# Psychopharmacological Decision Making in Bipolar Disorder During Pregnancy and Lactation: A Case-by-Case Approach to Using Current Evidence

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The safety of pharmacotherapy for bipolar disorder during pregnancy and lactation remains a subject of debate and uncertainty. Clinicians must balance concerns about anatomical and behavioral teratogenicity, maternal mental health, exposure to multiple drugs, and heightened risks for peripartum mood episodes. Risk-benefit analyses must consider factors such as illness severity, past pregnancy treatment outcomes, known drug responsivity, psychosocial supports, and key windows during fetal development. Pharmacological decision making usually changes over the course of pregnancy, given developments in maternal physiology and critical relapse risk periods. Among mood stabilizers, given current research, many experts eschew divalproex and carbamazepine, consider lamotrigine relatively benign, and voice strong opinions for or against lithium. Most second-generation antipsychotics are considered relatively safe, apart from possible extrapyramidal and other motor signs of withdrawal after delivery. In this review, the authors analyze the practical questions, current controversies, and available evidence regarding psychotropic drug therapy during pregnancy and lactation in bipolar disorder.

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## CLINICAL CONTEXT

Although most studies have found similar lifetime prevalence rates of bipolar disorder between men and women, gender differences may be evident in the impact of reproductive life events on affected women (1). Both clinical and epidemiological studies have found that women with bipolar disorder are at very high risk for postpartum relapse (2–4). They have also been found to have a higher risk of psychiatric admission during the postpartum period compared with women with schizophrenia or other psychiatric disorders, particularly in the first 6–8 weeks postpartum (3, 5). In some cases, new-onset postpartum psychosis or mania may represent the first episode of a new bipolar disorder diagnosis, whereas in other cases, the postpartum psychosis or mania may appear in isolation. Although postpartum relapse among women with bipolar disorder has been well described, there is debate about whether pregnancy itself positively or negatively affects relapse risk (6).

The precise rate of relapse has been difficult to quantify across a large number of prospective, retrospective, and birth cohort studies because of differences in study populations and methodologies. In a recent systematic review and meta-analysis, Wesseloo et al. found that patients with bipolar disorder had an overall postpartum relapse risk of 37% (2). Although researchers have widely assumed that women with bipolar disorder and previous postpartum episodes might be at the highest risk for relapse, the authors were not able to stratify risk by history of previous postpartum episodes because insufficient information was available. The authors also found that patients who used prophylactic pharmacotherapy during pregnancy had a significantly lower relapse rate (23%) compared with those who did not use medications (65%); the same prophylactic benefit held true for postpartum medication use as well.

Despite these apparent benefits, the decision to continue or stop medications during pregnancy is a difficult one, given the need to also consider the risks of perinatal medication exposure and the fact that medication use does not guarantee psychiatric stability. Therefore, clinicians weighing individual risks versus benefits may find it helpful to consider factors that can predict relapse as well as the effect of bipolar disorder on pregnancy outcomes. Risk factors predicting bipolar relapse may include history of perinatal affective psychosis or depression (4), severity of illness (7), relapse during pregnancy, primiparity, family history of postpartum episodes, and obstetric complications (2). Adverse pregnancy outcomes and high-risk behaviors during pregnancy reported in association with bipolar disorder include preterm birth, smoking, and alcohol and illicit drug use (8).

In this article, we use a brief case vignette to illustrate some of the questions and challenges that arise in the

treatment of women with bipolar disorder during the pregnancy and postpartum periods. We use a question-and-answer format to review the evidence base and expert recommendations. The article concludes with a set of general recommendations to help guide practitioners caring for women with bipolar disorder during and after pregnancy.

## CASE VIGNETTE

A 28-year-old woman with a past psychiatric history of bipolar disorder type I presents to you for consultation about medication management during pregnancy. She was first diagnosed with bipolar disorder in college after having three episodes of acute mania, the second of which led to hospitalization after she jumped out of a second-story window due to command auditory hallucinations to harm herself. She was started on lithium during that hospitalization, and she reports that she has been euthymic while on lithium. However, she reports having had over the past three years two major depressive episodes that occurred when she stopped her lithium. Her mother also has a diagnosis of bipolar disorder type I and had two episodes of postpartum depression. The patient tells you that she recently started a committed relationship and is interested in getting pregnant. She is asking for guidance about her medication options during her pregnancy.

