HHS Public Access

Author manuscript

Drugs Today (Barc). Author manuscript; available in PMC 2021 April 09.

Published in final edited form as:

Drugs Today (Barc). 2019 September ; 55(9): 537–544. doi:10.1358/dot.2019.55.9.3040864.

Brexanolone for the treatment of patients with postpartum depression

K.E. Morrison[1,2], **A.B. Cole**[3], **S.M. Thompson**[3], **T.L. Bale**[1,2]

[1]Departments of Pharmacology and Psychiatry, University of Maryland School of Medicine, Baltimore, Maryland, USA

[2]Center for Epigenetic Research in Child Health and Brain Development, University of Maryland School of Medicine, Baltimore, Maryland, USA

[3]Department of Physiology, University of Maryland School of Medicine, Baltimore, Maryland, USA

Summary

On March 19, 2019, the United States Food and Drug Administration (FDA) approved Zulresso (brexanolone) for intravenous use for the treatment of postpartum depression (PPD) in adult women. The decision was based on three recent clinical trials following an FDA priority review and breakthrough therapy designation. Brexanolone is now available through a restricted process called the Zulresso Risk Evaluation and Mitigation Strategy Program that requires the drug to be administered by a healthcare provider in a certified healthcare facility. Brexanolone represents an important new treatment option to address treatment-resistant depressive symptoms. In this article, we discuss the current critical need for PPD treatments, the mechanisms of brexanolone action, and the efficacy and drug safety studies that led to FDA approval. Additionally, we discuss some limitations of the current formulation, specific populations of women that might benefit from this treatment, and how new drugs on the horizon may increase the ability to treat PPD in a variety of patient populations.

Keywords

Brexanolone; Zulresso; $GABA_A$ receptor modulators; Neurosteroids; Postpartum depression; Antidepressants

Background

Mood disorders represent a class of emotional disturbances characterized by a loss of interest in previously enjoyable activities (anhedonia) and/or extreme sadness, and are one of the leading causes of disability in the world (1, 2). Women are twice as likely as men to suffer from mood disorders such as major depressive disorder (3). The perinatal period—

Correspondence: Tracy L. Bale, PhD, Professor, Departments of Pharmacology and Psychiatry Director, Center for Epigenetic Research in Child Health and Brain Development, University of Maryland School of Medicine, 655 W. Baltimore St., HSF3, Rm 9-171, Baltimore, MD 21201, USA. tbale@som.umaryland.edu.

Disclosures

The authors state no conflicts of interest.

before and after birth—is a time of increased risk for women to present with mood disorders (4).

Postpartum depression (PPD) is one of the most common complications of childbearing, with several independent estimates showing that about 11-19% of women suffer from postpartum depressive symptoms in the 3 months following birth (5–7). PPD has a serious and widespread negative impact on mothers, babies and families. Data from over 5,000 families shows that PPD was present in a significant proportion of mothers and was associated with undesirable maternal behaviors, including unhealthy feeding and sleep practices, and fewer positive parent-infant interactions (8).

A recent meta-analysis of 122 PPD studies revealed an association of PPD with outcomes such as negative maternal physical and psychological health, poor social relationships with partners, and difficulty in bonding with the infant (9). Infants of mothers with PPD had lower motor development scores at 6 months of age and lower language scores at 12 months of age than infants of nondepressed mothers, suggesting that maternal mood has a serious impact on important developmental milestones in the infant (10). These negative outcomes of PPD on the health of mothers, babies and their families are present worldwide, indicating that there is an underlying biological etiology of PPD (11–13).

While the consequences of PPD are well recognized, until now there has been little progress in the development of pharmacological treatments specifically for this unique population. Current pharmacological treatment for PPD is the same as for depressive disorders in nonpregnant adults, namely antidepressant drugs. There are many disadvantages of current first-choice antidepressants, which include selective serotonin reuptake inhibitors (SSRIs), serotonin and norepinephrine reuptake inhibitors (SNRIs), and atypical antidepressants such as bupropion. Each of these classes of drugs can require weeks to months to exert their antidepressant effects, leaving patients suffering for a significant amount of time following the start of treatment. For postpartum women and their infants, this delayed effectiveness can promote irreparable harm to the mother-infant bond and to the development of the infant in what is clearly a critical period. Additionally, there is a barrier to taking these drugs during and following pregnancy due to the passage of SSRIs through the placenta and into breastmilk. SSRIs are considered safe to use in pregnant and lactating women, but little is known about their long-term effects on the development of the infant, including their effects on the neonatal brain where serotonin is critical to neurodevelopment (14–17). This risk needs to be balanced with the often serious consequences of untreated depression in the mother. As such, clinicians have been seeking alternatives that are faster-acting and have lower risk profiles for infants.

