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Pharmacotherapy of postpartum depression: an update

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Abstract

Introduction—Postpartum depression (PPD) is a common and serious illness that affects up to 14% of women in the first month after childbirth. We present an update on the pharmacologic treatment of PPD, although there continues to be a lack of large, randomized controlled trials (RCTs).

Areas covered—A review of the literature on the use of antidepressants, hormonal supplements and omega-3 fatty acids for the prevention and the treatment of PPD published since the original review in 2009 and the authors' opinion on the current status of the pharmacological treatment of PPD are covered. An electronic search was performed by using PubMed, Medline and PsychINFO. Inclusion criteria were: i) empirical articles in peer-reviewed English-language journals; ii) well-validated measures of depression; and iii) a uniform scoring system for depression among the sample.

Expert opinion—Since the last Expert Opinion review, four antidepressant treatment studies and one prevention study of PPD have been published. Six RCTs evaluating the use of omega-3 fatty acids (four for prevention and two for treatment) have been published. There continues to be lack of data regarding the pharmacotherapy of PPD. However, serotonin reuptake inhibitors should be considered first-line for women with PPD after it has been determined that the proper diagnosis is not bipolar disorder. It is important to individualize treatment for women with PPD and consider the risks and benefits of treatment while breastfeeding.

Keywords

omega-3 fatty acids; pharmacotherapy; postpartum depression; prevention; treatment

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1. Introduction

Postpartum depression (PPD) is a common and serious disorder that affects women of all demographic and cultural backgrounds. In May 2013, the Diagnostic and Statistical Manual of Mental Disorders (5th ed.; *DSM–5*; American Psychiatric Association, 2013) was published with a modified specifier for major depressive episodes ‘with peripartum onset’ [1]. The previous DSMs, 4th (DSM-IV TR) time criterion specifier ‘with postpartum onset’ was applied to a major depressive episode onset within 4 weeks after birth [2]. Despite evidence that the time criterion should be expanded past 4 weeks postpartum [3], the new DSM-5 specifier is used when the onset of depressive symptoms occurs during pregnancy or in the 4 weeks following delivery. Although the specifier is important for standardizing inclusion for research protocols, it is less important from a public health standpoint, since depression impairs function at any point in motherhood. There is no true consensus as to what time frame constitutes the postpartum period [4]. For consistency with the previous Expert Opinion review [5], we will describe treatment studies that include the onset of depression in women through 12 months following birth.

Postpartum depressive episodes do not present as substantially different from depressive episodes outside of the postpartum period except that obsessions and ruminations focusing on the newborn and fitness for mothering are more common [6-8]. Postpartum anxiety often presents in addition to depression, and when both conditions coexist, the presentation is often more severe [9]. In the largest US PPD screening study to date (n = 10,000), 66% of the women with an Edinburgh Postnatal Depression Scale (EPDS) score greater than or equal to 10 sample had a comorbid diagnosis, most commonly anxiety [10]. PPD is one of the strongest predictors of suicidal ideation in new mothers [11].

The reported period prevalence of PPD varies widely. Part of the discrepancy comes from reporting both major and minor depressive syndromes as well as the large time range that is considered postpartum (up to 12 months postpartum in some studies). When the 3-month time window is considered and both major and minor depressions are included, the period prevalence is 19.2% and the point prevalence is 12.9% [12]. When major depression alone is considered, the 3-month postpartum period prevalence is 7.1% (4.7% point prevalence) and the 12-month period prevalence is 21.9% (3.9% point prevalence) [4,12]. The wide confidence intervals, indicating significant variability, make exact estimates difficult. Depending on the cut-off score used for various depression severity ratings, recent data suggest that 7 – 14% of women in the general population will screen positive for depression at 4 – 6 weeks postpartum [10]. Although the highest risk of PPD onset is within 4 weeks postpartum, women remain at increased risk throughout the first 5 months after child-birth [13]. Interestingly, while 40% of postpartum women with depression report the episode onset postpartum, 33.4% report antenatal onset and 26.5% report onset before pregnancy [10]. Women with PPD are more likely to have future, recurrent depressive episodes compared to controls. In one longitudinal cohort study, women with PPD were six times more likely to experience future depressive symptoms than matched controls who did not suffer from PPD after childbirth [14].

