

# Psychotropic Medications in Pregnancy and the Postpartum Period



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**ABSTRACT:** Many pregnant women suffer from mental health conditions while pregnant. As providers and patients make decisions about risks of the conditions and treatments during pregnancy, information to populate those discussions is needed. Taking into account the physiologic changes in pregnancy, we may need to optimize medication therapy. This article reviews and summarizes some of the most common mental health conditions suffered in pregnancy: depression, bipolar disorder, anxiety, and psychosis. It further discusses the different medications used to treat them, as well as risks associated with these medications.

**KEYWORDS:** pregnancy, psychotropic drugs, depression, teratology

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## Introduction to Psychotropics in Pregnancy

Several studies document that over three-quarters of pregnant women take medications in pregnancy, with one-third taking multiple drugs in pregnancy.<sup>1,2</sup> These rates are even higher if prenatal vitamins and iron supplements are added in. The drugs that are taken span a wide range of therapeutic classes and disease entities.

Psychiatric diagnoses are common therapeutic problems faced by women's health providers.<sup>3</sup> One study of 3000 women presenting to an obstetrics/gynecology clinic for any type of care found that 20% of the women screened positive for a psychiatric disorder.<sup>3</sup> Mental health diagnoses in pregnancy are associated with higher rates of complications such as preterm birth, hypertensive disorder, and low-birth weight babies.<sup>4,5</sup> In fact, maternal mental illness is identified as a leading indirect cause of maternal mortality.<sup>6</sup> Between 14% and 23% of pregnant women will experience a depressive disorder while pregnant.<sup>7</sup> In 2003, approximately 13% of women took an antidepressant at some point in pregnancy, a rate that has doubled since 1999.<sup>8</sup> With the high rate of mental health issues in pregnancy, the importance of the baseline condition effects on outcomes must be balanced with informed discussions about the risks and benefits of medication therapy for the conditions.<sup>9</sup> With the availability and proven efficacy of a number of new psychotropic medications, many women have a greater potential for symptom reduction and remission of their mood disorders.<sup>10</sup> Thus, it is crucial for women's health providers to understand the implications of psychotropic drugs in pregnancy.

The objective of this review article is to summarize the use of psychotropic drugs in pregnancy and to highlight research on risk and efficacy to help inform clinicians treating women with mental health disorders including depression, bipolar disorder (BPD), and anxiety. The authors performed Ovid and PubMed searches to find relevant articles about the individual drugs, drug classes, and pregnancy. The data found are summarized below.

## Pharmacology Changes in Pregnancy and General Considerations

Pharmacotherapy in pregnancy has unique challenges for providers. There are several key changes in maternal physiology that can affect the dosing and efficacy profiles of different drugs. Cardiovascular changes include increased cardiac output and blood volume expansion to allow for adequate perfusion of vital organs, including the placenta and developing fetus.<sup>11</sup> In addition, maternal total body water increases near the end of gestation, which may cause a dilution effect on certain drugs.<sup>12</sup> Plasma albumin decreases, which can impact protein-bound drugs. Gastric transit time is slowed in pregnancy and renal plasma flow and glomerular filtration rate are both increased.<sup>11</sup> Thus, physiological changes that accommodate the developing pregnancy can have profound impact on medications in pregnancy, potentially necessitating a higher dose of medication than would be commonly utilized for nonpregnant populations.<sup>13,14</sup> In addition, as each trimester passes, not only does the maternal physiology change but also the risks of taking medications change. In the first trimester,



concern about teratogenicity and major fetal anomalies during the initial development of fetal organs and systems is present. Second and third trimester risks are focused on fetal growth and development of adverse pregnancy outcomes such as pre-term birth or stillbirth.

These pregnancy changes and need to take medications are also balanced with the fear of teratogenic risk of medications. In general, teratogenic risk is overestimated by both patients and medical specialty providers.<sup>15</sup> Teratogenic risks for some classes like antidepressants are small.<sup>16</sup> However, there are thousands of calls from concerned women and providers to teratology services such as MotherRisk in Canada ([www.motherrisk.org](http://www.motherrisk.org)) and MotherSafe in Australia ([www.mothersafe.org.au](http://www.mothersafe.org.au)) each year.<sup>17</sup> The number of calls to these services continues to rise. The most common class of medications after over-the-counter drugs is for psychotropic medications, typically antidepressants.<sup>17</sup> To address the maternal and neonatal risks of both depression and antidepressant exposure algorithms to help guide providers and patients, the American Psychiatric Association and American College of Obstetricians and Gynecologists released a consensus report several years ago.<sup>18,19</sup> The remainder of this article will describe different psychotropic medications used in pregnancy, the clinical need for the medications, and the risks associated with them. This will be accomplished for several mental health conditions, including depression, BPD, and anxiety.