## QUESTIONS AND CONTROVERSY

A case such as this one raises numerous important clinical questions, some of which engender debate among obstetric and psychiatric providers in general practice. Most of these questions arise from the larger, complex question of how best to balance the clinical benefit of prophylactic psychotropic medications during pregnancy with fetal risks from in-utero medication exposure. We explore these questions in further detail in the following section, using the case to illustrate key points. We then summarize the evidence, if available, and provide recommendations for clinical management.

## TREATMENT STRATEGIES AND EVIDENCE

### What Aspects of the Patient's History Would Help Guide Your Recommendations for Treatment During Pregnancy?

In deciding whether to continue psychotropic medications during pregnancy, clinicians must consider each patient's individual risk factors for relapse. The patient in this case vignette has several of the aforementioned risk factors, including greater severity of illness, primiparity, and family history of postpartum episodes. She has relapsed twice before in the context of stopping her lithium and made a suicide attempt in the setting of a manic episode. Given these factors, the risks of stopping psychopharmacology need to be weighed heavily against the potential teratogenic and neonatal risks of the medication. It is worth nothing that if this patient had a less-severe form of illness (e.g., bipolar disorder type II with no manias by definition or no history of suicide attempts), the risk-benefit ratio of using psychotropics during pregnancy might have been different, favoring lower risk alternatives to lithium, such as lamotrigine or psychotherapy.

### Does Evidence Support Prophylactic Pharmacotherapy for Bipolar Disorder During Pregnancy?

Understanding the impact of prophylactic psychotropic medication on pregnancy and postpartum relapse rates is important in helping patients and their providers conduct a risk-benefit assessment and develop an individualized peripartum management plan. Medication prophylaxis is important for maintaining mood stability during pregnancy as well as for preventing postpartum relapse. Discontinuation of mood-stabilizing medication has been associated with an increased risk of relapse, particularly in the first trimester, with major depressive and mixed episodes (7).

One large meta-analysis and systematic review found that women without prophylactic pharmacotherapy during pregnancy had a postpartum relapse rate of 66%, compared with 23% for women who were taking medications (2). Most of the women taking prophylactic medications used lithium (9). Most of the studies of prophylactic pharmacotherapy for bipolar disorder during pregnancy have focused on use of lithium, which seems to have a protective effect during both the pregnancy and the postpartum period (7, 10). Fewer data are available on other agents, although several such agents, including second-generation antipsychotics and lamotrigine, are routinely used.

Rates of recurrence in the perinatal period have been lower among women taking medication than among women without prophylaxis. However, reported recurrence rates—even among women taking medications—remain high, ranging from 20% to 50%, depending on the study (4).

To best advise patients about using psychotropic medications during pregnancy or lactation, health care providers have to help patients weigh the risks of untreated illness against the risks of teratogenicity, perinatal complications, and neurodevelopmental problems. Although this has to be an individualized process for each patient, most experts have concluded that that the benefits of continuing medication during pregnancy still seem to outweigh the risks, particularly for women with history of more severe illness.

### What Factors Should You Consider in Interpreting the Literature on Medication Safety During Pregnancy?

To make sense of the literature in this area, practicing clinicians should keep in mind several important points. First, although many of the recent data about medications' safety during pregnancy are reassuring, birth defects may still occur, given the background rate in the U.S. general population of about 3% (11).

Second, prospective, double-blind, placebo-controlled studies with long-term follow-up are not available. Many of the available studies are small and have methodological limitations, such as lack of controls for important confounders (underlying psychiatric disorder, comorbid substance use, other medications, duration or dose of the exposure, etc.), confounds by indication, or insufficient statistical power.

Third, it is often difficult to separate the adverse effect of a medication from the underling psychiatric illness. Bipolar disorder itself has been associated with adverse pregnancy outcomes, such as preterm birth (8, 12).

Fourth, case reports and case series lack a denominator for the estimation of possible risk in the entire population of exposed individuals.

