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## Pharmacotherapy of Postpartum Depression: Current Approaches and Novel Drug Development.

Ariela Frieder, MD<sup>1</sup>, Madeleine Fersh, MD<sup>1</sup>, Rachel Hainline, BS<sup>2</sup>, and Kristina M. Deligiannidis, MD<sup>1,3,4</sup>

<sup>1</sup>Department of Psychiatry, Zucker Hillside Hospital, Northwell Health, New York, NY 11004, USA;

<sup>2</sup>Donald and Barbara Zucker School of Medicine at Hofstra/Northwell, Hempstead, NY 11549, USA;

<sup>3</sup>Departments of Psychiatry and Obstetrics & Gynecology, Donald and Barbara Zucker School of Medicine at Hofstra/Northwell, Hempstead, NY 11549, USA;

<sup>4</sup>Feinstein Institute for Medical Research, Manhasset, NY 11030, USA.

### Abstract

Postpartum depression is one of the most common complications of childbirth. Untreated postpartum depression can have substantial adverse effects on the well-being of the mother and child, negatively impacting child cognitive, behavioral, and emotional development with lasting consequences. There are a number of therapeutic interventions for postpartum depression including pharmacotherapy, psychotherapy, neuromodulation and hormonal therapy among others, most of which have been adapted from the treatment of major depressive disorder outside of the peripartum period. Current evidence of antidepressant treatment for postpartum depression is limited by the small number of randomized clinical trials, underpowered samples and lack of long-term follow-up. The peripartum period is characterized by rapid and significant physiological change in plasma levels of endocrine hormones, peptides and neuroactive steroids. Evidence supporting the role of neuroactive steroids and GABA in the pathophysiology of postpartum depression led to the investigation of synthetic neuroactive steroids and their analogs as potential treatment for postpartum depression. Brexanolone, a soluble, proprietary, intravenous preparation of synthetic allopregnanolone has been developed. A recent series of open-label and placebo-controlled randomized clinical trials of brexanolone in postpartum depression demonstrated rapid reduction of depressive symptoms, and have led to the submission for regulatory approval to the US Food and Drug Administration (decision due in March 2019). SAGE-217, an allopregnanolone analog, with oral bioavailability, was recently tested in a randomized, double-blind, placebo-controlled phase 3 study in severe postpartum depression, with reportedly positive results. Finally,

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**Corresponding author:** Kristina M. Deligiannidis, M.D., Associate Professor of Psychiatry and Obstetrics & Gynecology, Donald and Barbara Zucker School of Medicine at Hofstra/Northwell, Associate Professor, Center for Psychiatric Neuroscience, Feinstein Institute for Medical Research Director, Women's Behavioral Health, Zucker Hillside Hospital, 75-59 263rd Street, NY, NY 11004, USA, kdeligian1@northwell.edu; 718-470-8184; ORCID ID: 0000-0001-7439-2236.

#### CONFLICT OF INTEREST

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a 3 $\beta$ -methylated synthetic analog of allopregnanolone, ganaxolone, is being tested in both intravenous and oral forms, in randomized, double-blind, placebo-controlled phase 2 studies in severe postpartum depression.

## 1. Introduction

Globally, postpartum depression (PPD) afflicts up to approximately twenty percent of women during pregnancy or after giving birth[1], and negatively impacts offspring neurodevelopment and behavior[2–4]. PPD is underdiagnosed and undertreated[5]: a significant obstacle to developing PPD treatment is the lack of understanding of PPD pathophysiology. The aims of this manuscript were to review the clinical characteristics of PPD, the evidence base for currently used pharmacotherapies and their limitations, current research into PPD neurobiology and the recent development of novel PPD investigational therapeutics. For this purpose, we conducted a literature search of current and investigational pharmacotherapies. Papers were searched on MEDLINE, PsychINFO, Web of Science, Scopus, Embase, and PubMed with the following key words: postpartum, pregnancy, depression, antidepressant, selective serotonin reuptake inhibitor (SSRI), serotonin and norepinephrine reuptake inhibitor (SNRI), tricyclic, tetracyclic, monoamine oxidase inhibitor (MAOI), neuroactive steroid, neurosteroid, allopregnanolone, brexanolone, ganaxolone, pharmacotherapy, psychotropic and drug therapy. This review was limited to papers published in English. Additional articles were identified by reviewing bibliographies of review articles identified within the literature search. We only included randomized clinical trials, systematic reviews or meta-analyses of trials in unipolar PPD and one prospective cohort study in the prevention of PPD.

## 2. Clinical characteristics of PPD

### 2.1 Prevalence

PPD is one of the most common complications of childbirth and is associated with negative consequences to the woman, child, family, and society, making it a public health concern[1]. Global prevalence ranges from 4% to 25% and varies across and within countries[6–12] with rates highest in countries with greater income inequality, maternal mortality or infant mortality [1]. The Centers for Disease Control and Prevention (CDC) in the United States (U.S.) reported an overall PPD prevalence of 11.5% which ranged from 8 % to 20.1% [13]. The determination of PPD prevalence is complicated by the fact that rates are calculated using different diagnostic criteria, especially when defining time of onset or offset, and a variety of screening tools and tool cut-offs are used [14–17]. The Edinburgh Postnatal Depression Scale (EPDS)[18] is the most widely used self-report screening tool, a ten-item scale that has been validated for use during pregnancy and postpartum[19] and in multiple languages. The Diagnostic and Statistical Manual of Mental Disorders-Fifth Edition (DSM-5)[20] defines PPD as a major depressive episode (MDE) with peripartum onset when onset occurs within pregnancy or up to four weeks postpartum. However, the World Health Organization defines the postpartum period as up to one year after delivery[21]. Longer periods of illness onset can lead to higher prevalence estimates[22].

## 2.2 Symptoms and Risk Factors

PPD is frequently under-detected[5, 23] and under-treated[5, 24] leaving women with prolonged symptoms and significant impairment[25]. Several national groups recommend screening for PPD [26–28], however practitioners often do not screen for comorbid psychiatric disorders. Comorbid psychiatric disorders are common[29] and associated with higher symptom severity[30], increased treatment resistance[23] and suicidality[31]. Comorbid anxiety symptomatology is common in approximately half of women within the first year postpartum [32]. PPD has a heterogeneous presentation, with distinct subtypes and severity that vary with the timing of symptom onset [33, 34]. PPD and MDD however share a similar overall symptom profile, and women with PPD often present with persistent sadness[20, 34], anhedonia[20, 34], guilt[20], irritability[20, 35], psychomotor agitation[20, 35], impaired concentration[20, 35], sleep disturbances[20], lethargy[20], and weight and appetite changes[20]. Severe PPD can include suicidal thoughts [36], and a risk for child abuse [37] or even infanticide [38]. Thoughts of self-harm occur in approximately 5–14% women with PPD. Maternal suicide is the leading cause of direct maternal mortality in the first postpartum year, with one in seven deaths due to suicide [39, 40].

Risk factors for PPD include younger age, African-American race, public insurance, single status, lower education level, annual income less than \$20,000, low occupational prestige, and multiple offspring [41, 42]. Additionally, intimate partner violence, adverse childhood experiences[43], self-reported previous psychiatric diagnosis, low social support, and a higher number of stressful life events during pregnancy are significantly associated with PPD[9]. PPD is associated with higher rates of recurrence in both future peripartum and *non*-peripartum periods. Compared to women with no episode of postpartum affective disorder after their first birth, women with postpartum antidepressant use or PPD hospital contact had 6.2x and 6.6x increased risk of *non*-postpartum affective disorder in the years following first childbirth, respectively, and 27x and 46x higher recurrence risk rate of postpartum affective disorder following a second birth, respectively[12].

## 2.3 Impact of Untreated PPD

Untreated PPD can have substantial adverse effects on the well-being of the mother and child with lasting consequences. PPD with onset in pregnancy is associated with an increased risk for maternal substance abuse[44], pre-eclampsia[45], preterm delivery [46, 47] and infant low birth weight [46, 47]. PPD can impair a woman's ability to care for herself and infant, negatively impacting child cognitive, behavioral, and emotional development [2, 3]. PPD has been associated with impaired mother-infant bonding [48]. Children of women with PPD exhibit poor cognitive [49, 50], neuropsychological [51, 52], social and emotional skills [53, 54] across childhood through adolescence. PPD can be long lasting[55]: women with persistent depressive symptoms at eight months postpartum showed elevated depressive symptoms when their child was eleven years old[56]. Both the chronicity and severity of PPD predict later cognitive performance in children [56, 57].

### 3. Current treatment of PPD and its limitations

#### 3.1 Pharmacotherapy

There are a number of therapeutic interventions for PPD, most of which have been adapted from the treatment of MDD, as currently there are no pharmacotherapies specifically approved for PPD. We next briefly review the available randomized clinical trial (RCT) level data for PPD pharmacotherapy and refer the reader to a comprehensive review of treatment considerations (how to apply the evidence base) in the care of the PPD patient[58].

##### 3.1.1. Acute Treatment

**Selective Serotonin Reuptake Inhibitors (SSRIs):** First-line therapy for moderate-to-severe PPD is typically with an SSRI. Four open-label postpartum clinical studies [59–62], and eight RCTs [63–70] have evaluated SSRIs in PPD. We are not aware of any PPD RCTs testing SSRI efficacy during pregnancy. Although results are mixed, in terms of antidepressant efficacy, there remains a general consensus supporting the use of SSRIs in PPD (Table 1).

We are not aware of any RCT level data for escitalopram and fluvoxamine, only open-label evidence [61, 62], and there is no data for citalopram or vilazodone in PPD treatment. Overall, sertraline is the SSRI with the most evidence in the treatment of PPD [60, 63, 64]. A Cochrane review conducted a meta-analysis of three studies comparing treatment with SSRIs versus placebo for treatment of PPD and found that patients randomized to SSRI treatment were more likely to show response or remission of PPD at follow-up [71]. Data was limited for other medication comparisons so meta-analyses could not be conducted. A systematic review by De Crescenzo and colleagues found that SSRIs, nortriptyline and psychotherapy are efficacious for the acute treatment of PPD, but there is not enough evidence to demonstrate a clear superiority of one over another [72].

##### **Serotonin Norepinephrine Reuptake Inhibitors (SNRIs) and Other**

**Antidepressants:** We are not aware of any RCT level data for the use of SNRIs, including venlafaxine, duloxetine, milnacipran or desvenlafaxine, in the treatment of PPD. Open-label trials suggest venlafaxine[73] and desvenlafaxine[74] may lead to symptom resolution. There is no RCT level data for the use of bupropion, mirtazapine, trazodone or nefazodone as treatments for PPD, only open-label studies supporting the use of bupropion[75] and nefazodone[76].

**Tricyclic Antidepressants (TCA) and Monoamine Oxidase Inhibitors (MAOI):** To date, nortriptyline is the only TCA to have been studied in a controlled trial in PPD (Table 1).[68]. We are not aware of any RCT level data for the use of MAOIs for the treatment of PPD.

**Estradiol and Progestin Interventions:** Given the wealth of preclinical and clinical data that sex and reproductive hormones contribute to brain function[77] and the neurobiology of affective disorders[78], initial studies have investigated the potential role for estradiol and progestin-based therapeutic interventions in PPD. An RCT compared transdermal 17 $\beta$ -estradiol patches with placebo patches for the treatment of severe PPD. Over the first month

of treatment, women receiving estrogen showed greater and more rapid improvement in depressive symptoms as measured on the EPDS, but neither treatment nor control groups achieved complete symptom remission[79]. A recent randomized trial examined an eight-week course of postpartum transdermal 17 $\beta$ -estradiol vs sertraline or placebo for the treatment of PPD [80] but was stopped early when it was discovered that estradiol serum levels were lower than expected. Future research in the treatment of PPD with transdermal 17 $\beta$ -estradiol should be explored [81].

Some controlled trials examining the effects of synthetic progestin-based contraception have shown that intramuscular injection of norethisterone enanthate[82] and depot medroxyprogesterone acetate[83] were associated with increased postpartum depressive symptoms compared to those on placebo[82] or intrauterine device[83]. A retrospective review found no association[84]. The most recent Cochrane systematic review concluded that the role of natural progesterone has yet to be evaluated in an RCT but synthetic progestogens should not be used to prevent PPD and that they should be used in postpartum women with significant caution[85].

Current evidence of antidepressant treatment for PPD is limited by the small number of RCTs examining a small number of individually assessed antidepressants, underpowered sample sizes and lack of long-term follow-up or child outcomes [71]. Response and remission rates vary greatly between studies and many of the available studies examining treatment for PPD excluded women with severe depression or suicidal ideation, therefore limiting the generalizability of these findings in clinical practice. Studies of estradiol and progestin-based interventions are in their infancy and require further study.

### 3.1.2 Prophylactic Treatment

**Selective Serotonin Reuptake Inhibitors (SSRIs) and Tricyclic Antidepressants (TCAs):** Women with previous episodes of PPD have a recurrence risk of approximately 25%[86]. Refer to Table 2 for studies that have investigated pharmacotherapies for the prevention of PPD.[86–89]. A recent Cochrane review concluded that further studies with greater numbers of participants are necessary in order to make any conclusions about the effectiveness of antidepressants for the prevention of PPD[90].

