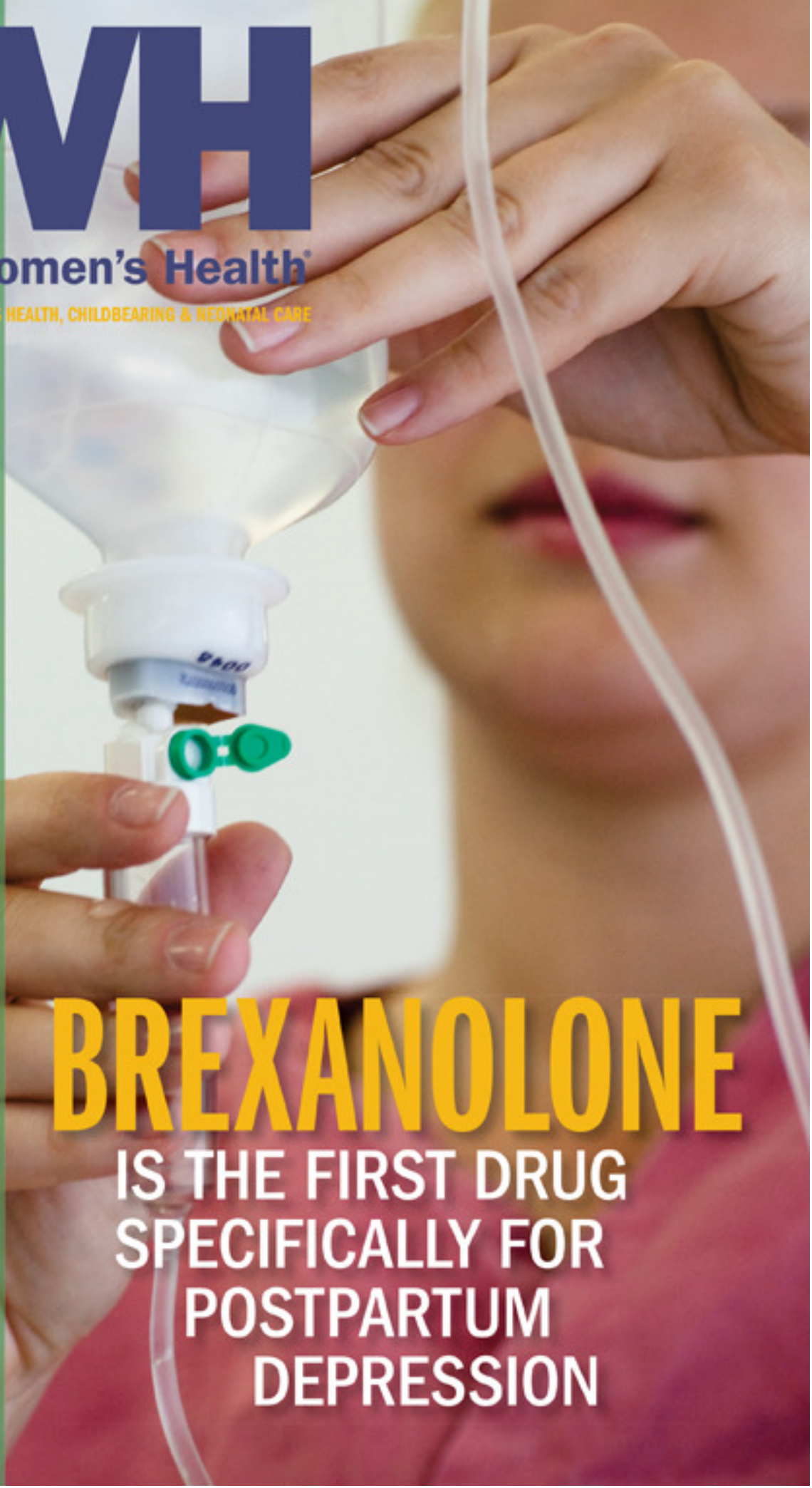

BREXANOLONE
IS THE FIRST DRUG SPECIFICALLY FOR POSTPARTUM DEPRESSION

Brexanolone Is the First Drug Specifically for Postpartum Depression

Heidi Collins Fantasia

ABSTRACT: Postpartum depression is a mood disorder that affects up to 20% of women in the first year after childbirth. Symptoms can range from mild depression and anxiety to severe mood alterations and psychosis. A mainstay of treatment has included selective serotonin reuptake inhibitors. However, it can take 2 to 6 weeks for clinical improvement with this approach. In March 2019, the U.S. Food and Drug Administration approved brexanolone, the first medication specifically indicated for the treatment of postpartum depression. Given as an intravenous infusion over the course of 60 hr, brexanolone has the potential to fill an unmet need for women with postpartum depression. In this column, I will provide an overview of brexanolone and discuss administration, adverse effects, and practice implications for nurses who work with childbearing women.