Fifth, statistically significant association may not be clinically meaningful if the number needed to harm is high. Similarly, a statistically significant increase in the relative risk of an adverse outcome may not be clinically meaningful if the absolute risk remains very low. Finally, even studies with large sample sizes may lack power to study very rare events, such as congenital malformations.

**What Are the Potential Risks of Remaining on Lithium During Pregnancy?**

Lithium is widely considered to be the gold standard mood stabilizer for the treatment and prevention of relapses, particularly manic episodes, in bipolar disorder type I. Treatment with lithium can reduce the risk of relapse during pregnancy and the postpartum period (2, 7), but its use is limited by concerns about teratogenicity and perinatal complications. Researchers have had difficulty interpreting the data regarding the association of lithium use with an increased risk of congenital malformations, perinatal complications, and neurodevelopmental effects because of the paucity of high-quality studies. Practice guidelines provide inconsistent and variable information about lithium's safety during pregnancy and recommendations for use, which makes individual risk-benefit discussions imperative (9).

Lithium freely crosses the placenta and equilibrates between maternal and fetal circulation (13). The association of lithium use during pregnancy with an elevated risk of congenital cardiac malformations, including Ebstein's anomaly, was first reported in the 1970s on the basis of data from the Register of Lithium Babies (14). A later analysis of the data estimated the risk to be just 10–20 times higher than risk in the general population: 1–2 of 1,000 live births, as compared with the background rate of 1 of 20,000 live births (15).

Results from three recent large cohort studies mostly indicate a lower risk of congenital malformations than previously reported, although they still suggest some risk (16–18). A prospective observational study from the Israeli Teratology Information Service demonstrated that the rate of major congenital abnormalities, including cardiovascular anomalies, was not significantly greater among babies exposed to lithium in the first trimester, once those anomalies that spontaneously resolved were excluded (16). Patorno et al. used U.S. Medicaid register data to compare lithium- and lamotrigine-exposed pregnancies and found a dose-dependent association between lithium exposure and cardiac malformations, including Ebstein's anomaly (17). A recent meta-analysis of six studies (18) found an increased risk of major malformations in lithium-exposed pregnancies compared with nonexposed pregnancies among women with a mood disorder, but there was no statistically significant increase in the risk of cardiac malformations.

A possible association between lithium and neural tube defects has been suggested by some rodent studies (19) and individual case reports (16). Further studies are needed to determine whether lithium is associated with an increased risk of neural tube defects.

An association between lithium use and obstetric complications, including miscarriages and preterm deliveries, has been reported, although these studies did not control fully for important confounding variables (16). Several more recent studies have not found higher rates of obstetric complications in lithium-exposed pregnancies compared with disease-matched controls (18). Lithium exposure may be associated with increased risk of neonatal complications, most notably "floppy infant syndrome," which presents with poor sucking, lethargy, tachypnea, respiratory distress syndrome, poor tone, and cyanosis (20). These effects may be dose related, given that one small, prospective study reported an increased risk of neonatal neurologic and respiratory problems, especially for neonatal serum levels higher than 0.64 mEq/L (13). Cases of neonatal hyperbilirubinemia, cardiac rhythm disturbances, hypothyroidism, and diabetes insipidus have been described as well (13, 21). Complications have been reported in cases of both toxic and low maternal and neonatal serum lithium levels, but no cases of infant death have been reported in association with late-pregnancy lithium exposure, and these complications have not been well studied.

Much less is known regarding the long-term effects of lithium on neurodevelopment of exposed children, but available data are reassuring. An observational retrospective cohort study of 15 children who were exposed to lithium in utero found the children to have normal growth, behavior, and general development when evaluated at 3–15 years of age (22). Cognitive tests were within normal limits, although most children had nonstatistically significant lower scores on the performance IQ subtest. A recent study found no difference in total, performance, or verbal IQ among children with in-utero lithium exposure, nonexposed children of mothers with a mood disorder, and control children (23). Additional studies, including neuroimaging studies, are needed to more fully elucidate potential long-term effects of in-utero lithium exposure.

