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DRUG EVALUATION

Evaluating brexanolone for the treatment of postpartum depression

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ABSTRACT

Introduction: Postpartum depression (PPD) is a serious and common complication of childbirth that can have deleterious effects not only on the mother but on the cognitive and behavioral development of exposed children. Brexanolone is a novel, soluble synthetic formulation of the natural hormone allopregnanolone and acts as a positive allosteric modulator of the gamma-aminobutyric acid A receptor (GABAA). Allopregnanolone levels dramatically decrease during the postpartum time-period and some studies indicate lower serum levels of allopregnanolone during pregnancy in women that go on to develop PPD.

Areas covered: The author provides an overview of brexanolone as a treatment option for PPD including coverage of its pharmacokinetics, efficacy, safety, and tolerability. Furthermore, the author gives her expert perspectives on its use and its standing in the treatment armamentarium moving forward.

Expert opinion: Brexanolone represents a breakthrough for psychiatry due to its novel mechanism of action, its rapid onset of action, and its sustained effects without continued administration. It is appropriate for use in women with moderate to severe PPD. Experience with the medication and further research is needed to clarify whether the current recommended dosing regimen is required for efficacy.

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KEYWORDS
Brexanolone; allopregnanolone; postpartum depression; major depression; GABA; neurosteroids

1. Introduction

Postpartum depression (PPD) is one of the most common complications of childbirth and is associated with significant adverse outcomes for the mother, the child, and the family as a whole [1,2]. Prevalence in the general population is approximately 10–15% [1,2] but is higher in women with a history of a preexisting mood disorder. The risk for PPD has been shown to be increased in women with a history of major depression [3], bipolar disorder [4], and PPD following previous pregnancies [5]. Repercussions of PPD are not insignificant. Suicides account for up to 20% of all postpartum deaths and represent one of the leading causes of peripartum mortality [6]. PPD has also been associated with impaired bonding [7] and to negatively affect parenting behavior [8,9]. Finally, PPD has significant negative effects on infant development, including lower IQ, slower language development, and increases in adverse childhood behavioral issues [10]. Thus, adequate treatment of PPD is imperative – not only for maternal outcomes but for child outcomes as well.

The Diagnostic and Statistical Manual (DSM) is used by psychiatrists and other clinicians to make specific psychiatric diagnoses and has undergone revisions over the years. In the DSM-IV version [11], the specifier 'postpartum' was added to the diagnosis of major depression if the onset of the depressive illness occurred within 4 weeks after delivery. The most recent version, DSM-5 [12], has changed from the specifier 'postpartum' to the term 'peripartum' which includes episodes of depression that begin during pregnancy or begin within the first 4 weeks postpartum. This change recognizes the fact that many cases of PPD actually begin during pregnancy and continue or worsen in the immediate postpartum time-period [12]. The term 'PPD' in this article therefore includes cases that began in pregnancy and continued postpartum as well as cases that began in the immediate postpartum time-period. The treatment of PPD has been limited by a paucity of studies and reluctance to use psychiatric medications during lactation and is further complicated by the need for lengthy medication trials due to the fact that antidepressants take weeks to months to fully work to treat a major depressive episode.

Clinically, PPD is essentially a major depressive episode that occurs during the immediate postpartum time-period, a period that has been demonstrated to have an elevated risk for the development of a major depressive episode [13]. A major depressive episode is defined as 2 weeks or longer of 5 or more of the following symptoms: persistent depression or low mood, anhedonia, change in appetite, sleep disturbance, psychomotor retardation or agitation, loss of energy, feelings of worthlessness or hopelessness, poor concentration, and thoughts of death or suicide [12]. PPD, then, meets criteria for a major depressive episode with symptom onset during pregnancy or in the immediate postpartum time-period.

