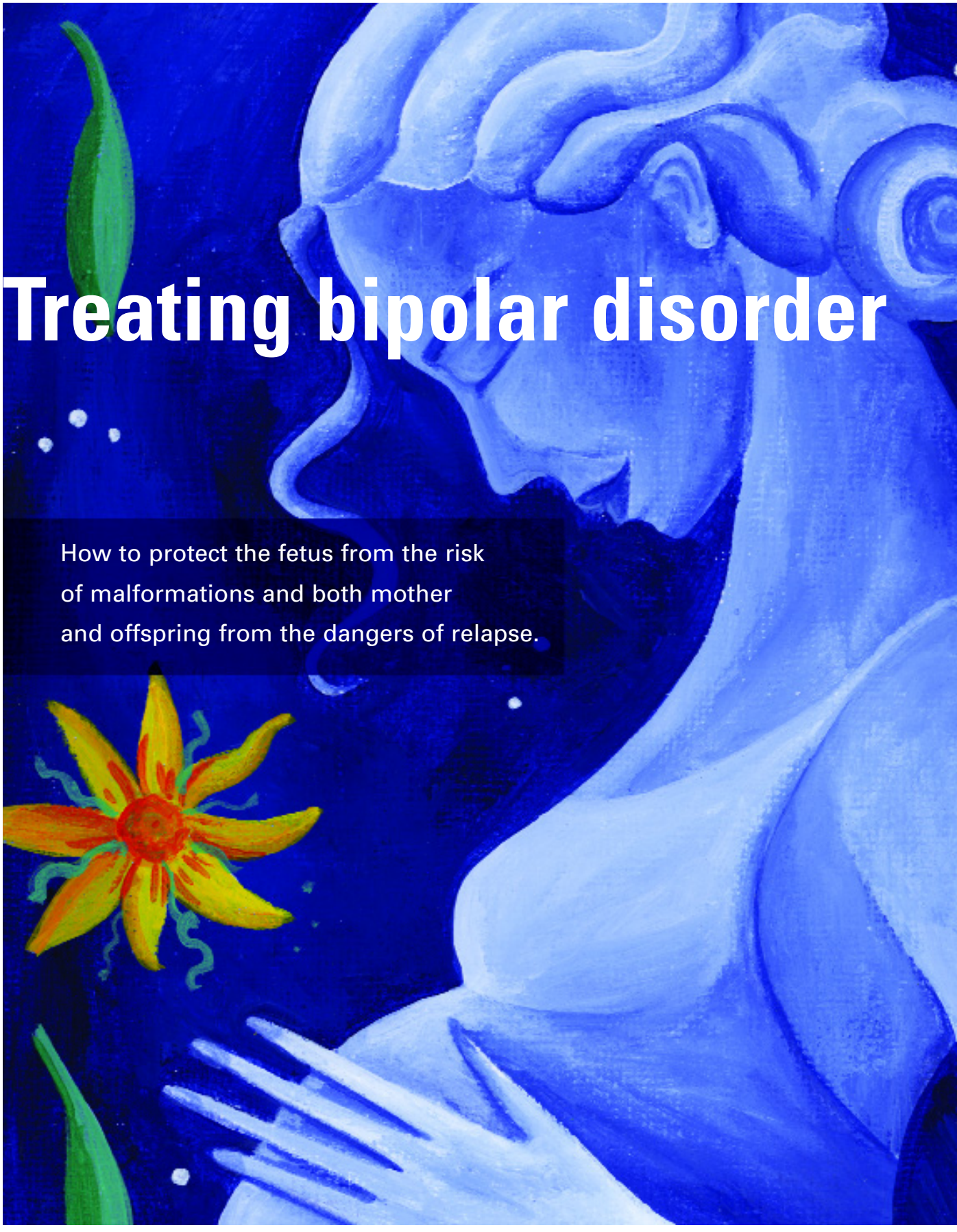
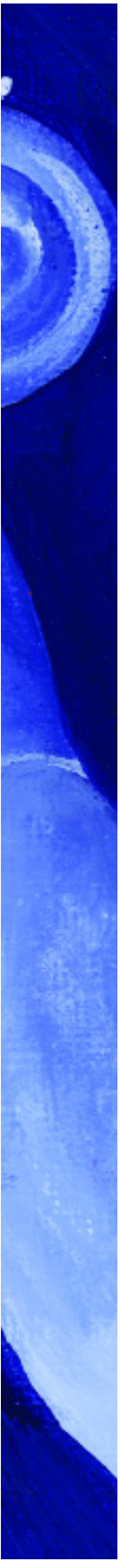