## Antidepressants

**Selective serotonin reuptake inhibitors.** Selective serotonin reuptake inhibitors (SSRIs) are a class of medications indicated for the treatment of depression and anxiety. SSRIs are the most commonly prescribed treatment for depression both outside of pregnancy and during pregnancy.<sup>18,20,21</sup> United States prevalence rates of SSRI use in pregnancy range from 8% to 13%.<sup>8,20</sup> Since up to 50% of pregnancies are unplanned, it is important for patients and health-care providers to be familiar with the impact of fetal exposure to SSRIs when prescribing these medications to women of reproductive age. While SSRIs are the mainstay of therapy and generally considered to be safe for use in pregnancy, there are some risks that must be considered. Areas of concern regarding in utero exposure to SSRIs include cardiac, pulmonary, and central nervous system.

In 2005, the Food and Drug Administration (FDA) reclassified paroxetine to category D due to concerns for increased risks for congenital heart malformations, specifically right ventricular outflow tract obstruction.<sup>20</sup> At the same time, sertraline, while not reclassified, had also been associated with an increased risk for ventricular septal defects.<sup>20</sup> A follow-up nationwide cohort study of 949,504 pregnant Medicaid recipients from 2000 to 2007 showed a relative risk of any cardiac defect of 1.25 (95% confidence interval [CI], 1.13–1.38) in an unadjusted analysis of women using an SSRI in the first trimester. However, when adjusted for patients with only a

depression diagnosis to control for confounding comorbid conditions, the relative risk was 1.12 (95% CI, 1.00–1.26). Additionally, a third fully adjusted analysis applied a propensity-score stratification to further control for depression severity and other potential cofounders, which revealed a relative risk of 1.06 (95% CI, 0.92–1.22). The study also analyzed categories of cardiac defects including right ventricular outflow tract obstruction, ventricular septal defects, and any cardiac malformation. Contrary to previous evidence, they found no significantly increased risk for paroxetine and right ventricular outflow tract obstruction and for ventricular septal defects with sertraline.<sup>20</sup>

A Danish cohort study examining 72,280 pregnancies using the EUROCAT register (database of congenital anomalies) from 1995 to 2008 showed an increased risk of severe congenital heart defects (CHD) with first-trimester SSRI exposure. Twelve percent of pregnant women filled an SSRI prescription in the first trimester, with citalopram being the most commonly redeemed (35.4%). Of the 845 exposed, 11 CHD were noted, with 6 categorized as severe. The odds ratio for all CHD was 1.75 (95% CI, 0.96–3.19) and that for severe CHD being 4.15 (95% CI, 1.82–9.44). Data on maternal age, smoking, and exposure to antiepileptic drugs and insulin were collected; however, due to the limitations of the EUROCAT register, data were not collected on additional cofounders. Interestingly, this study confirmed information from a previous Danish study that showed an increased risk of CHD in patients who were exposed to SSRIs 3–12 months prior to pregnancy but not exposed during pregnancy. Overall, the study showed a low incidence of all CHDs (1.3%) in exposed pregnancies but did show a four-fold increased risk for severe CHD (Adjusted Odds Ratio [AOR] 4.03 [95% CI, 1.75–9.26]).<sup>21</sup>