Given the perceived risks of first-trimester lithium exposure, some guidelines suggest that clinicians should consider a lithium taper but weigh it against the risk of relapse (taking into account the patient's overall illness burden,

severity, and suicide risk and the uniqueness of her lithium responsivity antepartum) (9). For patients who choose to continue lithium throughout their pregnancy, high-resolution ultrasound and fetal echocardiography are recommended at 16–18 weeks to identify any potential cardiac malformations secondary to lithium exposure (20). Clinicians should inform pregnant women about the risk of perinatal complications and closely coordinate care with pediatricians. Newborns should be carefully monitored, especially during the first 48 hours, for potential perinatal complications of maternal lithium use. Current expert recommendations do not include discontinuing lithium during late pregnancy or during delivery for patients with therapeutic lithium levels (24, 25), but clinicians should carefully monitor maternal lithium levels and ensure adequate hydration in the hope of minimizing the risk of neonatal toxicity.

**What Are the Alternative Pharmacological Treatment Options and Their Risks?**

*Valproate.* Antiepileptic medications are often used in the management of bipolar disorder. Valproate is approved by the U.S. Food and Drug Administration (FDA) for acute manic or mixed episodes and is widely used off label for prophylaxis. However, valproate should be avoided if possible during pregnancy because of an association with increased rates of congenital malformations and neurodevelopmental delays.

Exposure to valproate during the first trimester has been associated with an increased risk of neural tube defects, especially spina bifida, and an increased rate of total congenital malformations, including craniofacial, cardiac, genital, and skeletal or limb abnormalities (26–29). In certain studies, total rates of malformation were as high as 15% (28) or, in the case of spina bifida, 12–16 times that in the general population (26). Folate administration has been recommended in some reviews, but it is unclear whether this affects the overall rate of malformation in the fetus (30). Some literature indicates a dose-related relative risk in exposure to valproate, with risk starting at doses as low as 400 mg/day (28). Later in life, cognitive and behavioral abnormalities, such as reduced IQ, autism spectrum disorders, and attention-deficit/hyperactivity disorder, have also been reported in association with valproate exposure during pregnancy (29, 31).

It is important to keep in mind that most of the studies examining risks of valproate use during pregnancy were focused on women with epilepsy, so it is not known precisely how findings would generalize to bipolar disorder or other conditions. Valproate should be avoided if possible during pregnancy and among reproductive-age women in general, and the clinician should carefully discuss and document risks versus benefits and justification for use if the decision is made to use valproate during pregnancy despite the known risks.

*Carbamazepine.* Given limited use in general psychiatric practice, carbamazepine is less likely to be prescribed to women of reproductive age. However, congenital malformations are thought to be prevalent at higher rates compared with the unexposed population. A Cochrane review reported a pooled major malformation prevalence of 4.93% and a difference in risk from unexposed children ranging from to 1% to 2% (27). Reports have associated carbamazepine with an increased risk of neural tube malformations (32), urinary tract malformations (28), and orofacial cleft and craniofacial malformations (27), but methodological limitations make it difficult to draw conclusions about rates of specific malformations. Long-term outcomes suggest that exposure to carbamazepine in utero can cause future neurodevelopmental delays as well as decrease IQ (31).

*Lamotrigine.* Lamotrigine is FDA approved for the prevention of recurrent mood episodes in bipolar disorder type I and is often used off label for bipolar disorder type II or for acute bipolar depression. Given reassuring safety data, clinicians may favor it for women of reproductive age. Although an increased risk for oral clefts was reported by the North American Antiepileptic Drug Registry (33), this finding has not been replicated, and multiple subsequent large, register-based studies have shown the rate of total malformations in exposed pregnancies to be comparable to the rate among unexposed control participants (34). In a recent retrospective study of 20 years of data, lamotrigine had a low incidence of congenital malformations during pregnancy (28). Lamotrigine use in pregnancy is therefore considered relatively safe, and the drug is often used as an alternative to lithium or valproate.