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Postpartum depression (PPD) is a mood disorder that can affect women within the first year of childbirth. It is estimated that between 10% and 20% of women may develop PPD during the 12 months after birth (Kanes, Colquhoun, Gunduz-Bruce, et al., 2017; Kimmel, Cox, Schiller, Gettes, & Meltzer-Brody, 2018), but the first month after birth represents the time of greatest risk for developing this mood disorder (Burke, Susser, & Hermann, 2018). PPD results from fluctuations in reproductive hormones, specifically estrogen and the progesterone metabolite allopregnanolone (Kanes, Colquhoun, Gunduz-Bruce, et al., 2017). The rapid decline of these hormones after birth is thought to play a role in the development of PPD in some women. Additional clinical predictors for the development of PPD include a previous history of depression, family history of depression, and stressful life events (Kose & Cetin, 2017).

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CLINICAL IMPLICATIONS

- Postpartum depression can affect up to 20% of women during the first year after childbirth.
- Brexanolone is the first medication approved specifically for the treatment of postpartum depression.
- Brexanolone is given by intravenous infusion over the course of 60 hr.
- Improvement in mood alterations can occur immediately after infusion.
- Excessive sedation and loss of consciousness require continuous monitoring and supervision of women with infants and children.

Symptoms can range from mild to severe and include clinically significant depression, which often occurs with anxiety. Severe PPD includes depression with marked impairment in daily function (including self and infant care) and intrusive thoughts; in the presence of psychosis, PPD increases the risk of maternal suicide (Kose & Cetin, 2017).

First-line treatment of PPD has focused on screening and intervention with pharmacologic management of the mood alterations (depression and anxiety), with or without concurrent psychotherapy with a mental health provider (American College of Obstetricians and Gynecologists, 2018). Selective serotonin reuptake inhibitors are considered the first-line pharmacologic treatment for PPD because they are used to treat symptoms of depression and anxiety (Kimmel et al., 2018). A disadvantage of this approach is that it can take between 2 and 6 weeks for these medications to alleviate a woman's symptoms (Meltzer-Brody et al., 2018). Nonpharmacologic interventions for PPD, including counseling, also do not have an immediate effect and, in cases of severe PPD, are used in conjunction with pharmacologic agents.

In March 2019, the U.S. Food and Drug Administration (FDA) approved brexanolone, an injection for intravenous (IV) treatment of PPD in adult women. Brexanolone, marketed under the brand name Zulresso (Sage Therapeutics, Cambridge, MA), is the only medication approved by the FDA specifically to treat PPD with no other indication for use. In this column, I present an overview of brexanolone, highlight adverse effects, and discuss implications for nursing practice.

Overview of Brexanolone

Researchers have postulated that rapid alternations in the concentration of neuroactive steroids, such as allopregnanolone, during the peripartum period may contribute to affective dysregulation in women (Burke et al., 2018). Allopregnanolone rises with progesterone throughout pregnancy and peaks in the third trimester. Allopregnanolone is a modulator of γ-aminobutyric acid A (GABA-A) receptors, and if these receptors do not adjust to the fluctuations in hormone levels after birth, this may be one mechanism that contributes to the development of PPD (Kose & Cetin, 2017; Maguire, 2019). Brexanolone is a neuroactive steroid and a modulator of GABA-A receptors. Although the complete mechanism of action is not fully understood, the effect of brexanolone on these receptors is thought to be the pathway for its effect on mood (Frieder, Fersh, Hainline, & Deligiannidis, 2019; Kose & Cetin, 2017).

