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Treating bipolar disorder during pregnancy

Optimal outcomes require careful preconception planning, medication risk/benefit analysis

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Ms. M, age 31, has bipolar I disorder and takes lamotrigine, 200 mg/d, and aripiprazole, 10 mg/d. She was first hospitalized at age 20 for a manic episode and was discharged on lithium, 1,200 mg/d. She was hospitalized again at age 25 for a depressive episode that occurred after she stopped taking lithium because of undesirable side effects. She was switched to lamotrigine, 200 mg/d, which she tolerated well. Aripiprazole, 10 mg/d, was added 1 year later to address emergence of mild mood elevation symptoms.

During a recent follow-up appointment, Ms. M expresses interest in getting pregnant in the next 6 months. Her mood has been stable for 5 years and she asks if she should stop taking her medications in preparation for pregnancy. What would you recommend?

Because the typical age of onset for bipolar disorder (BD) is late adolescence or early adulthood, women are at risk for new onset or recurrence of mood episodes throughout their peak reproductive years. This article updates practitioners on the treatment of BD during pregnancy, including preconception planning and the risks and benefits of medication use during pregnancy. We also cover treatment considerations during the postpartum period, such as prophylaxis of mood episodes and mood stabilizer treatment for women who breast-feed.

Prenatal planning

Ideally, "prenatal planning" should begin long before women with BD prepare to have children. Because one-half of pregnancies in the United States are unplanned[1] and manic episodes may result in impulsivity and increased sexual activity, all women of reproductive age with BD should be counseled about birth control and risks of unplanned pregnancies. Discussions about risks of in utero exposure to psychotropics should occur when medications are first prescribed. Because certain mood stabilizers, (eg, carbamazepine) may decrease efficacy of oral contraceptives by inducing cytochrome P450 (CYP450) enzymes, women taking these medications also should be counseled about additional methods of birth control.[2]

Oral contraceptives also may affect mood stabilizer levels through similar mechanisms. Because of CYP450 induction, lamotrigine serum levels are lower during the 3 "active" weeks of exposure to exogenous estrogen. During the "pill-free" last week, lamotrigine levels may increase up to 54%.[3]

Because mood stabilizers such as valproate are associated with teratogenic risks, women with BD should be asked about contraception at every visit.[4] Valproate also has been associated with an increased risk of menstrual cycle irregularity. Some studies have shown that even before initiating mood stabilizers, women with BD have a higher incidence of menstrual cycle irregularity than women without BD, which suggests the link between polycystic ovarian syndrome (PCOS) and BD may be independent of medications and part of the endophenotype.[5]

The importance of prenatal vitamins should be discussed. The recommended folate dosage for women planning to become pregnant is 0.4 to 1 mg/d and 0.8 to 5 mg/d for women with either a previous pregnancy with neural tube defects or those taking an antiepileptic medication.[6]

Table 1[7] summarizes recommendations to improve prenatal planning in women

Clinical Point
Because mood stabilizers are associated with teratogenic risks, ask women with BD about contraception at every visit

Quick Poll
QUICK POLLS
Which treatment option would you choose for Mr. S's intermittent explosive disorder?

Mr. S, age 19, reports feeling overly angry over the slightest daily annoyances, and he relieves his anger by punching a wall and occasionally others. Mr. S, who has no history of psychiatric illness, says that he recently started hurting himself when he has outbursts, because earlier episodes of violence have ruined relationships. Which treatment option would you choose for Mr. S's intermittent explosive disorder?

- Prescribe fluoxetine, 20 mg/d, and titrate to 90 mg/d
- Encourage Mr. S to attend group therapy for anger management
- Prescribe fluoxetine and begin cognitive-behavioral therapy
- Prescribe oxcarbazepine, 600 mg/d, and titrate to 1,200 mg/d

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1. How to control weight gain when prescribing antidepressants
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3. Does bupropion exacerbate anxiety?
4. Which psychotropics carry the greatest

with BD. Goals include:

- meeting with the patient at least 3 months before conception to review current menstrual cycle functioning. If your patient exhibits any signs or symptoms of PCOS, consider referral to a gynecologist
- meeting with patient and partner/significant supports to discuss treatment decisions
- optimizing the patient's mood before conception, preferably for at least 3 to 6 months
- prescribing monotherapy at the lowest therapeutic dose if clinically feasible
- assessing the patient's personal preferences and beliefs regarding medication use during pregnancy and breast-feeding
- assessing the patient's capacity to understand the risks and benefits of medication continuation/discontinuation during pregnancy, including risk for relapse, current literature on teratogenicity, perinatal complications, and neurodevelopmental studies. Document that the patient provides informed consent.