Less is known about the efficacy of lamotrigine during the peripartum period. However, a small, population-based observational cohort study using Danish national registry data did not find a significant difference in the risk of postpartum psychiatric admission between women who used lamotrigine and those who used lithium during pregnancy (35). The study authors suggested that lamotrigine could be a reasonable treatment alternative for pregnant women with bipolar disorder, particularly for those with a history of significant depressive episodes. Limited data also suggest that there is not significant impact on the long-term neurodevelopment of children exposed to lamotrigine in utero (31).

*Antipsychotics.* Second-generation antipsychotics are often used as monotherapy for mood stability or in conjunction with mood stabilizers for mood control, and they increasingly are being used during pregnancy. Previous registry studies largely have reported on antipsychotic medications as a class and have yielded mixed results. Higher incidence of low birth weight, preterm birth, and neonatal complications have been reported in some studies, although confounders such as exposure to other medications, substance use (e.g., alcohol and nicotine), and prepregnancy diabetes and hypertension may limit any definitive conclusions about a specific causal relationship (34). The FDA added a risk of

neonatal complications after third-trimester exposure to the labeling for antipsychotics in 2011. Possible neonatal complications include abnormal movements, agitation, increased or decreased muscle tone, tremor, sleepiness, and breathing and feeding difficulties (36). Regarding the risk of congenital malformations associated with first-trimester use of second-generation antipsychotics, a large study using a U.S. Medicaid cohort provides some reassurance. Medications included in this study were aripiprazole, olanzapine, quetiapine fumarate, risperidone, and ziprasidone. The study found that the relative risk of congenital malformations among babies with first-trimester exposure to second-generation antipsychotics was not elevated over baseline risk once the authors adjusted for confounding factors (37). When the authors examined medications individually, however, they found a small increased risk in overall malformations and cardiac malformations for risperidone.

Concern has been raised about the risk of metabolic syndrome associated with second-generation antipsychotics and the impact on both mother and fetus. In a recently published review of second-generation antipsychotics' impact on gestational diabetes, Uguz (38) noted that the risk of maternal gestational diabetes mellitus (GDM) ranged from 2.63% to 13.0% among women using second-generation antipsychotics, in comparison with 2.0% to 2.17% among women using first-generation antipsychotics. However, the authors noted that in individual studies, there has not been a consistent, significant increase in risk of GDM, and they concluded that "results of most studies do not support a significant connection between antipsychotic treatment and the development of GDM when confounding variables were taken into account." By contrast, one recent study found that use of quetiapine and olanzapine during pregnancy was associated with a small increase in risk for gestational diabetes (39).

Unfortunately, only a limited number of studies have looked at the long-term outcomes of infants and children who were exposed in utero to antipsychotics, and clinicians should inform patients during risk-benefit conversations about such gaps in the safety data. One such study, which examined the risk of second-generation antipsychotics on child development, detected an increased delay at two months of age in areas of social-emotional, motor, and adaptive behavioral domains. However, there was no statistically significant difference by 12 months between infants exposed to second-generation antipsychotics and control infants (40).

Monotherapy with antipsychotics is considered safer than polypharmacy in general but also among women of reproductive age. In a study published by Sadowski et al., women exposed to polypharmacy with second-generation antipsychotics had higher prepregnancy weight, higher risk of complications for neonates leading to increased risk of stays in the intensive care unit, premature birth, and babies who were large for their gestational age, as compared with women exposed to monotherapy with second-generation antipsychotics (41). However, the researchers also noted that women on polypharmacy were more likely to smoke during pregnancy, less likely to use prenatal vitamins, and eight times less likely to breastfeed. They were also two to three times more likely to have hypertension, gestational diabetes, and hypothyroidism.

*Benzodiazepines.* Benzodiazepines are frequently used as adjunct medication in the treatment of bipolar disorder. Previous research suggested the potential for congenital malformations among fetuses exposed in utero to benzodiazepines, on the basis of early rodent studies examining diazepam and alprazolam. These studies suggested an increase in risk of cleft palate, but later studies did not substantiate this finding (42), and dosing was higher than human use. Similar rodent data on lorazepam come from one study that examined dosages 400 times the human dose, finding an increased incidence of cleft palate (43). Subsequent population-based cohort studies from Israel and England demonstrated that the frequency of congenital anomalies after in-utero exposure to benzodiazepines (i.e., alprazolam, lorazepam, diazepam, oxazepam, and clonazepam) was not significantly different from the frequency among control participants (44, 45).

