Pharmacologic Treatment of Perinatal Depression

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KEYWORDS

• Depression • Peripartum • Mental health • Medication • Treatment considerations

KEY POINTS

- Clinicians treating pregnant and postpartum women should be familiar with a range of pharmacologic treatment options, gain comfort with prescribing, and know when to consult a mental health provider.
- Treatment decisions should weigh the risks of medication exposure to fetus or infant with the risks of maternal psychiatric illness on the mother and her family.
- Clinicians should communicate to patients that perinatal depression is a treatable medical condition.

BACKGROUND AND PREVALENCE

Perinatal depression, defined as depressive symptoms occurring either during pregnancy (antenatal depression [AND]) or postpartum (postpartum depression [PPD])[1,2] is exceedingly common and has serious implications when not adequately identified and treated. It has been estimated that between 14% and 23% of women experience AND,[3] and up to 22% of women develop PPD within the first 12 months after delivery.[4] Yet, it has also been estimated that only 30% to 50% of women with AND or PPD are identified in clinical settings, and an even smaller number (14%–16%) receive any treatment for their symptoms.[5]

CONSEQUENCES OF PERINATAL DEPRESSION

Untreated AND has been associated with increased risks for preeclampsia and preterm birth, as well as the development of numerous chronic health complications in

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the mother, including diabetes, hypertension, and cardiovascular disease.[6–8] Furthermore, untreated AND is one of the greatest risk factors for the development of PPD.[3,9,10] Untreated PPD has been associated with unplanned weaning or lactation failure, toxic stress of the newborn, impaired bonding and attachment, and can adversely affect the mental and emotional health of the child through school-age.[11–19] PPD is often a trigger for onset of a chronic major depressive disorder, with almost 1 in 3 women continuing to struggle with depressive symptoms at least 4 years after delivery.[20] Most important, PPD is considered to be the greatest risk factor for maternal suicide and infanticide.[21]

WEIGHING THE RISKS: PSYCHOTROPIC MEDICATION AND PERINATAL DEPRESSION

The American Psychiatric Association and American Congress of Obstetrics and Gynecology both recommend either psychotherapy or antidepressant medication as first-line treatment for mild to moderate perinatal depression.[22] Many women express concern about the effects of medication on the fetus or nursing infant,[23] and prefer psychotherapy as the initial approach to their depressive symptoms.[23,24] Both cognitive–behavioral therapy and interpersonal therapy are efficacious treatments for mild to moderate perinatal depression.[25–27] A recent metaanalysis demonstrated that therapies with an interpersonal component (eg, interpersonal therapy) lead to the greatest reduction in depressive symptoms.[28] Interpersonal therapy is a particularly good fit for addressing perinatal depression given its:

1. Time-limited nature,
2. Goal of positively impacting interpersonal functioning, including the mother–infant relationship and relationship with the husband or partner, and
3. Focus on increasing social support more broadly, which is critically important for maternal well-being.[29]

Psychotherapy during the perinatal period should be delivered individually whenever possible because it leads to greater improvement in depressive symptoms compared with group therapy.[28] Although there have not been any randomized controlled trials (RCTs) of psychotherapy versus pharmacotherapy for perinatal depression, epidemiologic data suggest that, for moderate to severe symptoms, psychotherapy alone may not be sufficient, and augmentation with pharmacotherapy ought to be considered.[30] For those receiving both psychotherapy and pharmacotherapy, a multidisciplinary, integrated care team, including the prescribing physician and therapist, is critical for monitoring symptoms and working collaboratively to address both the psychosocial[31] and biological[32] aspects of perinatal depression.

When considering medication use in pregnancy, the thoughtful weighing of potential risks of untreated depressive symptoms in both the mother and developing baby compared with the risk of medication exposure is needed. No decision is completely risk free and the goal of treatment is minimization of risk with efficacy of treatment. All psychotropic medications cross the placenta and no psychotropic medication is approved by the US Food and Drug Administration (FDA) for use during pregnancy.[33] Given that gold standard RCTs for pregnant women and psychotropic medications are not available, we rely on data from case reports, case control studies, and administrative databases.[30] Potential risks to the fetus that must be considered include teratogenicity and neonatal toxicity and/or withdrawal, as well as long-term effects on development. When medication is required, often the best choice is the drug that previously demonstrated good efficacy for the individual, although this choice must be balanced against the safety of the particular drug during pregnancy. Medication

should be titrated to the lowest effective therapeutic dose, with a goal of full symptom remission. As pregnancy progresses, higher doses of psychotropic medication may be required owing to the marked changes in plasma volumes and drug clearance rates during pregnancy. Therefore, collaborative interdisciplinary care among obstetrics, psychiatry, and pediatrics is of utmost importance to ensure the best clinical outcomes.