The biological underpinnings of PPD are an active area of investigation. Some women appear to be sensitive to the normal hormonal fluctuations during pregnancy and postpartum such that declining estradiol (E2) and increases in monoamine oxidase enzymes result in poorer mood [15,16]. There are also some empirical data to support the hypothesis that a dysregulation of the hypothalamic–pituitary–adrenal (HPA) axis during pregnancy may predict a hyporesponsive HPA axis and depression during the postnatal period [17]. Genetic mechanisms have been investigated as well. Women with serotonin gene polymorphisms may be at increased risk for depression in the early (< 8 weeks) postpartum period but conflicting results make these data premature for clinical use at this time [18,19]. Women at risk for PPD may have an increased sensitivity to estrogen-based DNA methylation [20]. Two polymorphisms of the estrogen receptor α gene (ESR1) were strongly associated with PPD in another study [21], although replication in a larger sample is necessary for confirmation of these results.

Given the considerable morbidity and mortality associated with PPD, many investigators have sought to phenotype those women who are at greatest risk for depression during the perinatal period. Low socioeconomic status may be the strongest demographic risk factor for PPD as it is a proxy for other risks such as race/ethnicity, age and education [4]. Other risk factors include a personal history of depression or anxiety, previous PPD, and lack of social support [17]. In a prospective cohort study, 80% of women who discontinued antidepressants during pregnancy relapsed within in the first-year postpartum [22]. In contrast to previous studies [23,24], Robertson-Blackmore [25] found that childhood trauma increased the risk of antenatal depression but not PPD. In favor of the theory that some women are vulnerable to developing affective instability in the context of hormonal changes, in a recent retrospective case–control study, premenstrual mood disorders were identified as risk factors for PPD (odds ratio 1.97) [26].

PPD needs to be distinguished from other mental health conditions that affect the postnatal woman. The baby blues is a common, transient syndrome seen in women in the first-week postpartum. Most investigators have found that over 50% of women experience this syndrome [27]. Mood lability is common and generally resolves in 1 – 2 weeks without intervention. In addition, those who experience more severe baby blues are more likely to go on to meet criteria for PPD [28]. PPD should also be differentiated from postpartum psychosis that is a rare (1/1000 births) psychiatric emergency for which women present with delusions, hallucinations and a disorganized thought process [29]. Hospitalization is often necessary for women suffering from postpartum psychosis, as the risk for self-harm or infanticide is elevated [30].

The risks of PPD to the family system are numerous and serious. For example, maternal PPD increases the risk of paternal PPD and maladaptive development in infants and children [31-33]. The new mother is usually the primary care-taker for the infant and must be psychologically stable to keep the infant safe. Child abuse and neglect can be more common in women with postpartum depressive symptoms [34] possibly because, in some studies, childhood trauma is a risk factor for the development of PPD, perpetuating a cycle of victimization [23,24,35]. However, as stated earlier, not all studies support that childhood

abuse is a risk factor for PPD. Lastly, women with PPD are less likely to breastfeed, which is an ideal source of nutrition and supports maternal-infant attachment [36,37].

Several states mandate screening for perinatal depression during obstetrical care. However, if a woman does not attend this visit or she lives in a state without mandatory screening, she may not be identified as having PPD. Not surprisingly, women with depression are more likely to present to their obstetrician with a physical symptom rather than a psychological symptom that renders recognition of depression by the obstetrics provider less likely [38]. Screening can be done quickly and accurately with a number of scales but the EPDS [39] is most often recommended. The original publication regarding the EPDS reported a sensitivity of 86% and a specificity of 78% for a score 13 or higher and a sensitivity of 85% and a specificity of 77% for a score 10 or higher. More recently, a positive EPDS screen of 10 or greater was associated with an Axis I disorder (most commonly unipolar depression) in 98% of women screened [10]. However, since some positive screens will actually lead to a primary anxiety or bipolar diagnosis, screening should be followed by a diagnostic exam. Additional screening with the Mood Disorders Questionnaire [40] is suggested [41]. As comorbidity is known to complicate treatment course and response, it is important to identify comorbid disorders in women with PPD [42].

More is known about patient acceptability of depression treatments during pregnancy than postpartum [43]. Although the postpartum period is a time for increased risk of depression, women are less likely to be taking an antidepressant postpartum than non-perinatal women [44]. Women with a history of depression prefer antidepressants to psychotherapy for PPD and breastfeeding women tend to prefer psychotherapy [45]. A more recent study found that women with antenatal and PPD prefer a combination of medication and psychotherapy [46]. Asking women how much participation they would like to take in treatment decision-making is important [46].