In a major breakthrough, the first drug ever developed specifically for PPD was recently approved. Sage Therapeutics received U.S. Food and Drug Administration (FDA) approval for Zulresso (brexanolone), an intravenous formulation of allopregnanolone (18).

Pharmacology

Brexanolone is a synthetic proprietary intravenous formulation of the endogenous neurosteroid allopregnanolone and is chemically identical to allopregnanolone (19) (Fig. 1).

Although it is a steroid molecule, allopregnanolone acts rapidly via nongenomic mechanisms to modulate neurotransmitter receptor function (20). Allopregnanolone is a potent positive allosteric modulator of synaptic and extrasynaptic $GABA_A$ receptors ($GABA_ARs$), prolonging the opening time of chloride channels within $GABA_ARs$, which amplifies inhibitory neurotransmission (21). Allopregnanolone can also directly activate the receptor at micromolar concentrations (22–24). Allopregnanolone thus exerts similar effects to those of other $GABA_AR$ positive allosteric modulators, such as benzodiazepines, including their sedative effects (25–29), although there are subtle differences related to their unique binding sites, potency and selectivity for GABA receptor subtypes (30). It can therefore be expected that elevated allopregnanolone levels will enhance inhibitory synaptic function, as well as extrasynaptic inhibition, and thereby reduce overall neuronal activity (31). It remains unknown where in the brain the critical circuits underlying both the genesis and the treatment of PPD are located, and to what degree these circuits overlap.

Understanding the underlying biological mechanisms of PPD is an area of active investigation. There are several possibilities, including a hypersensitivity to the normal dynamic hormonal changes during pregnancy and postpartum, dysregulation of the hypothalamic–pituitary–adrenal (HPA) stress axis during pregnancy and postpartum, and genetic mechanisms such as single nucleotide polymorphisms in the serotonin transporter and estrogen receptor α genes (32–35). While the exact mechanisms are unclear, researchers generally agree that the dynamic changes in hormones during and following pregnancy are key in promoting the onset of PPD. The stress hormone cortisol and the ovarian hormones progesterone and estradiol all rise 3- to 10-fold during pregnancy, as do their metabolites, and then precipitously drop at parturition (36, 37). One neuroactive metabolite of progesterone is allopregnanolone. Consistent with the rise in progesterone during pregnancy, levels of allopregnanolone increase throughout gestation and peak at term, with levels increasing from 4 nmol/L at 8-10 weeks after conception to > 40 nmol/L at 36-38 weeks, and then plummeting back to 1 nmol/L at 4-6 weeks postpartum (31, 38, 39).

Because it is an allosteric modulator of GABA receptors, most theories about the relationship between allopregnanolone and PPD focus on GABAergic inhibition (40). Abnormally low levels of allopregnanolone during pregnancy are associated with increased depressive symptoms and increased negative emotional responses (41–43). Similarly, polymorphisms in genes for steroid hormone processing enzymes that decrease allopregnanolone production are associated with increased PPD risk (41). One hypothesis to explain PPD is that there are insufficient levels of allopregnanolone during pregnancy, leaving the inhibitory system too weak to cope with the elevated cortisol levels during pregnancy, the fall in allopregnanolone levels after birth, or the stresses associated with being a postpartum mother, including dysregulated sleep.

Alternatively, the naturally elevated levels of allopregnanolone during pregnancy may promote a homeostatic downregulation of $GABA_ARs$ and inhibitory synaptic function, thus leaving the brain without sufficient inhibitory tone in potentially critical synapses (44). Women at risk for PPD also have lower blood plasma GABA concentration during the postpartum period, and lower GABA levels are correlated with risk for PPD (45). Furthermore, it has been hypothesized that when allopregnanolone levels fall sharply at

parturition, $GABA_AR$ numbers and inhibitory synaptic function recover from their downregulated state too slowly in some women, resulting in weakened inhibition and thereby triggering the onset of PPD (43, 46). Deficits in GABAergic function would also contribute to depressive episodes by reducing sensitivity to allopregnanolone and preventing its endogenous anxiolytic, sedating and prosomnolence effects during and after pregnancy (47).