## 3.2 Psychotherapies, Complementary Health Practices and Neuromodulation

Women with PPD have moderate-to-high rates of decisional conflict when considering antidepressant treatment, particularly during pregnancy[91] and many find psychotherapies more acceptable than pharmacotherapies [92]. Globally, between 26–70% of pregnant women use complementary health practices for potential health benefits [93] and 54% of women with depression report past-year use of complementary health practices nationally [94]. As review of the psychotherapy and complementary health literature is outside the scope of this review, we refer the reader to Stuart & Koleva [95] and Dennis & Dowswell [96] for a comprehensive review of psychotherapies in PPD, and to Reza N et al [97] for complementary health practices in PPD.

Electroconvulsive therapy (ECT) is an important neuromodulatory choice in severe and refractory cases of PPD and postpartum psychosis. ECT is reported to result in higher rates of response as compared to treatment of non-postpartum depression and/or psychosis [98]. Although guidelines for the use of ECT in pregnancy have been published [99], there is no RCT level data for the use of ECT in the treatment of PPD. Additional neuromodulation techniques including repetitive transcranial magnetic stimulation [100–102] and transcranial direct current stimulation [103] are in initial trial stages for the treatment of PPD [104]. Further RCTs should examine the efficacy of ECT versus pharmacotherapy in severe PPD and the utility of other non-invasive neuromodulation interventions.

## **4. Current understanding of the neurobiology of postpartum depression and the development of potential targets for drug treatment**

### **4.1 Overall scope of current research**

As in MDD, the pathophysiology of PPD is likely multifactorial, leading to an array of distinct phenotypes [33, 34]. During the reproductive years women have approximately double the one-month and lifetime prevalence of MDD found in men [105] and as such, research has focused on the role of the reproductive endocrine system in PPD [106–114] but there are other active lines of research including inflammation [115, 116], chronobiology [117, 118], genetics [119], epigenetics [120] and neuroimaging [108, 121, 122]. The peripartum period is characterized by rapid and significant physiological change in plasma levels of endocrine hormones, peptides and neuroactive steroids (NAS) [123–128]. Several lines of research are actively examining the potential roles of cortisol [112, 113, 129–132], corticotropin-releasing hormone (CRH) [106, 133–136], adrenocorticotrophic hormone (ACTH) [137, 138] oxytocin [139–141], prolactin [142, 143], testosterone [144–146], NAS [121, 147], and thyroid function [148–151] in PPD.

### **4.2 Research into the hypothalamic-pituitary axis**

A body of research has examined hypothalamic-pituitary axis (HPA) axis function in PPD [152, 136]. Briefly, in healthy women, pregnancy is associated with physiological changes in the HPA axis [153] including suppressed hypothalamic CRH and increased basal plasma CRH [154–156], ACTH and cortisol concentrations [157–159]. In the postpartum period, plasma CRH, ACTH, and cortisol levels decline around four days following parturition, with HPA axis activity returning to non-pregnant levels around twelve weeks after delivery [110, 157, 160]. Some studies of maternal HPA response to pharmacological and physical stressors in healthy pregnant women suggest that there is a dampened response to these stressors across gestation [161–163]; other studies suggest comparable antepartum HPA responsivity to stress to non-pregnant women [164, 165]. One study which examined healthy euthymic pregnant women who developed postpartum depressive symptoms reported higher cortisol reactivity to psychosocial stress [114] and in an innovative study in simulated pregnancy, in the presence of elevated levels of gonadal steroids, women with a history of PPD demonstrated a greater cortisol response to ovine CRH stimulation as compared to healthy women, suggesting that euthymic women with a history of PPD have an enhanced sensitivity of the HPA axis to gonadal steroids [106]. Both of these studies [106, 114] suggest



that a heightened reactivity to stress, rather than baseline plasma levels of HPA axis hormones, may be a risk factor for developing PPD.

### 4.3 Research into neuroactive steroids and $\gamma$ -aminobutyric acid (GABA)

Preclinical research suggests that the NAS allopregnanolone plays a critical role in suppressed HPA axis responses to stress in pregnancy (for a comprehensive review see ref. [166]). NAS have been studied across neuropsychiatric illnesses [167–171] including PPD [172, 173]. NAS are metabolites of cholesterol-derived steroid hormones made in the nervous system and periphery that can rapidly alter the excitability of neurons by binding to membrane-bound receptors [174, 175]. Pregnane NAS include allopregnanolone (3 $\alpha$ , 5 $\beta$ -tetrahydroprogesterone; 3 $\alpha$ , 5 $\alpha$ -THP), pregnanolone (3 $\alpha$ , 5 $\beta$ -tetrahydroprogesterone; 3 $\alpha$ , 5 $\beta$ -THP), and tetrahydrodeoxycorticosterone (THDOC), while pregnenolone, progesterone and deoxycorticosterone are pregnane steroid precursors which also exhibit neuroactive effects [174, 176]. In the central nervous system (CNS), GABA is the predominant inhibitory neurotransmitter [177], and many NAS are positive allosteric modulators (PAMs) of the GABA<sub>A</sub> receptor (R), binding at an allosteric site on the membrane-bound, ligand-gated ion channel receptor and facilitating negatively-charged chloride ion flow into the post-synaptic neuron [178, 179]. GABAergic inhibition in the CNS is either phasic (low affinity; via synaptic GABA<sub>A</sub>R) or tonic (high affinity; via extrasynaptic GABA<sub>A</sub>R) and is determined by the location of and subunit composition of the pentameric GABA<sub>A</sub>R channel [180, 181]. Through their modulation of GABA<sub>A</sub>R, NAS affect both tonic and phasic GABAergic neurotransmission, resulting in a change in the excitatory-inhibitory balance in neural networks [182]. In non-medicated women with PPD, plasma postpartum allopregnanolone concentrations are significantly correlated with intrinsic functional connectivity of neural networks important for selfappraisal and emotional perception [121].

CNS and plasma concentrations of NAS rise during pregnancy then fall rapidly after parturition [127, 147, 183]. There are associated changes in regional GABA<sub>A</sub>R subunit composition and excitability in addition to changes in regional GABA concentrations across the peripartum period [184–188]. A groundbreaking study in GABA<sub>A</sub>R  $\delta$ -subunit knockout mice demonstrated that in healthy pregnant mice, as antepartum progesterone-derived NAS concentrations rose, there was a decrease in tonic and phasic inhibition mediated by a downregulation of GABA<sub>A</sub>R  $\delta$ - and  $\gamma$ 2-subunits, respectively, which rebounded postpartum [189]. However, GABA<sub>A</sub>R  $\delta$ -subunit knockout mice displayed depressive-like behavior and abnormal maternal behavior in the postpartum, a time of lowered NAS concentrations and altered tonic current compared to wildtype mice. The behavioral changes were reversed when a GABA<sub>A</sub>R  $\delta$ -subunit preferring agonist, enhancing inhibition, was administered [189]. Thus this study identified a possible mechanism for abnormal maternal postpartum behavior resulting from a failure of normal peripartum GABA<sub>A</sub>R neuroplasticity.

In rodents, region-specific changes in GABAergic inhibition occur in the peripartum period [184]. Elevated antepartum NAS are associated with inhibition of glutamic acid decarboxylase (GAD) mRNA expression, reducing brain GABA concentrations [186] while the postpartum is characterized by reduced allopregnanolone and enhanced neuronal GABA

synthesis, raising brain GABA concentrations in regions important to maternal care[185]. Dysregulation of NAS metabolism, including allopregnanolone and pregnanolone, and/or their interaction with GABA, has been implicated in PPD [121, 147, 189, 190]. Between-group differences in peripartum blood allopregnanolone concentrations could represent differential metabolism within the progesterone-based biosynthetic pathway, either peripherally and/or in the brain[174]. Altered peripartum allopregnanolone concentrations could then affect cortical GABA concentrations via their interaction with GAD or on phasic and tonic cortical inhibitory tone through the GABA<sub>A</sub> R.

NAS research in human subjects has included endocrine manipulation studies and observational studies of women at-risk for PPD, women with PPD and healthy peripartum women. In a landmark study by Bloch et al[107], supraphysiologic levels of synthetic estradiol and progesterone were administered to women with a history of PPD and those without and were later withdrawn, simulating the antepartum and postpartum gonadal steroid states. Upon estrogen and progesterone withdrawal, only women with a history of PPD developed depressive symptomatology suggesting that a subgroup of women are sensitive to gonadal steroid flux. Research has additionally examined potential differences in peripartum plasma NAS concentrations between healthy women and those at-risk for or diagnosed with PPD, but data remains mixed. Low allopregnanolone serum levels have been associated with postpartum blues[191] and in one study of PPD[192] but not others in PPD[108, 190]. Plasma progesterone and pregnanolone were higher in women at-risk for developing PPD compared to healthy peripartum women[147] and recent evidence revealed higher peripartum plasma allopregnanolone levels in women with PPD compared to healthy peripartum women with no difference in progesterone or pregnanolone concentrations [121]. In our recent study in women not taking psychotropics or hormonal contraception, postpartum allopregnanolone concentrations, as measured by liquid chromatography/tandem mass spectrometry, were higher in women in PPD and significantly positively correlated with Hamilton Depression Rating Scale total score (HAMD-17)[193] and resting-state functional connectivity differences between healthy postpartum women and women with PPD[121].

Altered cortical GABA concentrations have been implicated in the pathogenesis of MDD[194] and premenstrual dysphoric disorder[195]. Two studies have measured occipital cortex (OCC) GABA magnetic resonance spectroscopy (MRS) concentrations in PPD [121, 190] and one study measured anterior cingulate cortex (ACC) GABA concentrations [121]. In these two studies, there was no difference in either OCC or ACC GABA concentrations in women with PPD vs. healthy postpartum women, in contrast to findings in MDD [194, 196–199]. Postpartum cortical GABA MRS concentrations were quantitatively low in all postpartum women compared to healthy women during the follicular stage of the menstrual cycle (a low estradiol and progesterone state)[190] which may be a consequence of prolonged antepartum NAS exposure. Further research in this area is greatly needed.

## 5. Implications for novel pharmacologic treatment

Due to the low oral bioavailability and high in vivo clearance of endogenous allopregnanolone, it has been clinically studied using intravenous preparations in healthy



men and women. Intravenous allopregnanolone is associated with decreased saccadic eye velocity and sedation, with effects greater in women than men [200, 201]. Episodic but not semantic or working memory may be impaired in some women receiving intravenous allopregnanolone[202]. Startle response and prepulse inhibition of startle response are unaffected by acute intravenous administration of allopregnanolone, suggesting no anxiolytic effects in healthy women[203]. Additional studies have indicated that intravenous administration to healthy women in the follicular stage of the menstrual cycle is associated with reduced plasma levels of luteinizing hormone and follicle-stimulating hormone, but no change in plasma estradiol or progesterone, suggesting that allopregnanolone has a regulatory mechanism on the hypothalamic-pituitary-gonadal axis via GABA<sub>A</sub>R modulation [204].

The aforementioned evidence supporting the role of NAS and GABA in the pathophysiology of PPD supports the exploration of synthetic NAS and their analogs as potential treatments of PPD. Sage Therapeutics developed brexanolone (USAN; formerly SAGE-547 Injection), a soluble, proprietary, intravenous preparation of synthetic allopregnanolone. Brexanolone is a sterile solution of 5 mg/mL allopregnanolone in 250 mg/mL sulfobutylether- $\beta$ -cyclodextrin buffered with citrate and diluted with sterile water until it is isotonic [205, 206]. In whole-cell patch electrophysiology studies, brexanolone induces potent, concentration-dependent enhancement of GABA-mediated currents [205]. Drug interaction studies have demonstrated that brexanolone has the potential to alter the metabolism of CYP2C9 substrates when co-administered [205].

A recent series of open-label and placebo-controlled RCTs of brexanolone in PPD demonstrated rapid reduction of PPD symptoms. The first, a proof-of-concept, open-label study examined a single 60-hour brexanolone infusion in postpartum women (n=4) with PPD [207]. Participants included healthy women between the age of 18–45 and fourteen days to five months postpartum who were admitted to an inpatient psychiatric unit for a MDE with onset in third trimester of pregnancy or up to three months postpartum (i.e. study-defined PPD). Participants had a HAM-D<sub>17</sub> total score  $\geq 20$  at study entry. Dosing of brexanolone iv began with a twelve-hour titration period: 21.5  $\mu\text{g}/\text{kg}/\text{hr}$ . (hour 0–4), then 43  $\mu\text{g}/\text{kg}/\text{hr}$ . (hour 4–8), then 64.5  $\mu\text{g}/\text{kg}/\text{hr}$ . (hour 8–12). Maintenance dosing of 86  $\mu\text{g}/\text{kg}/\text{hr}$ . was continued for thirty-six hours (hour 12–48) to sustain a steady-state plasma concentration of approximately 150nm, designed to mimic plasma allopregnanolone levels in the third trimester[208]. Dose reduction then followed with rates of 64.5  $\mu\text{g}/\text{kg}/\text{hr}$ . (hour 48–52), 43  $\mu\text{g}/\text{kg}/\text{hr}$ . (hour 52–56), and finally 21.5  $\mu\text{g}/\text{kg}/\text{hr}$ . (hour 56–60). The primary outcomes were safety and tolerability and the key efficacy measure was the change in HAM-D<sub>17</sub> total score from baseline to the end of the infusion (hour 60). All adverse events were considered of mild to moderate severity and included sedation; rash; dizziness; flushing; oropharyngeal pain; and discomfort, pain, or erythema at the infusion site. HAM-D<sub>17</sub> total score declined from a baseline preinfusion mean of  $26.5 \pm 4.1$  to post-infusion score (hour 60) of  $1.8 \pm 1.5$  ( $p = 0.001$ ) [207].