SELECTIVE SEROTONIN REUPTAKE INHIBITORS, FIRST-LINE PHARMACOLOGIC TREATMENT

Selective serotonin reuptake inhibitors (SSRIs) are usually considered first-line pharmacologic treatment agents for perinatal depression, including both depressive and anxiety symptoms.[34] See **Table 1** for a list of SSRIs and specifics around dosing and unique considerations. SSRIs inhibit the reuptake of serotonin at the synaptic cleft, thereby amplifying serotonin signaling in the brain.[35] Efficacy and tolerability of different SSRIs have been largely similar in clinical trials.[36,37]

Small for Gestational Age, Preterm Delivery, and Spontaneous Abortion

There have been conflicting data about SSRI exposure during pregnancy and the potential risk of small for gestational age, preterm delivery, and spontaneous abortion. These risks have been associated with perinatal depression itself and the risk may lie with the illness rather than exposure.[38–40] Liu and colleagues[41] found that children of women who continued antidepressants were at greater risk of psychiatric disorders than women who discontinued antidepressants during pregnancy. Continuation may be a marker for more severe depression.

Teratogenicity

Most current data looking at exposure to all SSRIs show no consistent information to support specific teratogenic risks.[42]

Persistent Pulmonary Hypertension of the Newborn

Previous studies have reported conflicting data about increased risk of persistent pulmonary hypertension of the newborn (PPHN) with SSRI exposure during pregnancy, leading the FDA to revise their warning in 2011 to state that the risk is inconclusive.[43–45] However, the most up-to-date publication examining a cohort of more than 3 million women, and adjusting for potential confounding variables, concluded a very small increased absolute risk for PPHN with SSRI exposure (adjusted odds ratio of 1.28 for SSRIs vs 1.14 for non-SSRIs).[46]

Neonatal Toxicity and/or Withdrawal

With pregnancy exposure to SSRIs, there has been evidence of increased risk for medication withdrawal or poor neonatal adaptation syndrome (PNAS) at the time of delivery.[47,48] PNAS has been estimated to occur in up to 30% of exposed babies and can manifest as a range of symptoms, including irritability, respiratory distress, hypoglycemia, feeding difficulties, increased or decreased tone, sleep disturbance, and, more rarely, seizures, prolonged QT interval, or cardiac arrhythmias.[47] PNAS can present minutes to hours after birth and typically resolves within 1 to 2 days.[49] If present, PNAS is usually mild and transient, without residual issues. The likelihood of PNAS being more severe and requiring more significant intervention may occur in up to 3% of exposed neonates.[50] Some investigators have hypothesized that PNAS may be related to a neurologic phenomenon, rather than simply toxicity or withdrawal

Table 1
Medications, dosing, and unique considerations

Generic Name	Trade Name	Dosage Range	Unique Considerations/Indications
SSRIs[a]			
Sertraline	Zoloft, Serafem	50–200 mg,[b] increase by 25 mg or 50 mg, for very anxious patients 12.5 mg	Due to half-life small, even negligible amounts transmitted into breast milk.
Fluoxetine	Prozac	20–80 mg, increase by 10 mg or 20 mg	Longer half-life → withdrawal less likely if doses are missed, but also longer to get out of the system if there are adverse effects, likely greater amount in breast milk, thought to be more activating.
Citalopram	Celexa	20–40 mg, increase by 10 mg or 20 mg	FDA Drug Safety Communication that >40 mg could result in a life-threatening heart arrhythmia.
Escitalopram	Lexapro	10–20 mg,[b] increase by 5 mg or 10 mg	
Paroxetine	Paxil, Pexeva, Brisdelle	10–60 mg, increase by 10 mg or 20 mg, CR in 12.5 mg doses	Older data demonstrated potential for a 1.5- to 2.0-fold increase risk in cardiovascular malformations,[141] leading to a 2005 warning.[142] Recent data show no consistent information to support teratogenic risks.[42]
Fluvoxamine	Luvox, Faverin, Fevarin, Floxyfral, Dumyrox	25–150 mg, increase by 25 mg	More often used for treatment of obsessive compulsive disorder.
SNRIs[c]			
Venlafaxine	Effexor, Effexor XR	37.5–375.0 mg, increase by 37.5 mg	Older and most data available.
Duloxetine	Cymbalta, Irenka	20–120 mg, increase by 20 mg, 30 mg	
Milnacipran	Savella	100 mg BID–200 mg, increase by 12.5 mg, 25 mg, 50 mg	No studies currently available on use in pregnancy examining neither teratogenic risks nor available data about long-term developmental outcomes.