Persistent pulmonary hypertension of the newborn is a rare condition with a prevalence of 1.9 per 1000 live births.<sup>22</sup> During the immediate transition following birth, the neonatal lungs inflate and lung blood vessels relax, leading to proper neonatal oxygenation. Persistent pulmonary hypertension does not permit pulmonary vessel relaxation, resulting in poor oxygenation and subsequent respiratory distress.<sup>22</sup> The degree of persistent pulmonary hypertension can range from mild to severe hypoxia. Previous studies regarding fetal exposure to SSRIs have yielded inconclusive results ranging from no association to trimester-associated risk to increased overall risk. In 2014, a systematic review and meta-analysis of seven studies reported no significantly increased risk of persistent pulmonary hypertension with SSRI utilization in early pregnancy (OR 1.23; 95% CI, 0.58–2.60) but did report an increased risk for exposure in late pregnancy (OR 2.50; 95% CI, 1.32–4.73).<sup>22</sup> Due to the rare nature of this condition, the authors used the OR to approximate the RR. With an OR of 2.5 and a baseline risk of 1.9/1,000 live births, the absolute risk of persistent pulmonary hypertension was 2.85/1,000 live births for late pregnancy exposure. Thus, the number needed to harm (NNH) was 351 women. However, the OR



for early pregnancy exposure was 1.23, leading to an absolute risk of 0.44/1,000 lives births, resulting in an NNH of 2,288 women.<sup>22</sup> Overall, the risk of potential neonatal risks must be considered in relation to maternal risk of poorly treated depression with attention on late trimester exposure.

Another area of concern is the effect of SSRI exposure to the developing fetal central nervous system. A retrospective cohort study of children with intrauterine exposure to SSRIs matched 1:2 to children without intrauterine SSRI exposure when considering Chiari I malformations (CMI) at 1 and/or 2 years on MRI. The SSRI-exposed group had an increased risk of CMI diagnosis compared to the group with no maternal depression and no SSRI exposure (18% vs 2%,  $P = 0.003$ , OR 10.32, 95% CI 2.04–02.46).<sup>23</sup> Duration of exposure, exposure at conception, and family history of depression appeared to increase this risk. The authors conclude that it is uncertain if the SSRIs were the primary risk of CMI or if the severity of depression during pregnancy impacts the rate of CMI.

However, given that these absolute risks are small and the risks that untreated depression in pregnancy is also associated with adverse outcomes, SSRIs remain the first-line treatment of choice for pregnant women with depression.<sup>9,10,18,19</sup> Titrating the dose to antidepressant effect is often necessary due to the physiologic changes in pregnancy noted earlier. Women who breast feed after delivery can also continue to be treated with SSRI drugs as serum drug levels in infants who were breastfed by antidepressant-treated mothers were undetectable or low and no adverse impact was observed.<sup>24</sup>

**SNRIs.** The main SNRIs in clinical use include venlafaxine, desvenlafaxine, and duloxetine. While these drugs are used for first-line therapy, they are also utilized when patients have poor responses or intolerable side effects to SSRIs. These drugs are effective at treating depression and are associated with mild side effects of nausea, dizziness, and diaphoresis. Studies have demonstrated no increased risk of adverse pregnancy outcomes with venlafaxine compared to SSRIs and nonteratogenic drugs,<sup>25</sup> but a recent systematic review found an association with venlafaxine and an increased risk of spontaneous miscarriage (OR 2.1, 95% CI, 1.3–3.3).<sup>26</sup> While SSRI-induced neonatal abstinence syndrome has been found with antidepressant exposure, only 3% of the women were taking venlafaxine, and thus, no specific relationship was found.<sup>27</sup> In general, longer term follow-up of infants exposed to venlafaxine in utero have noted that these exposed infants have done well.<sup>28</sup> These drugs cross the placenta and also are secreted into breast milk. However, while venlafaxine is detected in the mother's milk with a mean infant dose of 3.49%, venlafaxine was not detected in infant plasma. In addition, there was no evidence of adverse effects in breastfeeding infants.<sup>24</sup> However, the American Academy of Pediatrics (AAP) classifies antidepressants together as drugs for which the effect on nursing infants is unknown but may be of concern.<sup>29</sup> Clinically, however, the risks must be weighed against the benefits of treating the

new mother for depression and the benefits of breastfeeding for mother and baby.