Pharmacological studies show that the subunit composition and activated phosphorylation state of $GABA_ARs$ influence the sensitivity of the receptor to allopregnanolone (48, 49). The δ subunit of $GABA_ARs$ is of particular interest to allopregnanolone and brexanolone actions because its incorporation into the $GABA_ARs$ that are located primarily at extrasynaptic sites where they respond to tonic levels of GABA increases the ability of allopregnanolone to potentiate GABA responses. Relative to other conformations of the $GABA_ARs$, those with the δ subunit require lower concentrations of allopregnanolone to reach EC_{50}, or the half maximal response (48). Expression of $GABA_AR$ δ subunit decreases during pregnancy and postpartum, which can be predicted to limit the ability of allopregnanolone to potentiate inhibition. In mice, deletion of the $GABA_AR$ δ subunit results in abnormal postpartum maternal behaviors (46, 50). Brexanolone treatment of mice improved these abnormal postpartum behaviors in this PPD-relevant preclinical model (51). These findings suggest that the composition and quantity of $GABA_ARs$ in the brain may determine how women respond to the dynamic hormonal changes of pregnancy and postpartum, leading to increased risk for PPD.

Regardless of mechanism, the shift in $GABA_AR$ sensitivity leaves the pregnant brain in a state of decreased GABAergic tone immediately prior to the most dramatic change in allopregnanolone levels, the sudden drop-off following parturition. Provision of supplemental allopregnanolone in the form of brexanolone can be predicted to counteract this change and restore normal function. As the action is thought to be directly on $GABA_ARs$ in the cell membrane, the effects of supplementing allopregnanolone levels with brexanolone are expected to occur rapidly. This allows clinicians to provide faster relief of symptoms upon diagnosis of PPD than has been possible with traditional antidepressants. Although these direct effects on $GABA_ARs$ likely lead to the rapid effectiveness of brexanolone, there may be other synaptic mechanisms underlying the prolonged relief of symptoms seen with this treatment, including delayed but sustained changes in $GABA_AR$ expression or function. Furthermore, allopregnanolone can be metabolized to 5α-dihydroprogesterone (5α-DHP), which binds with high affinity to intracellular progesterone receptors that regulate transcription and may underlie sustained functional changes (52).

A final open question is the role of sedation and regularization of sleep cycles in the antidepressive response to brexanolone. Because it is a positive allosteric modulator of $GABA_ARs$, allopregnanolone promotes sleep in a pattern similar to that seen with other agonistic modulators of $GABA_ARs$ (29). As any parent of a newborn will know, sleep disruption is a common consequence of childbirth. Patients administered brexanolone in an inpatient setting report that they experienced better sleep (53). Less fragmented sleep as well as emotional support and help with infant care from caregivers in the inpatient setting may

also contribute to the considerable placebo response observed in the brexanolone clinical trials.

Clinical Studies

Following the required clinical pharmacological studies in healthy volunteers to determine metabolism, abuse potential, safety, bioavailability and breast milk concentrations of brexanolone, clinical studies were undertaken. Pharmacokinetic studies revealed that brexanolone has a biphasic elimination, with an initial half-life of 40 minutes, resulting in rapid clearance of the drug.

Three double-blind, randomized, placebo-controlled trials were conducted at four clinical research centers (study 1) and subsequently 30 clinical research centers and specialized psychiatric units in the United States (studies 2 and 3) (53, 54). Brexanolone was administered in an inpatient setting with 60 hours of intravenous infusion at 60 μg/kg/h and 90 μg/kg/h doses and compared to placebo. To enhance tolerability, the dose was stepped up and then back down gradually over the 60 hours (30 μg/kg for 0-4 hours, 60 μg/kg for 4-24 hours, 60 μg/kg or 90 μg/kg for 24-52 hours, 60 μg/kg for 52-56 hours, and 30 μg/kg for 56-60 hours). An important factor to consider is that placebo treatment involved a similar 60-hour placebo injection with associated inpatient clinical care. Women included in the studies had ages ranging from 18 to 45 years, were ≤ 6 months postpartum, had a major depressive episode sometime during the third trimester of pregnancy or up to 4 weeks postpartum, were displaying some depression symptoms according to the 17-item Hamilton Rating Scale for Depression (HAM-D) score, and were willing to temporarily cease breastfeeding. Brexanolone was the primary treatment for the patient's PPD, as 71% of subjects did not receive additional antidepressants during the clinical trials.

The primary endpoint of the clinical trials was overall change in the 17-item HAM-D score at the end of the 60-hour infusion compared to baseline (start of infusion). HAM-D is one of the most widely used measures of depression severity (55). HAM-D responses were also assessed at 72 hours, 7 days and 30 days following the start of infusion. The secondary endpoint of the clinical studies was change from baseline in HAM-D total score at day 30. In all three independent clinical studies that were completed, a statistically significant improvement in HAM-D scores, compared with baseline scores, was achieved. The change in least square (LS) mean HAM-D scores ranged from 17.7 to 19.5 in response to brexanolone, although the response was less clearly different from placebo when measured with other depression scales. It must be noted that HAM-D includes questions related to sleep, which could have contributed to the lower score. Furthermore, placebo infusions in the inpatient setting also caused a reduction in LS mean HAM-D scores of 14.0 in these trials (53, 54).