Dose and Administration

Administration is by continuous IV infusion over 60 hr, which is approximately 2.5 days. The dosing schedule consists of titration, maintenance, and taper, in which the dose of brexanolone is gradually increased, kept steady, and then decreased during treatment (Kanes, Colquhoun, Doherty, et al., 2017). The starting dose during Hours 0 to 4 is 30 mcg/kg/hr. The dose is increased to 60 mcg/kg/hr for Hours 4 to 24. From Hours 24 to 52, the dose is increased to 90 mcg/kg/hr or kept at the previous dose of 60 mcg/kg/hr for women who cannot tolerate 90 mcg/kg/hr. During Hours 52 to 56, the dose is decreased to 60 mcg/kg/hr. The treatment is completed with a dose of 30 mcg/kg/hr during Hours 56 to 60 (Sage Therapeutics, 2019a).

There are specific instructions for preparation of the brexanolone infusion that are provided with the medication. Brexanolone must be diluted before administration and infused via a dedicated IV line. Brexanolone is suppled as a solution in 100 mg/20 ml vials (5 mg/ml). Once diluted, the product can be used only at room temperature for 12 hr, so a 60-hr infusion will require the preparation of five infusion bags. A 20-ml vial (containing 100 mg of brexanolone) is placed in an infusion bag and then diluted with 40 ml of sterile water for injection and 40 ml of 0.9% sodium chloride injection. The final concentration of brexanolone in the infusion bag is 1 mg/ml. After preparation, the infusion bag can be refrigerated for 96 hr. An infusion pump must be used to ensure accurate dosing (Sage Therapeutics, 2019a).

Potential Adverse Effects

Brexanolone has a black box warning for the potential for excessive sedation and sudden loss of consciousness (Sage Therapeutics, 2019a); these can occur at any time during the infusion. Dizziness, fatigue, dry mouth, headache, hot flashes/flushing, and IV site irritation were also reported (Kanes, Colquhoun, Doherty, et al., 2017; Kanes, Colquhoun, Gunduz-Bruce, et al., 2017; Meltzer-Brody et al., 2018). Because brexanolone has not been used outside of clinical trials at the time of this publication, there are no postmarking data available. Additional adverse effects could become apparent with more widespread use of the drug.

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Drug Interactions

Brexanolone should not be administered with other central nervous system depressants, including alcohol. Concomitant use with medications such as opioids, benzodiazepines, and hypnotics should be avoided. In clinical trials, use with other antidepressants increased sedation. During clinical trials, brexanolone was not evaluated with other medications for potential interactions (Kanes, Colquhoun, Doherty, et al., 2017; Kanes, Colquhoun, Gunduz-Bruce, et al., 2017; Meltzer-Brody et al., 2018; Sage Therapeutics, 2019a).

Contraindications

There are currently no known contraindications for brexanolone other than that its use is restricted for PPD only. It is not approved for the treatment of other mood disorders or mental health conditions that occur outside of the postpartum period (FDA, 2019).

Special Populations

Use of brexanolone is indicated for treatment of PPD that develops after birth; it is not recommended for treatment of depression during pregnancy or for depression that is not associated with childbirth. There are no data available regarding brexanolone use in pregnancy, but based on animal data with other drugs that enhance GABAergic inhibition, it is possible that brexanolone may cause fetal harm (Sage Therapeutics, 2019a). A pregnancy registry has been established for women who are exposed to brexanolone during pregnancy (see Box 1).

Brexanolone is excreted in breast milk in low levels and, based on very limited data, there have been no adverse effects reported in breastfed infants. However, women were excluded from clinical trials if they were breastfeeding, so there are no definitive safety data available (Kanes, Colquhoun, Doherty, et al., 2017; Kanes, Colquhoun, Gunduz-Bruce, et al., 2017; Meltzer-Brody et al., 2018). How treatment with brexanolone will affect breastfeeding is not known. The safety and efficacy of brexanolone in the treatment of PPD has not been established in adolescent women because women younger than 18 years were excluded from clinical trials.

Implications for Nursing Practice

Brexanolone is available only through a Risk Evaluation and Mitigation Strategy (REMS) program. This program, called *Zulresso REMS*, has been put in place because the potential

BOX 1 BREXANOLONE PREGNANCY REGISTRY

Women who are exposed to brexanolone while pregnant should speak with their health care provider about registering with the National Pregnancy Registry for Antidepressants via phone at 1-844-405-6185 or online at https://womensmentalhealth.org/clinical-and-research-programs/pregnancyregistry/antidepressants.