After delivery, there is a potential risk of neonatal withdrawal among infants exposed to standing doses of benzodiazepines in utero. Symptoms such as hypotonia, decreased sucking, cyanosis, and temperature dysregulation have been reported among infants born to mothers taking benzodiazepines (46–48). Given that the infant cytochrome p450 enzyme system is still developing, medications without long-lasting, active metabolites are less likely to accumulate and cause complications after delivery. Such medications include lorazepam and clonazepam. Using limited quantities on an as-needed basis is preferable if possible.

### Should Clinicians Make Any Changes in Routine Therapeutic Drug Monitoring or Dosing When Treating Pregnant Women With Bipolar Disorder?

Changes in drug metabolism and clearance during pregnancy and the postpartum period complicate medication management. Lithium levels require close monitoring because of the narrow therapeutic index and potential for toxicity with higher levels. Pregnancy-related increases in total body water, plasma volume, and glomerular filtration result in increased clearance and decreased lithium levels. Lithium blood levels have been shown to decrease in the first trimester (−24%), plateau in the second trimester (−36%), and then begin to slowly return to prepregnancy level in the third trimester (−21%) and postpartum period (49).

The lithium dose may need to be increased during pregnancy, although some experts prefer to keep the dose low during the first trimester given the potential teratogenicity. Clinicians should be aware of the risk of lithium toxicity as lithium levels begin to increase closer to delivery. Recommendations suggest that lithium levels should be checked every four weeks throughout pregnancy, with increased

frequency of monitoring in the third trimester (weekly from 34 weeks or during the last month, depending on the guideline being used) (15, 18, 24, 25, 34). Even more frequent monitoring is needed in the setting of complications, such as hyperemesis gravidarum or pre-eclampsia, which can affect lithium levels.

Although some guidelines have suggested decreasing or even discontinuing lithium at the onset of labor to avoid lithium toxicity as glomerular filtration rate returns to baseline, fluid volume contracts, and lithium levels subsequently rise, this must be weighed against the exceptionally high risk of relapse endured by women with bipolar disorder during the postpartum period (2, 9). Thus, continuation of lithium is recommended in the postpartum period, with dosing guided by serum levels checked at the onset of labor, 24 hours after delivery, and after each dose adjustment, at least twice weekly. Clinicians should take proper precautions to ensure adequate hydration throughout labor and should avoid medications that affect renal function (25, 34).

Lamotrigine is metabolized primarily by hepatic glucuronidation. Increases in estrogen during pregnancy induce glucuronidation, leading to increased clearance of lamotrigine (50). Lamotrigine clearance can increase up to five times normal levels during the later weeks of pregnancy, and, on average, women have been shown to need up to a 315% increase in dose by the third trimester (51). Patients may need repeated dose adjustments during pregnancy to maintain therapeutic drug levels, so clinicians should monitor levels closely. Some experts recommend obtaining a baseline serum level as early as possible and continuing to monitor serum lamotrigine level every four weeks throughout pregnancy, with dose adjustments as needed (52).

Within a few days of delivery, lamotrigine clearance decreases and plasma levels increase, so dose reduction is necessary to avoid toxicity. If dosage is increased more than four times during pregnancy, the dose should be decreased immediately by 20%−25% after delivery to prevent lamotrigine toxicity (52). Although lamotrigine dosing in bipolar disorder is generally guided by clinical response rather than serum levels, the above data highlight the need for therapeutic drug monitoring (TDM) of lamotrigine among pregnant women. If TDM is not available at all, the patient should receive close clinical monitoring, and the clinician should anticipate a possible dose increase of two to three times the preconception dose by the end of pregnancy. After delivery, the dose should be tapered rapidly back to preconception levels within two weeks (34).

### Does Evidence Support Nonpharmacological Treatment Options for Mood Stabilization and Relapse Prevention During and After Pregnancy?