**Tricyclic antidepressants.** Tricyclic antidepressants (TCAs) are the major category of psychotropic medications compared to SSRIs for the treatment of depression. Like many psychotropic medications, evidence for the risk/benefit of TCA use in pregnancy has been mixed. A meta-analysis of early studies from 1966 to 1995 did not find evidence for an increased risk of congenital malformations in 414 patients exposed to TCA in the first trimester.<sup>30</sup> A subsequent study comparing infants exposed to TCA (209 infants) versus SSRI (185 infants) did not find evidence of adverse effects in either group.<sup>31</sup> Another study of 167 pregnancies exposed to TCA did not find conclusive evidence for a link with birth defects, but did link TCA exposure with respiratory distress syndrome, metabolic, and endocrine abnormalities in the newborn.<sup>32</sup> While these data appear to portray a favorable risk profile for the use of TCA in pregnancy, all the studies were limited by a small sample size. A more recent study of women in Sweden captured a larger number of women exposed to TCA (1,662 pregnancies), although nearly 70% of these utilized one agent, clomipramine.<sup>33</sup> This study compared a range of perinatal outcomes between women treated with TCA and SSRI agents for depression and largely concluded that outcomes after TCA exposure were worse than those after SSRI exposure. A range of detrimental effects were present to a more severe degree in women using TCA, including preterm birth, low birth weight, low APGAR score, hypoglycemia, and jaundice. Finally, the risk for congenital cardiac malformations was judged to be higher with exposure to TCA than any SSRI other than paroxetine. While the Reis and Kallen study has provided an analysis of the largest cohort of patients exposed to TCA, it was limited by the predominant use of just one TCA (clomipramine) and general applicability of the study results. Another concern is that it is unclear whether the subjects were adequately matched for disease (depression) severity, which may independently affect perinatal outcomes. Further research is needed to reconcile the differences in perinatal risk proposed by the various studies of TCA use in pregnancy.

One TCA which has received increasing attention recently is mirtazapine, a tetracyclic antidepressant that is postulated to act through a variety of mechanisms. Although mirtazapine does not have any pregnancy-specific pharmacokinetic literature, it has been documented to have linear kinetics within the typical dose range and achieve steady state within 5 days. Elimination is primarily through renal and hepatic routes, with a longer elimination half-life noted in women. There are a few studies, primarily case reports or small case series, documenting safety and efficacy from the use of mirtazapine in pregnancy. Uguz has documented successful use of a low-dose mirtazapine regimen for the treatment of major depression without neonatal complications.<sup>34</sup> Another case report documented delivery of healthy twin infants after exposure to mirtazapine in pregnancy; no abnormalities were



detected at birth, and the infants demonstrated normal development at a 6-month follow-up.<sup>35</sup> Future investigations of specific medications may prove to be more useful than analysis of the entire class of TCA drugs in identifying promising therapies for women with depression during pregnancy.

TCA medications are generally excreted into breast milk in low quantities, often with undetectable infant plasma levels. The AAP classifies most TCA as drugs whose effect on nursing infant is unknown but may be of concern.<sup>29</sup>

**Other antidepressants.** Bupropion is a unique antidepressant of the aminoketone class that neither inhibits monoamine oxidase nor alters reuptake of serotonin or norepinephrine. The antidepressant activity is not fully characterized and the compound is used clinically also for smoking cessation. The final report of the Bupropion Pregnancy Registry committee and other prospective studies found no increased risk of major teratogenic effects.<sup>36</sup> Studies that have noted a possible increased risk of conditions such as childhood ADHD are potentially confounded by other factors such as smoking.<sup>37</sup> The preponderance of the evidence points to the use of bupropion in pregnancy as low risk. Bupropion is excreted into breast milk but despite an elevated milk:plasma ratio, a review of antidepressant treatment during breastfeeding found no information that bupropion exposure during nursing resulted in quantifiable amounts of the drug in the infant or any adverse effects.<sup>38</sup>

## Bipolar Medications

BPD is a mental illness categorized as an affective mood disorder and is estimated to have a lifetime prevalence of 1%–2% worldwide.<sup>39</sup> Typical onset of disease occurs in a person's early 20s, putting many women at risk of developing the illness at the height of their reproductive years.<sup>40</sup> The female gender itself predisposes a woman with BPD to suffering more depressive versus manic episodes than her male counterparts and is also associated with higher incidence of sexual promiscuity, sexually transmitted infections, unplanned pregnancy, sexual assault, and other comorbidities such as tobacco and alcohol abuse.<sup>41</sup> In the pregnant woman with BPD, her risk of postpartum psychosis can be as great as 20%–30%, compared with 0.2% for the nonaffected population.<sup>42</sup>