Desvenlafaxine	Pristiq, Khedezia	25–400 mg	No studies currently available on use in pregnancy examining neither teratogenic risks nor available data about long-term developmental outcomes. No evidence >50 mg is helpful.
Other antidepressants: Their own unique mechanisms of action			
Buproprion	Wellbutrin SR, Wellbutrin XL, Zyban, Aplenzin, and Forfivo XL	150–450 mg, increase by 150 mg, SR BID dosing	Not to exceed 450 mg owing to an increased risk of seizure, greater concern for seizure in those with a history of seizure or those engaging in purging behaviors. Helpful for smoking cessation[144] and even evidence for lower prematurity risk for smokers.[145] May help ADHD and other addictive disorders, such as overeating.
Mirtazepine	Remeron	15–45 mg, increase by 7.5 mg, 15 mg	Antiemetic effects in addition to antidepressant and anxiolytic effects,[146,147] and helps with sleep and decreased appetite.
Trazodone, nefazodone	Oleptro, Desyrel, Serzone	50–400 mg, ½ tablet (25 mg)-100 mg for sleep	Sleep aid[148] at lower dosages, higher dosages more antidepressant affects. No differences in the rate of major malformations.[93]
Tricyclic TCAs[d]			
Desipramine, nortriptyline	Norpramin, Pamelor, Aventyl	Dose varies for each TCA	Less anticholinergic, so less orthostatic hypotension and constipation, which are common in pregnancy.[149,150]
Amoxapine, impramine, doxepin, clomipramine, trimipramine, amitriptyline, protriptyline	Asendin, Tofranil, Sinequan, Silenor, Anafranil, Sumontil, Vivactil, Elavil, Vanatrip	Dose varies for each TCA, blood levels are possible to obtain	
MAOIs[e]			
Isocarboxazid, phenelzine, selegiline, tranylcypromine	Marplan, Nardil, Emsam, Parnate	Dose varies for each MAOI	Requires special diet, interacts with some medications to cause life-threatening hypertensive crisis.

(*continued on next page*)

Table 1
(*continued*)

Generic Name	Trade Name	Dosage Range	Unique Considerations/Indications
Mood stabilizer and antidepressant			
Lamotrigine	Lamictal	>50 mg, start at 25 mg daily and increase by 25 mg every 2 wk to decrease risk of Stevens–Johnson syndrome	Some evidence to use for augmentation in treatment-resistant depression,[151,152] OCD,[153,154] and, therefore, possibly obsessive compulsive symptoms of perinatal depression,[155] and for mood dysregulation and aggressive behaviors of borderline personality disorder, which is often comorbid with depression.[156]
Atypical antipsychotics (ariprazole, quetiapine, olanzapine, risperidone, ziprasidone, lurasidone, paliperidone)	Abilify, Seroquel, Zyprexa, Risperdal, Geodon, Latuda, Invega		With augmentation of depression resulted in modest but statistically significant increased likelihood of remission during 12 wk of treatment compared with switching to bupropion monotherapy[157]; small study found less likely to have a postpartum mood episode.[158]
Lithium		Increase by 150 mg, 300 mg; Therapeutic blood level 0.4–0.8 for depression augmentation, 0.8–1.2 for mood stabilization	Helpful for monotherapy and augmentation of unipolar depression,[159,160] and postpartum psychosis in addition to Bipolar Disorder.[161] Increases the likelihood of maintaining mood stability during pregnancy and preventing postpartum relapse[162–164] as does immediately restarting postpartum[162,165]

Abbreviations: ADHD, attention deficit hyperactivity disorder; BID, 2 times per day; CR, controlled release; FDA, US Food and Drug Administration; MAOI, monoamine oxidase inhibitor; OCD, obsessive–compulsive disorder; SNRI, Serotonin norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor; TCA, tricyclic antidepressant; XR, extended release.