In addition to medication management, providers must incorporate therapeutic and behavioral intervention strategies for patients. Most of the literature on psychotherapy in the postpartum period focuses on treatment of depression and anxiety disorders. However, many women with bipolar disorder experience symptoms of depressed mood. The most commonly studied therapies—cognitive-behavioral therapy and interpersonal psychotherapy—have been shown to have significant benefits for women with postpartum depression (53, 54). Additionally, nondirective and supportive therapies as well as family and mother-baby dyad therapy have been shown to have a positive impact on maternal mental health as well as to improve maternal attachment and mother-infant interactions (55, 56). Therapy for the bipolar patient can be considered in conjunction with appropriate pharmacologic management.

Additionally, sleep hygiene is considered an important component in the prevention and treatment of postpartum mania as well as depression (57). Early studies showed a correlation between insomnia and onset of postpartum psychosis (58). More recent studies have promoted maternal sleep by encouraging private rooms while the patient is in the hospital, nursing-led nighttime feeds, and sleep medication for patients during the first week postpartum (10).

For mothers who pose a risk to themselves or their offspring, inpatient admission on a psychiatric unit is necessary. Additionally, electroconvulsive therapy (ECT) is used in the treatment of mania or in cases of severe depression that pose an imminent risk to mother or child or fail to respond adequately to pharmacotherapy. However, concerns about use of this modality during pregnancy are based on the possibilities of maternal hypoxia and hypotension (59) as well as more significant risks due to induced release of oxytocin and vasoactive hormones that may produce uterine contractions or bleeding (60–62) or even placental abruption (61). ECT during pregnancy has been associated with serious complications approximately 9% of the time (59), but rarely has fetal death been reported (63).

Some reports have shown that with adequate preprocedure hydration and with appropriate monitoring, ECT during pregnancy does not seem to pose a severe risk for the fetus (64, 65). In a review of 339 cases reported from 1941 to 2007, the authors concluded that the risk of adverse events was low (66). Reproductive psychiatry experts have considered ECT to be relatively safe with modifications in technique, compared with the risks of untreated severe mental illness (20, 66, 67).

### Can a Woman With Bipolar Disorder on Psychotropic Medication Safely Breastfeed her Baby?

Recommendations on lithium exposure during breastfeeding among newborns are controversial, with limited literature and mixed outcomes. Numerous guidelines and reports recommend against lithium use while breastfeeding (68). Breast milk contains approximately 50% of the mother's lithium level, and serum levels among infants are seen at approximately 50% of that level, or about a fourth of the maternal serum level (69). Documented concerns for newborns include hypotonia, dehydration, and impairment of thyroid function because of limited renal clearance in newborns (69–71).

**BOX 1. Recommendations for the Treatment of Women With Bipolar Disorder During Pregnancy**

- Provide psychoeducation on risks of untreated psychiatric illness (impact on mother and fetus as well as long-term outcomes among children) versus the risks of pharmacology.
- When possible, consider using monotherapy.
- Continue a previously "successful" medication, and avoid discontinuing or reducing medication unless clinically indicated.
- Collaboration among the psychiatrist, obstetrician, and neonatologist or pediatrician is essential.
- Pregnant patients should be evaluated carefully and monitored closely throughout pregnancy and in the first year postpartum.
- Include the patient's partner and family in discussion to help improve compliance and reduce strife.
- Valproate should be avoided for women of childbearing age unless alternatives are not appropriate. If valproate is used, the clinician should discuss with the patient the potential risks during pregnancy, talk with the patient about a contraception plan, and document accordingly.
- Electroconvulsive therapy (ECT) should be considered for severe, refractory cases of mood disorders during pregnancy or in the presence of symptoms such as suicidality, psychosis, dangerous behaviors, and catatonia, which may lead to acute safety concerns. In such cases, ECT may be used concurrently with pharmacotherapy.
- Clinicians should maintain good documentation of conversations about the risks of psychotropics versus the risk of untreated psychiatric illness.
- Clinicians should inform patients about existing gaps in the medication safety literature, particularly in the area of long-term neurodevelopmental effects of in-utero medication exposure.
- Psychotherapy and psychosocial interventions are important considerations in the treatment of women, often in conjunction with pharmacological management.

Although it is important to consider that mothers may choose to stop their lithium rather than opt out of breastfeeding, only a rare situation would adequately allow for monitoring of infant lithium exposure.