The initial Expert Opinion review [5] evaluated 19 journal articles that met the following inclusion criteria: i) empirical articles in peer-reviewed English language journals; ii) well-validated measures of depression; and iii) a uniform scoring system for depression among the sample. Seven articles addressed the efficacy of antidepressants or hormonal supplements for the *prevention* of PPD and 12 articles examined the efficacy of antidepressants or hormonal supplements for the *treatment* of PPD. The authors concluded that antidepressants were efficacious for women with PPD with the most compelling data for serotonin reuptake inhibitors (SSRIs), particularly, fluoxetine, paroxetine and sertraline. There was not enough data on hormonal supplements to make a recommendation regarding their use. Paroxetine and sertraline were recommended as agents of choice in breastfeeding women. The purpose of this review on the pharmacotherapy of PPD is to update this Expert Opinion, taking into account the additional published literature over the past 4 years.

2. Method

An electronic search was performed using PubMed, Medline and PsychINFO. Articles were identified from January 2009 to December 2013 that contained the key terms used in the original review, including depression, depressive illness, postpartum, postnatal, treatment,

prevention, therapy, pharmacotherapy, antidepressant, hormonal therapy, estrogen and progesterone. Inclusion criteria were: i) empirical articles in peer-reviewed English-language journals; ii) well-validated measures of depression; and iii) a uniform scoring system for depression among the sample.

3. Results

Since the last Expert Opinion review, no new antidepressant or hormonal supplement *prevention* trials were published. An additional four antidepressant *treatment* studies have been published (Table 1). In addition, one meta-analysis was published evaluating treatment studies and one for prevention studies of PPD, which are useful to note as they combine all data to date. Six randomized controlled trials (RCTs) evaluating the use of omega-3 fatty acids (four for treatment Table 2 and two for prevention Table 3) have been published and are reviewed.

3.1 Antidepressants and prevention of PPD

PPD prevention programs fall into one of three main categories: universal (all pregnant women), selective (women with specific risk factors) and indicated (symptomatic) [4]. While a number of studies evaluated non-pharmacologic PPD prevention strategies [47], no new human studies were found using antidepressants for the prevention of PPD.

3.2 Antidepressants and treatment of PPD

3.2.1 Open-label trials—Fifteen women with PPD onset within 12 months of child-birth completed a 10-week open-label study of citalopram [48]. Ninety-three percent of subjects were responders (50% or greater reduction in Montgomery–Asberg Depression Rating Scale [MADRS] scores). The mean number of weeks to remission (MADRS score of 10 or less) was 7.23 (SD 1.68). The citalopram was started at a dose of 10 mg and increased to 20 mg over 10 weeks based on subject ratings. The authors do not indicate why such a low dose of citalopram was chosen although in one subject the dose was increased to 40 mg and in another subject quetiapine was added, both for anxiety symptoms. The subjects in this study achieved improvement on a low SSRI antidepressant dose but it took almost 8 weeks for symptoms to remit. Open-label trials often have high response rates, so an RCT would be helpful to confirm these results.

3.2.2 Randomized controlled trials—In a single-center, 6-week, randomized double-blind trial of sertraline for 36 women with PPD, sertraline was significantly more effective than placebo [49]. The trial design included a 1-week placebo lead-in. PPD was defined as a depressive episode that onset within 3 months postpartum with antenatal onset excluded. Sertraline or placebo was titrated from 50 to 200 mg as deemed clinically necessary. Compared to women in the placebo group, a greater proportion of women in the sertraline group met study criteria for treatment response (59 vs 26%, $p = 0.05$). A *post hoc* analysis restricted to subjects with PPD onset within 4 weeks of childbirth showed an even larger differential in the proportion of responders between the antidepressant and placebo groups (50 vs 6.7%, $p = 0.02$). In this sample, women with earlier onset PPD had a shorter duration of illness and a greater incidence of past psychiatric diagnosis but this was not statistically

significant. If confirmed in a larger sample, this may suggest that women with PPD onset acutely after childbirth, who develop depression in the context of neuroactive steroid withdrawal, may have a different disease course from those who develop PPD at later time points.

A randomized, 18-week trial compared antidepressants (various antidepressants, mostly SSRIs) prescribed by a general practitioner to general supportive care and listening visits by a trained research health visitor in 254 women [50]. PPD onset was within 6 months postpartum. Women were randomized to medication or general supportive care for 4 weeks. After the acute phase, the listening visits were started and women could at any time choose to change or add the alternate treatment. Prior to trial entry, women reported a preference to be randomized to listening visits over medication. EPDS score was the main outcome. At 4 weeks, women were twice as likely to have responded (EPDS < 13) on antidepressants compared to those randomized to listening visits, which was general supportive care for the acute phase (45 vs 20%, OR 3.4 [95% CI 1.8 – 6.5], $p < 0.001$). At 18 weeks, there was no difference between women originally randomized to medication versus listening visits but many women were receiving both interventions by study end. These data suggest that symptom improvement is more rapid in women who receive antidepressant treatment and that antidepressant medications may become acceptable to women who are initially resistant to pharmacotherapy.