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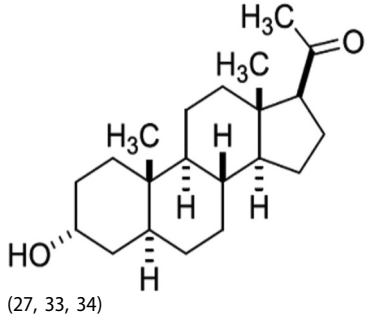
Article highlights

- Postpartum depression is a serious complication of pregnancy with significant morbidity and mortality.
- Brexanolone is the first pharmacologic agent specifically approved for the treatment of postpartum depression.
- Brexanolone can be thought of as a synthetic version of the neurosteroid allopregnanolone which acts as a positive allosteric modulator of the gamma-aminobutryic acid A receptor thus regulating the major inhibitory neurotransmitter in the brain.
- Brexanolone is given as a 3 day intravenous infusion and requires continuous pulse oximetry monitoring.
- Brexanolone reduces postpartum depression symptoms within hours of administration, results in remission in a large portion of patients and has sustained effects for at least 30 days after infusion.
- Brexanolone with its novel mechanism of action and its rapid, significant and sustained response is an exciting breakthrough agent for psychiatry.

Box 1. Drug Summary Box

Drug Name	Brexanolone
Phase	Launched
Indication	Postpartum Depression
Pharmacology description	Positive allosteric modulator of gamma-aminobutyric acid (GABA) receptor type A
Route of Administration	Intravenous infusion over 60 hours
Chemical Structure	
Pivotal Trials	(27, 33, 34)

The exact pathophysiology underlying PPD remains unclear and is likely multifactorial with genetics/epigenetics, neuroendocrine changes, inflammation, neurotransmitter changes, and environmental risk factors all playing a role [14]. Further, PPD is likely heterogeneous as a diagnosis and different pathophysiological mechanisms may be at play in different women. Hypothalamic-pituitary-adrenal (HPA) axis dysfunction has been proposed as an underlying mechanism for PPD and preclinical work has demonstrated that HPA axis dysfunction induces postpartum depression-like behaviors in animal models (reviewed in [15]). The major inhibitory neurotransmitter system in the brain, the gamma-aminobutyric acid (GABA) system tightly regulates neurons in the hypothalamus via neurosteroid-sensitive GABA-A ($GABA_A$) receptors. During pregnancy and the postpartum time period, there are significant changes in HPA axis functioning, neuroactive steroids, and $GABA_A$ receptors. Animal models have demonstrated that reduced $GABA_A$ receptor functioning is associated with depression-like behavior and abnormal maternal behavior in the postpartum period (reviewed in [15]). Thus, GABAergic hypofunctioning coupled with HPA axis overactivity, potentially triggered in susceptible women by pregnancy-induced changes in the GABA system, neurosteroid levels, and the HPA axis, may underlie at least some cases of PPD.

2. Overview of the market

Prior to brexanolone, there were no FDA-approved medications specifically for PPD, although standard antidepressant treatments have typically been used to treat this condition. Despite the fact that PPD is common, few clinical trials have been conducted, but overall the data support the use of standard antidepressant treatments for PPD. For example, a 2014 Cochrane Review examined the results of three randomized, placebo controlled trials of Selective Serotonin Reuptake Inhibitors (SSRIs) and found that SSRIs were significantly more effective than placebo in response and remission rates of postpartum depressive symptoms [16]. Serotonin Norepinephrine Reuptake Inhibitors (SNRIs), tricyclic antidepressants, and other atypical antidepressants can also be used though this is based on little data specific to PPD. For example, there have been open-label studies supporting the use of bupropion [17], venlafaxine [18], and desvenlafaxine [19] but no randomized, placebo controlled trials. Thus, to date, treatment of PPD has been primarily based on data that supports the treatment of major depression in general and on little data specific to PPD.