By contrast, the other medications reviewed above have more favorable safety data for lactation. Most practice guidelines conclude that breastfeeding and taking lamotrigine are compatible, and the rate of adverse events during lactation is low (72). The mean serum level of lamotrigine among breastfed infants was found in one study to be 32.5% of the maternal serum level, but it ranged from 6% to 50% of maternal serum levels (52). The only reported adverse event of lamotrigine exposure through breast milk was a 16-day-old infant who experienced a brief apneic episode while sleeping and again three hours later while breastfeeding (73).

Carbamazepine and valproate are also considered relatively safe during breastfeeding, with serum levels among infants measured at less than therapeutic dosages in children (74) and only a few reported case studies of hepatic dysfunction or cholestatic jaundice (75, 76). However, most articles have recommended close monitoring of exposed infants (77). The data for antipsychotic safety during lactation are limited, but neonatal exposure is thought to be less than during pregnancy, so continuing the medication is recommended (34). Some experts suggest that among the antipsychotics, quetiapine and olanzapine should be considered as first-line treatment options, whereas risperidone may be compatible with breastfeeding under medical supervision (78).

Researchers previously thought benzodiazepines were contraindicated with breastfeeding because of concerns about sedation and withdrawal symptoms, but more recent data suggest that the overall risk of exposure is minimal. One prospective study found that only 1.6% of infants exposed to benzodiazepines showed signs of sedation. This number did not seem to correlate with any specific variable, such as dose or number of hours breastfed (79).

## What Additional Interventions Help Prevent Relapse During and After Pregnancy?

A comprehensive plan for maintaining mood stability during pregnancy and minimizing risk of postpartum relapse should be developed for all women with bipolar disorder. These discussions should begin well before pregnancy occurs, because pregnancy might be unplanned. In addition to risk-benefit discussions about medication prophylaxis during pregnancy and after delivery, each patient's individualized management plan should include an obstetric birth plan that includes preferential mode of delivery and management recommendations for acute psychiatric symptoms that may develop. Providers should also work with patients and their partners to identify early prodromal signs and symptoms of relapse and develop a list of specific intervention strategies. Developing a plan for baby feeding, proposing strategies for stress reduction and sleep maintenance, and ensuring adequate supports are all also important for minimizing risk of relapse.

During the postpartum period, it is important to continue to closely monitor and adjust medication doses as needed to avoid toxicity, maintain a therapeutic level, and maintain efficacy. Because postpartum insomnia may increase the risk of a manic episode, patients should be counseled to avoid sleep deprivation and to make arrangements to have a partner or another individual to assist with nighttime feedings.

## Can Psychiatrists Perform Interventions to Help Women Plan for a Future Pregnancy?

Psychiatrists treating women of reproductive age should routinely inquire about and document the patient's level of sexual activity, last menstrual period, method of contraception, and plans for future pregnancy. Patients and their partners (if applicable) should be counseled about potential risks versus benefits of taking specific medications during pregnancy, and medications should be selected with the patient's future

pregnancy planning in mind. In some circumstances, it may be appropriate to switch medications in advance of pregnancy planning because of potential safety concerns about continuing particular medications during pregnancy. Informed consent conversations and treatment recommendations should be documented.

## CONCLUSIONS AND RECOMMENDATIONS

Box 1 includes some helpful general recommendations for the treatment of women with bipolar disorder during pregnancy. It is important that each patient work with her health care provider to conduct a personal risk-benefit assessment and develop an individualized treatment plan. Medication prophylaxis is important for maintaining mood stability during pregnancy as well as for preventing postpartum relapse, but it has to be balanced against potential adverse effects of fetal and neonatal medication exposure. Such adverse effects include potential long-term neurodevelopmental consequences, which have been studied far less than more immediate effects and for which very limited data are available. Although all women with bipolar disorder are at increased risk for postpartum relapse, some additional risk factors for relapse have been identified, and clinicians may use these to help stratify risk and inform clinical decision making for the individual patient. Additionally, psychosocial and supportive interventions are an important consideration in helping the mother-baby dyad.

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