The open-label study was followed by the first double-blind, randomized, placebo-controlled phase 2 study of brexanolone in women with severe PPD (n=21) [206]. Participants included healthy women aged 18–45 who were within six months postpartum and had an onset of

MDE no earlier than third trimester and no later than four weeks following delivery (i.e. study-defined PPD). Participants had a HAM-D<sub>17</sub> total score  $\geq 26$  at study entry and could remain on stable doses of antidepressants. Randomization was 1:1 brexanolone to placebo with dosing occurring over sixty hours: 30  $\mu\text{g}/\text{kg}/\text{hr}$ . (hour 0–4), 60  $\mu\text{g}/\text{kg}/\text{hr}$ . (hour 4–24), then 90  $\mu\text{g}/\text{kg}/\text{hr}$ . (hour 24–52), 60  $\mu\text{g}/\text{kg}/\text{hr}$ . (hour 52–56), 30  $\mu\text{g}/\text{kg}/\text{hr}$ . (hour 56–60h). The primary outcome measure was the change in HAM-D<sub>17</sub> total score from baseline to hour 60. Safety and tolerability were assessed. Participants were followed through day 30. At the end of the 60-hour infusion, the mean reduction in HAM-D<sub>17</sub> total score was 21.0 (SE = 2.9) in the brexanolone group and 8.8 points (SE = 2.8) in the placebo group, with a mean difference between groups of  $-12.2$  points (95% CI  $-20.77$  to  $-3.67$ ,  $p = 0.0075$ ). Depression remission (HAM-D<sub>17</sub>  $\leq 7$ ) at hour 60 was observed in seven out of ten participants in the brexanolone group and one out of eleven in the placebo group (OR  $-23.33$ , 95% CI  $-1.56$  to  $1152.71$ ;  $p = 0.0364$ ). Treatment-emergent adverse events in the brexanolone group with mild severity included dizziness (2/10) and somnolence (2/10) and with moderate severity included sinus tachycardia (1/10) and somnolence (1/10) [206].

This study was followed by two double-blind, randomized, placebo-controlled phase 3 trials of brexanolone in women with moderate and severe PPD[209]. Participants included healthy women aged 18–45 who were within six months postpartum and had an onset of a MDE no earlier than third trimester and no later than four weeks following delivery (i.e. study-defined PPD). Participants had a HAM-D<sub>17</sub> total score  $\geq 26$  (Study B) or 20–25 (Study C) at study entry and could remain on stable doses of antidepressants. The primary outcome measure was the change in HAM-D<sub>17</sub> total score from baseline to hour 60. Safety and tolerability were assessed. Participants were followed through day thirty. Study B (n = 138) randomized patients 1:1:1 to placebo, brexanolone iv 60  $\mu\text{g}/\text{kg}/\text{hr}$ . (BRX60), and brexanolone iv 90  $\mu\text{g}/\text{kg}/\text{hr}$ . (BRX90). The dosing schedule remained the same as in the previous placebo-controlled trial of BRX90 [206], with the only difference for participants in the BRX60 group that from hour 24–52, they received 60  $\mu\text{g}/\text{kg}/\text{hr}$ . instead of 90  $\mu\text{g}/\text{kg}/\text{hr}$ . When comparing HAM-D<sub>17</sub> total scores from baseline to the end of the infusion (hour 60), least squared mean reduction following BRX90 infusion was  $-17.7$  (SE 1.2) compared with  $-14.0$  (SE 1.1) for placebo (BRX-PBO  $-3.7$ , 95% CI  $-6.9$  to  $-0.5$ ,  $p = 0.0252$ ). For BRX60, the least squared mean reduction was  $-19.5$  (SE 1.2) (BRX-PBO  $-5.5$ , 95% CI  $-8.8$  to  $-2.2$ ,  $p = 0.0013$ ). Study C (n = 108) randomized patients 1:1 to placebo and BRX90 and was otherwise conducted with the same protocol as Study B. Least squared mean reduction in HAM-D<sub>17</sub> total score following BRX90 at hour 60 was  $-14.6$  (SE 0.8) versus  $-12.1$  (SE 0.8) for placebo (BRX-PBO  $-2.5$ , 95% CI  $-4.5$  to  $-0.5$ ,  $p = 0.0160$ ). In both studies[209], through the final follow up visit at study day 30, participant symptoms did not return to their baseline HAM-D<sub>17</sub> score. Treatment-emergent adverse events were mild-to-moderate and most commonly included somnolence, dizziness, and headache. Serious adverse events included altered state of consciousness and syncope (one participant) and suicidal ideation and intentional overdose attempt during follow-up (one participant). Severe adverse events included somnolence and loss of consciousness (one participant), fatigue (one participant) and pre-syncope (one participant). Five participants across both studies reported excessive somnolence, and all recovered fully within approximately one hour of interrupting the infusion[209].

Study authors additionally presented data on HAM-D<sub>17</sub> remission and response, Clinical Global Impression Scale-Global Improvement response, HAM-D<sub>17</sub> individual items and integrated efficacy data from the full placebo-controlled study population. Despite robust placebo responses in Studies B and C, data show statistically significant, rapid antidepressant effects in PPD[209].

The U.S. Food and Drug Administration (FDA) Psychopharmacologic Drugs Advisory Committee and Drug Safety and Risk Management Advisory Committee met on November 2, 2018 to review the ZULRESSO™ (brexanolone) injection New Drug Application (NDA) for the treatment of PPD[210]. The FDA proposed a risk evaluation and mitigation strategy (REMS) to reduce the risk of serious adverse events resulting from loss of consciousness/pre-syncope associated with the use of brexanolone[210]. A required REMS can include several risk minimization strategies that go beyond professional labeling. Should ZULRESSO™ be approved, the FDA proposed that administration only occur in certain healthcare settings that have health care professionals available to monitor the patient for sedation and intervene if necessary. The FDA also proposed that patients treated with brexanolone be enrolled in a registry to allow collection of additional data to further characterize the risk of loss of consciousness/pre-syncope[210]. The Prescription Drug User Fee Act date for the NDA's priority review was set to occur in March, 2019. Sage Therapeutics reported that if ZULRESSO™ is approved, it is "expected to be scheduled by the U.S. Drug Enforcement Administration, consistent with other approved GABAergic therapies[211]." Should ZULRESSO™ become the first FDA-approved medication for the treatment of PPD, it will be important to know the product's compatibility with breastfeeding, as in the most recent RCTs, women had stopped lactating or had temporarily ceased breastfeeding while receiving brexanolone until four days after the end of infusion[209]. Recent data provided by Sage Therapeutics and made publically available at the FDA Advisory Board meeting indicate that "the calculated maximum RID [relative infant dose] for brexanolone during infusion is 1.3%[210]." In general, a RID less than 10% is considered acceptable in a healthy postnatal infant [212], though RID does not provide information on the bioavailability of the drug in the infant.

Sage Therapeutics has additionally developed an orally bioavailable, potent PAM at both extrasynaptic and synaptic GABA<sub>A</sub>-R [213]. SAGE-217, an allopregnanolone analog, with oral bioavailability[213], was recently tested in an outpatient randomized, double-blind, placebo-controlled phase 3 study in severe PPD (NCT02978326). Published study results were pending at the time of writing, however the sponsor released top line results in January, 2019[214]. Participants included 151 adult women with severe PPD with a HAM-D<sub>17</sub> total score ≥ 26 who received two weeks of treatment with either SAGE-217 30mg or placebo and then were followed for four weeks. "Statistically significant differences in the reduction in HAM-D<sub>17</sub> total score of SAGE-217 versus placebo were first observed on Day 3 (-12.5 vs. -9.8; p=0.0255) and the effect was maintained at each timepoint through two weeks of treatment (-17.8 vs. -13.6; p=0.0029), the primary endpoint of the study[214]." "After two weeks of treatment with SAGE-217, 45% of patients achieved remission (HAM-D<sub>17</sub> ≤ 7) compared with 23% of patients who received placebo (p=0.0122); at the end of the four week follow-up, 53% of patients receiving SAGE-217 achieved remission compared with 30% of patients who received placebo[214]." The most common adverse events (5%) in

either group were somnolence, headache, dizziness, upper respiratory infection, diarrhea, nausea, sedation, vomiting, abnormal dreams and hyperhidrosis. There were no reports of loss of consciousness or syncope in either group[214].

Marinus Pharmaceuticals is currently conducting trials of the 3 $\beta$ -methylated synthetic analog of allopregnanolone, ganaxolone, in PPD. Ganaxolone is an extrasynaptic and synaptic GABA<sub>A</sub>-R PAM, similar to allopregnanolone, but unlike allopregnanolone, in binding studies, ganaxolone is reported to show no affinity for estrogen or progesterone receptors [205]. The iv formulation is being tested in a phase 2 double-blind, placebo-controlled, multiple-dose escalation study in severe PPD (NCT03228394) while the oral formulation is being tested in a phase 2 double-blind, placebo-controlled study in moderate PPD (NCT03460756). Published study results were pending at the time of writing, however the sponsor released some limited ganaxolone iv top-line data in December, 2018[215]. “There was a clear dose response relationship seen for three groups of patients receiving ganaxolone iv at median doses of 60, 90 and 140  $\mu$ g/kg/h. The 140  $\mu$ g/kg/h dose group (n=10) demonstrated the most robust results, with a clinically meaningful 5.6-point reduction in HAM-D<sub>17</sub> compared to placebo at 48 hours that was durable through the last visit, day 34[215].” “The most common reported adverse events were sedation and dizziness [215].”

## 6. Conclusions

PPD is a common and disabling disorder. A variety of effective pharmacotherapies, psychotherapies, psychosocial and neuromodulation interventions are available but most are understudied, especially in RCTs. Unfortunately, available treatments are significantly underutilized in the community. While PPD is more openly discussed in recent times, there still remains significant stigma for some women to seek treatment. Even when women do seek treatment, they may have limited access to providers with specialized training in perinatal mental health, especially in poorer nations where mental health may not be prioritized. Within the discipline of psychiatry, reproductive psychiatric training should be expanded in residency [216] and fellowship programs as the treatment of peripartum psychiatric illness is complex and requires collaboration among multiple providers, including obstetrics, pediatrics, psychiatry and nursing/midwifery.

In addition to improving currently available treatments and increasing access to those treatments, novel therapeutics are needed which specifically target the underlying pathophysiology of the disorder. Research into the underpinnings of PPD has increased, yet the complete underlying neurobiology is still poorly understood. With consistent evidence that psychiatric illnesses are neural network disorders representing complex, multimodal patterns of neurobiological abnormalities, the need for future research into the underpinning of these disorders is paramount. Increasing our understanding of the neurobiology of PPD will aid us in more effectively detecting, diagnosing, and treating PPD during pregnancy and postpartum periods.

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## REFERENCES

- Hahn-Holbrook J, Cornwell-Hinrichs T, Anaya I. Economic and Health Predictors of National Postpartum Depression Prevalence: A Systematic Review, Meta-analysis, and Meta-Regression of 291 Studies from 56 Countries. *Frontiers in psychiatry*. 2017;8:248. doi:10.3389/fpsyt.2017.00248. [PubMed: 29449816]
- Goodman SH, Rouse MH, Connell AM, Broth MR, Hall CM, Heyward D. Maternal depression and child psychopathology: a meta-analytic review. *Clin Child Fam Psychol Rev*. 2011;14(1): 1–27. doi: 10.1007/s10567-010-0080-1. [PubMed: 21052833]
- O'Connor TG, Heron J, Golding J, Beveridge M, Glover V. Maternal antenatal anxiety and children's behavioural/emotional problems at 4 years. Report from the Avon Longitudinal Study of Parents and Children. *Br J Psychiatry*. 2002;180:502–8. [PubMed: 12042228]
- Madigan S, Oatley H, Racine N, Fearon RMP, Schumacher L, Akbari E et al. A Meta-Analysis of Maternal Prenatal Depression and Anxiety on Child Socio-Emotional Development. *Journal of the American Academy of Child & Adolescent Psychiatry*. doi:10.1016/j.jaac.2018.06.012.
- Cox EQ, Sowa NA, Meltzer-Brody SE, Gaynes BN. The Perinatal Depression Treatment Cascade: Baby Steps Toward Improving Outcomes. *J Clin Psychiatry*. 2016;77(9):1189–200. doi:10.4088/JCP.15r10174. [PubMed: 27780317]
- Dietz PM, Williams SB, Callaghan WM, Bachman DJ, Whitlock EP, Hornbrook MC. Clinically identified maternal depression before, during, and after pregnancies ending in live births. *Am J Psychiatry*. 2007;164(10):1515–20. doi:10.1176/appi.ajp.2007.06111893. [PubMed: 17898342]
- Takehara K, Tachibana Y, Yoshida K, Mori R, Kakee N, Kubo T. Prevalence trends of pre- and postnatal depression in Japanese women: A population-based longitudinal study. *J Affect Disord*. 2018;225:389–94. doi:10.1016/j.jad.2017.08.008. [PubMed: 28846961]
- Anokye R, Acheampong E, Budu-Ainooson A, Obeng EI, Akwasi AG. Prevalence of postpartum depression and interventions utilized for its management. *Ann Gen Psychiatry*. 2018;17:18. doi: 10.1186/s12991-018-0188-0. [PubMed: 29760762]
- Bell AF, Carter CS, Davis JM, Golding J, Adejumo O, Pyra M et al. Childbirth and symptoms of postpartum depression and anxiety: a prospective birth cohort study. *Arch Womens Ment Health*. 2016;19(2):219–27. doi:10.1007/s00737-015-0555-7. [PubMed: 26202722]
- Franca UL, McManus ML. Frequency, trends, and antecedents of severe maternal depression after three million U.S. births. *PLoS One*. 2018;13(2):e0192854. doi: 10.1371/journal.pone.0192854. [PubMed: 29444165]
- Shakeel N, Sletner L, Falk RS, Slinning K, Martinsen EW, Jenum AK et al. Prevalence of postpartum depressive symptoms in a multiethnic population and the role of ethnicity and integration. *J Affect Disord*. 2018;241:49–58. doi:10.1016/j.jad.2018.07.056. [PubMed: 30096592]
- Rasmussen MH, Strom M, Wohlfahrt J, Videbech P, Melbye M. Risk, treatment duration, and recurrence risk of postpartum affective disorder in women with no prior psychiatric history: A population-based cohort study. *PLoS Med*. 2017;14(9):e1002392. doi:10.1371/journal.pmed.1002392. [PubMed: 28949960]
- Ko JY, Rockhill KM, Tong VT, Morrow B, Farr SL. Trends in Postpartum Depressive Symptoms - 27 States, 2004, 2008 and 2012. . *MMWR Morb Mort Wkly Rep*. 2017;66:153–8. doi:10.15585/mmwr.mm6606a1.