3. Introduction to the compound

Brexanolone is a soluble synthetic formulation of the naturally occurring neuroactive steroid allopregnanolone that can be administered intravenously to produce stable physiological serum concentrations. It acts on the gamma-aminobutyric acid A receptor ($GABA_A$) and was originally developed by SAGE Therapeutics for the treatment of status epilepticus [20] but was also simultaneously developed for the treatment of PPD. It is the first FDA-approved medication for PPD and was approved in March of 2019 after being granted a Priority Review and a Breakthrough Therapy designation by the FDA. It is administered as a 60-h stepped dosage infusion from 30 µg/kg/hour up to a high of 90 µg/kg/hour, though available studies have demonstrated efficacy with a 60 µg/kg/hour dosage as well. Remarkably, brexanolone results in a rapid treatment response, with a significant decrease in depressive symptoms (and separation from placebo) as early as 24 hours after the start of the infusion and can therefore be classified as a Rapidly Acting Antidepressant with a similar timing of response as ketamine and esketamine. However, unlike ketamine's generally brief response, based on the available data, response to brexanolone appears to be maintained for at least 30 days after the infusion despite discontinuation of the medication. In addition, like ketamine and esketamine, brexanolone has a novel mechanism of action that is unique since most other antidepressant medications work via the monoamine neurotransmitter systems. Thus,

brexanolone is the first treatment approved specifically for PPD and has a novel mechanism of action, a rapid onset of action, and a sustained response despite discontinuation of the medication.

4. Chemistry

Brexanolone is chemically identical to endogenous allopregnanolone and, like allopregnanolone, acts as a positive allosteric modulator of the gamma-aminobutyric acid A receptor ($GABA_A$) in the brain. GABA acts as an inhibitory neurotransmitter, and $GABA_A$ receptors are five-unit transmembrane ion channels that are found in intrasynaptic and extra synaptic sites as well as on glial cells. A number of preclinical and clinical studies have implicated reduced neuroactive steroid levels, in particular allopregnanolone, in mood and anxiety disorders (reviewed in [21,22]). For example, in animal models, neuronal levels of allopregnanolone rise during an acute stress, but with chronic stress decrease and correlate with depressive and anxiety-like behaviors [22]. Allopregnanolone levels rise across the course of pregnancy and precipitously drop after delivery, and some [23,24] but not all studies [25] have found that lower levels of allopregnanolone in pregnancy are associated with the development of PPD. Brexanolone is thus thought to target the decreased levels of allopregnanolone following childbirth, which may trigger a depressive episode in susceptible women, thus alleviating their depressive symptoms.

5. Pharmacodynamics

Brexanolone potentiates GABA-mediated currents by acting on the $GABA_A$ receptor and enhancing the receptor's function, potentiating GABA transmission. As noted above, the GABAergic system tightly regulates the HPA axis and inhibits HPA activity. Thus, brexanolone is thought to correct HPA axis dysfunction by targeting the GABAergic system. The exposure–response relationship of brexanolone and the time course of pharmacodynamic response are unknown, and thus, the requirement for a 60-h continuous infusion is solely based on the previous study designs and currently available data.

(1) **Pharmacokinetics and metabolism** [26]

Brexanolone is administered as a stepped intravenous infusion over 60 hours. The starting dose is 30 µg/kg/hour for the first 4 hours, then 60 µg/kg/hour for hours 4–24 and then 90 µg/kg/hour for hours 24–52. The dose is then lowered to 60 µg/kg/hour for the next 4 hours (hours 52–56) and finally to 30 µg/kg/hour for the last 4 hours.

Brexanolone exhibits dose proportional pharmacokinetics from 30 µg/kg/hour to 270 µg/kg/hour and the mean steady state exposure at 60 µg/kg/hour was approximately 52 ng/mL and for 90 µg/kg/hour was 79 mg/mL. The volume of distribution was approximately 3 L/kg which suggests an extensive tissue distribution. Plasma protein binding is greater than 99%, independent of plasma concentration. For elimination, the terminal half-life is approximately 9 hours and the total plasma clearance is approximately 1 L/h/kg. Brexanolone is extensively metabolized by non-CYP pathways including keto-reduction, glucuronidation and sulfation. Brexanolone has three major circulating metabolites that are pharmacologically inactive and do not contribute to efficacy. Brexanolone is primarily excreted in feces (47%) and urine (42%) with less than 1% unchanged. Importantly, no clinically significant differences in pharmacokinetics were observed in populations with renal or hepatic impairment. Although the effect of end stage renal disease on brexanolone pharmacokinetics is unknown, it is recommended that brexanolone not be used in this population because the solubilizing agent, betadex sulfobutyl ether sodium, can accumulate in these patients. There have been no studies to evaluate the effects of other drugs on brexanolone. No clinically significant differences in the pharmacokinetics of phenytoin were observed with concomitant use of brexanolone.