Treating bipolar disorder

How to protect the fetus from the risk of malformations and both mother and offspring from the dangers of relapse.

Current PSYCHIATRY



during pregnancy

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Prescribing drug therapy for pregnant bipolar women requires psychiatrists to balance the potential for neonatal malformations against the high risk of relapse when patients discontinue their medications.[1] To help you achieve this balance, we offer an evidence-based approach that includes:

- analysis of the FDA's teratogenicity categories for psychotropics
- review of the safety profiles of drugs used in mood stabilization
- an algorithm for managing patients who are considering conception or are pregnant.

PSYCHOTROPIC RISKS TO OFFSPRING

All psychotropic medications diffuse across the placenta, which exposes the fetus to some degree. Risks include teratogenicity, obstetrical complications, perinatal syndromes, and long-term postnatal behavioral sequelae.

Teratogenicity. A medication is considered teratogenic when prenatal exposure significantly increases the risk of congenital deformities over

Table 1

FDA Use-in-Pregnancy ratings for medications

The FDA system weighs the degree to which research findings have ruled out risk to the fetus

Category	Interpretation
A	Controlled studies show no risk
B	No evidence of risk in humans
C	Risk cannot be ruled out
D	Positive evidence of risk
X	Contraindicated in pregnancy

Source: *Physicians' Desk Reference.* Montvale, NJ: Medical Economics Co., 2003.

the baseline risk, which is 2% in the United States.[2] The cause of most congenital malformations is unknown. Risk for teratogenicity occurs in the first 12 weeks of gestation, as organs are formed.

Obstetrical complications include preterm delivery, low birth weight, and delivery complications such as low Apgar scores or behavioral effects requiring intensive care.

Perinatal syndromes include physical and behavioral symptoms noticed shortly after birth (such as jitteriness). These consequences are putatively related to drug use at or near birth and have limited duration.

Postnatal behavioral sequelae include long-term neurobehavioral abnormalities in children who were exposed to psychotropics in utero.

BALANCING RISKS

Risks with medication. The FDA's "use in pregnancy" rating system (*Table 1*) uses available data to assess the degree of teratogenic risk. These guidelines can be confusing and are one of many tools to use when considering a possible drug treatment.

Most psychotropics are category "C" or "D," which imply a chance of harm to the exposed fetus. Category "B" drugs would appear safer, but this rating could simply indicate a lack of adequate human data or that no data have shown harm in animals.

Moreover, a category "D" drug may be chosen more often during pregnancy than a category "C" drug. This may occur when more human data exist on using the category "D" drug in patients with a particular disorder (such as using lithium versus valproate or olanzapine in pregnant bipolar women).

No psychotropics are classified as "A," meaning either some risks are associated with every psychotropic or the risk of some agents has not been adequately explored. Furthermore, no psychotropics are FDA-approved for use during pregnancy.

Risks without medication. Teratogenicity notwithstanding, psychotropic intervention is the most effective treatment for women with bipolar disorder. Patients who discontinue mood-stabilizing medication after conception increase their risk of relapse into depression or mania,[3] either of which could lead to complications and untoward effects on the fetus.

A manic, pregnant patient may engage in risky behaviors that endanger her and the fetus

Depression during pregnancy has been linked to low birth weight and preterm delivery.[4,5] These effects may be mediated by the illness itself or by other factors that indirectly affect birth outcomes. For example, depression during pregnancy is associated with decreased appetite, substance use and abuse, and lower use of prenatal care.[6]

Untreated mania may also be associated with perinatal risks, as a pregnant patient in a manic state may engage in impulsive, high-risk behaviors that endanger her and the fetus.[7]

MOOD STABILIZERS

The FDA categorizes as "D" the three most com-

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monly used mood stabilizers: lithium, valproate, and carbamazepine (*Table 2*). This rating implies that studies have demonstrated fetal risk but the drug's potential benefit may still outweigh the risk.