Safety

Brexanolone targets GABAergic synapses and extrasynaptic $GABA_A$Rs nonspecifically throughout the brain, leading to concerns about adverse sedation-related events. Indeed, sedation-related events, including dizziness, somnolence, sedation, fatigue and loss of consciousness, occurred at a higher rate in brexanolone-treated patients (27%; 38/140) than

in placebo-treated patients (14%; 15/107) in the first 24 hours of the 60-hour infusion (53, 54). In studies 2 and 3, 5/130 (4%) patients had excessive sedation following brexanolone treatment that was considered a severe adverse event leading the patients to withdraw from the study (54). Due to these safety concerns, the approval of Zulresso was delayed by 3 months while the FDA implemented risk evaluation and mitigation strategies (REMS) to minimize the risk for loss of consciousness. REMS is an established mechanism for the FDA to ensure favorable outcomes and has been used successfully in the past. The key components of REMS with Elements to Assure Safe Use include enrollment of the prescriber in REMS, enrollment of all patients in a registry to collect data and further characterize any loss of consciousness, and restrictions on the drug's distribution to certified healthcare settings. Observation of patients by a healthcare provider in a certified facility allows for the confirmation of the discontinuation of the sedation events following treatment. Importantly, any excessive sedation observed in brexanolone patients was reversed within 15 minutes of stopping the infusion.

There were few other adverse effects reported in the clinical trials. Importantly, there was no evidence of increased suicidality (53, 54). While women enrolled in the clinical trials were required to cease breastfeeding for the duration of the infusion, a lactation study demonstrated a low Relative Infant Dose (RID) of 1.3% at maximum, which is well below the recommended threshold of < 10% RID (56). Ultimately, it was recommended that breastfeeding during infusion be discussed by the mother and physician.

Conclusions

PPD is a significant health issue for new mothers, and the lack of effective treatment is a considerable issue for maternal mental health. It is exciting that the FDA has approved Zulresso (brexanolone), the first antidepressant developed specifically for PPD. The mechanism underlying the rationale for brexanolone treatment for PPD is based on a strong scientific foundation and is supported by numerous preclinical and clinical studies. Amid this excitement, there are issues that need to be addressed, including better identification of the target population, further refinement of the pharmacology and lowering the barriers to access. Increased recognition of the risks of PPD and screening for symptoms in new mothers are needed to improve current low rates of diagnosis and treatment (57).

Major depression, including PPD, is a heterogeneous disorder that likely has more than one biological etiology. Now that brexanolone has been approved, clinical experience will hopefully reveal which patients are likely to respond positively to this treatment. Adverse childhood experiences (ACEs), which encompass all types of abuse, neglect and other potentially traumatic experiences that occur prior to the age of 18, predict a variety of negative health outcomes, especially for women during periods in the lifespan in which there are dynamic periods of hormonal changes, including for PPD (58–60). Studies examining the impact of ACEs on maternal outcomes in pregnancy in mice and humans showed the same negative correlation between maternal ACE history and HPA axis stress reactivity, suggesting that careful consideration of patient psychiatric history is important in determining the best treatment options (61). Other relevant factors that should be considered include maternal HPA axis reactivity and measures of sleep disturbance and anxiety.

Due to high intrinsic clearance and low volume of distribution, brexanolone is ideally suited for parenteral administration with a fast-on/fast-off kinetic profile (62). Practically, the requirement for intravenous administration in an inpatient setting is a major barrier to widespread use, both financially and socially. The requirement of a monitored 60-hour inpatient hospitalization and fees combined with a drug price suggested at around USD 34,000 per treatment have raised concerns among the public. To this end, Sage Therapeutics has another compound, SAGE-217 (zuranolone), in development. This compound differs from brexanolone in the addition of a methyl group at C3 and a pyrazole substitution at C-21, which together confer oral bioavailability to the compound while maintaining modulatory efficacy at the $GABA_A$Rs. Sage also states that SAGE-217 has low intrinsic clearance with potential for once-daily dosing (63). Although the phase III clinical trial results have yet to be published, Sage has announced that SAGE-217 provided a significant improvement in the HAM-D score compared with placebo (64). This effectively means that SAGE-217 could provide the therapeutic benefits seen in brexanolone, but in a once-daily oral dose that should significantly drop the overall cost of treatment. Short-course oral treatment with SAGE-217 in an outpatient setting will hopefully reduce this potential barrier to access.