6. Clinical efficacy

FDA approval of brexanolone for the treatment of PPD was based on data collected from four published studies. The first study was an open-label, proof-of-concept study in severe PPD in which they had originally planned to enroll 10 participants [27]. The study was stopped early based on the significant results seen in 4 participants. In this study, PPD was defined as beginning no earlier than the third trimester and no later than 12 weeks after delivery. Inclusion required a score of ≥20 on the Hamilton Rating Scale for Depression (HAM-D) [28], a stable dose of an antidepressant for 2 weeks or longer (if taking antidepressants), and permanent weaning from breastfeeding. Dosing was 21.5 µg/kg/hour for 4 h, 43 µg/kg/hour for 4 h, 64.5 µg/kg/hour for 4 h, and then 36 h of 86 µg/kg/hour followed by a stepped taper of the infusion over 12 hours. No serious adverse events were noted and two participants reported sedation. The mean HAM-D score decreased from 26.5 before the infusion to 4.8 at 12 hours after the start of the infusion and to 1.8 at the end of the infusion (60 hours after the start of the infusion). Other measures of psychiatric symptoms were similarly strikingly reduced, including the Edinburgh Postnatal Depression Scale (EPDS) [29], The Generalized Anxiety Disorder 7-item scale (GAD-7) [30], the Patient Health Questionnaire (PHQ-9) [31], and Clinical Global Impression-Improvement scale [32]. The trial was halted early in order to move to double-blind, placebo-controlled designs.

The first randomized controlled study (Phase II) of brexanolone enrolled a total of 21 women, 10 of whom received brexanolone and 11 received placebo [33]. The trial was multicenter and participants were enrolled at four sites. The dosing was simplified to 30 µg/kg/hr for the first 4 hours, 60 µg/kg/hr for hours 4–24, 90 µg/kg/hr for hours 24–52 and then stepped down to 60 µg/kg/hr for 4 hours, and finally 30 µg/kg/hr for 4 hours. PPD was again defined as onset beginning no earlier than the third trimester and no later than 12 weeks after delivery, and participants could not be more than 6 months from delivery at the time of enrollment. Participants were required to have more severe symptoms with a HAM-D score of ≥26. Stable antidepressant use was allowed, and participants were required to have ceased breastfeeding or to agree

not to breastfeed until after day 12 of the study. The primary outcome measure was the change from the baseline HAM-D score at the end of the infusion (60 hours). Participants were followed up to 30 days after the start of the infusion. The results were again striking in that the mean reduction in HAM-D score was 21.0 points (SE 2.9) in the brexanolone group and 8.8 points in the placebo group (SE 2.8) at 60 hours post the start of the infusion. The two groups became statistically different from each other based on the HAM-D by 24 hours after the start of the infusion. Remission, defined as HAM-D score of ≤7 at 60 hours after the start of the infusion, was achieved in 7 out of 10 brexanolone-infused participants and 1 out of 11 placebo-infused participants. The groups remained statistically different from each other throughout the 30 day follow-up period.