Bloch *et al*. [51] conducted a single-center, 8-week, randomized, double-blind placebo-controlled study of sertraline add-on to brief dynamic psychotherapy (BDP) for women suffering mild-to-moderate (MADRS score < 30), first episode PPD. Episode onset was within 2 months postpartum. Sertraline titration was as follows: 25 mg for the first week, 50 mg for 3 weeks, then up to 100 mg for 4 weeks or kept at 50 mg based on the psychiatrist's decision. The mean sertraline dose at 8 weeks was 67.5 ± 21.5 mg. All patients received 12 weeks of BDP starting with the onset of the sertraline titration. Forty women were included in the primary 8-week intent-to-treat analysis. Two women in the active group became hypomanic at week 8. There was no statistically significant difference between groups although the response rate (50% or greater decrease on MADRS or EPDS) was 55% (placebo + BDP) vs 70% (sertraline + BDP) and remission rate (MADRS < 10 or EPDS < 7) was 50% (placebo + BDP) vs 65% (sertraline + BDP). The authors suggested that including women with more severe depression may have led to significant results based on data that shows that the benefits of antidepressants are more striking in more severely depressed populations. Other hypotheses raised by the authors include the possibility that women with low E2 levels may be less medication responsive, that sertraline was dosed too low or that the small sample size may have also impacted the study results. The most likely hypothesis is that the sertraline dose may have been too low for some of the women as many women with PPD need higher doses of sertraline to achieve response [52]. In the first randomized comparative antidepressant trial for PPD, the following sertraline doses were required for the 25 women who achieved remission: 1 ≤ 100 mg/day, 12 = 100 mg/day, 5 = 125 or 150 mg/day and 7 = 200 mg/day [53].

In a qualitative review of RCTs for PPD, trials that looked at an SSRI were compared to trials that used other antidepressants or psychotherapy [54]. In total, six RCTs (n = 595) had

examined an SSRI, including two additional studies since the last Expert Opinion review [50,51]. The authors concludethat SSRI treatment for PPD varied from 43 to 87.5% for some improvement and 37 to 65% for complete symptom remission. Although there was little consistency between studies, the authors conclude there is support for the use of SSRIs for PPD. In one of the largest studies of the treatment of non-perinatal depression, a response rate of 47% and a remission rate of 28 – 33% were achieved with an SSRI [55]. Therefore, the PPD rates of response and remission to a single antidepressant trial are similar to those observed in the non-perinatal population.

3.2.3 Treatment-resistant PPD—What about the other 30 – 40% of women with PPD who do not respond to an initial antidepressant trial? Robakis and Williams [42] published a suggested approach for treatment-resistant depression (TRD) during the perinatal period. The algorithm was intended for both pregnant and postpartum women as they did not publish a separate algorithm for PPD. They base their recommendations on data published for TRD outside of perinatal period and this algorithm has not been specifically tested. The algorithm suggests starting with an SSRI. For women with a partial response, they suggest three trials of augmenting agents before moving to neuromodulation. For women with no response to an SSRI, they suggest three trials of different antidepressants before moving to neuromodulation. This is clearly an area that needs more research. TRD may occur when an inadequate dose of medication is prescribed, when there is a misdiagnosis or when a woman has comorbidities such as substance abuse or anxiety.

3.3 Hormonal treatment of PPD

There is continuing interest in the use of hormones for the treatment of PPD. In women, there are three estrogens: estrone (E1), E2 and estriol (E3). E2, the most potent of the bio-estrogens, promotes neuronal growth and survival, is pro-serotonergic and decreases oxidative stress [56]. Oral estrogens typically are conjugated equine estrogens with a predominance of E1 [57]. Of the bio-identical estrogens, 17-β-E2 has greater ESR affinity than E1 or E3 [58]. Transdermal 17 β-E2 bypasses hepatic metabolism and results in 1:1 ratio of E2 to E1. Since transdermal E2 avoids the induction of hepatic coagulation factor, it does not increase the risk of venothrombolic events as much as conjugated equine estrogens do. It also is more available to the brain. The risk of endometrial cancer occurs in 1% of long-term estrogen users who develop endometrial hyperplasia due to not cycling the endometrium with progesterone. Although decreased milk production can occur, there is negligible passage of transdermal E2 for doses up to 100 mcg/day into breast milk [59].