[a] All treat depression and anxiety, higher dosages needed for anxiety, Black Box warning for use in children secondary to an increased risk of suicidal thoughts at initiation (still used to treat depression, anxiety, which will decrease risk of suicide), increase dosage for 1 week for menses for premenstrual mood worsening or anxiety.

[b] Some providers may increase to 250 mg or 30 mg.

[c] Treat depression and anxiety, and have also shown to be effective treatments for chronic pain.[143]

[d] First discovered in the 1950s, revolutionized treatment of depression and preceded SSRIs,[88] but are associated with higher mortality rates owing to overdose.[89] Helpful for chronic pain.

[e] Gracious and Wisner[90] indicate a use in patients with atypical depression that have not otherwise responded.

from medication.[51] Importantly, tapering medication to avoid PNAS during the third trimester is not advised, because it has not been shown to improve neonatal health or outcomes, and could place the mother at significant risk of worsened symptoms and decline.[51] Breastfeeding may additionally help to minimize or ease any potential serotonin withdrawal symptoms for the infant in the early postpartum period.[52]

Long-Term Developmental Outcomes

The risk for autism spectrum disorders associated with SSRI exposure during pregnancy is controversial. Maternal depression has been found to be potentially neurotoxic, and is a considerable confounding variable.[53] Some studies have shown potential risk for autism spectrum disorders with SSRI exposure[54–56]; however, when adjusted for confounders, including the risk of maternal depression, statistical significance is usually lost.[57–59] Other developmental outcomes that must be considered with perinatal exposure to psychotropic medications include language, growth, and motor development. Review of available data demonstrates no effects of in utero SSRI exposure on head circumference, weight, or length during the first year of life.[60] Examination of the literature on IQ and behaviors of sibling pairs in mother's with and without SSRI exposure during pregnancy showed that the child's IQ was predicted by maternal IQ. Maternal depression has an impact on problematic behaviors in the children.[53] Last, a longitudinal study of the development in children with in utero SSRI exposure found no differences in mental indices; psychomotor scores were mildly lower during the first year of life, and then normalized thereafter.[61]

SEROTONIN NOREPINEPHRINE REUPTAKE INHIBITORS, IMPORTANT ALTERNATIVES

Serotonin norepinephrine reuptake inhibitors (SNRIs), as detailed in **Table 1**, are important alternatives in the treatment of perinatal depressive and anxiety symptoms especially when nonresponsive to SSRIs or if the patient has previously done well on an SNRI.[62,63] SNRIs have a mixed mechanism of action on both serotonin and norepinephrine and have demonstrated good efficacy for treatment refractory depression[35,64] There are fewer data available for SNRI use during pregnancy than for SSRIs.

There has been 1 study in rats showing potential increased risk for cardiac anomalies with venlafaxine exposure in utero.[65] However, available human data, including an aggregate metaanalysis of multidatabase studies including 2.3 million Nordic births, concluded there was no evidence for venlafaxine-related cardiovascular birth defects.[66] The literature comprises a systematic review from 2016, a separate comprehensive appraisal of 29 available studies in 2015, and a 2001 prospective controlled study of 150 exposures to in utero venlafaxine, all of which failed to find an increased rate of major malformations.[67–69] Although there are fewer data with Duloxetine, available studies to date have not found evidence of an apparent increased risk of congenital malformations.[67,69,70]

Data from the Quebec Pregnancy Cohort between 1998 and 2009 investigating risk between SNRI/SSRI exposure and risk for PPHN did not find a statistically significant association; however, the lack of power for the SNRI arm of the study makes the risk assessment ultimately unclear, because there was a small but significantly increased risk with SSRI exposure during the second half of pregnancy in that study.[71]

There is 1 study examining placental transfer of 2 SSRIs (paroxetine and fluoxetine) and 1 SNRI (venlafaxine), which found no pattern of PNAS association with placental transfer of different antidepressants owing to large interindividual variability for each medication[72] However, as with SSRIs, there is potential increased risk for SNRI toxicity or withdrawal/PNAS. Symptom manifestation and presentation for SNRIs is

likely relatively similar.[73] Also, as observed with PNAS management with SSRIs, breastfeeding may help to ease any potential risk for withdrawal symptoms from SNRIs.[73,74]