The next publication reported the results of two multicenter double-blind, placebo-controlled (Phase III) trials [34]. Inclusion and exclusion criteria were similar to the double-blind placebo-controlled trial described above. Enrollment in Study 1 required a HAM-D score of ≥26 and in Study 2 a HAM-D score between 20 and 25 was required. In Study 1 participants were randomly assigned (1:1:1) to receive a brexanolone dose of 90 µg/kg/hr (BRX90), a brexanolone dose of 60 µg/kg/hr (BRX60) or placebo. In Study 2 participants received either a brexanolone dose of 90 µg/kg/hr or placebo. All brexanolone doses were stepped up following the schedule described above, except that those randomized to BRX60 did not increase to a dose of 90 µg/kg/hr. The primary outcome measure for both studies was the change from baseline in mean HAM-D total score at 60 hours post infusion. Follow-up was again to 30 days after the initiation of the infusion. Study 1 enrolled 138 participants, 45 received BRX90, 47 received BRX60, and 46 received placebo. Study 2 enrolled 108 participants with 54 receiving BRX90 and 54 receiving placebo. In Study 1, the least squares mean reduction in HAM-D score from baseline to 60 hours after the start of infusion was 19.5 points (SE 1.2) in the BRX60 group, 17.7 points (SE 1.2) in the BRX90 group, and 14.0 points (SE 1.1) in the placebo group. The mean difference between the placebo group and both brexanolone groups was statistically significant. In Study 2, the mean reduction in HAM-D score in the BRX90 group was 14.6 points (SE 0.8) and in the placebo group was 12.1 (SE 0.8) which was also significantly different. Separation from placebo occurred by 24 hours in the BRX60 group and by 48 hours in the BRX90 groups. The proportion of participants achieving remission was higher in the brexanolone groups than in the placebo groups in both studies.

Of note, a meta-analysis of all three randomized controlled trials has been published which confirmed that brexanolone induces a rapid antidepressant effect that lasts for at least 1-week post-infusion [35]

7. Safety and tolerability

In the published trials, brexanolone was generally well tolerated. The most frequently reported adverse events in the brexanolone groups were headache, dizziness, and somnolence [27,33,34]. The package insert states that the common side effects of brexanolone include sleepiness, dry mouth, passing out, and flushing of the skin or face [26].

Notably, approximately 5% of participants who received brexanolone had excessive sedation, including loss of consciousness, which was relieved by stopping the infusion immediately [26]. These events led the FDA to require constant pulse-oximetry monitoring and a Risk Evaluation and Mitigation Strategy (REMS) program as detailed below. In addition, the label has a boxed warning for 'Excessive Sedation and Sudden Loss of Consciousness.'

During the clinical trials, women were required to have ceased breastfeeding or to agree not to breastfeed until 7–12 days (depending on the study) after the initiation of the infusion. In the data published in abstract form [36,37], a lactation study was undertaken in 12 women which demonstrated transference of brexanolone into breastmilk. However, the relative infant dose was found to be quite low at 1–2% of the maternal weight-adjusted dosage. The available data, according to the study, do not suggest a significant risk for adverse reactions in breastfed infants and the product label suggests that the risks and benefits of breastfeeding and exposure to brexanolone should be considered individually.

8. Regulatory affairs

Brexanolone is classified as a Class IV controlled substance. Its use requires that the patient, provider, and the institution should be registered with the REMS program in order to ensure safe use. Administration of the medication requires continuous pulse-oximetry monitoring, and a trained healthcare provider must be available immediately to monitor the pulse oximetry and to assess for excessive sedation every 2 hours during waking hours and every 4 during sleeping hours. This generally requires nursing to be constantly available in order to stop the infusion should the patient lose consciousness, be excessively sedated or experience decreased oxygen saturation.

9. Conclusion

Brexanolone (Box 1) has been found to be rapidly effective in the treatment of PPD (defined as beginning no earlier than the third trimester of pregnancy and no later than 12 weeks after delivery) and was generally well tolerated with the most common side effect being sedation. Both response and remission rates were higher in the brexanolone treated groups as compared to placebo based on the primary outcome measure of the least squares mean reduction in HAM-D score from baseline to 60 hours after start of the infusion. For psychiatry in general, brexanolone's new mechanisms of action targeting $GABA_A$ receptors are exciting and open up a new avenue to explore in the treatment of major depression in general and PPD specifically. Brexanolone is also rapidly acting and has a sustained response for at least 30 days after infusion and therefore represents a new direction in psychiatric care that heretofore has been limited to the rapidly acting, but short-lived response to ketamine injection. In summary, brexanolone

is an exciting opportunity for psychiatry in terms of research as well as clinical care.

