Treating bipolar disorder

How to protect the fetus from the risk of malformations and both mother and offspring from the dangers of relapse.
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. 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...
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 symp-
toms noticed shortly after birth
(such as jitteriness). These con-
sequences are putatively related to
drug use at or near birth and have limited dura-
tion.
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 preg-
nancy” rating system (Table 1) uses available data to
assess the degree of teratogenic risk. These guide-
lines can be confusing and are one of many tools to
use when considering a possible drug treatment.

<table>
<thead>
<tr>
<th>Category</th>
<th>Interpretation</th>
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<tbody>
<tr>
<td>A</td>
<td>Controlled studies show no risk</td>
</tr>
<tr>
<td>B</td>
<td>No evidence of risk in humans</td>
</tr>
<tr>
<td>C</td>
<td>Risk cannot be ruled out</td>
</tr>
<tr>
<td>D</td>
<td>Positive evidence of risk</td>
</tr>
<tr>
<td>X</td>
<td>Contraindicated in pregnancy</td>
</tr>
</tbody>
</table>


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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 preg-
nant bipolar women).

No psychotropics are classified as “A,” meaning
either some risks are associated with every psy-
chotropic 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 notwith-
standing, psychotropic intervention is the most
effective treatment for
women with bipolar disor-
der. 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.

Depression during pregnancy has been
linked to low birth weight and preterm
delivery.4 “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.5

Untreated mania may also be associated with
perinatal risks, as a pregnant patient in a manic
state may engage in impulsive, high-risk behav-
iors that endanger her and the fetus.6

**MOOD STABILIZERS**
The FDA categorizes as “D” the three most com-
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, anencephaly, 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.11 These malformations disappear with age.11 Teratogenicity increases with the use of multiple anticonvulsants and possibly with higher maternal plasma levels and toxic metabolites.11

**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

**ANTIPSYCHOTICS**

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

**Table 3**

<table>
<thead>
<tr>
<th>Category</th>
<th>Medication</th>
<th>Teratogenicity</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Tricyclics</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amitriptyline</td>
<td>Category C</td>
<td></td>
</tr>
<tr>
<td>Clomipramine</td>
<td>Category C</td>
<td></td>
</tr>
<tr>
<td>Desipramine</td>
<td>Safety in pregnancy not known</td>
<td></td>
</tr>
<tr>
<td>Imipramine</td>
<td>Safety in pregnancy not known</td>
<td></td>
</tr>
<tr>
<td>Nortriptyline</td>
<td>Safety in pregnancy not known</td>
<td></td>
</tr>
<tr>
<td><strong>Selective serotonin reuptake inhibitors</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Citalopram</td>
<td>Category C</td>
<td></td>
</tr>
<tr>
<td>Fluoxetine</td>
<td>Category C</td>
<td></td>
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<tr>
<td>Fluvoxamine</td>
<td>Category C</td>
<td></td>
</tr>
<tr>
<td>Paroxetine</td>
<td>Category C</td>
<td></td>
</tr>
<tr>
<td>Sertraline</td>
<td>Category C</td>
<td></td>
</tr>
<tr>
<td><strong>Other antidepressants</strong></td>
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</tr>
<tr>
<td>Bupropion</td>
<td>Category B</td>
<td>Safety in pregnancy and nursing not known</td>
</tr>
<tr>
<td>Phenelzine</td>
<td>Safety in pregnancy and nursing not known</td>
<td></td>
</tr>
<tr>
<td>Tranylcypromine</td>
<td>Safety in pregnancy and nursing not known</td>
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**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. The absolute risk is <1 in 1,000 cases.
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), 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 perinatal 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

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.11

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

Pregravid?

Yes

- Discuss planned conception
- Review risks associated with conceiving on her medication
- Discuss risk for relapse off medications
- Discuss alternatives to her current medication, including psychotherapies, less-teratogenic psychotropics, and ECT

No

- No
- Yes

Already pregnant?

Yes

First trimester?

Yes

- Discuss specific medication and its risk for teratogenicity
- Consider switching to a relatively safer alternative (e.g., from valproate to lithium) if no history of treatment nonresponse to the safer alternative
- Assess current mood and length of wellness, as well as severity of prior illness
- Discuss increased potential for relapse with abrupt discontinuation of a mood stabilizer
- Consider continuing medication in 1st trimester if prior course was characterized by multiple admissions, impaired judgment, or suicidal ideation

No

- Continue medications if she is taking them and mood is stable
- Discuss risk for postpartum relapse
- To decrease risk for postpartum relapse, discuss option to restart medications at end of 3rd trimester if mood is stable and patient is not on medications
- Restart medications if mood is unstable and patient is not on medications
- Discuss lactation and medication use

No

Wanting to conceive?

Yes

- No
- Yes

Continue medication until closer to decision to conceive

No

2nd and 3rd trimesters?

Yes

- Continue medications if she is taking them and mood is stable
- Discuss risk for postpartum relapse
- To decrease risk for postpartum relapse, discuss option to restart medications at end of 3rd trimester if mood is stable and patient is not on medications
- Restart medications if mood is unstable and patient is not on medications
- Discuss lactation and medication use

No

- No
- Yes
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. 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.

**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. 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. 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 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.

References


**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


DISCLOSURE

Dr. Altshuler receives research support from Abbott Laboratories, is a consultant to Abbott Laboratories, Forest Laboratories, and Eli Lilly & Co., and is a speaker for GlaxoSmithKline and Janssen Pharmaceutica.

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