Brexanolone Injection for Postpartum Depression

Psychological Health Center of Excellence Psych Health Evidence Briefs December 2019

Q. What is brexanolone injection?

A. Brexanolone is a novel, rapid-acting antidepressant, and is the first medication specifically indicated for the treatment of postpartum depression (PPD). Brexanolone injection was approved by the U.S. Food and Drug Administration (FDA) in early 2019 for the treatment of PPD in adults, under the brand name Zulresso. Administration requires an on-site healthcare provider to monitor the patient over the course of the infusion, which is administered intravenously over 60 hours (2.5 days).

Q. What is the potential mechanism of action underlying brexanolone?

A. Brexanolone is a $GABA_A$ receptor modulator, and is chemically identical to the progesterone metabolite allopregnalone, an endogenous neurosteroid. During pregnancy, allopregnalone levels rise, peaking in the third trimester. Postpartum, levels of allopregnalone decrease rapidly, and this rapid decline in hormones results in downregulation of $GABA_A$ receptors, which is thought to be related to the development of PPD in some women (Osborne et al., 2017). The exact mechanism of action of brexanolone as a treatment for PPD is not fully understood, but it is proposed to occur by "resetting" dysregulated brain function via modulation of $GABA_A$ receptor activity (Sage Therapeutics, 2018).

Q. Is brexanolone recommended as a treatment for PPD in the Military Health System (MHS)?

A. No. The *2016 VA/DoD Clinical Practice Guideline for the Management of Major Depressive Disorder* was published prior to FDA approval of brexanolone for the treatment of PPD, and does not include brexanolone as a treatment for any type of depression.

The MHS relies on the VA/DoD clinical practice guidelines (CPGs) to inform best clinical practices. The CPGs are developed under the purview of clinical experts and are derived through a transparent and systematic approach that includes, but is not limited to, systematic reviews of the literature on a given topic and development of recommendations using a graded system that takes into account the overall quality of the evidence and the magnitude of the net benefit of the recommendation. A further description of this process and CPGs on specific topics can be found on the VA clinical practice guidelines website.

Q. Do other authoritative reviews recommend brexanolone as a treatment for PPD?

A. No. Other authoritative reviews have not substantiated the use of brexanolone for PPD.

Several other recognized organizations conduct systematic reviews and evidence syntheses on psychological health topics using similar grading systems as the VA/DoD CPGs. These include the Agency for Healthcare Research and Quality (AHRQ) and Cochrane.

- AHRQ: No comparative effectiveness reviews including studies on brexanolone for PPD were identified.
- Cochrane: No systematic reviews of brexanolone for PPD were identified.

Q. Is there any recent research on brexanolone as a treatment for PPD?

A. An October 2019 literature search identified three randomized controlled trials (RCTs) of brexanolone as a treatment for PPD (reported in two articles; Kanes et al., 2017; Meltzer-Brody et al., 2018), which are included in a 2019 meta-analysis (Zheng et al., 2019). The meta-analysis included 267 women with PDD, 156 receiving brexanolone injection and 111 receiving a placebo injection. Two studies included women with severe PPD, and one included women with moderate PPD. One study examined two different dosages of brexanolone. For all three studies, the primary endpoint was change from baseline in Hamilton Rating Scale for Depression (HAM-D) score at 60 hours (end of treatment), and the length of follow-up was 30 days. Each of the individual RCTs found significant reductions in HAM-D scores at 60 hours compared to placebo, and differences remained significant at 30 days in two of the studies, but data provided were not

meta-analyzable (the studies reported only change scores). The meta-analysis of treatment response found that women receiving brexanolone injection had significantly greater treatment response than placebo, beginning after 24 hours, peaking at 36 hours, and lasting until day seven of follow-up. Similar results were found for treatment remission, with significant differences starting at 24 hours, peaking at 60 hours, and lasting until 72 hours. Rates of treatment discontinuation for any reason were significantly higher in the brexanolone group, though rates were similar for treatment discontinuation due to intolerability and adverse drug reactions. The most common adverse effects reported were dizziness, somnolence, and headaches.