In a small study that looked at both animals and humans, E2 withdrawal was associated with anhedonia (behavioral despair) in rats but there was no association between E2 levels and negative affect in non-pregnant women is considered high risk for the development of PPD due to a previous history of PPD [60]. However, in women who did develop PPD at 4 weeks postpartum, there was a negative association between daily perinatal salivary E2 levels and negative affect ($r = -0.34$, $p < 0.001$). Other studies have shown an association between depressed affect and E2 levels in women at risk for PPD (Bloch and Sacher). Although there is a current investigation underway of the efficacy of transdermal 17 β-E2 to replicate and

extend a 1996 study by Gregoire *et al*. [61], (personal communication Wisner), there are no new cases or studies published.

3.4 Hormonal prevention of PPD

There were no new hormonal prevention studies. In a retrospective chart review of women receiving depot medroxyprogesterone acetate for birth control prior to hospital discharge (n = 55) compared to women who did not use hormonal contraception (n = 192), there was no statistical significance between EPDS scores at the 6-week postpartum visit (5.02 vs 6.17, p = 0.16) [62].

3.5 Alternative pharmacological treatments for treatment and prevention of PPD

3.5.1 Omega-3 fatty acids—The only alternative pharmacological agent for PPD that has been consistently studied is omega-3 polyunsaturated fatty acids (PUFAs). Docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA) are the preferred sources of omega-3 PUFAs as they are the most biologically available. It is recommended that pregnant women consume at least 300 mg of DHA daily [63]. Thought to increase inflammatory dysregulation, low levels of DHA have been associated with increased rates of PPD in some [64-66] but not all studies [67-69]. For example, in one study, decreased maternal omega-3 fatty acid levels at 28 weeks gestational age are associated with increased EPDS scores at 3 months postpartum [66]. A total of four RCTs have evaluated omega-3 PUFAs supplementation for the prevention of PPD and two RCTS for the treatment of PPD.

3.6 Prevention studies

Llorente *et al*. [70] published the first RCT of 89 women who planned to exclusively breastfeed. Women were supplemented with DHA (200 mg/day) for the first 4 months postpartum. While supplemented women had higher levels of plasma DHA, there was no difference in Beck Depression Inventory (Beck) (BDI) scores at 3 weeks, 2 and 4 months postpartum. Forty-nine women underwent a diagnostic interview and seven (three placebo, four supplemented) met criteria for major depressive disorder (MDD) at some point during the 4 months. As part of an RCT of healthy pregnant women [71], evaluating infant neurodevelopment, 119 pregnant women (mean gestational age at enrollment 16.5 weeks) were treated with placebo, DHA (220 mg) or DHA + arachidonic acid (220 mg each) from week 16 of pregnancy through 3 months postpartum. Depressive symptoms were measured at 6 weeks postpartum using the EPDS. Women were considered depressed if the EPDS score was 12 or greater. Although the study found a low incidence of PPD (n = 7, 5.9%), there was no difference in depression scores between the three groups. The largest trial evaluated DHA (800 mg/day) versus placebo in 2399 pregnant women recruited before 21 weeks gestational age [72]. Women were evaluated at 6 weeks and 6 months postpartum for depressive symptoms defined as an EPDS score 12 or greater. There was no difference in depressive symptoms between groups at either time point. Most recently, in 118 women with a history of antenatal depressive symptoms, there was no difference in the prevention of PPD at 6 – 8 weeks postpartum between supplementing with EPA-rich fish oil, DHA-rich fish oil and soy oil placebo [73,74]. Serum EPA and DHA levels during pregnancy did not predict depression scores (BDI) postpartum. Therefore, DHA supplementation does not

appear to prevent PPD in women with or without antenatal depression. In addition, it does not seem to matter whether supplementation is started before or after the pregnancy.

3.7 Treatment studies

An early study that did not include a placebo group showed that omega-3 PUFAs reduced depression scores by 50% postpartum [75]. However, in a randomized controlled follow-up trial of omega-3 supplementation in perinatal women [76], no difference was seen between active and placebo groups. In that study, postpartum women (n = 36) were within 6 months postpartum and diagnosed with MDD. They had to meet DSM criteria (onset within 4 weeks postpartum) and have EPDS scores greater than or equal to 9 at enrollment. Subjects received 1.9 g/day (1.1 g of EPA and 0.8 g of DHA) in a total of four capsules per day. The placebo was corn oil. All subjects received 8 weeks of manualized supportive psychotherapy with 8 weeks of omega-3s or placebo pills. Similar to the above study, Rees *et al*. [77] evaluated whether omega-3 PUFAs treated both antenatal and PPD, but lasted only 6 weeks. In postpartum women [14], there was no statistically significant difference between treatment and placebo groups. Postpartum women had to have depressive episode onset within 6 months postpartum and at least a score of 13 on the EPDS, 18 on the HAM-D or 25 on the MADRS. Subjects received 6 g/day fish oil (27.3% DHA and 6.9% EPA). High omega-3 intake women were excluded.