14. Kroenke K, Spitzer RL, Williams JB. The PHQ-9: validity of a brief depression severity measure. *Journal of general internal medicine*. 2001;16(9):606–13. [PubMed: 11556941]
15. Hanusa BH, Scholle SH, Haskett RF, Spadaro K, Wisner KL. Screening for depression in the postpartum period: a comparison of three instruments. *J Womens Health (Larchmt)*. 2008;17(4):585–96. doi:10.1089/jwh.2006.0248. [PubMed: 18345995]
16. Beck CT, Gable RK. Postpartum Depression Screening Scale: development and psychometric testing. *Nursing research*. 2000;49(5):272–82. [PubMed: 11009122]
17. Brodey BB, Goodman SH, Baldasaro RE, Brooks-DeWeese A, Wilson ME, Brodey IS et al. Development of the Perinatal Depression Inventory (PDI)-14 using item response theory: a comparison of the BDI-II, EPDS, PDI, and PHQ-9. *Arch Womens Ment Health*. 2016;19(2):307–16. doi:10.1007/s00737-015-0553-9. [PubMed: 26271280]
18. Cox JL, Holden JM, Sagovsky R. Detection of postnatal depression. Development of the 10-item Edinburgh Postnatal Depression Scale. *Br J Psychiatry*. 1987;150:782–6. [PubMed: 3651732]
19. Flynn HA, Sexton M, Ratliff S, Porter K, Zivin K. Comparative performance of the Edinburgh Postnatal Depression Scale and the Patient Health Questionnaire-9 in pregnant and postpartum women seeking psychiatric services. *Psychiatry Res*. 2011;187(1–2):130–4. doi:10.1016/j.psychres.2010.10.022. [PubMed: 21122923]
20. APA. *Diagnostic and Statistical Manual of Mental Disorders, DSM-5*. Fifth Edition ed. Washington, D C.: American Psychiatric Publishing; 2013.
21. Robertson E, Celasun N, Stewart DE. Risk factors for postpartum depression. *Postpartum depression: Literature review of risk factors and interventions*. Department of Mental Health and Substance Abuse: World Health Organization; 2003 p. 1–63.
22. Report CfDCaPCMaMW. Prevalence of Self-Reported Postpartum Depressive Symptoms-17 States, 2004–2005. In: Services DoHaH, editor. Atlanta, GA 2008.
23. Sharma V, Khan M, Corpse C, Sharma P. Missed bipolarity and psychiatric comorbidity in women with postpartum depression. *Bipolar Disord*. 2008;10(6):742–7. doi:10.1111/j.1399-5618.2008.00606.x. [PubMed: 18837870]
24. Vesga-Lopez O, Blanco C, Keyes K, Olfson M, Grant BF, Hasin DS. Psychiatric disorders in pregnant and postpartum women in the United States. *Arch Gen Psychiatry*. 2008;65(7):805–15. doi:10.1001/archpsyc.65.7.805. [PubMed: 18606953]
25. Hung CI, Liu CY, Yang CH. Untreated duration predicted the severity of depression at the two-year follow-up point. *PLoS One*. 2017;12(9):e0185119. doi:10.1371/journal.pone.0185119. [PubMed: 28934289]
26. Earls MF. Incorporating Recognition and Management of Perinatal and Postpartum Depression Into Pediatric Practice. *Pediatrics*. 2010;126(5):1032–9. doi:peds.2010-2348 [pii] 10.1542/peds.2010-2348. [PubMed: 20974776]
27. ACOG. The American College of Obstetricians and Gynecologists Committee Opinion no. 630. Screening for perinatal depression. *Obstet Gynecol*. 2015;125(5):1268–71. doi:10.1097/01.AOG.0000465192.34779.dc. [PubMed: 25932866]
28. O'Connor E, Rossom RC, Henninger M, Groom HC, Burda BU. Primary Care Screening for and Treatment of Depression in Pregnant and Postpartum Women: Evidence Report and Systematic Review for the US Preventive Services Task Force. *JAMA*. 2016;315(4):388–406. doi: 10.1001/jama.2015.18948. [PubMed: 26813212]
29. Dindo L, Elmore A, O'Hara M, Stuart S. The comorbidity of Axis I disorders in depressed pregnant women. *Arch Womens Ment Health*. 2017;20(6):757–64. doi:10.1007/s00737-017-0769-y. [PubMed: 28842756]
30. Hirschfeld RM. The Comorbidity of Major Depression and Anxiety Disorders: Recognition and Management in Primary Care. *Primary care companion to the Journal of clinical psychiatry*. 2001;3(6):244–54.
31. Newport DJ, Levey LC, Pennell PB, Ragan K, Stowe ZN. Suicidal ideation in pregnancy: assessment and clinical implications. *Arch Womens Ment Health*. 2007;10(5):181–7. doi: 10.1007/s00737-007-0192-x. [PubMed: 17726640]
32. Dennis CL, Brown HK, Wanigaratne S, Fung K, Vigod SN, Grigoriadis S et al. Prevalence, Incidence, and Persistence of Postpartum Depression, Anxiety, and Comorbidity among Chinese



- Immigrant and Nonimmigrant Women: A Longitudinal Cohort Study. *Can J Psychiatry*. 2018;63(1):44–53. doi:10.1177/0706743717720689. [PubMed: 28748744]
33. Putnam K, Robertson-Blackmore E, Sharkey K, Payne J, Bergink V, Munk-Olsen T et al. Heterogeneity of postpartum depression: a latent class analysis. *Lancet Psychiatry*. 2015;2(1):59–67. doi:10.1016/s2215-0366(14)00055-8. [PubMed: 26359613]
  34. Putnam KT, Wilcox M, Robertson-Blackmore E, Sharkey K, Bergink V, Munk-Olsen T et al. Clinical phenotypes of perinatal depression and time of symptom onset: analysis of data from an international consortium. *Lancet Psychiatry*. 2017;4(6):477–85. doi:10.1016/S2215-0366(17)30136-0. [PubMed: 28476427]
  35. Bernstein IH, Rush AJ, Yonkers K, Carmody TJ, Woo A, McConnell K et al. Symptom features of postpartum depression: are they distinct? *Depress Anxiety*. 2008;25(1):20–6. doi: 10.1002/da.20276. [PubMed: 17187349]
  36. Pope CJ, Xie B, Sharma V, Campbell MK. A prospective study of thoughts of self-harm and suicidal ideation during the postpartum period in women with mood disorders. *Arch Womens Ment Health*. 2013;16(6):483–8. doi:10.1007/s00737-013-0370-y. [PubMed: 23784481]
  37. Plant DT, Pariante CM, Sharp D, Pawlby S. Maternal depression during pregnancy and offspring depression in adulthood: role of child maltreatment. *Br J Psychiatry*. 2015;207(3):213–20. doi: 10.1192/bjp.bp.114.156620. [PubMed: 26045352]
  38. Spinelli MG. Maternal infanticide associated with mental illness: prevention and the promise of saved lives. *Am J Psychiatry*. 2004;161(9):1548–57. doi:10.1176/appi.ajp.161.9.1548. [PubMed: 15337641]
  39. Lindahl V, Pearson JL, Colpe L. Prevalence of suicidality during pregnancy and the postpartum. *Arch Womens Ment Health*. 2005;8(2):77–87. doi:10.1007/s00737-005-0080-1. [PubMed: 15883651]
  40. Draper ES, Gallimore ID, Kurinczuk JJ, Smith PW, Bobby T, Smith LK et al. MBRACE-UK Perinatal Mortality Surveillance Report, UK Perinatal Deaths for Births from January to December 2016. In: *The Infant Mortality and Morbidity Studies DoHS*, editor. University of Leicester, UK: The Infant Mortality and Morbidity Studies; 2018.
  41. Wisner KL, Sit DK, McShea MC, Rizzo DM, Zoretich RA, Hughes CL et al. Onset timing, thoughts of self-harm, and diagnoses in postpartum women with screen-positive depression findings. *JAMA psychiatry*. 2013;70(5):490–8. doi:10.1001/jamapsychiatry.2013.87. [PubMed: 23487258]
  42. Segre LS, O'Hara MW, Arndt S, Stuart S. The prevalence of postpartum depression: the relative significance of three social status indices. *Soc Psychiatry Psychiatr Epidemiol*. 2007;42(4):316–21. doi:10.1007/s00127-007-0168-1. [PubMed: 17370048]
  43. Mershy JP, Janczewski CE. Adverse Childhood Experiences and Postpartum Depression in Home Visiting Programs: Prevalence, Association, and Mediating Mechanisms. *Maternal and child health journal*. 2018;22(7):1051–8. doi:10.1007/s10995-018-2488-z. [PubMed: 29435785]
  44. Homish GG, Cornelius JR, Richardson GA, Day NL. Antenatal risk factors associated with postpartum comorbid alcohol use and depressive symptomatology. *Alcoholism, clinical and experimental research*. 2004;28(8):1242–8.
  45. Hu R, Li Y, Zhang Z, Yan W. Antenatal depressive symptoms and the risk of preeclampsia or operative deliveries: a meta-analysis. *PLoS One*. 2015;10(3):e0119018. doi:10.1371/journal.pone.0119018. [PubMed: 25789626]
  46. Grote NK, Bridge JA, Gavin AR, Melville JL, Iyengar S, Katon WJ. A meta-analysis of depression during pregnancy and the risk of preterm birth, low birth weight, and intrauterine growth restriction. *Arch Gen Psychiatry*. 2010;67(10):1012–24. doi: 10.1001/archgenpsychiatry.2010.111. [PubMed: 20921117]
  47. Yedid Sion M, Harlev A, Weintraub AY, Sergienko R, Sheiner E. Is antenatal depression associated with adverse obstetric and perinatal outcomes? *J Matern Fetal Neonatal Med*. 2016;29(6):863–7. doi:10.3109/14767058.2015.1023708. [PubMed: 25777791]
  48. Badr LK, Ayvazian N, Lameh S, Charafeddine L. Is the Effect of Postpartum Depression on Mother-Infant Bonding Universal? *Infant Behav Dev*. 2018;51:15–23. doi: 10.1016/j.infbeh.2018.02.003. [PubMed: 29533871]

