

# Treatment of Bipolar Disorder During Pregnancy

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The treatment of bipolar disorder during pregnancy or in those women who wish to conceive poses a unique set of dilemmas with which clinicians should be familiar. Given the teratogenicity of some psychotropic medications used to treat bipolar disorder and incomplete reproductive safety data for agents frequently employed to manage the illness, patients and clinicians should collaborate as they weigh options regarding appropriate pharmacologic therapy during pregnancy. Ultimately, risk-benefit decisions are made that must factor in the risk of relapse of psychiatric illness during pregnancy and its attendant morbidity versus the risk of fetal exposure to these agents. No clinical decision is risk-free, and patients with comparable information about risks and benefits of treatment options may make different decisions. However, awareness of the latest reproductive safety data across the family of compounds used to treat bipolar disorder, including antipsychotics, antidepressants, mood stabilizers, and anticonvulsants, allows for the most informed decisions. This article (1) describes the treatment dilemmas faced by bipolar women who are either pregnant or who wish to conceive, (2) reviews the teratogenic risks associated with commonly used psychotropic medications used to treat the illness, and (3) provides some clinical guidelines for treating this population during pregnancy.

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Women with bipolar disorder who are pregnant or who wish to conceive face difficult choices concerning treatment of underlying illness, leaving them (and those who prescribe for them) caught between a teratologic rock and a clinical hard place.<sup>1</sup> These patients must be informed about both the effects of fetal exposure to psychotropic medication as well as the critical importance of maintaining euthymia during pregnancy.

## TREATMENT DILEMMAS UNIQUE TO PREGNANCY

Historically, pregnancy has been regarded as protective against psychiatric disorders, including bipolar disorder. This belief was based partly on the low rate of psychiatric hospitalizations during pregnancy among women with bipolar disorder reported first by Kendell and colleagues.<sup>2</sup> The rate of hospitalization dramatically increased during the postpartum period, highlighting the lower hospitalization risk during pregnancy. Clearly, admission to the hospital in such a study is not a particularly sensitive indication of psychiatric illness, and such an investigation might easily fail to capture pregnant women experiencing

symptoms of affective dysregulation that are not severe enough to justify hospitalization. Interestingly, Grof and colleagues<sup>3</sup> have described an improvement in the clinical course of bipolar illness during pregnancy when comparing subjects across three 9-month periods (including the 9 months immediately before pregnancy, the pregnancy, and postpartum). However, the generalizability of this report may be limited, because the subjects had been responsive to lithium treatment and were not receiving maintenance therapy with mood stabilizer at the time of the study.

Conversely, Viguera and colleagues<sup>4</sup> found a substantial rate of relapse in euthymic pregnant patients with bipolar I and II disorder who discontinued mood stabilizer treatment. During the first 40 weeks after discontinuation of lithium treatment, rates of recurrence for pregnant patients were similar to rates of recurrence for nonpregnant patients (52% and 58%, respectively), suggesting that pregnancy is risk-neutral, neither conferring risk for relapse of bipolar disorder nor protecting against it.

Maintenance treatment of bipolar disorder during pregnancy has proved to be protective against relapse. In a study comparing pregnant bipolar women who discontinued mood stabilizer versus those who maintained treatment with mood stabilizer during pregnancy, Viguera<sup>5</sup> found a high risk of recurrence for those patients who discontinued mood stabilizer (81%) compared with a low rate of recurrence for those taking mood stabilizers (29%). Overall, these data are consistent with a recent study<sup>6</sup> regarding risk of relapse of unipolar depression during pregnancy, suggesting that clinician and patient must be aware of relative risks of various treatment options during

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pregnancy with the cardinal goal of minimizing risk for recurrence of illness during pregnancy.

In light of the variability of information regarding the relative risks of pharmacologic treatment during pregnancy received by women with bipolar disorder who wish to become pregnant, Viguera and colleagues<sup>7</sup> have described the advice given to such patients when they are making reproductive decisions. Before receiving perinatal psychopharmacologic consultation about the relative risks of either maintaining or discontinuing psychotropic treatment during pregnancy, 29 of 70 survey respondents had been advised by health care professionals to avoid pregnancy (69% by psychiatrists or other mental health care professionals and 14% by primary care physicians or obstetricians). Many of these women had also been advised against pursuing pregnancy by their spouses (21%) or by a parent or sibling (45%). Nevertheless, after consultation, 63% of these women chose to pursue pregnancy. These data illustrate the concerns that women with bipolar disorder, their clinicians, and their families have about pregnancy and about using psychotropic agents across gestation. The proportion of women who suffer from bipolar disorder and who ultimately choose to become pregnant after thoughtfully weighing the risks underscores the importance of providing accurate and frank information about the risk of relapse if psychotropic treatment is discontinued on one hand as well as comprehensive information regarding the known risks of fetal exposure to agents used to treat the disorder on the other.