The data to date do not support the use of omega-3 PUFAs supplementation for the treatment or prevention of PPD. It has been argued that higher doses of supplementation may have resulted in improved results [74]; however, an earlier trial that assessed different dose ranges did not find differences between low and high doses [75].

4. Conclusion

To date, studies of the efficacy of antidepressants and hormonal supplements for the prevention of PPD remain at three RCTs and four open-label studies. There are eight open-label studies and eight RCTs studies of the efficacy of antidepressants and hormonal supplements for the treatment of PPD. Since the last Expert Opinion review one additional open-label study and three RCTs of antidepressant treatment for PPD have been published. Sertraline has now been studied in three randomized controlled PPD treatment trials [49,51,53]. Wisner *et al*. [53] and Hantsoo *et al*. [49] used doses up to 200 mg/day, while Bloch *et al*. [51] used doses up to 100 mg/day. All three trials used different timing definitions for depression episode onset. Sertraline was an efficacious intervention between 50 and 67% of women responding to treatment at 6 – 8 weeks. There were no recent E2 treatment studies and no new prevention studies published. In a meta-analysis of 22 interventions to prevent PPD onset, 3 were biological [47]. The biological studies included were all examined in the previous Expert Opinion review [5]. There was a 27% reduction in the prevalence of depressive episodes for all interventions combined and categorizing the intervention as psychological or biological did not impact the effect size.

Since antidepressants are controversial during breastfeeding despite their relatively low risk, researchers have looked for alternatives. A randomized controlled study looking at nutritional supplementation with selenium during pregnancy did not find a significant

impact on the prevention of PPD [78]. One well-studied pharmacological alternative is omega-3 PUFAs. Whether DHA or EPA is more important in supplementation is still a matter of debate. Despite the association with low DHA levels and the development of postpartum depressive symptoms, evidence suggests that DHA supplementation alone is not an efficacious treatment or prevention strategy for PPD.

5. Expert opinion

5.1 General considerations

The change in the DSM-5 specifier to 'peripartum onset' will lead to even more variation in the interpretation of future PPD studies. Since about one-third of women with PPD actually have episode onset during pregnancy, the peripartum specifier is intuitively reasonable. However, the continued restriction to 4 weeks postpartum is not in line with recent data suggesting that risk increases through [13,79] 3 – 5 months postpartum. Accurately defining PPD is important from a research perspective. From a clinical perspective, it may be less important because maternal depression at any point impacts the child's mental health and we recommend following the patient's lead with respect to referring to an episode of MDD as PPD. Either way, women with PPD are more likely to go on to experience other episodes of MDD so prognosis is not drastically altered by calling the illness PPD or a major depressive episode.

With the new DSM-5 specifier, it is important to consider whether there is any evidence that episodes that are identified in the postpartum period should be treated differently from episodes that onset before or during pregnancy. To date, there are no studies that look at whether women respond differently to antidepressants based on the onset of the peripartum episode with the exception of the one study by Hantsoo and colleagues suggesting a preferential treatment response to SSRIs among those women with onset of PPD after delivery but within 4 weeks of childbirth. Future studies should consider that the changing physiology during pregnancy increases antidepressant clearance during the third trimester [80] and that beyond the first 3 weeks postpartum, there is refractory metabolism by the P450 live enzymes such that doses should be started low and titrated more slowly. In fact, it may be wise for most postpartum women to start at the equivalent of 25 mg of sertraline as they are more likely to complain of side effects when starting at what may be considered a typical starting dose for non-parturient women.

When considering how to titrate antidepressants postpartum, it is important to emphasize that an individualized approach is necessary. Since anxiety is commonly seen with PPD and metabolism may be slower in the first few weeks postpartum, starting the antidepressant at a low dose is recommended. Some women will respond to the starting antidepressant dose but most women will need titration over 8 weeks to their optimal dose [53]. In a study by Wisner *et al*. [53], women remitted most commonly at doses of sertraline between 100 and 200 mg.