49. Smith-Nielsen J, Tharner A, Krogh MT, Vaever MS. Effects of maternal postpartum depression in a well-resourced sample: Early concurrent and long-term effects on infant cognitive, language, and motor development. *Scandinavian journal of psychology*. 2016;57(6):571–83. doi:10.1111/sjop.12321. [PubMed: 27611177]
50. Shen H, Magnusson C, Rai D, Lundberg M, Le-Scherban F, Dalman C et al. Associations of Parental Depression With Child School Performance at Age 16 Years in Sweden. *JAMA psychiatry*. 2016;73(3):239–46. doi:10.1001/jamapsychiatry.2015.2917. [PubMed: 26842307]
51. Kawai E, Takagai S, Takei N, Itoh H, Kanayama N, Tsuchiya KJ. Maternal postpartum depressive symptoms predict delay in non-verbal communication in 14-month-old infants. *Infant Behav Dev*. 2017;46:33–45. doi:10.1016/j.infbeh.2016.11.006. [PubMed: 27870989]
52. Martini J, Petzoldt J, Knappe S, Garthus-Niegel S, Asselmann E, Wittchen HU. Infant, maternal, and familial predictors and correlates of regulatory problems in early infancy: The differential role of infant temperament and maternal anxiety and depression. *Early Hum Dev*. 2017;115:23–31. doi:10.1016/j.earlhumdev.2017.08.005. [PubMed: 28869923]
53. Meiser S, Zietlow AL, Reck C, Trauble B. The impact of postpartum depression and anxiety disorders on children's processing of facial emotional expressions at pre-school age. *Arch Womens Ment Health*. 2015;18(5):707–16. doi:10.1007/s00737-015-0519-y. [PubMed: 25833807]
54. Kersten-Alvarez LE, Hosman CM, Riksen-Walraven JM, van Doesum KT, Smeekens S, Hoefnagels C. Early school outcomes for children of postpartum depressed mothers: comparison with a community sample. *Child psychiatry and human development*. 2012;43(2):201–18. doi:10.1007/s10578-011-0257-y. [PubMed: 22011810]
55. Klier CM, Rosenblum KL, Zeller M, Steinhardt K, Bergemann N, Muzik M. A multirisk approach to predicting chronicity of postpartum depression symptoms. *Depress Anxiety*. 2008;25(8):718–24. doi:10.1002/da.20419. [PubMed: 18729148]
56. Netsi E, Pearson RM, Murray L, Cooper P, Craske MG, Stein A. Association of Persistent and Severe Postnatal Depression With Child Outcomes. *JAMA psychiatry*. 2018;75(3):247–53. doi:10.1001/jamapsychiatry.2017.4363. [PubMed: 29387878]
57. Letourneau NL, Tramonte L, Willms JD. Maternal depression, family functioning and children's longitudinal development. *Journal of pediatric nursing*. 2013;28(3):223–34. doi:10.1016/j.pedn.2012.07.014. [PubMed: 22940454]
58. Kimmel MC, Cox E, Schiller C, Gettes E, Meltzer-Brody S. Pharmacologic Treatment of Perinatal Depression. *Obstetrics and gynecology clinics of North America*. 2018;45(3):419–40. doi:10.1016/j.ogc.2018.04.007. [PubMed: 30092919]
59. Roy A, Cole K, Goldman Z, Barris M. Fluoxetine treatment of postpartum depression. *Am J Psychiatry*. 1993;150(8):1273.
60. Stowe ZN, Casarella J, Landry J, Nemeroff CB. Sertraline in the treatment of women with postpartum major depression. *Depression*. 1995;3(1–2):49–55. doi:10.1002/depr.3050030109.
61. Suri R, Burt VK, Altshuler LL, Zuckerbrow-Miller J, Fairbanks L. Fluvoxamine for postpartum depression. *Am J Psychiatry*. 2001;158(10):1739–40. doi:10.1176/appi.ajp.158.10.1739. [PubMed: 11579021]
62. Misri S, Abizadeh J, Albert G, Carter D, Ryan D. Restoration of functionality in postpartum depressed mothers: an open-label study with escitalopram. *J Clin Psychopharmacol*. 2012;32(5):729–32. doi:10.1097/JCP.0b013e31826867c9.
63. Milgrom J, Gemmili AW, Ericksen J, Burrows G, Buist A, Reece J. Treatment of postnatal depression with cognitive behavioural therapy, sertraline and combination therapy: a randomised controlled trial. *Aust N Z J Psychiatry*. 2015;49(3):236–45. doi:10.1177/0004867414565474. [PubMed: 25586754]
64. Hantsoo L, Ward-O'Brien D, Czarkowski KA, Gueorguieva R, Price LH, Epperson CN. A randomized, placebo-controlled, double-blind trial of sertraline for postpartum depression. *Psychopharmacology (Berl)*. 2014;231(5):939–48. doi:10.1007/s00213-013-3316-1.
65. Bloch M, Meiboom H, Lorberblatt M, Bluvstein I, Aharonov I, Schreiber S. The effect of sertraline add-on to brief dynamic psychotherapy for the treatment of postpartum depression: a randomized, doubleblind, placebo-controlled study. *J Clin Psychiatry*. 2012;73(2):235–41. doi:10.4088/JCP.11m07117. [PubMed: 22401479]

66. Sharp DJ, Chew-Graham C, Tylee A, Lewis G, Howard L, Anderson I et al. A pragmatic randomised controlled trial to compare antidepressants with a community-based psychosocial intervention for the treatment of women with postnatal depression: the RESPOND trial. *Health technology assessment (Winchester, England)*. 2010;14(43):iii-iv, ix-xi, 1–153. doi:10.3310/hta14430.
67. Yonkers KA, Lin H, Howell HB, Heath AC, Cohen LS. Pharmacologic treatment of postpartum women with new-onset major depressive disorder: a randomized controlled trial with paroxetine. *J Clin Psychiatry*. 2008;69(4):659–65. [PubMed: 18363420]
68. Wisner KL, Hanusa BH, Perei JM, Peindl KS, Piontek CM, Sit DK et al. Postpartum depression: a randomized trial of sertraline versus nortriptyline. *J Clin Psychopharmacol*. 2006;26(4):353–60. doi:10.1097/01.jcp.0000227706.56870.dd. [PubMed: 16855451]
69. Misri S, Reebye P, Corral M, Milis L. The use of paroxetine and cognitive-behavioral therapy in postpartum depression and anxiety: a randomized controlled trial. *J Clin Psychiatry*. 2004;65(9):1236–41. [PubMed: 15367052]
70. Appleby L, Warner R, Whitton A, Faragher B. A controlled study of fluoxetine and cognitive behavioural counselling in the treatment of postnatal depression. *Bmj*. 1997;314(7085):932–6. [PubMed: 9099116]
71. Molyneaux E, Howard LM, McGeown HR, Karia AM, Trevillion K. Antidepressant treatment for postnatal depression. *The Cochrane database of systematic reviews*. 2014(9):Cd002018. doi:10.1002/14651858.CD002018.pub2.
72. De Crescenzo F, Perelli F, Armando M, Vicari S. Selective serotonin reuptake inhibitors (SSRIs) for post-partum depression (PPD): a systematic review of randomized clinical trials. *J Affect Disord*. 2014;152–154:39–44. doi:10.1016/j.jad.2013.09.019.
73. Cohen LS, Viguera AC, Bouffard SM, Nonacs RM, Morabito C, Collins MH et al. Venlafaxine in the treatment of postpartum depression. *J Clin Psychiatry*. 2001;62(8):592–6. [PubMed: 11561929]
74. Misri S, Swift E, Abizadeh J, Shankar R. Overcoming functional impairment in postpartum depressed or anxious women: a pilot trial of desvenlafaxine with flexible dosing. *Therapeutic advances in psychopharmacology*. 2016;6(4):269–76. doi:10.1177/2045125316656297. [PubMed: 27536346]
75. 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):445–9. doi:10.1017/s1461145705005079. [PubMed: 15817137]
76. Suri R, Burt VK, Altshuler LL. Nefazodone for the treatment of postpartum depression. *Arch Womens Ment Health*. 2005;8(1):55–6. doi:10.1007/s00737-005-0071-2. [PubMed: 15868388]
77. Marrocco J, McEwen BS. Sex in the brain: hormones and sex differences. *Dialogues Clin Neurosci*. 2016;18(4):373–83. [PubMed: 28179809]
78. Rubinow DR, Schmidt PJ. Sex differences and the neurobiology of affective disorders. *Neuropsychopharmacology*. 2018. doi:10.1038/s41386-018-0148-z.
79. Gregoire AJ, Kumar R, Everitt B, Henderson AF, Studd JW. Transdermal oestrogen for treatment of severe postnatal depression. *Lancet (London, England)*. 1996;347(9006):930–3.
80. Wisner KL, Sit DK, Moses-Kolko EL, Driscoll KE, Prairie BA, Stika CS et al. Transdermal Estradiol Treatment for Postpartum Depression: A Pilot, Randomized Trial. *J Clin Psychopharmacol*. 2015;35(4):389–95. doi:10.1097/jcp.0000000000000351. [PubMed: 26061609]
81. Moses-Kolko EL, Berga SL, Kairo B, Sit DK, Wisner KL. Transdermal estradiol for postpartum depression: a promising treatment option. *Clin Obstet Gynecol*. 2009;52(3):516–29. doi:10.1097/GRF.0b013e3181b5a395. [PubMed: 19661765]
82. Lawrie TA, Hofmeyr GJ, De Jager M, Berk M, Paiker J, Viljoen E. A double-blind randomised placebo controlled trial of postnatal norethisterone enanthate: the effect on postnatal depression and serum hormones. *British journal of obstetrics and gynaecology*. 1998;105(10):1082–90. [PubMed: 9800931]
83. Singata-Madliki M, Hofmeyr GJ, Lawrie TA. The effect of depot medroxyprogesterone acetate on postnatal depression: a randomised controlled trial. *The journal of family planning and*

- reproductive health care. 2016;42(3):171–6. doi:10.1136/jfprhc-2015-101334. [PubMed: 27030698]
84. Tsai R, Schaffir J. Effect of depot medroxyprogesterone acetate on postpartum depression. *Contraception*. 2010;82(2):174–7. doi:10.1016/j.contraception.2010.03.004. [PubMed: 20654759]
  85. Dennis CL, Ross LE, Herxheimer A. Oestrogens and progestins for preventing and treating postpartum depression. *The Cochrane database of systematic reviews*. 2008(4):Cd001690. doi: 10.1002/14651858.CD001690.pub2.
  86. Wisner KL, Perel JM, Peindl KS, Hanusa BH, Findling RL, Rapport D. Prevention of recurrent postpartum depression: a randomized clinical trial. *J Clin Psychiatry*. 2001;62(2):82–6. [PubMed: 11247106]
  87. Yonkers KA, Vigod S, Ross LE. Diagnosis, pathophysiology, and management of mood disorders in pregnant and postpartum women. *Obstet Gynecol*. 2011;117(4):961–77. doi:10.1097/AOG.0b013e31821187a7. [PubMed: 21422871]
  88. Wisner KL, Perei JM, Peindl KS, Hanusa BH, Piontek CM, Findling RL. Prevention of postpartum depression: a pilot randomized clinical trial. *Am J Psychiatry*. 2004;161(7): 1290–2. doi:10.1176/appi.ajp.161.7.1290. [PubMed: 15229064]
  89. Khazaie H, Ghadami MR, Knight DC, Emamian F, Tahmasian M. Insomnia treatment in the third trimester of pregnancy reduces postpartum depression symptoms: a randomized clinical trial. *Psychiatry Res*. 2013;210(3):901–5. doi:10.1016/j.psychres.2013.08.017. [PubMed: 23993464]
  90. Molyneaux E, Telesia LA, Henshaw C, Boath E, Bradley E, Howard LM. Antidepressants for preventing postnatal depression. *The Cochrane database of systematic reviews*. 2018;4:Cd004363. doi:10.1002/14651858.CD004363.pub3.
  91. Walton GD, Ross LE, Stewart DE, Grigoriadis S, Dennis CL, Vigod S. Decisional conflict among women considering antidepressant medication use in pregnancy. *Arch Womens Ment Health*. 2014;17(6):493–501. doi:10.1007/s00737-014-0448-1. [PubMed: 25104244]
  92. Goodman JH. Women's attitudes, preferences, and perceived barriers to treatment for perinatal depression. *Birth*. 2009;36(1):60–9. doi: 10.1111/j.1523-536X.2008.00296.x. [PubMed: 19278385]
  93. Hall HR, Jolly K. Women's use of complementary and alternative medicines during pregnancy: a cross-sectional study. *Midwifery*. 2014;30(5):499–505. doi:10.1016/j.midw.2013.06.001. [PubMed: 23849906]
  94. Wu P, Fuller C, Liu X, Lee HC, Fan B, Hoven CW et al. Use of complementary and alternative medicine among women with depression: results of a national survey. *Psychiatr Serv*. 2007;58(3): 349–56. doi:10.1176/ps.2007.58.3.349. [PubMed: 17325108]
  95. Stuart S, Koleva H. Psychological treatments for perinatal depression. *Best practice & research Clinical obstetrics & gynaecology*. 2014;28(1):61–70. doi:10.1016/j.bpobgyn.2013.09.004. [PubMed: 24269903]
  96. Dennis CL, Dowswell T. Psychosocial and psychological interventions for preventing postpartum depression. *The Cochrane database of systematic reviews*. 2013(2):Cd001134. doi: 10.1002/14651858.CD001134.pub3.
  97. Reza N, Deligiannidis KM, Eustis EH, Battle CL. Complementary Health Practices for Treating Perinatal Depression. *Obstetrics and gynecology clinics of North America*. 2018;45(3):441–54. doi:10.1016/j.ogc.2018.04.002. [PubMed: 30092920]
  98. Rundgren S, Brus O, Bave U, Landen M, Lundberg J, Nordanskog P et al. Improvement of postpartum depression and psychosis after electroconvulsive therapy: A population-based study with a matched comparison group. *J Affect Disord*. 2018;235:258–64. doi:10.1016/j.jad.2018.04.043. [PubMed: 29660641]
  99. Ward HB, Fromson JA, Cooper JJ, De Oliveira G, Almeida M. Recommendations for the use of ECT in pregnancy: literature review and proposed clinical protocol. *Arch Womens Ment Health*. 2018. doi:10.1007/s00737-018-0851-0.
  100. Myczkowski ML, Dias AM, Luvisotto T, Arnaut D, Bellini BB, Mansur CG et al. Effects of repetitive transcranial magnetic stimulation on clinical, social, and cognitive performance in postpartum depression. *Neuropsychiatric disease and treatment*. 2012;8:491–500. doi: 10.2147/ndt.s33851. [PubMed: 23118543]