Table 1

Pregnancy and BD: Medication management guidelines

Comprehensive prenatal counseling should begin at least 3 months before pregnancy. Folate supplementation is advised
Medication should be avoided if clinically feasible (particularly during the first trimester). Avoid abrupt discontinuation. Increase psychosocial and clinical supports
If medication is pursued: • Use minimum effective dose • Monotherapy is preferable • Avoid changing effective medications unless there is significant safety or clinical advantage • Increase frequency of clinical monitoring as indicated
Comprehensive postpartum counseling should begin before and be reinforced throughout pregnancy, emphasizing: • importance of sleep • postpartum prophylaxis • risks/benefits of breast-feeding • importance of social support and identification of support structure, including psychoeducation session with support team
BD: bipolar disorder Source: Adapted from reference 7

CASE CONTINUED: Medication decisions

Ms. M's first question is, "Should I stop taking my medications?" Ms. M and her psychiatrist review the risks and benefits of medication exposure during pregnancy (Table 2) and decide against discontinuing all medications because of her history of relapse when she stopped lithium. Because Ms. M's mood has been stable for 5 years, she and her psychiatrist decide to limit her medications to lamotrigine monotherapy at her current dose, and agree to slowly taper aripiprazole. One week later, Ms. M calls and states she has a positive pregnancy test and is wondering if she should stop aripiprazole all at once. Ms. M is advised to continue with the original plan to slowly taper aripiprazole.

Table 2

Potential risks of continuing or discontinuing medications for BD during pregnancy

Risks of discontinuing	Risks of continuing
Mood relapse during pregnancy or postpartum Risks of alternative treatment(s): • failure to respond to different emergency treatment • potential exposure to polypharmacy	Medication-specific risks: • congenital malformation (carbamazepine, lithium, valproate) • neurodevelopmental risks (valproate)
BD: bipolar disorder	

Medication risks/benefits

Women with BD have a high rate of relapse associated with abrupt discontinuation of pharmacotherapy during pregnancy. As such, patients and their partners and families should be cautioned against rapid discontinuation of medications.[8] The risk to mother and fetus is particularly high for women with a history of recurrent, severe mood episodes. These patients face not only a high risk of recurrence of mood episodes, but also the inherent danger of impulsivity, poor self-care, and suicidality associated with mania, depression, and mixed states. In these cases, continuing a medication (other than known teratogens such as valproate) that has effectively stabilized mood may be preferred to discontinuation; these decisions are made after careful risk/benefit assessment.

> **Clinical Point**
>
> Advise patients with BD that abruptly discontinuing pharmacotherapy during pregnancy will increase their risk of relapse

Carefully reviewing the patient's history is essential to assessing the risks and benefits of tapering medications before pregnancy. Consider the frequency and severity of your patient's mood episodes, and whether a switch in mood state was rapid or had a prodromal phase. If a patient currently has a stable mood, a history of mild to moderate mood episodes, a history of prodromal symptoms (eg, gradually increasing sleep disturbances and mood deterioration), and no history of rapid switches, gradually discontinuing medications before or during pregnancy may be considered. However, encourage women to enlist their partners and family members to monitor for warning symptoms and advocate for early medication intervention. Because insomnia is a sign of relapse for many patients, educate women and their families about the importance of maintaining a regular sleep/wake cycle and alerting care providers if this cycle changes.

Mood stabilizers with the greatest risk for teratogenicity are valproate, carbamazepine, and lithium.[9] Valproate is associated

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with a 6% to 13% risk of congenital malformation, including neural tube defects (1% to 2%) and cardiac or craniofacial defects. Risks increase at doses >800 mg/d.[10] Potential perinatal complications associated with valproate include heart rate deceleration, abnormal tone (hypotonia or hypertonia), and growth retardation.[11] Neurobehavioral sequelae include lower IQ scores and increased risk of autism.[12]

Carbamazepine is associated with a 2% to 5% risk of congenital malformation, including neural tube defects and cardiac or craniofacial defects.[4] Perinatal complications associated with carbamazepine include vitamin K deficiency.[4] The neurobehavioral sequelae of carbamazepine are controversial; most prospective studies do not suggest long-term cognitive deficits.[13] It is strongly recommended that valproate and carbamazepine be avoided, if possible, in women with BD who plan to become pregnant in the near future.

