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

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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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CONFLICT OF INTEREST

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a 3β-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]. Co-morbid 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 17β-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 17β-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 17β-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], adrenocorticotropic 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 γ-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 (3α, 5β-tetrahydroprogesterone; 3α, 5α-THP), pregnanolone (3α, 5β-tetrahydroprogesterone; 3α, 5β-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-$_A$ 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-$_A$R) or tonic (high affinity; via extrasynaptic GABA-$_A$R) and is determined by the location of and subunit composition of the pentameric GABA-$_A$R channel [180, 181]. Through their modulation of GABA-$_A$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-$_A$R subunit composition and excitability in addition to changes in regional GABA concentrations across the peripartum period [184–188]. A groundbreaking study in GABA-$_A$R δ-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-$_A$R δ- and γ2-subunits, respectively, which rebounded postpartum[189]. However, GABA-$_A$R δ-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-$_A$R δ-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-$_A$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-$_A$ 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 $GABA_AR$ 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-β-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_{17} total score ≥ 20 at study entry. Dosing of brexanolone iv began with a twelve-hour titration period: 21.5 μg/kg/hr. (hour 0–4), then 43 μg/kg/hr. (hour 4–8), then 64.5 μg/kg/hr. (hour 8–12). Maintenance dosing of 8 6 μg/kg/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 μg/kg/hr. (hour 48–52), 43 μg/kg/hr. (hour 52–56), and finally 21.5 μg/kg/hr. (hour 56–60). The primary outcomes were safety and tolerability and the hey efficacy measure was the change in HAM-D_{17} 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_{17} total score declined from a baseline preinfusion mean of 26.5 ± 4.1 to post-infusion score (hour 60) of 1.8 ± 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_{17} total score ≥ 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 μg/kg/hr. (hour 0–4), 60 μg/kg/hr. (hour 4–24), then 90 μg/kg/hr. (hour 24–52), 60 μg/kg/hr. (hour 52–56), 30 μg/kg/hr. (hour 56–60h). The primary outcome measure was the change in HAM-D_{17} 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_{17} 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_{17}≤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_{17} total score ≥ 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_{17} 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 μg/kg/hr. (BRX60), and brexanolone iv 90 μg/kg/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 μg/kg/hr. instead of 90 μg/kg/hr. When comparing HAM-D_{17} 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_{17} 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_{17} 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_{17} remission and response, Clinical Global Impression Scale-Global Improvement response, HAM-D_{17} 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 $GABA_A$-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_{17} 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_{17} 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_{17}≤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 3β-methylated synthetic analog of allopregnanolone, ganaxolone, in PPD. Ganaxolone is an extrasynaptic and synaptic $GABA_A$-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 μg/kg/h. The 140 μg/kg/h dose group (n=10) demonstrated the most robust results, with a clinically meaningful 5.6-point reduction in HAM-D_{17} 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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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 $GABA_A$ 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

Study	Intervention	Trial duration	Total sample size	Summary of findings
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	Diphenhydraminemine, 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.