101. Garcia KS, Flynn P, Pierce KJ, Caudle M. Repetitive transcranial magnetic stimulation treats postpartum depression. *Brain Stimul.* 2010;3(1):36–41. doi:10.1016/j.brs.2009.06.001. [PubMed: 20633429]
102. Andriotti T, Stavale R, Nafee T, Fakhry S, Mohamed MMA, Sofiyeva N et al. ASSERT trial-How to assess the safety and efficacy of a high frequency rTMS in postpartum depression? A multicenter, double blinded, randomized, placebo-controlled clinical trial. *Contemporary clinical trials communications.* 2017;5:86–91. doi: 10.1016/j.conctc.2017.01.004. [PubMed: 29740625]
103. Vigod S, Dennis CL, Daskalakis Z, Murphy K, Ray J, Oberlander T et al. Transcranial direct current stimulation (tDCS) for treatment of major depression during pregnancy: study protocol for a pilot randomized controlled trial. *Trials.* 2014;15:366. doi: 10.1186/1745-6215-15-366. [PubMed: 25234606]
104. Kim DR, Snell JL, Ewing GC, O'Reardon J. Neuromodulation and antenatal depression: a review. *Neuropsychiatric disease and treatment.* 2015;11:975–82. doi:10.2147/ndt.s80480. [PubMed: 25897234]
105. Blazer DG, Kessler RC, McGonagle KA, Swartz MS. The prevalence and distribution of major depression in a national community sample: the National Comorbidity Survey. *Am J Psychiatry.* 1994;151(7):979–86. [PubMed: 8010383]
106. Bloch M, Rubinow DR, Schmidt PJ, Lotsikas A, Chrousos GP, Cizza G. Cortisol response to ovine corticotropin-releasing hormone in a model of pregnancy and parturition in euthymic women with and without a history of postpartum depression. *J Clin Endocrinol Metab.* 2005;90(2):695–9. doi:10.1210/jc.2004-1388 [pii] 10.1210/jc.2004-1388. [PubMed: 15546899]
107. 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]
108. Deligiannidis KM, Sikoglu EM, Shaffer SA, Frederick B, Svenson AE, Kopoyan A et al. GABAergic neuroactive steroids and resting-state functional connectivity in postpartum depression: a preliminary study. *J Psychiatr Res.* 2013;47(6):816–28. doi:10.1016/j.jpsychires.2013.02.010. [PubMed: 23499388]
109. Harris B, Lovett L, Newcombe RG, Read GF, Walker R, Riad-Fahmy D. Maternity blues and major endocrine changes: Cardiff puerperal mood and hormone study II. *BMJ.* 1994;308(6934):949–53. [PubMed: 8173402]
110. Magiakou MA, Mastorakos G, Rabin D, Dubbert B, Gold PW, Chrousos GP. Hypothalamic corticotropin-releasing hormone suppression during the postpartum period: implications for the increase in psychiatric manifestations at this time. *J Clin Endocrinol Metab.* 1996;81(5):1912–7. [PubMed: 8626857]
111. Stuebe AM, Grewen K, Pedersen CA, Propper C, Meltzer-Brody S. Failed lactation and perinatal depression: common problems with shared neuroendocrine mechanisms? *J Womens Health (Larchmt).* 2012;21(3):264–72. doi:10.1089/jwh.2011.3083. [PubMed: 22204416]
112. Hellgren C, Akerud H, Skalkidou A, Sundstrom-Poromaa I. Cortisol awakening response in late pregnancy in women with previous or ongoing depression. *Psychoneuroendocrinology.* 2013;38(12):3150–4. doi:10.1016/j.psyneuen.2013.08.007. [PubMed: 24041544]
113. Meinlschmidt G, Martin C, Neumann ID, Heinrichs M. Maternal cortisol in late pregnancy and hypothalamic-pituitary-adrenal reactivity to psychosocial stress postpartum in women. *Stress.* 2010;13(2):163–71. doi: 10.3109/10253890903128632. [PubMed: 20214437]
114. Nierop A, Bratsikas A, Zimmermann R, Ehlert U. Are stress-induced cortisol changes during pregnancy associated with postpartum depressive symptoms? *Psychosom Med.* 2006;68(6):931–7. doi:10.1097/01.psy.0000244385.93141.3b. [PubMed: 17132840]
115. Corwin EJ, Pajer K, Paul S, Lowe N, Weber M, McCarthy DO. Bidirectional psychoneuroimmune interactions in the early postpartum period influence risk of postpartum depression. *Brain, behavior, and immunity.* 2015;49:86–93. doi:10.1016/j.bbi.2015.04.012.
116. Boufidou F, Lambrinoudaki I, Argeitis J, Zervas IM, Pliatsika P, Leonardou AA et al. CSF and plasma cytokines at delivery and postpartum mood disturbances. *J Affect Disord.* 2009;115(1–2):287–92. doi:10.1016/j.jad.2008.07.008. [PubMed: 18708264]



117. Sharkey KM, Pearlstein TB, Carskadon MA. Circadian phase shifts and mood across the perinatal period in women with a history of major depressive disorder: a preliminary communication. *J Affect Disord.* 2013;150(3):1103–8. doi:10.1016/j.jad.2013.04.046. [PubMed: 23706877]
118. Parry BL, Meliska CJ, Sorenson DL, Lopez AM, Martinez LF, Nowakowski S et al. Plasma melatonin circadian rhythm disturbances during pregnancy and postpartum in depressed women and women with personal or family histories of depression. *Am J Psychiatry.* 2008;165(12):1551–8. doi:10.1176/appi.ajp.2008.08050709. [PubMed: 18829869]
119. Costas J, Gratacos M, Escaramis G, Martin-Santos R, de Diego Y, Baca-Garcia E et al. Association study of 44 candidate genes with depressive and anxiety symptoms in post-partum women. *J Psychiatr Res.* 2010;44(11):717–24. doi:10.1016/j.jpsychires.2009.12.012. [PubMed: 20092830]
120. Guintivano J, Arad M, Gould TD, Payne JL, Kaminsky ZA. Antenatal prediction of postpartum depression with blood DNA methylation biomarkers. *Mol Psychiatry.* 2014;19(5):560–7. doi:10.1038/mp.2013.62. [PubMed: 23689534]
121. Deligiannidis KM, Fales CL, Kroll-Desrosiers AR, Shaffer SA, Villamarin V, Tan Y et al. Intrinsic resting-state functional connectivity, cortical  $\gamma$ -aminobutyric acid and peripheral neuroactive steroids in peripartum and peripartum depressed women: a functional magnetic imaging and resonance study. . Accepted, in press, *Neuropsychopharmacology* and available at *BioRxiv* 411405. 2018. doi:Available from: <https://doi.org/10.1101/411405>.
122. Silver M, Moore CM, Villamarin V, Jaitly N, Hall JE, Rothschild AJ et al. White matter integrity in medication-free women with peripartum depression: a tract-based spatial statistics study. *Neuropsychopharmacology.* 2018;43(7):1573–80. doi:10.1038/s41386-018-0023-y. [PubMed: 29453442]
123. B lactum ST. Reproductive and developmental processes In: Jachson C, editor. *Maternal, Fetal and Neonatal Physiology.* Philadelphia, PA, USA: Elsevier Health Sciences; 2007 p. 100–2.
124. Tulchinshy D, Hobel CJ, Yeager E, Marshall JR. Plasma estrone, estradiol, estriol, progesterone, and 17-hydroxyprogesterone in human pregnancy. I. Normal pregnancy. *American journal of obstetrics and gynecology.* 1972;112(8):1095–100. [PubMed: 5025870]
125. Bammann BL, Coulam CB, Jiang NS. Total and free testosterone during pregnancy. *American journal of obstetrics and gynecology.* 1980;137(3):293–8. [PubMed: 7189643]
126. Levine A, Zagoory-Sharon O, Feldman R, Weller A. Oxytocin during pregnancy and early postpartum: individual patterns and maternal-fetal attachment. *Peptides.* 2007;28(6):1162–9. doi:10.1016/j.peptides.2007.04.016. [PubMed: 17513013]
127. Hill M, Parizeh A, Klak J, Hampl R, Sulcova J, Havlihova H et al. Neuroactive steroids, their precursors and polar conjugates during parturition and postpartum in maternal and umbilical blood: 3.3beta-hydroxy-5-ene steroids. *J Steroid Biochem Mol Biol.* 2002;82(2–3):241–50. [PubMed: 12477491]
128. Hill M, Cibula D, Havlihova H, Kancheva L, Fait T, Kancheva R et al. Circulating levels of pregnanolone isomers during the third trimester of human pregnancy. *J Steroid Biochem Mol Biol.* 2007;105(1–5):166–75. doi:10.1016/j.jsbmb.2006.10.010. [PubMed: 17583491]
129. Deligiannidis KM, Kroll-Desrosiers AR, Svenson A, Jaitly N, Barton BA, Hall JE et al. Cortisol response to the Trier Social Stress Test in pregnant women at risk for postpartum depression. *Arch Womens Ment Health.* 2016;19(5):789–97. doi:10.1007/s00737-016-0615-7. [PubMed: 26951216]
130. Halligan SL, Herbert J, Goodyer I, Murray L. Disturbances in morning cortisol secretion in association with maternal postnatal depression predict subsequent depressive symptomatology in adolescents. *Biol Psychiatry.* 2007;62(1):40–6. doi:10.1016/j.biopsych.2006.09.011. [PubMed: 17188253]
131. Nierop A, Bratsihis A, Klinhenberg A, Nater UM, Zimmermann R, Ehlert U. Prolonged salivary cortisol recovery in second-trimester pregnant women and attenuated salivary alpha-amylase responses to psychosocial stress in human pregnancy. *J Clin Endocrinol Metab.* 2006;91(4):1329–35. doi:10.1210/jc.2005-1816 [pii] 10.1210/jc.2005-1816. [PubMed: 16434458]
132. O'Connor TG, Tang W, Gilchrist MA, Moynihan JA, Pressman EK, Blackmore ER. Diurnal cortisol patterns and psychiatric symptoms in pregnancy: short-term longitudinal study.



- Biological psychology. 2014;96:35–41. doi:10.1016/j.biopsycho.2013.11.002. [PubMed: 24239618]
133. Meltzer-Brody S, Stuebe A, Dole N, Savitz D, Rubinow D, Thorp J. Elevated corticotropin releasing hormone (CRH) during pregnancy and risk of postpartum depression (PPD). *J Clin Endocrinol Metab.* 2011;96(1):E40–7. doi:10.1210/jc.2010-0978. [PubMed: 20943787]
  134. Zaconeta AM, Amato AA, Barra GB, Casulari da Motta LD, de Souza VC, Karnikowski MG et al. Cerebrospinal Fluid CRH Levels in Late Pregnancy Are Not Associated With New-Onset Postpartum Depressive Symptoms. *J Clin Endocrinol Metab.* 2015;100(8):3159–64. doi: 10.1210/jc.2014-4503. [PubMed: 26066672]
  135. Glynn LM, Sandman CA. Evaluation of the association between placental corticotrophin-releasing hormone and postpartum depressive symptoms. *Psychosom Med.* 2014;76(5):355–62. doi:10.1097/psy.000000000000066. [PubMed: 24915294]
  136. Yim IS, Glynn LM, Dunkel-Schetter C, Hobel CJ, Chicz-DeMet A, Sandman CA. Risk of postpartum depressive symptoms with elevated corticotropin-releasing hormone in human pregnancy. *Arch Gen Psychiatry.* 2009;66(2):162–9. doi: 10.1001/archgenpsychiatry.2008.533. [PubMed: 19188538]
  137. Ferguson EH, Di Florio A, Pearson B, Putnam KT, Girdler S, Rubinow DR et al. HPA axis reactivity to pharmacologic and psychological stressors in euthymic women with histories of postpartum versus major depression. *Arch Womens Ment Health.* 2017;20(3):411–20. doi: 10.1007/s00737-017-0716-y. [PubMed: 28251369]
  138. 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. doi:10.1007/s00213-0164217-x.
  139. Skrundz M, Bolten M, Nast I, Hellhammer DH, Meinlschmidt G. Plasma oxytocin concentration during pregnancy is associated with development of postpartum depression. *Neuropsychopharmacology.* 2011;36(9):1886–93. doi:10.1038/npp.2011.74. [PubMed: 21562482]
  140. King L, Robins S, Chen G, Yerko V, Zhou Y, Nagy C et al. Perinatal depression and DNA methylation of oxytocin-related genes: a study of mothers and their children. *Horm Behav.* 2017;96:84–94. doi:10.1016/j.yhbeh.2017.09.006. [PubMed: 28918249]
  141. Kroll-Desrosiers AR, Nephew BC, Babb JA, Guilarte-Walker Y, Moore Simas TA, Deligiannidis KM. Association of peripartum synthetic oxytocin administration and depressive and anxiety disorders within the first postpartum year. *Depress Anxiety.* 2017;34(2): 137–46. doi:10.1002/da.22599. [PubMed: 28133901]
  142. Okun ML, Luther J, Prather AA, Perel JM, Wisniewski S, Wisner KL. Changes in sleep quality, but not hormones predict time to postpartum depression recurrence. *J Affect Disord.* 2011;130(3):378–84. doi:10.1016/j.jad.2010.07.015. [PubMed: 20708275]
  143. O’Hara MW, Schlechte JA, Lewis DA, Wright EJ. Prospective study of postpartum blues. Biologic and psychosocial factors. *Arch Gen Psychiatry.* 1991;48(9):801–6. [PubMed: 1929770]
  144. Parizek A, Mikesova M, Jirak R, Hill M, Koucky M, Paskova A et al. Steroid hormones in the development of postpartum depression. *Physiological research / Academia Scientiarum Bohemoslovaca.* 2014;63 Suppl 2:S277–82.
  145. Hohlagschwandtner M, Husslein P, Klier C, Ulm B. Correlation between serum testosterone levels and peripartum mood states. *Acta obstetrica et gynecologica Scandinavica.* 2001;80(4): 326–30. [PubMed: 11264607]
  146. Aswathi A, Rajendiren S, Nimesh A, Philip RR, Kattimani S, Jayalakshmi D et al. High serum testosterone levels during postpartum period are associated with postpartum depression. *Asian journal of psychiatry.* 2015;17:85–8. doi:10.1016/j.ajp.2015.08.008. [PubMed: 26372084]
  147. Deligiannidis KM, Kroll-Desrosiers AR, Mo S, Nguyen HP, Svenson A, Jaitly N et al. Peripartum neuroactive steroid and gamma-aminobutyric acid profiles in women at-risk for postpartum depression. *Psychoneuroendocrinology.* 2016;70:98–107. doi:10.1016/j.psyneuen.2016.05.010. [PubMed: 27209438]