Lithium. The International Registry of Lithium reported increased rates of cardiovascular malformations—such as Ebstein's anomaly—in children whose mothers took lithium during pregnancy.

Relative risk for Ebstein's anomaly in children with fetal exposure to lithium may be 20 times higher than the risk in unexposed children, although the absolute risk with lithium exposure remains low (1 in 1,000 births).[1,8]

No significant neurobehavioral teratogenicity has been reported in infants exposed in utero to lithium, although few cases have been studied. One study reported that 22 lithium-exposed infants attained developmental milestones at a pace comparable to that of unexposed controls.[9]

"Floppy baby" syndrome, in which infants experience hypotonicity and cyanosis, is the most recognized adverse effect in infants exposed to lithium in utero.[10] Its frequency is unknown, but rare. Neonatal hypothyroidism and nephrogenic diabetes insipidus have also been documented.

Anticonvulsants. To date, no studies have examined the outcomes of children whose mothers took anticonvulsants for bipolar disorder during pregnancy, though the research concerning epileptic mothers is extensive.

Neural tube defects. Data associate anticonvulsant exposure with a significantly greater risk for malformations than in the general population. Specifically, anticonvulsants may cause neural tube defects such as spina bifida, ancephaly, and encephaly in 2 to 5% of those exposed, as well as craniofacial anomalies, microcephaly, growth retardation, and heart defects.[11-14]

More minor malformations—such as rotated ears, depressed nasal bridge, short nose, elongated upper lip, and fingernail hypoplasia—have been reported in infants exposed to anticonvulsants in utero.[14] These malformations disappear with age.[13] Teratogenicity increases with the use of multiple anticonvulsants and possibly with higher maternal plasma levels and toxic metabolites.[15]

Conclusion. The three most commonly used mood stabilizers are all teratogenic. The least risk may occur with lithium (0.1%) versus valproate (2 to 5%) or carbamazepine (1 to 3%). These risks must be weighed against the up to 50% chance of relapse with medication discontinuation.[3]

Table 2

FDA's teratogenicity ratings of mood stabilizers and other antimanic agents

Category	Medication	Teratogenicity
Mood stabilizers	Lithium	Category D
	Carbamazepine	Category D
	Valproate	Category D
Anticonvulsants	Gabapentin	Category C
	Lamotrigine	Category C
	Topiramate	Category C
Antipsychotics	Olanzapine	Category C
	Risperidone	Category C
	Chlorpromazine	Safety in pregnancy not known
	Haloperidol	Category C
	Trifluoperazine	Safety in pregnancy not known

Source: *Physicians' Desk Reference.* Montvale, NJ: Medical Economics Co., 2003.

ANTIPSYCHOTICS

Antipsychotics are often used to treat mania because of their rapid effects and sedative properties. Most antipsychotics—specifically, haloperi-

Table 3

FDA's teratogenicity ratings of common antidepressants

Category	Medication	Teratogenicity
Tricyclics	Amitriptyline	Category C
	Clomipramine	Category C
	Desipramine	Safety in pregnancy not known
	Imipramine	Safety in pregnancy not known
	Nortriptyline	Safety in pregnancy not known
Selective serotonin reuptake inhibitors	Citalopram	Category C
	Fluoxetine	Category C
	Fluvoxamine	Category C
	Paroxetine	Category C
	Sertraline	Category C
Other antidepressants	Bupropion	Category B
	Phenelzine	Safety in pregnancy and nursing not known
	Tranylcypromine	Safety in pregnancy and nursing not known

Source: *Physicians' Desk Reference.* Montvale, NJ: Medical Economics Co., 2003.

dol, olanzapine, and risperidone—are labeled "C," specifying that fetal risk cannot be ruled out.