5.2 Preventive treatment

There remains only one randomized, placebo-controlled trial with positive results for the prevention of PPD [81]. This study evaluated sertraline versus placebo started 24 h after

birth (n = 22). Recurrence rates were 7% (sertraline group) versus 50% (placebo group) (p = 0.02). Without treatment, women with a history of PPD have a 50% chance of relapse [15,15,53,82]. Depending on the severity of the depressive episode, prevention may be indicated or chosen by the patient. The choice of a serotonergic medication makes the most sense given the data that while sertraline decreased the risk of relapse, nortriptyline did not [81,83]. If prevention is indicated, we recommend choosing an SSRI (if no history of medication, choose sertraline), documenting a discussion about the use of medication during breast-feeding and starting right after birth. If a patient has a history of PPD or a non-peripartum depressive episode, it is reasonable to choose the antidepressant to which she had the best response.

5.3 Active treatment

Antidepressants, not hormonal supplements, are first-line for women with moderate-to-severe PPD. Based on the general depression treatment guidelines, women should be continued for at least 9 – 12 months once they have achieved remission of symptoms [84,85]. Augmentation with benzodiazepines, antipsychotics and mood stabilizers may be necessary in complicated or treatment-resistant cases. Hormonal supplements are used less often and psychiatrists are less comfortable pre-scribing hormonal treatments [57,86]. The risk of short-term estrogen therapy is generally low although there are contrain-dications, including, but not limited to, tobacco use, significant cardiovascular disease, a personal or family history of breast cancer or a history of clotting disorders. The appropriate amount of time to maintain estrogen treatment for PPD is unknown. Therefore, based on the current evidence, we do not recommend E2 for the treatment of PPD.

It is important to use quantitative data to monitor improvement. It is a common practice to ask patients how they feel in relation to before they started treatment. However, it is essential to augment a patient's qualitative report with a standard measure of response and remission to better monitor her progress over time [87]. We recommend the use of a patient-based assessment scale paired with the clinician's assessment. At each visit, the patient should fill out the EPDS or another validated perinatal depression scale and the clinician should note the clinical global improvement [88]. This allows for the patient and clinician to track her monthly progress and make decisions together about when to continue or change her plan of care.

5.4 Breastfeeding and antidepressants

The benefits of breastfeeding are well-described [89]. In women who choose to breastfeed, most antidepressants are low risk [90]. All psychotropics pass into breast milk as the same molecular qualities that allow them to pass from the gut through the blood-brain barrier, allow them to passively diffuse to breast milk. There are a few ways to choose an antidepressant for a breastfeeding woman with PPD. One can consider the maternal milk/plasma (M/P) ratio or the relative infant dose (RID). If the M/P ratio is < 1 and/or the RID is < 10%, the infant exposure is likely low. Based on these parameters, citalopram, venlafaxine and fluoxetine should be avoided [90,91] unless a woman has experienced a particularly effective treatment response to these agents. We prefer to consider the clinical data that evaluate infant adverse outcomes when exposed *in vivo* to antidepressants [92]. Based on

clinical data, there are few adverse outcomes reported with antidepressants and breastfeeding with the exception of monoamine oxidase inhibitors for which there is no data. Women should be advised to monitor their infant's behavior before starting the antidepressant to establish a baseline then monitor for irritability, agitation, excessive crying, post-feeding vomiting or sedation after antidepressant initiation. Antidepressant serum level monitoring in infants is not recommended unless there is a clinical suspicion for toxicity. In general, it makes sense to choose an antidepressant based on the expected efficacy and tolerability to the individual patient. We do not recommend pumping at the T_{max} and dumping that milk as this has not been shown to change clinical outcomes. In addition, it gives a confusing message to the patient about the safety of the medication in breastfeeding.

BTL Bibliography

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

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Article highlights

- The definition of postpartum depression (PPD) according to the Diagnostic and Statistical Manual of Mental Disorders (5th ed.) was changed to major depressive episodes ‘with peripartum onset,’ meaning the depressive episode has to start in the 4 weeks surrounding (as opposed to after) childbirth.
- When the 3-month time window is considered and both major and minor depressions are included, the period prevalence is 19.2% and the point prevalence is 12.9%.
- Since the last Expert Opinion review, four antidepressant treatment studies and one prevention study of PPD have been published. Six randomized controlled trials evaluating the use of omega-3 fatty acids (four for prevention and two for treatment) have been published.
- Despite an overall dearth of studies, currently, there is the most data for the use of sertraline for the prevention and treatment of PPD.
- At this time, the evidence does not support the use of omega-3 fatty acids for the prevention and treatment of PPD.
- The risk of breastfeeding while taking a serotonin reuptake inhibitor is relatively low and women can be encouraged to breastfeed while being treated with an antidepressant.