> **Clinical Point**
>
> The mood stabilizers with the greatest risk for teratogenicity are valproate, carbamazepine, and lithium

Prospective studies of lithium have shown a 2.8% rate of congenital malformations, which is much lower than the 11% rate found in retrospective studies.[14] Ebstein's anomaly—downward displacement of the tricuspid valve—is estimated to occur in .05% to 0.1% of infants exposed to lithium, which is 10 to 20 times the base rate, but a low absolute risk.[11]

> **Clinical Point**
>
> Some researchers have suggested suspending lithium during labor may lower the risk of lithium toxicity

It is recommended women taking lithium during pregnancy complete a fetal high resolution ultrasound and echocardiogram at 16 to 18 weeks.[11] Perinatal complications associated with lithium include prematurity, hypotonia, hypothyroidism, hepatic abnormalities, respiratory distress, and nephrogenic diabetes insipidus.[15] When prescribing lithium, divided doses are recommended to maintain a stable serum level. Serum lithium levels should be monitored frequently, and higher doses may be needed because of increased glomerular filtration rate and plasma volume throughout pregnancy.[10] Because of fluid shifts at delivery—including blood loss during delivery and postpartum diuresis and diaphoresis—there is a risk of lithium toxicity at this time. Some researchers have suggested suspending lithium treatment during labor or 24 to 48 hours before planned induction or Caesarean section may lower this risk, with re-administration after delivery when medically stable.[16] Women should be followed closely for signs of lithium toxicity and have lithium levels monitored as clinically indicated.[16] There is insufficient data to support any neurobehavioral sequelae of in utero exposure to lithium; however, there are few long-term follow up studies using standardized measures.[17]

Lamotrigine is associated with a 1.9% to 4.6% rate of congenital malformations, including cleft lip/palate (8.9/1,000 vs 0.5 to 1.2/1,000 baseline).[4] Studies suggest that rates of malformations (cardiac, genitourinary, gastrointestinal, neural tube defect) are dose-dependent: 1.3% at dosages <100 mg/d, 1.9% at 100 to 200 mg/d, and 5.4% at >200 mg/d.[18] Because cleft lip and palate are formed by late second trimester, it is recommended to attempt to keep the lamotrigine dose <200 mg/d during the first and second trimesters. Higher doses of lamotrigine may be needed in the third trimester because of increased renal clearance.[19] There is insufficient data to support any lamotrigine-associated neurobehavioral effects, and unlike studies of valproate, follow-up evaluations of lamotrigine-exposed children have not shown lower IQs.[20]

Evidence about the reproductive safety of other mood stabilizers used in BD is limited. A recent population-based cohort study did not show increased risk of major malformations in children exposed to topiramate, gabapentin, or oxcarbazepine during the first trimester of pregnancy.[21] Topiramate often is used in combination with other mood stabilizers for weight control, and studies suggest that polypharmacy with topiramate, especially at higher doses and with valproate, increases the risk of major congenital malformations, especially cleft lip and cleft palate.[22] Consequently, topiramate is not recommended for women planning to conceive.

Antipsychotics. Although there is increasing information about outcomes of neonates exposed to atypical antipsychotics during pregnancy, the literature still is limited. The greatest number of studies have evaluated olanzapine, risperidone, and quetiapine and show the rate of congenital malformations is 0.9% to 4.1%, which is consistent with general population rates.[23-26] Perinatal complications associated with these atypical antipsychotics include neonatal extrapyramidal syndrome (EPS), possible neonatal adaptation/withdrawal syndrome, and an increased risk of the infant being either large or small for gestational age. Because atypical antipsychotics may increase the risk of metabolic syndrome, women should be counseled about the possible increased risk for gestational diabetes with these medications. None of these drugs have been associated with neurobehavioral sequelae, but long-term follow-up studies of exposed infants are lacking.

For aripiprazole, asenapine, ziprasidone, iloperidone, and lurasidone there is insufficient data about rate of congenital malformations, obstetric complications, and neurobehavioral sequelae. However, perinatal complications associated with these medications include risk of EPS and withdrawal symptoms.[25,26]

Continued...

1 2 Next Page »

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