Chlorpromazine and haloperidol have been most studied during pregnancy but in relation to treating hyperemesis gravidarum and psychosis, not bipolar disorder. Results regarding antipsychotics' teratogenic and behavioral risks are mixed,[16-21] probably because the various compounds have different effects on the fetus.

The underlying illness—rather than the medications—may increase the rate of anomalies seen with exposure to antipsychotics:

- Rieder et al[22] reported an increased rate of perinatal death in infants of schizophrenic mothers but no significant association between the mothers' use of antipsychotics and perinatal death.
- Sobel[23] compared psychotic women with and without histories of chlorpromazine exposure during pregnancy. Rates of fetal damage were similar and approximately twice that of the general population.

A meta-analysis of 74,337 live births revealed that first-trimester exposure to low-potency antipsychotics increases the relative risk of fetal anomalies in nonpsychotic women. Phenothiazines may increase the 2% baseline incidence of malformations to 2.4%.[1] No specific organ malformation following fetal exposure to phenothiazines has been consistently identified.

Olanzapine was recently approved for treating mania. Very little data exist regarding its impact on fetal development when used during pregnancy, although studies on small numbers of women have not revealed teratogenicity.[24,25]

Conclusion. Psychotic illness itself may increase the risk of poor fetal outcome to a greater extent than does antipsychotic use. Prenatal exposure to low-potency phenothiazines may further increase this risk, although only slightly. The effect of prenatal exposure to atypical antipsychotics requires further study.

BENZODIAZEPINES

Benzodiazepines are rarely a primary treatment for mania or depression. Thus, a comprehensive review of their effect on fetal outcome is beyond the scope of this review. A meta-analysis of exposure in the first trimester suggests a very small but significant increase in risk for cleft palate.[1] The absolute risk is <1 in 1,000 cases.

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ANTIDEPRESSANTS

Whereas treatment of acute mania is considered a medical emergency, women with bipolar disorder may also relapse into depression during pregnancy. An antidepressant should not be used without a mood stabilizer when treating bipolar I disorder, although a mood stabilizer alone may be inadequate to treat depression. Using tricyclics and selective serotonin reuptake inhibitors (SSRIs) during pregnancy has not been associated with teratogenicity (*Table 3*),[26] although perinatal effects have been reported.[1]

Tricyclics. In case-control studies involving more than 300,000 live births, 414 incidences of first-trimester exposure to tricyclics were followed. Information from these patients found no significant association between fetal exposure to tricyclics and increased rates of congenital malformations.[1] The few studies that have been performed suggest no long-term effects from in utero exposure.[26] Although these results suggest that prenatal exposure to tricyclics is relatively safe, more research is needed.

SSRIs. To date, no significant teratogenic effects of SSRIs have been identified in offspring of treated women.

The manufacturer's register for fluoxetine contains approximately 2,000 cases of treated patients, with no excess cases of congenital anomalies or malformations following prenatal exposure. Citalopram has the next largest database of in utero exposure (n=365), again with no increased risk for teratogenicity. Several smaller systematic reports are available on in utero exposure to sertraline, paroxetine, or escitalopram.[26]

Most studies of pregnant women taking fluoxetine in the first trimester have found no increased risk of obstetrical complications—including spontaneous pregnancy loss, preterm labor, or low birth weight—compared with women not taking fluoxetine. Taking fluoxetine during the third trimester may increase the risk for perinatal complications,[27] although this has been inconsistently reported and requires further study. Effects of other SSRIs in the third trimester have not been systematically explored.