10. Expert opinion

Brexanolone is clearly a breakthrough for psychiatry both in terms of identifying a novel mechanism of action that has not been directly targeted before in the treatment of major depressive episodes and its rapid onset of action and its sustained effects after discontinuation of the medication. It is also the first medication to be FDA approved for the treatment of PPD, an important common variant of major depression that occurs after the birth of a child. The medication is generally well tolerated, and there do not appear to be lasting side effects.

Downsides of brexanolone include the fact that it needs to be administered in an inpatient setting that has been REMS approved and requires constant pulse oximetry monitoring and discontinuation of the drug in the setting of oversedation. These conditions make brexanolone difficult to administer on psychiatry inpatient units, and many sites are administering brexanolone in medical and obstetrics units instead. Given its rapid onset of action and short course of therapy, brexanolone should be attractive to women experiencing PPD though some may be reluctant to agree to an inpatient stay away from their new child or may not have access to alternative child care arrangements. Brexanolone is also expensive (approximately 34,000 USD plus the costs of inpatient care) and therefore obtaining insurance coverage may be difficult for some cases. That being said, when one considers the costs associated with PPD, the need for long-term treatment with standard antidepressants, and the effects of PPD on infant development and IQ, brexanolone and its rapid and sustained response may ultimately be more cost-effective.

There are a number of research questions that need to be explored including whether or not the full 60-h infusion is required and whether lower doses of brexanolone are as effective as the higher doses. Because the drug was brought rapidly to market by the FDA given its Breakthrough Therapy status, these questions were not explored. Further, approximately 28% [27,33,34] of the clinical trial participants received concomitant antidepressant medications, at stable doses, during the trials, and it remains unclear if brexanolone alone versus brexanolone plus an antidepressant results in superior or equivalent results. Longer-term outcomes of patients who receive brexanolone also need to be identified. Biomarkers of brexanolone response also need to be explored – for example, do women who respond to brexanolone have lower levels of allopregnanolone postpartum or during pregnancy compared to women who do not respond to brexanolone? Finally, another research question is whether brexanolone can be used to prevent PPD in women identified as high risk for PPD – for example, using biomarkers [38–40] or identifying women who become depressed during pregnancy or who have a history of PPD with prior pregnancies. Prevention of onset of psychiatric illness is possible for PPD since the timing of onset is predictable and prevention of illness would be a great step forward for psychiatry.

For now, given the REM program, expense, and need for inpatient treatment, brexanolone treatment will likely be limited to women with more severe cases of PPD who would potentially require inpatient treatment even without the option of brexanolone. In the long-run, as sites gain experience with the medication, given its rapid onset of action, brexanolone should be made available to less severe cases in order to mitigate the effects of PPD on the mother, the child, and the family rapidly. While other antidepressant options exist, standard antidepressant treatments have side effects and a long onset of action that ultimately may make them less attractive than the short-term, rapid treatment that brexanolone offers. Overall, brexanolone represents an exciting opportunity for psychiatry in general as well as for women with PPD.

Declaration of interest

JL Payne has, over the past five years, received research funding from Sage Therapeutics. She has also served as a consultant for Sage Therapeutics and Janssen Pharmaceuticals and has a patent entitled 'Epigenetic Biomarkers of Postpartum Depression'. The author has no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

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References

Papers of special note have been highlighted as either of interest (•) or of considerable interest (••) to readers.