There are few data available for long-term developmental effects of SNRI exposure in pregnancy. One study examining 62 exposed children ages 3 to 7 years found that IQ was predicted by maternal IQ and not SNRI exposure or duration of SNRI exposure.[53] There is 1 available study looking at desvenlafaxine exposure during pregnancy in Swiss albino mice that found potential risk for increase in anxiety and fearfulness in offspring that could be indicative of possible impact on brain development.[75]

BUPROPION AND MIRTAZAPINE, UNIQUE PROPERTIES

Bupropion inhibits norepinephrine and dopamine reuptake and is the only antidepressant of its kind.[35] The most common side effects are dry mouth, insomnia, and nausea.[76–78] Mirtazapine, a noradrenergic and specific serotonergic antidepressant, has been shown to be comparable with SSRIs in the acute phase treatment of non–pregnancy-related depression.[79,80] See **Table 1** for more on their unique properties and indications.

The literature has been conflicting on risk of bupropion exposure during pregnancy and adverse effects on the fetus. Some studies show no association of first trimester bupropion exposure with congenital or cardiovascular malformations compared with other antidepressants or bupropion exposure outside of the first trimester.[81] Interestingly, the data from this initial report were reanalyzed using more stringent case definitions and concluded that there is a small increased risk, although also acknowledging an inability to account for confounders.[82] Other reports have also shown a positive association between first trimester bupropion use and left outflow tract heart defects, but the magnitude of the observed increased risk was small.[83] More recently, Louik and colleagues[84] in 2014, using data from Slone Epidemiology Center's Case-control Birth Defect Study, concluded that they could not confirm the association with left-sided cardiac defects, but did find an increased risk of ventricular septal defect.

Given this conflicting and relatively small literature, as well as the difficulty accounting for confounders, the risk of bupropion exposure versus nontreatment should be considered carefully, as with any medication in pregnancy. Patients should be counseled that bupropion and its metabolites have been found to cross the placenta,[85] but this should factor be weighed against the risks of depression or smoking for the patient and the baby.

A review of the literature on mirtazapine in pregnancy and lactation included 31 papers with 390 cases of neonates, and concluded that mirtazapine is not associated with increased risk of malformations; however, there was not enough information to make any conclusions on risks of mirtazapine during lactation.[86] Of note, typical exposure through lactation involves even more factors, such as amount in the mother's blood, protein binding and oral bioavailability,[87] which often manifests as reduced transfer to the newborn.

TRICYCLIC ANTIDEPRESSANTS, MONOAMINE OXIDASE INHIBITORS, AND TRAZODONE

Tricyclic antidepressants (TCAs), first discovered in the 1950s, revolutionized the treatment of depression and preceded SSRIs.[88] TCAs are associated with higher mortality rates owing to overdose.[89] Monoamine oxidase inhibitors were also first discovered in the 1950s.[88] There is very little data on monoamine oxidase inhibitors.[90] Trazodone also has limited data. All 3 agents are discussed in **Table 1**. Limb anomalies in earlier studies of TCAs have not been confirmed and neonatal behavioral effects

from fetal exposure have not been reported.[91] Monoamine oxidase inhibitors included in a study with other antidepressants did not identify adverse fetal outcomes.[92] A study of 147 women taking nefazadone or trazodone were compared with 2 other groups—women taking other antidepressants or women taking another nonpsychotropic medication thought to be nonteratogenic—and found no differences in the rate of major malformations.[93] Conceivably, the same concerns as for SSRIs may be present, such as for possible increased risk of PPHN.[94] Similar to SSRIs, neonatal symptoms, such as transient withdrawal symptoms, have been reported.[91] TCAs studied in the Quebec Pregnancy Cohort were associated with eye, ear, face, neck, and digestive defects, although the confidence interval for the eye, ear, face, and neck defects was very close to 1.0.[95] Several cohorts of exposed children have been followed with no identified negative neurobehavioral effects of TCAs.[96–98]

AUGMENTATION MEDICATIONS (LITHIUM, ATYPICAL ANTIPSYCHOTICS, AND LAMOTRIGINE)

See **Table 1** for more details about lithium, atypical antipsychotics and lamotrigine used for augmentation. Recent literature has shown that lithium's association with cardiac malformations is smaller than previously thought,[99] and must be weighed against the risks of the illness itself. Although limited, data for lithium and second-generation antipsychotics indicate effects are reassuring with regards to child development.[100] Despite some earlier concerns, subsequent studies have suggested that lamotrigine is not associated with an increased risk of congenital malformations.[101] The long-term safety profile of lamotrigine during pregnancy is promising. In a review that included 8 studies, lamotrigine had no adverse outcomes on infant IQ or neurodevelopment.[102]