In summary, the approval of brexanolone for the treatment of PPD is a positive step forward for the treatment of women's mental health. While there are currently some barriers to access, rapid-acting treatments such as Zulresso are likely to have a significant effect on the long-term health of the mother, baby and family.

References

1. NIH fact sheets – Mood disorders. National Institutes of Health (NIH), https://report.nih.gov/NIHfactsheets/ViewFactSheet.aspx?csid=48. Accessed Jun 20, 2019.
2. Üstün TB, Ayuso-Mateos JL, Chatterji S, Mathers C, Murray CJ Global burden of depressive disorders in the year 2000. Br J Psychiatry 2004, 184: 386–92. [PubMed: 15123501]
3. Altemus M, Sarvaiya N, Neill Epperson C Sex differences in anxiety and depression clinical perspectives. Front Neuroendocrinol 2014, 35(3): 320–30. [PubMed: 24887405]
4. Ross LE, McLean LM Anxiety disorders during pregnancy and the postpartum period: a systematic review. J Clin Psychiatry 2006, 67(8): 1285–98. [PubMed: 16965210]
5. Ko JY, Rockhill KM, Tong VT, Morrow B, Farr SL Trends in postpartum depressive symptoms - 27 states, 2004, 2008, and 2012. MMWR Morb Mortal Wkly Rep 2017, 66(6): 153–8. [PubMed: 28207685]
6. Howard LM, Molyneaux E, Dennis CL, Rochat T, Stein A, Milgrom J Non-psychotic mental disorders in the perinatal period. Lancet 2014, 384(9956): 1775–88. [PubMed: 25455248]
7. Gavin NI, Gaynes BN, Lohr KN, Meltzer-Brody S, Gartlehner G, Swinson T Perinatal depression: a systematic review of prevalence and incidence. Obstet Gynecol 2005, 106(5 Pt 1): 1071–83. [PubMed: 16260528]
8. Paulson JF, Dauber S, Leiferman JA Individual and combined effects of postpartum depression in mothers and fathers on parenting behavior. Pediatrics 2006, 118(2): 659–68. [PubMed: 16882821]
9. Slomian J, Honvo G, Emonts P, Reginster JY, Bruyère O Consequences of maternal postpartum depression: a systematic review of maternal and infant outcomes. Womens Health (Lond) 2019, 15: 1745506519844044.
10. O'Leary N, Jairaj C, Molloy EJ, McAuliffe FM, Nixon E, O'Keane V Antenatal depression and the impact on infant cognitive, language and motor development at six and twelve months postpartum. Early Hum Dev 2019, 134: 41–6. [PubMed: 31176100]