Table 1

New antidepressant treatment studies

Article	Study type	Sample size (N)	Depression definition	Intervention	Duration of treatment	Measures	Outcome/Results
Hantsoo *et al*. 2013 [49]	Randomized controlled	36	DSM-IV-TR criteria for MDD within 3 months postpartum	Sertraline (50–200 mg, based on clinical judgment)	6 weeks	CGI, HAM-D	Response (score of ≤ 10 on HAM-D, at least a 50% decrease in HAM-D score from baseline, and at least a score of 'much improved' on the improvement scale of the CGI): 59% (active) vs 26% (placebo); p = 0.05 Remission (score of ≤ 7 on HAM-D): 63% (active) vs 21% (placebo); p = 0.05
Bloch *et al*. 2012 [51]	Randomized controlled	40	DSM-IV-TR criteria for MDD within 2 months postpartum	BDP concurrent with sertraline (25–100 mg, based on clinical judgment)	8 weeks	EPDS, MADRS	Response (reduction in MADRS score by 50% or more): 70% (active) vs 55% (placebo) Remission (final score of < 10 on the MADRS or score of < 7 on the EPDS): 65% (active) vs 50% (placebo)
Misri *et al*. 2012 [48]	Open-label	15	DSM-IV-TR criteria for MDD within 12 months postpartum and MADRS ≥ 25	Citalopram (10 mg titrated to 20 mg over 10 weeks)	10 weeks	MADRS	Response (reduction in MADRS score by 50% or more): 93%; p < 0.01 Remission (MADRS score of ≤ 10): 93%; mean number of weeks to remission was 7.23 weeks; p < 0.01
Sharp *et al*. 2010 [50]	Randomized controlled	254	International Classification of Diseases version 10 criteria for MDD within 6 months postpartum	Various antidepressants	18 weeks	EPDS	Response (EPDS < 13): 45% (active) vs 20% (placebo); p < 0.001

BDP: Brief dynamic psychotherapy; CGI: Clinical Global Impressions; EPDS: Edinburgh Postnatal Depression Scale; HAM-D: Hamilton Depression Rating Scale; MADRS: Montgomery-Asberg Depression Rating; MDD: Major depressive disorder.

Table 2

Omega-3 prevention studies

Article	Study type	Sample size (N)	Intervention	Duration of treatment	Measures	Outcome/Results
Mozurkewich *et al*. 2013 [74]	Randomized controlled	118	EPA (1060 mg) + DHA (274 mg) or DHA (900 mg) + EPA (180 mg)	Treatment started between 12 and 20 weeks of pregnancy lasting through 8 months postpartum	BDI, EPDS, MINI	No difference between either active and placebo groups
Makrides *et al*. 2010 [72]	Randomized controlled	2399	DHA (800 mg/day)	Treatment started by 21st week of pregnancy lasting through 6 months postpartum	EPDS	No difference between active and placebo groups
Doornbos *et al*. 2009 [71]	Randomized controlled	119	DHA (220 mg/day) or DHA + arachidonic acid (220 mg/day)	Treatment started in 16th week of pregnancy lasting through 3 months postpartum	EPDS	No difference between either active and placebo groups
Llorente *et al*. 2003 [70]	Randomized controlled	89	DHA (200 mg/day)	Treatment started after birth lasting through 4 months postpartum	BDI	No difference between active and placebo groups

BDI: Beck depression inventory; DHA: Docosahexaenoic acid; EPA: Eicosapentaenoic acid; EPDS: Edinburgh Postnatal Depression Scale; MINI: Mini-International Neuropsychiatric Interview.

Table 3

Omega-3 fatty acids treatment studies

Article	Study type	Sample size (N)	Depression definition	Intervention	Duration of treatment	Measures	Outcome/Results
Freeman *et al*. 2008 [76]	Randomized controlled	51	DSM-IV-TR criteria for MDD and EPDS ≥ 9	DHA + EPA (1.9 g/day total, split into 1.1 g of EPA and 0.8 g of DHA)	8 weeks	EPDS, HAM-D	No difference between active and placebo groups
Rees *et al*. 2008 [77]	Randomized controlled	26	DSM-IV-TR criteria for MDD within 6 months postpar tum, EPDS ≥ 13, and either HAMD-17 ≥ 17 or MADRS ≥ 25	DHA + EPA (6.0 g/day total, split into 27.3% DHA and 6.95% EPA)	6 weeks	EPDS, HAMD-17, MADRS	No difference between active and placebo groups

BDP: Brief dynamic psychotherapy; EPDS: Edinburgh Postnatal Depression; HAM-D: Hamilton Rating Scale for Depression; MADRS: Montgomery-Asberg Depression Rating Scale; MDD: Major depressive disorder.