NEW DEVELOPMENTS IN DRUG SAFETY LABELING AND MONITORING

This review does not include information on the FDA pregnancy risk categories (A, B, C, D, and X), which began in 1979.[103] This labeling system has been criticized for not adequately reflecting the complexity of decision making about medication use during pregnancy. This system is not conducive to assessing relative risk within categories, has often been viewed as hierarchical rather than descriptive, and does not readily allow for updating based on new findings.[103,104]

In December 2014, the FDA published the Content and Format of Labeling for Human Prescription Drug and Biological Products; Requirements for Pregnancy and Lactation Labeling, also referred to as the "Pregnancy and Lactation Labeling Rule." The rule was implemented on June 30, 2015. It requires medication labels to include a risk summary and clinical considerations, including information relevant for decision making, such as the risk of untreated conditions, complications, and interventions, and data. It prioritizes the inclusion of new information available from drug registries and postmarketing surveillance. Medications approved after 2001 will be required to implement this new labeling by June of 2020, and those approved before 2001, to remove letter ratings by June 30, 2018.[103,105] More information is available at https://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/Labeling/ucm093307.html.

ESTRADIOL AND PROGESTIN TREATMENTS

Many investigators have hypothesized that alterations in reproductive hormones contribute to PPD because of the temporal association between the precipitous

decrease in hormone concentrations that occur with childbirth and the onset of mood symptoms.[106] Reproductive hormones have been shown to play a role in basic emotion processing, arousal, cognition, and motivation, and they regulate each of the biological systems implicated in depression (eg, thyroid, immune, and hypothalamic–pituitary–adrenal axis function and genetic expression).[32] Reproductive hormones also regulate neurotransmitter synthesis, release, and transport, impacting the neural systems implicated in depression.[32] Experimental studies have shown that some women with a history of PPD are differentially sensitive to the effects of changes of estrogen and progesterone on mood.[107] One pilot study of pregnant women with a history of PPD showed that prophylactic administration of oral Premarin, a conjugated estrogen, prevented PPD recurrence in 10 of the 11 women studied.[108] A later double-blind, placebo-controlled trial of 61 women with PPD that began within 3 months after delivery showed that women treated with transdermal estradiol (n = 34) showed a greater decrease in depressive symptoms than those who received placebo (n = 27), although almost one-half of the women in each group were also taking antidepressants.[109] Finally, another study of 23 women with severe PPD, many of whom had not experienced benefit from treatment with either antidepressant medication or psychotherapy, and were found to have low concentrations of serum estradiol, were considered to be in "gonadal failure," and showed symptom remission after 8 weeks of sublingual estrogen treatment.[110] Estradiol may be an effective treatment for PPD; however, a large RCT is needed before recommending hormonal treatment in the postpartum period given the known risks of impaired lactation and venous thromboembolism with oral estrogen preparations. The only large-scale RCT to date was stopped early after finding that treatment with 200 μg transdermal estradiol did not result in significantly increased serum estradiol concentrations.[111] There is even less evidence for progesterone treatment for PPD. One study found norethisterone enanthate, a synthetic progestogen, administered within 48 hours of delivery, was associated with a significantly higher risk of developing PPD.[112] Of note, in a small study of nonpregnant women across the spectrum from anorexia nervosa to normal weight to obese, progesterone levels were not associated with depressive or anxiety symptoms; however, allopregnanolone levels were.[113] Intravenous allopregnanolone therapy is promising and discussed in the Future Directions section.

GENERAL RULES OF THUMB AND TREATMENT ALGORITHM

The rule of thumb for treating perinatal women is that one size does not fit all, and each patient should have an individualized discussion with her provider about the risks of medication weighed against her own risks of not taking medication during pregnancy or lactation. Women who decide they want to come off medications should do so with the supervision of a physician, and ideally preconceptionally. Abrupt medication discontinuation has been associated with high relapse rates. In a prospective sample of 201 euthymic women on stable doses of antidepressants at the time of conception, 68% who discontinued medications during pregnancy experienced relapse of symptoms, and 60% of those who stopped their medication restarted it later in pregnancy.[114] Predictors of relapse included having 4 or more prior depressive episodes and suffering illness for more than 5 years.[114] The most judicious approach is to use the least amount of medication that helps a woman feel better and keeps her well. As noted, it is important to recognize that higher dosages are often required than prepregnancy dosages owing to increased blood volume and increased metabolism during pregnancy. Managing sleep and comorbidities, while providing a multidisciplinary treatment approach, will improve outcomes with medication treatment of perinatal depression.