11. Callo-Quinte G, Del-Ponte B, Ruivo ACO et al. Maternal depression symptoms and use of child healthcare services at The Pelotas 2004 Birth Cohort. J Affect Disord 2019, 253: 303–7. [PubMed: 31078828]
12. Sharmin KN, Sarwar N, Mumu SJ, Taleb DA, Flora MS Postnatal depression and infant growth in an urban area of Bangladesh. Midwifery 2019, 74: 57–67. [PubMed: 30927633]
13. Hassert S, Sharon SR, Payakkakom A, Kodyšovã E Postpartum depressive symptoms: risks for Czech and Thai mothers. J Perinat Educ 2018, 27(1): 38–49. [PubMed: 30858680]
14. Lugo-Candelas C, Cha J, Hong S et al. Associations between brain structure and connectivity in infants and exposure to selective serotonin reuptake inhibitors during pregnancy. JAMA Pediatr 2018, 172(6): 525–33. [PubMed: 29630692]
15. Gingrich JA, Malm H, Ansorge MS et al. New insights into how serotonin selective reuptake inhibitors shape the developing brain. Birth Defects Res 2017, 109(12): 924–32. [PubMed: 28714607]
16. Brown AS, Gyllenberg D, Malm H et al. Association of selective serotonin reuptake inhibitor exposure during pregnancy with speech, scholastic, and motor disorders in offspring. JAMA Psychiatry 2016, 73(11): 1163–70. [PubMed: 27732704]
17. Malm H, Brown AS, Gissler M et al. Gestational exposure to selective serotonin reuptake inhibitors and offspring psychiatric disorders: a national register-based study. J Am Acad Child Adolesc Psychiatry 2016, 55(5): 359–66. [PubMed: 27126849]
18. FDA approves first treatment for post-partum depression. Food and Drug Administration (FDA), Mar 19, 2019. http://www.fda.gov/news-events/press-announcements/fda-approves-first-treatment-post-partum-depression. Accessed Jun 20, 2019.
19. Brexanolone injection, for intravenous use. Sponsor briefing document. Nov 2, 2018. https://www.fda.gov/media/121348/download.
20. Paul SM, Purdy RH Neuroactive steroids. FASEB J 1992, 6(6): 2311–22. [PubMed: 1347506]
21. Lambert JJ, Cooper MA, Simmons RD, Weir CJ, Belelli D Neurosteroids: endogenous allosteric modulators of $GABA_A$ receptors. Psychoneuroendocrinology 2009, 34(Suppl. 1): S48–58. [PubMed: 19758761]
22. Hosie AM, Wilkins ME, da Silva HM, Smart TG Endogenous neurosteroids regulate $GABA_A$ receptors through two discrete transmembrane sites. Nature 2006, 444(7118): 486–9. [PubMed: 17108970]
23. Liu QY, Chang YH, Schaffner AE, Smith SV, Barker JL Allopregnanolone activates $GABA_A$ receptor/Cl^- channels in a multiphasic manner in embryonic rat hippocampal neurons. J Neurophysiol 2002, 88(3): 1147–58. [PubMed: 12205136]
24. Chen ZW, Bracamontes JR, Budelier MM et al. Multiple functional neurosteroid binding sites on $GABA_A$ receptors. PLoS Biol 2019, 17(3): e3000157. [PubMed: 30845142]
25. Norberg L, Bäckström T, Wahlström G Anaesthetic effects of pregnanolone in combination with allopregnanolone, thiopental, hexobarbital and flurazepam: an EEG study in the rat. Br J Anaesth 1999, 82(5): 731–7. [PubMed: 10536552]
26. Tim by E, Balgård M, Nyberg S et al. Pharmacokinetic and behavioral effects of allopregnanolone in healthy women. Psychopharmacology (Berl) 2006, 186(3): 414–24. [PubMed: 16177884]
27. van Broekhoven F, Bäckström T, van Luijtelaar G, Buitelaar JK, Smits P, Verkes RJ Effects of allopregnanolone on sedation in men, and in women on oral contraceptives. Psychoneuroendocrinology 2007, 32(5): 555–64. [PubMed: 17470385]
28. Follesa P, Cagetti E, Mancuso L et al. Increase in expression of the $GABA_A$ receptor α_4 subunit gene induced by withdrawal of, but not by long-term treatment with, benzodiazepine full or partial agonists. Brain Res Mol Brain Res 2001, 92(1-2): 138–48. [PubMed: 11483250]
29. Lancel M, Faulhaber J, Schiffelholz T, Romeo E, Di Michele F, Holsboer F, Rupprecht R Allopregnanolone affects sleep in a benzodiazepine-like fashion. J Pharmacol Exp Ther 1997, 282(3): 1213–8. [PubMed: 9316828]
30. Rudolph U, Möhler H $GABA_A$ receptor subtypes: therapeutic potential in Down syndrome, affective disorders, schizophrenia, and autism. Annu Rev Pharmacol Toxicol 2014, 54:483–507. [PubMed: 24160694]