1. Gavin NI, Gaynes BN, Lohr KN, et al. Perinatal depression: a systematic review of prevalence and incidence. Obstet Gynecol. 2005;106(5 Pt 1):1071–1083.
2. Toohey J. Depression during pregnancy and postpartum. Clin Obstet Gynecol. 2012;55(3):788–797.
3. Frank E, Kupfer DJ, Jacob M, et al. Pregnancy-related affective episodes among women with recurrent depression. Am J Psychiatry. 1987;144(3):288–293.
4. Payne JL, Roy PS, Murphy-Eberenz K, et al. Reproductive cycle-associated mood symptoms in women with major depression and bipolar disorder. J Affect Disord. 2007;99(1–3):221–229. .
5. Cox JL, Murray D, Chapman G. A controlled study of the onset, duration and prevalence of postnatal depression. Br J Psychiatry. 1993;163(1):27–31.
6. Lindahl V, Pearson JL, Colpe L. Prevalence of suicidality during pregnancy and the postpartum. Arch Women's Mental Health. 2005;8(2):77–87.
7. Akman I, Kusçu K, Ozdemir N, et al. Mothers' postpartum psychological adjustment and infantile colic. Arch Dis Child. 2006;91(5):417–419. .
8. Flynn HA, Davis M, Marcus SM, et al. Rates of maternal depression in pediatric emergency department and relationship to child service utilization. Gen Hosp Psychiatry. 2004;26(4):316–322.
9. McLearn KT, Minkovitz CS, Strobino DM, et al. The timing of maternal depressive symptoms and mothers' parenting practices with young children: implications for pediatric practice. Pediatrics. 2006;118(1):174.