Beyond stabilization of acute symptoms, long-term treatment of BPD has typically involved use of psychotropic medications such as mood stabilizers, anticonvulsants, and antipsychotics, either alone or in combination. Many of these treatments, however, have long been associated with fetal congenital malformations, neurodevelopmental problems, or other adverse neonatal events. On the other hand, abruptly stopping treatment during pregnancy increases a woman's risk of relapse.<sup>43</sup> Managing BPD in pregnancy is a challenging task for any health-care provider and requires recognizing the risks and benefits associated with each medication, as well as that associated with removing treatment during pregnancy.

**No medical treatment.** As a risk factor for neonatal morbidity, having BPD alone is associated with infants born severely large for the gestational age, and especially among women previously hospitalized for the illness, there are significantly higher risk of congenital malformations, neonatal morbidity, and neonatal hospital readmission.<sup>44</sup>

While some studies have shown a protective effect of pregnancy on the symptoms of BPD,<sup>43,45</sup> childbirth and the postpartum period can be seen to increase the risk of relapse up to 50%.<sup>46</sup> Untreated BPD in pregnant and postpartum women has been linked to an increase in the hazardous and impulsive behavior, already noted to be higher at baseline in women versus men.<sup>41</sup> This includes a more rapid manic-to-depression cycling course and a significant increase in suicidal ideations, attempts, or death; suicide may even account for one-fifth of total postpartum deaths.<sup>40,47</sup> Decision to forego treatment of a pregnant patient with BPD must include an assessment of her baseline frequency and quality of episodes, number of prior hospitalizations, any history of postpartum psychosis, and there must be a well-discussed plan for any acute exacerbations.

**Lithium.** Lithium has been a first-line treatment in BPD, effective in both manic and depressive episodes and also in reducing the risk of suicidality.<sup>48</sup> It is not without risks, however. In 1973, a major report from the International Registry of Lithium Babies published data suggesting that the rate of congenital malformations, especially that of Ebstein's anomaly, was excessively increased than that of the general population.<sup>49</sup> Subsequent studies put the risk for Ebstein's anomaly and other major congenital malformations much lower than previously thought with only a slight increase in the risk of cardiac anomalies specifically (one case per 1,000–2,000 births).<sup>50,51</sup>

An often reported significant effect of lithium therapy is birth of large for gestational age (LGA) infants, with affected babies weighing an average of ~100 gm heavier than their nonexposed counterparts.<sup>51,52</sup> Neonatal hypotonicity or "floppy baby" syndrome is also a noted adverse outcome of neonatal lithium toxicity, often resolving completely after the drug clearance.<sup>9,40</sup> There are no data that support or describe any detrimental long-term behavioral or developmental effects on neonates of mothers treated with lithium.<sup>49,51</sup>

Lithium therapy is not contraindicated during pregnancy. The risk of maternal instability after abrupt discontinuation of therapy compared with the risk of adverse fetal effects is a main reason to maintain lithium therapy in such patients.<sup>40</sup> If a woman continues Lithium therapy during conception and pregnancy, it is recommended that she undergo a fetal echocardiography in addition to her routine anatomy ultrasound.<sup>52</sup> In a well-controlled BPD patient in whom expectant management is appropriate, either medication tapering or drug discontinuation during the first trimester is a reasonable choice. Lithium is excreted into breast milk, and the infant serum levels are near therapeutic levels. For these reasons, this



is classified as a drug that should be used with caution in nursing mothers.<sup>29</sup>

**Antiepileptic drugs (AEDs).** Anticonvulsant drugs can be used for both the long-term and acute treatment of BPD. These drugs have shown a higher teratogenicity rate than lithium when used during pregnancy, especially when used in combination or at a preexisting low-folate level at the time of conception.<sup>53</sup> Typical features of fetuses exposed to antiepileptic medications include problems with neural tube embryology, growth restriction, and hypoplasia of the midface and finger.<sup>54</sup> These major malformations can be seen in around 25% of children exposed to AED in utero.<sup>55</sup> The three most common AEDs used for BPD are valproate (VPA), carbamazepine (CBZ), and lamotrigine.