31. Gilbert Evans SE, Ross LE, Sellers EM, Purdy RH, Romach MK 3α-Reduced neuroactive steroids and their precursors during pregnancy and the postpartum period. Gynecol Endocrinol 2005, 21(5): 268–79. [PubMed: 16373246]
32. Bloch M, Schmidt PJ, Danaceau M, Murphy J, Nieman L, Rubinow DR Effects of gonadal steroids in women with a history of postpartum depression. Am J Psychiatry 2000, 157(6): 924–30. [PubMed: 10831472]
33. Glynn LM, Davis EP, Sandman CA New insights into the role of perinatal HPA-axis dysregulation in postpartum depression. Neuropeptides 2013, 47(6): 363–70. [PubMed: 24210135]
34. Binder EB, Newport DJ, Zach EB et al. A serotonin transporter gene polymorphism predicts peripartum depressive symptoms in an at-risk psychiatric cohort. J Psychiatr Res 2010, 44(10): 640–6. [PubMed: 20045118]
35. Pinsonneault JK, Sullivan D, Sadee W, Soares CN, Hampson E, Steiner M Association study of the estrogen receptor gene ESR1 with postpartum depression—a pilot study. Arch Womens Ment Health 2013, 16(6): 499–509. [PubMed: 23917948]
36. Allolio B, Hoffmann J, Linton EA, Winkelmann W, Kusche M, Schulte HM Diurnal salivary cortisol patterns during pregnancy and after delivery: relationship to plasma corticotrophin-releasing-hormone. Clin Endocrinol (Oxf) 1990, 33(2): 279–89. [PubMed: 2225483]
37. Schock H, Zeleniuch-Jacquotte A, Lundin E et al. Hormone concentrations throughout uncomplicated pregnancies: a longitudinal study. BMC Pregnancy Childbirth 2016, 16(1): 146. [PubMed: 27377060]
38. Luisi S, Petraglia F, Benedetto C et al. Serum allopregnanolone levels in pregnant women: changes during pregnancy, at delivery, and in hypertensive patients. J Clin Endocrinol Metab 2000,85(7): 2429–33. [PubMed: 10902789]
39. Parízek A, Hill M, Kancheva R et al. Neuroactive pregnanolone isomers during pregnancy. J Clin Endocrinol Metab 2005, 90(1): 395–403. [PubMed: 15486056]
40. Lüscher B, Möhler H Brexanolone, a neurosteroid antidepressant, vindicates the GABAergic deficit hypothesis of depression and may foster resilience. F1000Res 2019, 8: pii: F1000.
41. Hellgren C, Åkerud H, Skalkidou A, Bäckström T, Sundström-Poromaa I Low serum allopregnanolone is associated with symptoms of depression in late pregnancy. Neuropsychobiology 2014, 69(3): 147–53. [PubMed: 24776841]
42. Crowley SK, O'Buckley TK, Schiller CE, Stuebe A, Morrow AL, Girdler SS Blunted neuroactive steroid and HPA axis responses to stress are associated with reduced sleep quality and negative affect in pregnancy: a pilot study. Psychopharmacology (Berl) 2016, 233(7): 1299–310. [PubMed: 26856852]
43. Osborne LM, Gispen F, Sanyal A, Yenokyan G, Meilman S, Payne JL Lower allopregnanolone during pregnancy predicts postpartum depression: an exploratory study. Psychoneuroendocrinology 2017, 79: 116–21. [PubMed: 28278440]
44. Mody I $GABA_AR$ modulator for postpartum depression. Cell 2019,176(1–2): 1. [PubMed: 30633900]
45. Deligiannidis KM, Kroll-Desrosiers AR, Mo S et al. Peripartum neuroactive steroid and γ-aminobutyric acid profiles in women at-risk for postpartum depression. Psychoneuroendocrinology 2016, 70: 98–107. [PubMed: 27209438]
46. Maguire J, Mody I $GABA_AR$ plasticity during pregnancy: relevance to postpartum depression. Neuron 2008, 59(2): 207–13. [PubMed: 18667149]
47. Luscher B, Shen Q, Sahir N The GABAergic deficit hypothesis of major depressive disorder. Mol Psychiatry 2011, 16(4): 383–406. [PubMed: 21079608]
48. Brown N, Kerby J, Bonnert TP, Whiting PJ, Wafford KA Pharmacological characterization of a novel cell line expressing human $\alpha_4\beta_3\delta$ $GABA_A$ receptors. Br J Pharmacol 2002,136(7): 965–74. [PubMed: 12145096]
49. Koksma JJ, van Kesteren RE, Rosahl TW, Zwart R, Smit AB, Lüddens H, Brussaard AB Oxytocin regulates neurosteroid modulation of $GABA_A$, receptors in supraoptic nucleus around parturition. J Neurosci 2003, 23(3): 788–97. [PubMed: 12574407]
50. Maguire J, Ferando I, Simonsen C, Mody I Excitability changes related to $GABA_A$, receptor plasticity during pregnancy. J Neurosci 2009, 29(30): 9592–601. [PubMed: 19641122]