Case reports and one controlled study have addressed possible neonatal perinatal symptoms from in utero exposure to SSRIs.[28,29] Preliminary data show no adverse neurobehavioral function in exposed neonates.[26]

Electroconvulsive therapy (ECT) has been proven effective for acute mania and depression, demonstrating few deleterious effects on neonates. ECT has few side effects and may be safer than drug therapy in this population. Two reviews support the efficacy and relative safety of ECT treatment during pregnancy, although more evidence is needed.[30,31]

> No teratogenic effects of SSRIs have been identified in offspring of treated women

RECOMMENDATIONS

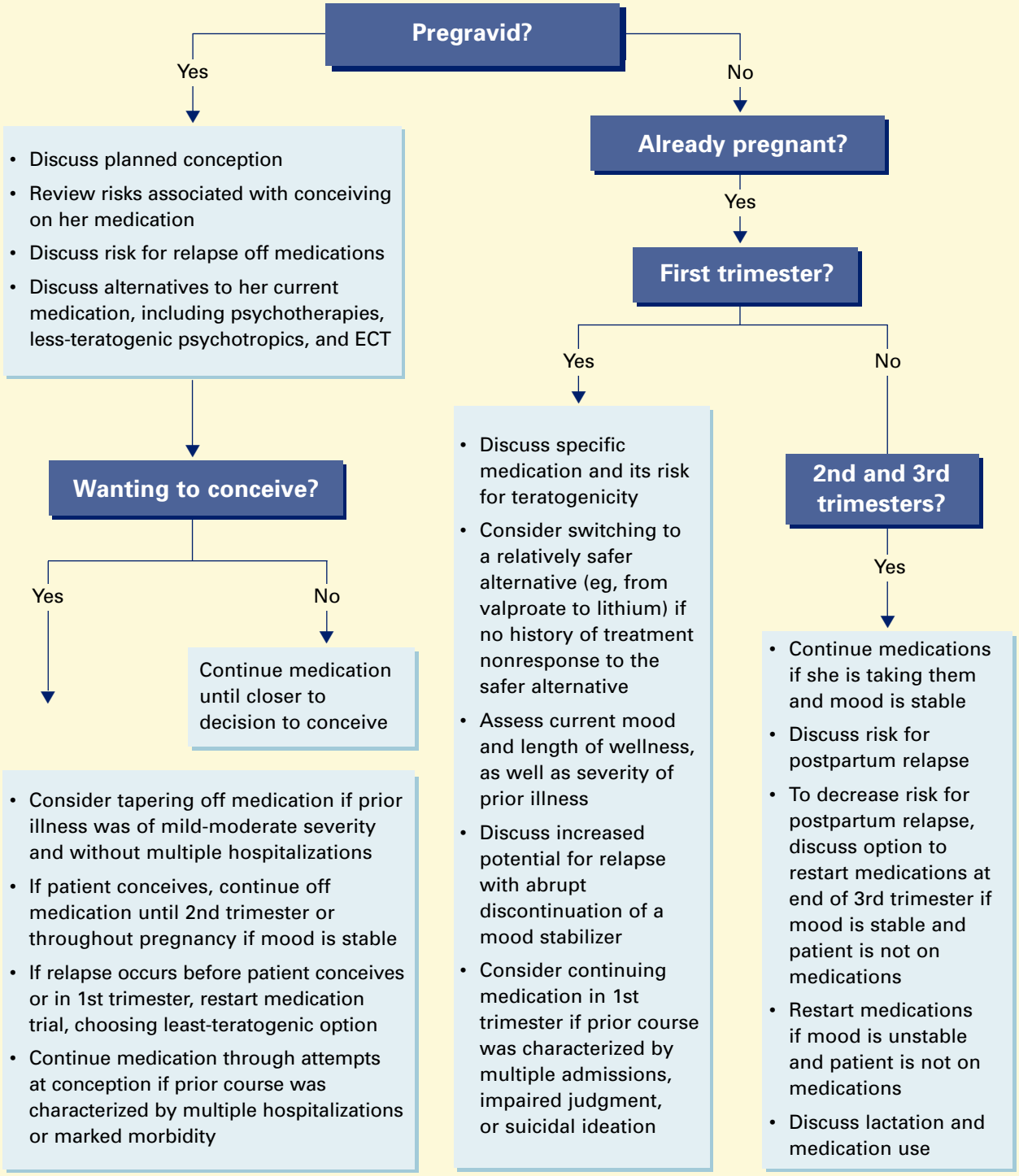
Discuss pregnancy and medication risks with all bipolar women, regardless of proximal plans for pregnancy. If psychotropic medication is used, prescribe carefully during the first trimester, using the minimum number of drugs and the lowest dosages needed to restore or maintain well-being.[32]

Pros and cons of switching. Some clinicians may encourage a patient to taper a medication during the first trimester because of its unknown or high teratogenicity. Depending on the patient's illness severity, this might not be the optimal decision. A more conservative option would be to switch to a lower-risk drug during pregnancy.