148. Groer MW, Vaughan JH. Positive thyroid peroxidase antibody titer is associated with dysphoric moods during pregnancy and postpartum. *Journal of obstetric, gynecologic, and neonatal nursing : JOGNN / NAACOG*. 2013;42(1):E26–32. doi:10.1111/j.1552-6909.2012.01425.x.
149. Albacar G, Sans T, Martin-Santos R, Garcia-Esteve L,Guillamat R, Sanjuan J et al. Thyroid function 48h after delivery as a marker for subsequent postpartum depression. *Psychoneuroendocrinology*. 2010;35(5):738–42. doi:10.1016/j.psyneuen.2009.10.015. [PubMed: 19939574]
150. Pedersen CA, Johnson JL, Silva S, Bunevicius R, Meltzer-Brody S, Hamer RM et al. Antenatal thyroid correlates of postpartum depression. *Psychoneuroendocrinology*. 2007;32(3):235–45. doi: 10.1016/j.psyneuen.2006.12.010. [PubMed: 17346901]
151. Sylven SM, Elenis E, Michelakos T, Larsson A, Olovsson M, Poromaa IS et al. Thyroid function tests at delivery and risk for postpartum depressive symptoms. *Psychoneuroendocrinology*. 2013;38(7):1007–13. doi:10.1016/j.psyneuen.2012.10.004. [PubMed: 23137714]
152. Sandman CA, Glynn LM. Corticotropin-Releasing Hormone (CRH) Programs the Fetal and Maternal Brain. *Future Neurol*. 2009;4(3):257–61. [PubMed: 19680459]
153. Duthie L, Reynolds RM. Changes in the maternal hypothalamic-pituitary-adrenal axis in pregnancy and postpartum: influences on maternal and fetal outcomes. *Neuroendocrinology*. 2013;98(2): 106–15. doi:10.1159/000354702. [PubMed: 23969897]
154. McLean M, Bisits A, Davies J, Woods R, Lowry P, Smith R. A placental clock controlling the length of human pregnancy. *Nat Med*. 1995;1(5):460–3. [PubMed: 7585095]
155. Sandman CA, Glynn L, Schetter CD, Wadhwa P, Garite T, Chic-DeMet A et al. Elevated maternal cortisol early in pregnancy predicts third trimester levels of placental corticotropin releasing hormone (CRH): priming the placental clock. *Peptides*. 2006;27(6): 1457–63. doi: 10.1016/j.peptides.2005.10.002. [PubMed: 16309788]
156. Sasaki A, Liotta AS, Luckey MM, Margioris AN, Suda T, Krieger DT. Immunoreactive corticotropin-releasing factor is present in human maternal plasma during the third trimester of pregnancy. *J Clin Endocrinol Metab*. 1984;59(4):812–4. doi: 10.1210/jcem-59-4-812. [PubMed: 6332823]
157. Mastorakos G, Ilias I. Maternal and fetal hypothalamic-pituitary-adrenal axes during pregnancy and postpartum. *Ann N Y Acad Sci*. 2003;997:136–49. [PubMed: 14644820]
158. Noltén WE, Lindheimer MD, Rueckert PA, Oparil S, Ehrlich EN. Diurnal patterns and regulation of cortisol secretion in pregnancy. *J Clin Endocrinol Metab*. 1980;51(3):466–72. [PubMed: 7410530]
159. Jung C, Ho JT, Torpy DJ, Rogers A, Doogue M, Lewis JG et al. A longitudinal study of plasma and urinary cortisol in pregnancy and postpartum. *J Clin Endocrinol Metab*. 2011;96(5): 1533–40. doi:10.1210/jc.2010-2395. [PubMed: 21367926]
160. O’Keane V, Lightman S, Patrick K, Marsh M, Papadopoulos AS, Pawlby S et al. Changes in the maternal hypothalamic-pituitary-adrenal axis during the early puerperium may be related to the postpartum ‘blues’. *Journal of neuroendocrinology*. 2011;23(11):1149–55. doi:10.1111/j.13652826.2011.02139.x. [PubMed: 22004568]
161. Buss C, Entringer S, Reyes JF, Chic-DeMet A, Sandman CA, Waffarn F et al. The maternal cortisol awakening response in human pregnancy is associated with the length of gestation. *American journal of obstetrics and gynecology*. 2009;201(4):398 e1–8. doi:10.1016/j.ajog.2009.06.063. [PubMed: 19716542]
162. Entringer S, Buss C, Shirtcliff EA, Cammack AL, Yim IS, Chic-DeMet A et al. Attenuation of maternal psychophysiological stress responses and the maternal cortisol awakening response over the course of human pregnancy. *Stress*. 2010;13(3):258–68. doi: 10.3109/10253890903349501. [PubMed: 20067400]
163. Schulte HM, Weisner D, Allolio B. The corticotrophin releasing hormone test in late pregnancy: lack of adrenocorticotrophin and cortisol response. *Clinical endocrinology*. 1990;33(1):99–106. [PubMed: 2169361]
164. de Weerth C, Buitelaar JK. Physiological stress reactivity in human pregnancy--a review. *Neuroscience and biobehavioral reviews*. 2005;29(2):295–312. doi:10.1016/j.neubiorev.2004.10.005. [PubMed: 15811500]

165. Giesbrecht GF, Campbell T, Letourneau N, Kaplan BJ. Advancing gestation does not attenuate biobehavioural coherence between psychological distress and cortisol. *Biological psychology*. 2013;93(1):45–51. doi:10.1016/j.biopsycho.2013.01.019. [PubMed: 23410761]
166. Brunton PJ. Neuroactive steroids and stress axis regulation: Pregnancy and beyond. *J Steroid Biochem Mol Biol*. 2016;160:160–8. doi:10.1016/j.jsbmb.2015.08.003. [PubMed: 26259885]
167. Butterfield MI, Stechuchak KM, Connor KM, Davidson JR, Wang C, MacKuen CL et al. Neuroactive steroids and suicidality in posttraumatic stress disorder. *Am J Psychiatry*. 2005;162(2):380–2. doi:10.1176/appi.ajp.162.2.380. [PubMed: 15677605]
168. Lopez-Rodriguez AB, Acaz-Fonseca E, Giatti S, Caruso D, Viveros MP, Melcangi RC et al. Correlation of brain levels of progesterone and dehydroepiandrosterone with neurological recovery after traumatic brain injury in female mice. *Psychoneuroendocrinology*. 2015;56:1–11. doi:10.1016/j.psyneuen.2015.02.018. [PubMed: 25770855]
169. Guille C, Spencer S, Cavus I, Epperson CN. The role of sex steroids in catamenial epilepsy and premenstrual dysphoric disorder: implications for diagnosis and treatment. *Epilepsy & behavior : E&B*. 2008;13(1):12–24. doi:10.1016/j.yebeh.2008.02.004.
170. Backstrom T, Haage D, Lofgren M, Johansson IM, Stromberg J, Nyberg S et al. Paradoxical effects of GABA-A modulators may explain sex steroid induced negative mood symptoms in some persons. *Neuroscience*. 2011;191:46–54. doi: 10.1016/j.neuroscience.2011.03.061. [PubMed: 21600269]
171. Luchetti S, Bossers K, Van de Bilt S, Agrapart V, Morales RR, Frajese GV et al. Neurosteroid biosynthetic pathways changes in prefrontal cortex in Alzheimer's disease. *Neurobiol Aging*. 2011;32(11):1964–76. doi:10.1016/j.neurobiolaging.2009.12.014. [PubMed: 20045216]
172. Schiller CE, Meltzer-Brody S, Rubinow DR. The role of reproductive hormones in postpartum depression. *CNS Spectr*. 2014:1–12. doi:10.1017/s1092852914000480.
173. Schiller CE, Schmidt PJ, Rubinow DR. Allopregnanolone as a mediator of affective switching in reproductive mood disorders. *Psychopharmacology (Berl)*. 2014;231(17):3557–67. doi:10.1007/s00213014-3599-x.
174. Paul SM, Purdy RH. Neuroactive steroids. *FASEB journal: official publication of the Federation of American Societies for Experimental Biology*. 1992;6(6):2311–22. [PubMed: 1347506]
175. Baulieu EE. Steroid hormones in the brain: several mechanisms? In: Fuxe F, Gustaffson JA, Wetterberg L, editors. *Steroid Hormone Regulation of the Brain*. Oxford, UK: Pergamon Press; 1981 p. 3–14.
176. Rupprecht R Neuroactive steroids: mechanisms of action and neuropsychopharmacological properties. *Psychoneuroendocrinology*. 2003;28(2):139–68. doi:S0306453002000641 [pii]. [PubMed: 12510009]
177. Avoli M, Krnjevic K. The Long and Winding Road to Gamma-Amino-Butyric Acid as Neurotransmitter. *The Canadian journal of neurological sciences Le journal canadien des sciences neurologiques*. 2016;43(2):219–26. doi:10.1017/cjn.2015.333. [PubMed: 26763167]
178. Callachan H, Cottrell GA, Hather NY, Lambert JJ, Nooney JM, Peters JA. Modulation of the GABAA receptor by progesterone metabolites. *Proceedings of the Royal Society of London Series B, Biological sciences*. 1987;231(1264):359–69.
179. Lambert JJ, Peters JA, Sturgess NC, Hales TG. Steroid modulation of the GABAA receptor complex: electrophysiological studies. *Ciba Foundation symposium*. 1990;153:56–71; discussion –82. [PubMed: 1963400]
180. Olsen RW, Sieghart W. International Union of Pharmacology. LXX. Subtypes of gamma-aminobutyric acid(A) receptors: classification on the basis of subunit composition, pharmacology, and function. Update. *Pharmacol Rev*. 2008;60(3):243–60. doi:10.1124/pr.108.00505. [PubMed: 18790874]
181. Semyanov A, Walker MC, Kullmann DM. GABA uptake regulates cortical excitability via cell type-specific tonic inhibition. *Nat Neurosci*. 2003;6(5):484–90. doi: 10.1038/nn1043. [PubMed: 12679782]
182. Stell BM, Brickley SG, Tang CY, Farrant M, Mody I. Neuroactive steroids reduce neuronal excitability by selectively enhancing tonic inhibition mediated by delta subunit-containing

- GABAA receptors. *Proc Natl Acad Sci U S A*. 2003;100(24):14439–44. doi:10.1073/pnas.2435457100 2435457100 [pii]. [PubMed: 14623958]
183. Parizek A, Hill M, Kancheva R, Havlikova H, Kancheva L, Cindr J et al. Neuroactive pregnanolone isomers during pregnancy. *J Clin Endocrinol Metab*. 2005;90(1):395–403. doi:10.1210/jc.2004-0444. [PubMed: 15486056]
184. Mostallino MC, Sanna E, Concas A, Biggio G, Follesa P. Plasticity and function of extrasynaptic GABA(A) receptors during pregnancy and after delivery. *Psychoneuroendocrinology*. 2009. doi:S03064530(09)00203-0 [pii] 10.1016/j.psyneuen.2009.06.013.
185. Zhao C, Gammie SC. Glutamate, GABA, and glutamine are synchronously upregulated in the mouse lateral septum during the postpartum period. *Brain Res*. 2014;1591:53–62. doi:10.1016/j.brainres.2014.10.023. [PubMed: 25451092]
186. Smolen A, Smolen TN, Han PC. Alterations in regional brain GABA concentration and turnover during pregnancy. *Pharmacol Biochem Behav*. 1993;44(1):63–9. [PubMed: 8430130]
187. Maguire J, Mody I. Steroid hormone fluctuations and GABA(A)R plasticity. *Psychoneuroendocrinology*. 2009;34 Suppl 1:S84–90. doi:10.1016/j.psyneuen.2009.06.019. [PubMed: 19632051]
188. Maguire J, Ferando I, Simonsen C, Mody I. Excitability changes related to GABAA receptor plasticity during pregnancy. *J Neurosci*. 2009;29(30):9592–601. doi:10.1523/JNEUROSCI.2162-09.2009. [PubMed: 19641122]
189. Maguire J, Mody I. GABA(A)R plasticity during pregnancy: relevance to postpartum depression. *Neuron*. 2008;59(2):207–13. doi:S0896-6273(08)00537-0 [pii] 10.1016/j.neuron.2008.06.019. [PubMed: 18667149]
190. Epperson CN, Gueorguieva R, Czarkowski KA, Stiklus S, Sellers E, Krystal JH et al. Preliminary evidence of reduced occipital GABA concentrations in puerperal women: a 1H-MRS study. *Psychopharmacology (Berl)*. 2006;186(3):425–33. doi:10.1007/s00213-006-0313-7.
191. Nappi RE, Petraglia F, Luisi S, Polatti F, Farina C, Genazzani AR. Serum allopregnanolone in women with postpartum “blues”. *Obstet Gynecol*. 2001;97(1):77–80. [PubMed: 11152912]
192. Osborne LM, Gispén F, Sanyal A, Yenokyan G, Meilman S, Payne JL. Lower allopregnanolone during pregnancy predicts postpartum depression: An exploratory study. *Psychoneuroendocrinology*. 2017;79:116–21. doi:10.1016/j.psyneuen.2017.02.012. [PubMed: 28278440]
193. Williams JB. A structured interview guide for the Hamilton Depression Rating Scale. *Arch Gen Psychiatry*. 1988;45(8):742–7. [PubMed: 3395203]
194. Sanacora G, Mason GF, Rothman DL, Behar KL, Hyder F, Petroff OA et al. Reduced cortical gamma-aminobutyric acid levels in depressed patients determined by proton magnetic resonance spectroscopy. *Arch Gen Psychiatry*. 1999;56(11): 1043–7. [PubMed: 10565505]
195. Epperson CN, Haga K, Mason GF, Sellers E, Gueorguieva R, Zhang W et al. Cortical gamma-aminobutyric acid levels across the menstrual cycle in healthy women and those with premenstrual dysphoric disorder: a proton magnetic resonance spectroscopy study. *Arch Gen Psychiatry*. 2002;59(9):851–8. [PubMed: 12215085]
196. Sanacora G, Mason GF, Rothman DL, Krystal JH. Increased occipital cortex GABA concentrations in depressed patients after therapy with selective serotonin reuptake inhibitors. *Am J Psychiatry*. 2002;159(4):663–5. [PubMed: 11925309]
197. Sanacora G, Gueorguieva R, Epperson CN, Wu YT, Appel M, Rothman DL et al. Subtype-specific alterations of gamma-aminobutyric acid and glutamate in patients with major depression. *Arch Gen Psychiatry*. 2004;61(7):705–13. doi:10.1001/archpsyc.61.7.705. [PubMed: 15237082]
198. Gabbay V, Mao X, Klein RG, Ely BA, Babb JS, Panzer AM et al. Anterior cingulate cortex gamma-aminobutyric acid in depressed adolescents: relationship to anhedonia. *Arch Gen Psychiatry*. 2012;69(2):139–49. doi: 10.1001/archgenpsychiatry.2011.131. [PubMed: 21969419]
199. Gabbay V, Bradley KA, Mao X, Ostrover R, Kang G, Shungu DC. Anterior cingulate cortex gamma-aminobutyric acid deficits in youth with depression. *Translational psychiatry*. 2017;7(8):e1216. doi:10.1038/tp.2017.187. [PubMed: 28892070]
200. van BroeRhoven F, Bächström T, van Luijtelaar G, Buitelaar JK, Smits P, VeAes RJ. Effects of allopregnanolone on sedation in men, and in women on oral contraceptives.