51. Melón L, Hammond R, Lewis M, Maguire J A novel, synthetic, neuroactive steroid is effective at decreasing depression-like behaviors and improving maternal care in preclinical models of postpartum depression. Front Endocrinol (Lausanne) 2018,9: 703. [PubMed: 30532739]
52. Dong E, Matsumoto K, Uzunova V et al. Brain 5α-dihydroprogesterone and allopregnanolone synthesis in a mouse model of protracted social isolation. Proc Natl Acad Sci U S A 2001, 98(5): 2849–54. [PubMed: 11226329]
53. Kanes S, Colquhoun H, Gunduz-Bruce H et al. Brexanolone (SAGE-547 injection) in post-partum depression: a randomised controlled trial. Lancet 2017, 390(10093): 480–9. [PubMed: 28619476]
54. 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 2018,392(10152): 1058–70. [PubMed: 30177236]
55. Hamilton M A rating scale for depression. J Neurol Neurosurg Psychiatry 1960, 23: 56–62. [PubMed: 14399272]
56. Bennett PN (Ed.) Drugs and Human Lactation. Elsevier Science: Aalborg 1996.
57. Georgiopoulos AM, Bryan TL, Wollan P, Yawn BP Routine screening for postpartum depression. J Fam Pract 2001,50(2): 117–22. [PubMed: 11219558]
58. Remigio-Baker RA, Hayes DK, Reyes-Salvail F Adverse childhood events and current depressive symptoms among women in Hawaii: 2010 BRFSS, Hawaii. Matern Child Health J 2014, 18(10): 2300–8. [PubMed: 24178156]
59. Chapman DP, Whitfield CL, Felitti VJ, Dube SR, Edwards VJ, Anda RF Adverse childhood experiences and the risk of depressive disorders in adulthood. J Affect Disord 2004, 82(2): 217–25. [PubMed: 15488250]
60. Felitti VJ, Anda RF, Nordenberg D et al. Relationship of childhood abuse and household dysfunction to many of the leading causes of death in adults. The Adverse Childhood Experiences (ACE) Study. Am J Prev Med 1998,14(4): 245–58. [PubMed: 9635069]
61. Morrison KE, Epperson CN, Sammel MD et al. Preadolescent adversity programs a disrupted maternal stress reactivity in humans and mice. Biol Psychiatry 2017,81(8): 693–701. [PubMed: 27776734]
62. Blanco MJ, La D, Coughlin Q, Newman CA, Griffin AM, Harrison BL, Salituro FG Breakthroughs in neuroactive steroid drug discovery. Bioorg Med Chem Lett 2018, 28(2): 61–70. [PubMed: 29223589]
63. Martínez Botella G, Salituro FG, Harrison BL et al. Neuroactive steroids. 2. 3α-Hydroxy-3β-methyl-21-(4-cyano-1H-pyrazol-1'-yl)-19-nor-5β-pregnan-20-one (SAGE-217): a clinical next generation neuroactive steroid positive allosteric modulator of the $(\gamma\text{-aminobutyric acid})_A$ receptor. J Med Chem 2017, 60(18): 7810–9. [PubMed: 28753313]
64. Sage Therapeutics announces SAGE-217 meets primary and secondary endpoints in phase 3 clinical trial in postpartum depression [news release]. Sage Therapeutics, Inc., Jan 7, 2019.

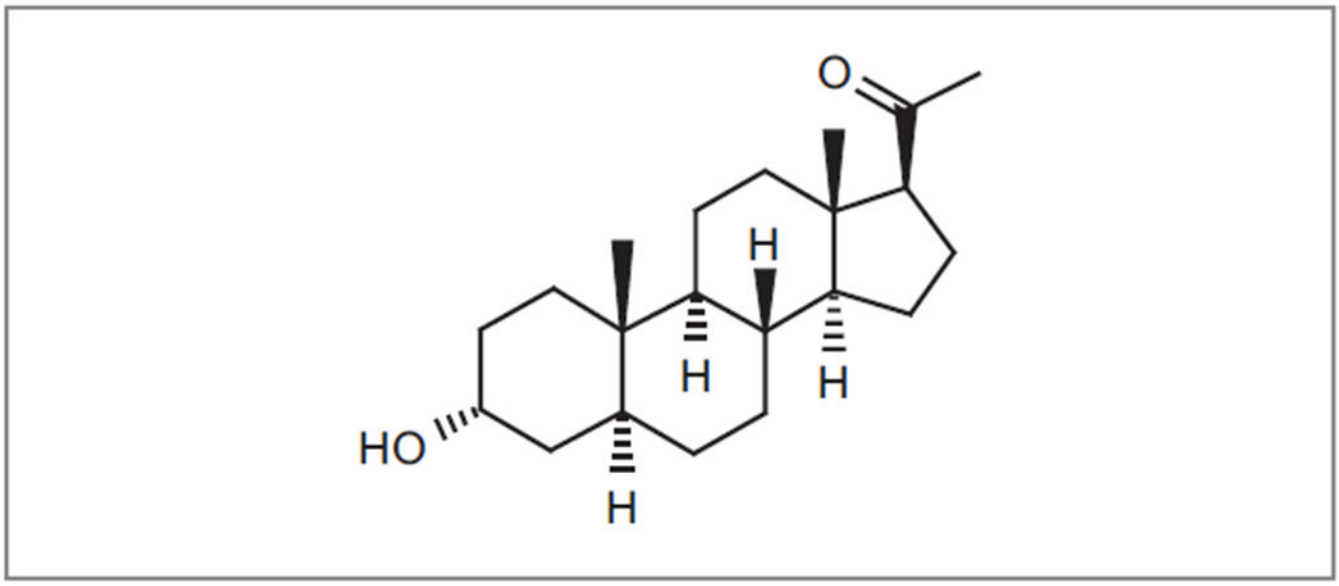

Figure 1.
Chemical structure of brexanolone.