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for excessive sedation may increase the risk for injury. The requirements of this program restrict the prescription and use of brexanolone to health care facilities that have enrolled in the program and pharmacies that have registered with the program. Additionally, women also need to enroll in the program before infusion. Information about the REMS program is available at the website www.zulressorems.com or can be requested by calling 1-844-472-4379.

At the time of this writing, brexanolone was anticipated to be available some time in 2019 after the U.S. Drug Enforcement Agency assigned the medication to a scheduling category (Sage Therapeutics, 2019b). In clinical trials, some women reported euphoric mood, but because of the short-term administration and tapered dosing, abuse potential was not able to be determined (Sage Therapeutics, 2019a). The optimal setting for the infusion of brexanolone has not been determined. Hospitals, infusion centers, and psychiatric facilities could possibly accommodate women receiving treatment, but individual organizations will need to determine if they will offer this service.

During an IV infusion of brexanolone, women must receive continuous pulse oximetry monitoring and be supervised when interacting with their infants or other children. This is to increase safety if loss of consciousness occurs (Sage Therapeutics, 2019a). Women must be continuously monitored by a health care provider during the infusion and be assessed for excessive sedation every 2 hr when awake. Staff at facilities where the infusion occurs will need to develop specific administration protocols and ensure that staffing levels are adequate to allow for increased patient monitoring by nurses. Additionally, women may be breastfeeding, and protocols will need to address the safest way for women feed their infants and maintain lactation during the infusion. The manufacturer suggests that women always have a family member with them to help care for any children (Sage Therapeutics, 2019a), but how that will be operationalized in health care facilities is unknown.

Other questions remain regarding treatment with brexanolone. According to media coverage of brexanolone

> This treatment could provide rapid relief to women with severe PPD and fill an unmet need among this population

approval, the estimated out-of-pocket cost of the drug is anticipated to be approximately $34,000 (Sage Therapeutics, 2019b). That does not include costs for the infusion, continuous monitoring, health care providers, and the required hospital stay. The manufacturer is negotiating with insurance companies regarding payment for brexanolone, and information about coverage options will be forthcoming. Women who cannot afford the costs associated with treatment (whether full cost or subsidized by insurance) may not be able to access this treatment.

There are currently no long-term data on the sustainability of the therapeutic effect of brexanolone after treatment is completed. In published clinical trials, follow-up was limited to 30 days (Kanes, Colquhoun, Gunduz-Bruce, et al., 2017; Meltzer-Brody et al., 2018). Guidelines for how and when women will be transitioned to oral antidepressants after infusion, the timing of the transition, and whether treatment with brexanolone will affect the dose of oral antidepressants is not known.

Because data on brexanolone are limited to premarketing clinical trials, individual health care providers, in collaboration with hospitals and facilities that decide to offer brexanolone infusion, will need to develop criteria for use and selection of those who are treated. In published clinical trials of brexanolone, PPD was diagnosed after administration of the Hamilton Rating Scale for Depression, a validated depression screening tool (Kanes, Colquhoun, Doherty, et al., 2017; Kanes, Colquhoun, Gunduz-Bruce, et al., 2017; Meltzer-Brody et al., 2018). However, other validated tools for PPD depression screening exist, such as the Edinburgh Postnatal Depression Scale (Cox, Holden, & Sagovsky, 1987) and the Postpartum Depression Screening Scale (Beck & Gable, 2000, 2001), both of which have different scoring criteria that assist in establishing a formal diagnosis of PPD. There is no evidence-based guidance on which screening tool is more appropriate or more effective for determining whether a woman has PPD when brexanolone is being considered. Additionally, women who participated in the brexanolone clinical trials were diagnosed with PPD after birth. Whether the drug could be used prophylactically for women with a previous and serious episode of PPD was not addressed during the clinical trials.

Conclusion

Brexanolone is the first medication approved to specifically and only treat PPD; it has been shown to improve depression and mood symptoms immediately after infusion

(Kanes, Colquhoun, Doherty, et al., 2017; Kanes, Colquhoun, Gunduz-Bruce, et al., 2017; Kose & Cetin, 2017). This treatment could provide rapid relief to women with severe PPD and fill an unmet need among this population. Although questions remain related to cost, insurance coverage, eligibility, logistics of treatment, and management of PPD after infusion completion, the use of brexanolone has the potential to change the way health care providers treat women with PPD and may improve the lives of women who are affected by this mood disorder. **NWH**

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