10. Grace SL, Evindar A, Stewart DE. The effect of postpartum depression on child cognitive development and behavior: a review and critical analysis of the literature. Arch Womens Ment Health. 2003;6(4):263–274.
- **This paper reviews the effects of postpartum depression on exposed children's cognitive development and behavior.**
11. American Psychiatric Association. Diagnostic and statistical manual of mental disorders. 4th ed ed. American Psychiatric Press, Washington, DC; 2000.
12. American Psychiatric Association. Diagnostic and statistical manual of mental disorders. 5th ed. American Psychiatric Publishing, Inc., Arlington, VA; 2013.
13. Vesga-Lopez O, Blanco C, Keyes K, et al. Psychiatric disorders in pregnant and postpartum women in the United States. Arch Gen Psychiatry. 2008;65(7):805–815.
14. Payne JL, Maguire J. Pathophysiological mechanisms implicated in postpartum depression. Front Neuroendocrinol. 2019;52:165–180.
15. Walton N, Maguire J. Allopregnanolone-based treatments for postpartum depression: why/how do they work? Neurobiology of Stress. 2019;11:100198.
- **An outstanding review of the potential mechanism of action of brexanolone and other similar agents in treating postpartum depression.**
16. Molyneaux E, Howard LM, McGeown HR, et al. Antidepressant treatment for postnatal depression. Cochrane Database Syst Rev. 2014;11(9):CD002018.
17. Nonacs RM, Soares CN, Viguera AC, Pearson K, Poitras JR, Cohen LS. Bupropion SR for the treatment of postpartum depression: a pilot study. Int J Neuropsychopharmacol. 2005;8(3):445.
18. Cohen LS, Viguera AC, Bouffard SM, et al. Venlafaxine in the treatment of postpartum depression. J Clin Psychiatry. 2001;62(8):592–596.
19. Misri S, Swift E, Abizadeh J, et al. Overcoming functional impairment in postpartum depressed or anxious women: a pilot trial of desvenlafaxine with flexible dosing. Ther Adv Psychopharmacol. 2016;6(4):269–276.
20. Rosenthal ES, Claassen J, Wainwright MS, et al. Brexanolone as adjunctive therapy in super-refractory status epilepticus. In Annals of Neurology. 2017;82(3):342-352.
21. Schule C, Nothdurfter C, Rupprecht R. The role of allopregnanolone in depression and anxiety. Prog Neurobiol. 2014;113:79–87.
22. Zorumski CF, Paul SM, Covey DF, et al. Neurosteroids as novel antidepressants and anxiolytics: GABA-A receptors and beyond. Neurobiology of Stress. 2019;11:100196.
23. Hellgren C, Åkerud H, Skalkidou A, et al. Low serum allopregnanolone is associated with symptoms of depression in late pregnancy. Neuropsychobiology. 2014;69(3):147.
24. Osborne LM, Gispen F, Sanyal A, et al. Lower allopregnanolone during pregnancy predicts postpartum depression: an exploratory study. Psychoneuroendocrinology. 2017;79:116–121.
25. Deligiannidis KM, Sikoglu EM, Shaffer SA, et al. GABAergic neuroactive steroids and resting-state functional connectivity in postpartum depression: a preliminary study. J Psychiatr Res. 2013;47(6):816–828. .
26. Zulresso package insert. 2019. [cited 2020 Dec 15]. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/211371lbl.pdf
27. Kanes SJ, Colquhoun H, Doherty J, et al., Open-label, proof-of-concept study of brexanolone in the treatment of severe postpartum depression. Hum Psychopharmacol. 32(2): e2576. 2017.
- **This paper presents the results of the first open-label study of brexanolone for postpartum depression.**
28. Hamilton M. A rating scale for depression. J Neurol Neurosurg Psychiatry. 1960;23(1):56–62.
29. Cox JL, Chapman G, Murray D, et al. Validation of the Edinburgh postnatal depression scale (EPDS) in non-postnatal women. J Affect Disord. 1996;39(3):185–189.
30. Spitzer RL, Kroenke K, Williams JBW, et al. A brief measure for assessing generalized anxiety disorder: the GAD-7. Arch Intern Med. 2006;166(10):1092–1097.
31. Kroenke K, Spitzer RL, Williams JB, et al. Validity of a brief depression severity measure. J Gen Intern Med. 2001;16(9):606–613.
32. Guy W. ECDEU assessment manual for psychopharmacology. Rockville, MD: Department of Health, Education, and Wellfare; 1976.
33. Kanes S, Colquhoun H, Gunduz-Bruce H, et al., Brexanolone (SAGE-547 injection) in post-partum depression: a randomised controlled trial. Lancet. 390(10093): 480–489. 2017.
- **This paper presents the data from the first randomized, placebo controlled trial of brexanolone for the treatment of postpartum depression.**
34. Meltzer-Brody S, Colquhoun H, Riesenberg R, et al., Brexanolone injection in post-partum depression: two multicentre, double-blind, randomised, placebo-controlled, phase 3 trials. Lancet. 392(10152): 1058–1070. 2018.
- **This paper presents the data from the two phase 3 randomized, placebo controlled trials of brexanolone for the treatment of postpartum depression.**
35. Zheng W, Cai DB, Zheng W, et al. Brexanolone for postpartum depression: a meta-analysis of randomized controlled studies. Psychiatry Res. 2019;279:83–89.
36. Hoffman E, Wald J, Colquhoun H. Evaluation of breast milk concentrations following brexanolone iv administration to healthy lactating women. Am J Obstet Gynecol. 2019;220(1):S554.
37. Hoffman E, Wald J, Dray D, et al. Brexanolone injection administration to lactating women: breast milk allopregnanolone levels. Obstet Gynecol. 2019;133(Suppl1):115S.
38. Guintivano J, Arad M, Gould TD, et al. Antenatal prediction of postpartum depression with blood DNA methylation biomarkers (vol 19, pg 560, 2013). Mol Psychiatry. 2014;19(5):633.
39. Osborne L, Clive M, Kimmel M, et al. Replication of epigenetic postpartum depression biomarkers and variation with hormone levels. Neuropsychopharmacology. 2016;41(6):1648–1658.
40. Payne JL, Osborne LM, Cox O, et al. DNA methylation biomarkers prospectively predict both antenatal and postpartum depression. Psychiatry Res. 2020;285:112711.