Breastfeeding is promoted by all major medical groups for the first year of the child's life to improve both maternal and infant health outcomes.[115] Therefore, to minimize stress on the mother, for most medications pumping and dumping (ie, pumping and then throwing out all milk while taking a medication or after taking the medication throwing out the first pump of milk after taking the medication) is not advised[87] However, there may be cases where the risk–benefit ratio supports this practice, such as in the case of a treatment agent that may have high likelihood of passing into breast milk. As noted, the amount of medication exposure in breast milk is thought to be far less than exposure during pregnancy through transplacental passage. Data from the National Institutes of Health have demonstrated that SSRIs are compatible with breastfeeding.[74] It is important to collaborate with the infant's pediatrician when a mother is taking a psychotropic medication during lactation, and to monitor the infant for sedation, proper weight gain, and achievement of developmental milestones. For any medication other than lithium, the literature does not support checking infant blood levels.[116] For questions, an important resource is LACTMED, https://toxnet.nlm.nih.gov/newtoxnet/lactmed.html, a database from the National Institutes of Health, with information on medication patients may have taken during pregnancy.

We have developed a treatment algorithm based on the literature and the clinical experience of our perinatal psychiatry team (**Fig. 1**). For a patient who has not tried medication before, sertraline is a good first choice given it is often well-tolerated, has efficacy for anxiety symptoms along with depressive symptoms, is an older medication with a relatively large evidence base, and has low breast milk concentrations in mother–infant dyad studies.[116] In general, medications that are less lipophilic, with shorter half-lives, are less likely to cross the placenta or cross into breast milk. However, if a patient is doing well with, or has done well with, another type of antidepressant, then it is better to continue with that medication, especially if other medications have not been effective for the patient. Alternatively, if a patient is not responding to a medication, it is important to consider other complicating factors and rethink the diagnosis. For STAR*D participants with major depression (general outpatients including men and women ages 18–75), severity, poor treatment adherence, and poor physical health increased the risk of depression failing to, or taking a longer time to remit. Social factors such as unemployment was also associated with nonremission.[117] Clinicians must also carefully screen for history of mania or hypomania to rule out bipolar spectrum illness, as a different treatment algorithm should then be applied, and antidepressants could significantly worsen symptoms if used alone.[2,35,118,119] Those presenting with first episodes of depression in the postpartum period are more likely to develop bipolar affective disorder and psychotic symptoms.[120] In addition, those with bipolar disorders I or II are associated with PPD rates as high as 50%.[121] The psychosis specifier of major depressive disorder is found more often in women who are postpartum than in those with depressive episodes during pregnancy, as well as nonpregnant women.[122,123] Psychotic symptoms can sometimes be hard to gather, so spending some time talking with patients and with their family and supports will help to identify those symptoms. If there is a question of psychosis, emergency referral to perinatal psychiatry is important.

FUTURE DIRECTIONS FOR PHARMACOLOGIC TREATMENT OF PERINATAL DEPRESSION

There is new evidence that the neurosteroid, allopregnanolone, a major metabolite of progesterone, may potentially contribute to the etiology and treatment of PPD.[32,124] Allopregnolone is a positive allosteric modulator of synaptic and extrasynaptic GABA-A receptors[125,126] and animal models have demonstrated that it has significant