**Valproate.** VPA or valproic acid is associated with the largest number of fetal and neonatal abnormalities compared to all other BPD treatments and can affect almost every organ system. The risk is dose dependent and is increased when used with other AEDs, especially if the patient has already delivered an affected child.<sup>54,56</sup> Neural tube defects, which are typically lumbosacral in nature, are among its most devastating effects, and the risk of NTDs can reach 1%–2%.<sup>55,56</sup> Other malformations reported are facial clefting, hypospadias, and skeletal abnormalities.<sup>57</sup> Additionally, VPA has been clearly shown to have effects on the cognitive, verbal, behavioral, and neurodevelopmental abilities,<sup>56,58</sup> and the FDA released a drug-safety announcement regarding these findings in 2011. In general, it is highly recommended that women in their reproductive years be counseled regarding the effects of VPA on a fetus, and, if desiring pregnancy, should attempt to change to another medication for BPD control. VPA is only excreted into breast milk in low concentrations and is classified as compatible with breastfeeding.<sup>29</sup>

**Carbamazepine.** Overall, the use of carbamazepine has been more favored than the use of other antiepileptics for use during pregnancy. In most major studies, the overall malformation rates are lower than those compared with VPA,<sup>59,60</sup> with rates ranging from 2.5% to 6.6%.<sup>52,53,59,60</sup> The most common malformations noted with carbamazepine use are neural tube defects, decreased head circumference and body length, and specific facies (short nose, hypertelorism, upslanting palpebral fissures).<sup>61,62</sup> In regards to neurodevelopmental outcomes, there has been no significant difference reported in the literature in infants with carbamazepine exposure to nonexposed children.<sup>63</sup> While it should be used with caution, carbamazepine may be a safer overall choice than VPA if treatment options must include an antiepileptic drug for the treatment of BPD. However, caution must still be used due to its risk of fetal effects, and an extensive ultrasound and fetal echocardiography are recommended.<sup>61</sup> Carbamazepine is considered compatible with breastfeeding due to low excretion into milk.<sup>29</sup>

**Lamotrigine.** Relative to its other antiepileptic counterparts, data on lamotrigine are limited, particularly in regard to

its use during pregnancy. In most studies to date, it has been reported to be less hazardous than other AEDs.<sup>64–66</sup> Women of reproductive age who use lamotrigine have been shown to be less likely to have an unplanned pregnancy, and, if pregnant, appear to have an increased protection against bipolar depression.<sup>67</sup> Use of the drug is associated with congenital malformations, with a most common rate of 2%–3% reported.<sup>67</sup> Slightly increased rates of facial clefting, hypospadias, and intestinal anomalies have been discussed; however, most of those rates are very near control rates.<sup>55,59</sup> To date, there have been no significant studies linking lamotrigine use in pregnancy with the risk of adverse neonatal neurodevelopmental outcomes.<sup>58</sup> Lamotrigine is present in variable quantities in breast milk.<sup>68</sup> Because of this, the AAP classifies it as a drug for which the effect on a nursing infant is unknown but may be of concern.<sup>29</sup>

### Antianxiety

Treatment for anxiety during pregnancy is controversial given the limited pharmacotherapeutic options. Most recommendations begin with early screening and treatment with nonpharmaceutical interventions in a multidisciplinary setting first (exercise, psychotherapy, etc).<sup>69,70</sup> Approximately 10%–15% of pregnant women will experience depression and/or anxiety symptoms, with a high rate of relapse with discontinuation of pharmacotherapy during pregnancy.<sup>71,72</sup> Maternal depression and anxiety have been correlated with spontaneous preterm delivery, cesarean delivery, as well as long-term maternal and neonatal well-being.<sup>73–75</sup>

**Benzodiazepines.** Benzodiazepines (BDZs) are the most commonly prescribed treatment for generalized anxiety disorder despite FDA Pregnancy Categories of D or X. Recent studies estimate the use of prescribed BDZ use at 4% for pregnant women in the United States.<sup>76,77</sup> Early safety reports of BZD's teratogenicity were overstated, but there remains conflicting evidence on the fetal effects and neonatal outcomes. Initial studies described a significant association between major malformations, increased rates of spontaneous abortion, or skeletal anomalies. However, many studies and several meta-analyses have shown no evidence of these associations.<sup>74,76,78–80</sup> There are data from case-control studies associating oral cleft with BDZ use, though this is refuted by cohort studies.<sup>76</sup>