- Psychoneuroendocrinology. 2007;32(5):555–64. doi:10.1016/j.psyneuen.2007.03.009. [PubMed: 17470385]
201. Timby E, Balgard M, Nyberg S, Spigset O, Andersson A, PoranHewicz-Asplund J et al. Pharmacologic and behavioral effects of allopregnanolone in healthy women. *Psychopharmacology (Berl)*. 2006;186(3):414–24. doi:10.1007/s00213-005-0148-7.
  202. Kash K, Bäckström T, Nilsson L-G, Sundström-Poromaa I. Allopregnanolone impairs episodic memory in healthy women. *Psychopharmacology*. 2008;199(2):161. doi: 10.1007/s00213-008-1150-7. [PubMed: 18551282]
  203. Kash K, Bachstrom T, Lundgren P, Sundstrom Poromaa I. Allopregnanolone has no effect on startle response and prepulse inhibition of startle response in patients with premenstrual dysphoric disorder or healthy controls. *Pharmacol Biochem Behav*. 2009;92(4):608–13. doi: 10.1016/j.pbb.2009.02.014. [PubMed: 19268499]
  204. Timby E, Hedstrom H, Bachstrom T, Sundstrom-Poromaa I, Nyberg S, Bixo M. Allopregnanolone, a GABAA receptor agonist, decreases gonadotropin levels in women. A preliminary study. *Gynecol Endocrinol*. 2011;27(12):1087–93. doi: 10.3109/09513590.2010.540603. [PubMed: 21190418]
  205. Bialer M, Johannessen SI, Levy RH, Perucca E, Tomson T, White HS. Progress report on new antiepileptic drugs: A summary of the Twelfth Eilat Conference (EILAT XII). *Epilepsy Res*. 2015;111:85–141. doi:10.1016/j.eplepsyres.2015.01.001. [PubMed: 25769377]
  206. Kanes S, Colquhoun H, Gunduz-Bruce H, Raines S, Arnold R, Schacterle A et al. Brexanolone (SAGE-547 injection) in post-partum depression: a randomised controlled trial. *Lancet (London, England)*. 2017;390(10093):480–9. doi:10.1016/S0140-6736(17)31264-3.
  207. Kanes SJ, Colquhoun H, Doherty J, Raines S, Hoffmann E, Rubinow DR et al. Open-label, proof-of-concept study of brexanolone in the treatment of severe postpartum depression. *Human psychopharmacology*. 2017;32(2). doi:10.1002/hup.2576.
  208. Luisi S, Petraglia F, Benedetto C, Nappi RE, Bernardi F, Fadalti M 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. doi:10.1210/jcem.85.7.6675. [PubMed: 10902789]
  209. Meltzer-Brody S, Colquhoun H, Riesenberg R, Epperson CN, Deligiannidis KM, Rubinow DR et al. Efficacy and safety of brexanolone iv, a GABAA receptor modulator, in women with postpartum depression: results from two double-blind, randomised, placebo-controlled phase 3 studies. *Lancet (London, England)*. 2018. doi:10.1016/S0140-6736(18)31551-4.
  210. Administration USFaD. 2018 Meeting Materials, Psychopharmacologic Drugs Advisory Committee Meeting. U.S. Food and Drug Administration, Silver Spring, MD 2018 <https://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/PsychopharmacologicDrugsAdvisoryCommittee/ucm598677.htm?fbclid=IwAR2bq2yaYOqzn0u-p0yAFjsgVWNwalq87l7ZzQO8cuJ3SQ8eLlfgrewIdj4>. Accessed November 30 2018.
  211. Therapeutics S Sage Therapeutics Receives Notification of PDUFA Extension for ZULRESSO™ (brexanolone) Injection. Cambridge, MA 2018.
  212. Newton ER, Hale TW. Drugs in Breast Milk. *Clin Obstet Gynecol*. 2015;58(4):868–84. doi: 10.1097/grf.000000000000142. [PubMed: 26457856]
  213. Martinez Botella G, Salituro FG, Harrison BL, Beresis RT, Bai Z, Blanco MJ et al. Neuroactive Steroids. 2. 3alpha-Hydroxy-3beta-methyl-21-(4-cyano-1H-pyrazol-1'-yl)-19-nor-5beta-pregnan-20-one (SAGE-217): A Clinical Next Generation Neuroactive Steroid Positive Allosteric Modulator of the (gamma-Aminobutyric Acid)A Receptor. *J Med Chem*. 2017;60(18):7810–9. doi:10.1021/acs.jmedchem.7b00846. [PubMed: 28753313]
  214. Therapeutics S Sage Therapeutics Announces SAGE-217 Meets Primary and Secondary Endpoints in Phase 3 Clinical Trial in Postpartum Depression, Cambridge, MA 2019 <https://investor.sagerx.com/news-releases/news-release-details/sage-therapeutics-announces-sage-217-meets-primary-and-secondary>. Accessed January 7, 2019 2019.
  215. Pharmaceuticals M. Marinus Pharmaceuticals Announces Positive Ganaxolone Data in Women with Postpartum Depression. 2018 <https://globenewswire.com/news-release/2018/12/10/1664282/0/en/Marinus-Pharmaceuticals-Announces-Positive-Ganaxolone-Data-in-Women-With-Postpartum-Depression.html>. Accessed January 7, 2019 2019.

216. Osborne LM, Hermann A, Burt V, Driscoll K, Fitelson E, Meltzer-Brody S et al. Reproductive Psychiatry: The Gap Between Clinical Need and Education. *Am J Psychiatry*. 2015;172(10):946–8. doi:10.1176/appi.ajp.2015.15060837. [PubMed: 26423479]
217. Kashani L, Eslatmanesh S, Saedi N, Niroomand N, Ebrahimi M, Hosseinian M et al. Comparison of Saffron versus Fluoxetine in Treatment of Mild to Moderate Postpartum Depression: A Double-Blind, Randomized Clinical Trial. *Pharmacopsychiatry*. 2017;50(2):64–8. doi: 10.1055/s-0042-115306. [PubMed: 27595298]
218. Yonkers KA, Gotman N, Smith MV, Forray A, Belanger K, Brunetto WL et al. Does antidepressant use attenuate the risk of a major depressive episode in pregnancy? *Epidemiology*. 2011;22(6):848–54. doi:10.1097/EDE.0b013e3182306847. [PubMed: 21900825]
219. Xu Y, Li Y, Huang X, Chen D, She B, Ma D. Single bolus low-dose of ketamine does not prevent postpartum depression: a randomized, double-blind, placebo-controlled, prospective clinical trial. *Archives of gynecology and obstetrics*. 2017;295(5): 1167–74. doi: 10.1007/s00404-017-4334-8. [PubMed: 28357557]



**Key Points:**

- Pharmacotherapies are available for the treatment of postpartum depression, but randomized clinical trial data to guide treatment remains limited.
- Evidence supporting the role of neuroactive steroids and GABA in the pathophysiology of postpartum depression has led to the investigation of synthetic neuroactive steroids and their analogs as potential treatment for postpartum depression.
- Recent randomized clinical trial data on brexanolone, a GABA<sub>A</sub> receptor modulator, provides evidence of efficacy in the treatment of postpartum depression; this has led to the drug being registered with the US Food and Drug Administration. SAGE-217, an allopregnanolone analog, has also been reported to have positive results in the treatment of postpartum depression.

**TABLE 1:****Randomized Controlled Trials of Antidepressants in the Acute Treatment of Postpartum Depression**

<b>Study</b>	<b>Intervention</b>	<b>Trial duration</b>	<b>Total sample size</b>	<b>Summary of findings</b>
Appleby et al. (1997)[70]	Fluoxetine, placebo, with each group added to either 1 or 6 counseling sessions	12 weeks	87	There was additional benefit from six counseling sessions or adding fluoxetine, but no detected advantage to adding both or one counseling session.
Misri et al. (2004)[69]	Paroxetine alone, paroxetine plus cognitive behavioral therapy (CBT)	12 weeks	35	Paroxetine monotherapy group and paroxetine plus CBT group were efficacious, but there was no additional benefit derived from the addition of the CBT.
Wisner et al. (2006) [68]	Sertraline, Nortriptyline	8 week comparative with 16 week continuation phase	109	There were no significant differences in response or remission between the two antidepressants at 4, 8, and 24 weeks postpartum.
Yonkers et al. (2008) [67]	Paroxetine, placebo	8 weeks	70	Paroxetine showed significantly higher remission rates versus placebo (37% compared to 15%). The paroxetine group did not show significantly higher response rates than placebo (43% compared to 31%).
Sharp et al. (2010) [66]	Various antidepressants (mostly selective serotonin reuptake inhibitors), supportive counseling	18 weeks	254	At 4 weeks postpartum, participants receiving antidepressants showed significant symptom resolution, however at 18 weeks postpartum there was no significant difference between those receiving antidepressants and those receiving supportive counseling.
Bloch et al. (2012) [65]	Sertraline, placebo, with each group added to brief psychodynamic therapy	8 weeks	40	Sertraline did not add additional benefit to brief psychodynamic therapy.
Hantsoo et al. (2014) [64]	Sertraline, placebo	6 weeks	38	The benefits of sertraline were more pronounced when PPD onset was within 4 weeks of childbirth.
Milgrom et al. (2015) [63]	Sertraline, specialized CBT program	12 weeks	45	Specialized CBT program for PPD was superior as monotherapy when compared with sertraline. The trial is unique in that it included a statistically independent evaluation of CBT monotherapy for PPD compared to both antidepressant and combination therapy.
Kashani et al. (2017) [217]	Fluoxetine, saffron	6 weeks	68	The response rates were not significantly different between the two groups.

**TABLE 2:**

## Pharmacotherapy Studies in the Prevention of Postpartum Depression

Study	Design	Study duration	Intervention	Total sample size	Summary of findings
Wisner et al. (2001) [86]	Randomized clinical trial	20 weeks	Nortriptyline, placebo	56	No significant differences were detected in rates of recurrence or time to relapse between women receiving nortriptyline and women receiving placebo.
Wisner et al. (2004) [88]	Randomized clinical trial	17 weeks	Sertraline, placebo	25	Treatment with sertraline was associated with fewer depressive relapses and a significantly longer time to relapse.
Yonkers et al. (2011) [218]	Prospective cohort	variable	Various	778	There was no clear difference in risk of a depressive episode in pregnancy between women who took antidepressants and women who did not.
Khazaie et al. (2013) [89]	Randomized clinical trial	6 weeks	Diphenhydraminamine, trazodone, placebo	54	Both diphenhydramine and trazodone were effective in preventing postpartum depressive symptoms at 2 and 6 weeks after delivery. No differences in depressive symptoms were observed between the trazodone and diphenhydramine groups.
Xu et al. (2017) [219]	Randomized clinical trial	6 weeks	Single intra-operative low-dose intravenous ketamine, placebo	330	No significant differences were detected in the prevalence of PPD between the two groups at 3 days and 6 weeks post-delivery.