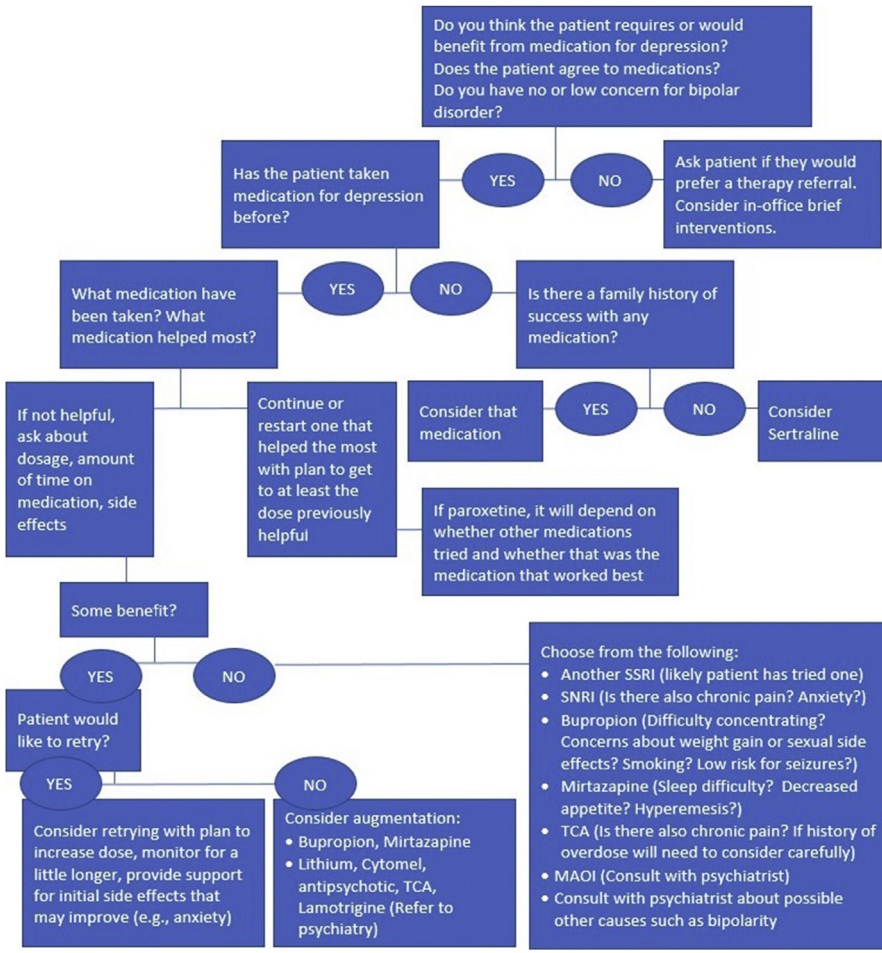

Fig. 1. Treatment algorithm for perinatal depression. MAOI, monoamine oxidase inhibitor; SSRI, selective serotonin reuptake inhibitor; TCA, tricyclic antidepressant.

effects on anxiety and depression.[32] Allopregnanolone concentrations rapidly decrease after childbirth, after reaching peak physiologic levels in the third trimester of pregnancy.[32,124] It is hypothesized that the failure of GABA-A receptors to adapt to the rapid fluctuations at childbirth may be a trigger for PPD.[127–130] This line of inquiry is being explored by the development of brexanolone, a proprietary formulation of allopregnanolone as a treatment for PPD. A positive small open-label trial,[131] and more recently, a positive phase II RCT of brexanolone showed rapid and clinically meaningful reductions in depressive symptoms as compared with placebo.[132] Sage Therapeutics (Cambridge, MA) announced in November 2017 that they obtained statistically significant mean reduction depressive symptoms with brexanolone compared with placebo at 60 hours, and was durable over 30 days in 2 placebo-controlled multicenter phase III trials.[133]

Another possible novel area of intervention may be the microbiota–gut–brain axis. Preliminary findings from an RCT testing the use of a probiotics in pregnancy warrant further study with regard to depressive and anxiety symptoms.[134,135] Although there is

no evidence as of yet to support the use of probiotic pills, the gut microbiota may be an important mediator of antidepressant effects given that certain microbes are involved in tryptophan and serotonin metabolism, and in drug metabolism.[136,137] Additional microbiome research may allow for better understanding of how medications are metabolized and best used during the perinatal period.

There is great need for innovative models regarding delivery of care to perinatal women. The literature demonstrates that only a small percentage of perinatal women are adequately screened and treated for perinatal depression[5,138] owing to multiple barriers.[139] Integrated care models that embed mental health providers in obstetric settings and specialized perinatal psychiatry inpatient units may further ensure patients better access and care.[140]

SUMMARY

Perinatal depression is a treatable medical condition. There are many evidence-based treatments, but novel treatment paradigms are also needed to target the underlying pathogenesis of perinatal depression and to increase the efficacy of treatment. Treatment can have important reductions in suffering for women and their families.

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