Neonates exposed to long-term BDZ may require a taper to avoid poor neonatal adaptation (PND).<sup>81</sup> This condition is likely related to fetal and neonatal toxicity and includes low birth weight, poor muscle tone, irritation, and agitation.<sup>73,81,82</sup> Lorazepam has been shown to have lower fetal cord blood concentration than other BDZs but has not been shown to decrease effects on the neonate.<sup>82</sup> Breastfeeding may be protective and should be encouraged in mothers using BDZ not only for the passive medication administration but also to promote bonding between mother and infant and to prevent postpartum depression and anxiety, all of which present minimal risk to the newborn.<sup>82</sup>



**Bupirone.** Bupirone is a non-BDZ with a similar effectiveness as BDZ but requires 2–3 weeks of consistent use to become effective. There have been no reported cases of PND with the use of bupirone, though maternal withdrawal can occur with abrupt cessation.<sup>80,81</sup> There are limited safety data in pregnancy, but results thus far are promising. For breastfeeding women, the AAP classifies essentially all anxiolytics together that there may be concern because of effects on the developing brain that may not be apparent until later in life.<sup>29</sup> Conclusive studies, however, are lacking and thus individualized counseling on risks and benefits should be undertaken.

## Summary and Conclusions

There is little doubt that the identification and treatment of mental health disorders are a public health priority. In addition, during pregnancy where there are additional considerations, this is particularly important in order to optimize maternal and infant outcomes. Psychotropic medications are often needed to treat these conditions. Because pregnancy studies are not abundant for various historical and ethical reasons,<sup>83</sup> the information known about the impact of psychotropic medications in pregnancy is not complete.<sup>9,19,84</sup> The development of teratology registries and “help lines” has helped with data gathering on medication exposure in early pregnancy. However, there are conflicting findings and in general, treatment with psychotropic drugs and other drugs in pregnancy is left up to a shared informed decision with the patient and provider.

Individualized pharmacotherapy may help in the future to optimize psychotropic drug therapy in pregnancy while minimizing the risks. Taking into account physiological changes in pregnancy can help clinicians arrive at an adequate dose more rapidly. In addition, the advent of pharmacogenomics and accounting for drug metabolizing enzyme and transporter changes in pregnancy may aid in developing therapeutic models for these drugs in pregnancy.<sup>85</sup> Many of the psychotropic drugs are metabolized by enzymes that are impacted by commonly prescribed medications in pregnancy, such as antacids, gastrointestinal medications, and cardiovascular drugs (<http://medicine.iupui.edu/CLINPHARM/ddis/main-table>). Because so many pregnant women take multiple medications, it is important to take all these factors into consideration when prescribing or continuing a psychotropic medication.

In conclusion, there are risks and benefits with all medications in pregnancy. Psychotropic medications are no different. Understanding the risks of the mental health disorder in pregnant woman and the developing baby are important considerations when making clinical decisions with patients about treatment options. Weighing pregnancy characteristics, impact of the mental health condition, and the potential risks and benefits of the drug will help patients and providers arrive at a shared decision about therapy. The importance of

developing good databases of psychotropic medications and potential effects is paramount. In addition, long-term studies are needed to determine the impact of both the mental health condition and the drug therapy on the developing infant. The impact of the drug on breastfeeding and the possible impact on breast-fed infants is another consideration for research priorities. Given that many pregnant women suffer from mental health conditions during pregnancy, it is important for providers to understand the implications and options for treatment with psychotropic medications.

## Author Contributions

Conceived and designed the experiments: DMH, KWM, PJD, SMR, ASP. Analyzed the data: DMH, KWM, PJD, SMR, ASP. Wrote the first draft of the manuscript: DMH, KWM, PJD, SMR, ASP. Contributed to the writing of the manuscript: DMH, KWM, PJD, SMR, ASP. Agree with manuscript results and conclusions: DMH, KWM, PJD, SMR, ASP. Jointly developed the structure and arguments for the paper: DMH, KWM, PJD, SMR, ASP. Made critical revisions and approved final version: DMH, KWM, PJD, SMR, ASP. All authors reviewed and approved of the final manuscript.

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