Q. What conclusions can be drawn about the use of brexanolone as a treatment for PPD in the MHS?

A. The *2016 VA/DoD Clinical Practice Guideline for the Management of Major Depressive Disorder* does not include brexanolone, which emerged as a treatment option after its publication. Three RCTs have found a rapid antidepressant effect of brexanolone injection in women with moderate to severe PPD compared to placebo. Commentaries on these trials note that differences in the women randomized into each group, such as timing of diagnosis and concomitant use of other GABAergic drugs, may be of concern (Tufts, 2019; Tang & Parekh, 2019). There is an FDA Black Box Warning for Zulresso for excessive sedation and sudden loss of consciousness. As a result, healthcare facilities must enroll in the FDA's REMS (Risk Evaluation and Management Strategy) for Zulresso, which requires monitoring by a healthcare professional every two hours during administration of the injection, treatment initiation early in the day to avoid excessive sedation, pulse oximetry monitoring, and accompanied interactions with children during administration (Sage Therapeutics, 2019). Beyond this potential treatment barrier, the cost of brexanolone injection is $34,000 ("Brexanolone (Zulresso)," 2019). More trials are needed to assess the comparative effectiveness of brexanolone against the current standard of care, the long-term efficacy and safety, and the optimal delivery and treatment combination.

**Find the full series of Psych Health Evidence Briefs, provide feedback and subscribe to receive future briefs at http://www.pdhealth.mil/research/evidence-synthesis/evidence-briefs.*

References

Brexanolone (Zulresso) for postpartum depression. (2019). *JAMA*, *322*(1), 73–74.

Department of Veterans Affairs/Department of Defense. (2016). *VA/DoD clinical practice guideline for management of major depressive disorder. Version 3.0*. Washington (DC): Department of Veterans Affairs/Department of Defense.

Kanes, S., Colquhoun, H., Gunduz-Bruce, H., Raines, S., Arnold, R., Schacterle, A., ... Meltzer-Brody, S. (2017). Brexanolone (SAGE-547 injection) in post-partum depression: A randomised controlled trial. *Lancet*, *390*, 480–489.

Meltzer-Brody, S., Colquhoun, H., Riesenberg, R., Epperson, C. N., Deligiannidis, K. M., Rubinow, D. R., ... Kanes, S. (2018). Brexanolone injection in post-partum depression: Two multicentre, doubleblind, randomised, placebo-controlled, phase 3 trials. *Lancet*, *392*, 1058–1070.

Osborne, L. M., Gispen, F., Sanyal, A., Yenokyan, G., Meilman, S., & Payne, J. L. (2017). Lower allopregnalone during pregnancy predicts postpartum depression: An exploratory study. *Psychoneuroendocrinology*, *79*, 116–121.

Sage Therapeutics. (2018). *Brexanolone injection, for intravenous use* (Brexanolone injection, IV sponsor briefing document). Joint Meeting of the Psychopharmacologic Drug Advisory Committee and Drug Safety and Risk Management Advisory Committee. Retrieved from https://www.fda.gov/media/121348/download

Sage Therapeutics. (March 2019). *Zulresso*. Retrieved from https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/211371lbl.pdf

Tang, G. Y., & Parekh, J. (2019). Brexanolone injection for post-partum depression. *Lancet*, *394*, 379.

Tufts, J. A. (2019). Brexanolone injection for post-partum depression. *Lancet*, *394*, 379.

Zheng, W., Cai, D. B., Zheng, W., Sim, K., Ungvari, G. S., Peng, X. J., ... Xiang, Y. T. (2019). Brexanolone for postpartum depression: A meta-analysis of randomized controlled studies. *Psychiatry Research*, *279*, 83–89.

Released December 2019 by the Psychological Health Center of Excellence
301-295-7681 | pdhealth.mil