Lithium has both antidepressant and antimanic properties and is less teratogenic compared with first-trimester exposure to an anticonvulsant. However, if lithium has not been successful for

Algorithm

Suggested approach to the bipolar patient who wishes to conceive or is pregnant



the woman's mania prophylaxis in the past and she has demonstrated antimanic response to an anticonvulsant, switching to lithium or another anticonvulsant is not recommended.

Folate and neural tube defects. As first-trimester exposure to carbamazepine or valproate increases the risk for neural tube defects, using the lowest available dosage may decrease the risk for spina bifida, at least with valproate.

Low maternal folate levels are often associated with neural tube defects from any cause.[33] Valproate lowers folate levels by inhibiting one of the enzymes necessary for its formation, which may be a mechanism for the increased risk of spina bifida.[34]

Folate supplementation. To date, no study has demonstrated that giving folate supplements to women taking anticonvulsants during pregnancy reduces the risk of neural tube defects.[35] Nonetheless, we recommend that women who continue to take valproate or carbamazepine during pregnancy receive folate, 3 to 4 mg/d, as a precaution.

Treating manic relapse. Data show high rates of relapse in patients who stop taking lithium, particularly if done abruptly.[3] Counsel women taking lithium to plan their pregnancies to allow enough time to taper off the medication prior to conception, if they want to try this. Lithium should be decreased slowly—approximately 50% every 2 weeks—to avoid relapse.

Treat aggressively if relapse occurs during pregnancy. Consider:

- psychiatric hospitalization in case of suicidality or psychosis
- reinstituting drug therapy with a less-teratogenic agent
- ECT for a manic or depressive episode.

As the pregnancy advances and the mother's volume of distribution increases, dosage increases may be needed to maintain therapeutic drug levels.

Treating depressive relapse. Should depression occur in pregnancy, SSRIs or tricyclics added to mood stabilizer therapy have been shown to be effective, with few teratogenic effects.

Cognitive-behavioral and interpersonal psychotherapies also have shown efficacy in pregnant women with major depressive disorder[36] and may be effective for women with bipolar disorder in pregnancy. Cognitive psychotherapies, when used with medication, have been reported effective in preventing relapse in nongravid bipolar patients.[36-37]

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continued

Bottom Line

Psychotropics may be used during pregnancy when the risk of untreated maternal bipolar disorder outweighs the potential medication risks to the fetus. Evaluate this decision with the bipolar woman, while considering her prior course of illness and response to medications.

Related resources

Psychiatric disorders during pregnancy. Massachusetts General Hospital Center for Women's Health. Perinatal Resource Center. www.womensmentalhealth.org/topics/pregnancy_lib.html

DRUG BRAND NAMES

Amitriptyline • Elavil
Bupropion • Wellbutrin
Carbamazepine • Tegretol
Chlorpromazine • Thorazine
Citalopram • Celexa
Clomipramine • Anafranil
Desipramine • Norpramin
Fluoxetine • Prozac
Fluvoxamine • Luvox
Gabapentin • Neurontin
Haloperidol • Haldol
Imipramine • Tofranil
Lamotrigine • Lamictal
Lithium • Lithobid et al
Methylphenidate • Ritalin et al
Nortriptyline • Pamelor
Olanzapine • Zyprexa
Paroxetine • Paxil
Phenelzine • Nardil
Risperidone • Risperdal
Sertraline • Zoloft
Topiramate • Topamax
Tranylcypromine • Parnate
Trifluoperazine • Stelazine
Valproate • Depakote et al

DISCLOSURE

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Ms. Richards reports no financial relationship with any company whose products are mentioned in this article, or with manufacturers of competing products.

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