#### PHARMACOLOGIC TREATMENT OF BIPOLAR DISORDER DURING PREGNANCY: WEIGHING THE RISKS

Since pregnancy appears not to be protective against recurrence of bipolar disorder, patients and clinicians must weigh the risks of fetal exposure to medication against the risk of maternal relapse. Many commonly used antimanic agents either are known teratogens or have sparse systematically gathered reproductive safety data.<sup>8,9</sup> Pharmacologic treatment may be continued during pregnancy when the risk to the mother and fetus from the disorder outweighs the teratogenic risks of pharmacotherapy; these decisions are specific to each individual and are typically made on a case-by-case basis. Arbitrary avoidance of fetal exposure to psychiatric medications is not necessarily the goal. Rather, clinicians should be able to provide as much current reproductive safety data as possible on the various treatments as well as data on risk for relapse during pregnancy in order to assist patients in making these decisions. Women with similar illness histories may make very different decisions regarding treatment options. No decision is risk-free and no decision is perfect, but clinicians should work collaboratively with patients to weigh the relative effects of medication use during pregnancy and the associ-

Table 1. U.S. Food and Drug Administration Categories for Drug Use During Pregnancy<sup>a</sup>

Category	Interpretation
A	<b>Controlled studies show no risk.</b> Adequate, well-controlled studies in pregnant women have not shown an increased risk of fetal abnormalities.
B	<b>No evidence of risk in humans.</b> Adequate, well-controlled studies in pregnant women have revealed no evidence of harm to the fetus despite adverse findings in animals, or, in the absence of adequate human studies, animal studies have revealed no evidence of fetal risk.
C	<b>Risk cannot be ruled out.</b> Adequate, well-controlled human studies and animal studies are lacking, or animal studies have shown a risk to the fetus. There is a chance of fetal harm if the drug is administered during pregnancy, but the potential benefits may outweigh the risk.
D	<b>Positive evidence of risk.</b> Studies in humans, or investigational or post-marketing data, have demonstrated risk to the fetus. Nevertheless, potential benefits from the use of the drug may outweigh the potential risk. For example, the drug may be acceptable if needed in a life-threatening situation or serious disease for which safer drugs cannot be used or are ineffective.
X	<b>Contraindicated in pregnancy.</b> Studies in animals or humans, or investigational or postmarketing reports, have demonstrated positive evidence of fetal abnormalities or risk. The use of the product is contraindicated in women who are or may become pregnant.

<sup>a</sup>Based on Meadows.<sup>11</sup>

ated risk for relapse if pharmacologic treatment is discontinued. The clinician can help each patient make an informed decision based on her illness history, available reproductive safety data for the relevant pharmacologic treatments being used to sustain euthymia, and the patient's individual wishes.

#### Psychotropic Drug Use in Pregnancy

Although clinicians use as few medications as necessary when managing bipolar disorder, many patients are treated with multiple medications including anti-psychotics, antidepressants, and mood stabilizers, including anticonvulsants. Some patients may also explore the potential use of complementary or alternative treatments for the treatment of underlying illness despite the very sparse data supporting efficacy of these agents to treat bipolar disorder.<sup>10</sup> While those treating pregnant women with psychotropics frequently seek reproductive safety information regarding such agents from the U.S. Food and Drug Administration (FDA) pregnancy category labels (Table 1),<sup>11</sup> it should be kept in mind that no psychotropic drug is approved by the FDA for use during pregnancy. The current category labeling system provides little information regarding the extent of global teratovigilance data for a given compound (see <http://www.womensmentalhealth.org>). Nonetheless, patients and clinicians frequently rely on the product label as a primary source of reproductive safety information for a given

medication. No single source provides comprehensive information, and so patients and clinicians often need to go beyond the package label, the category label, and even FDA letters to clinicians to obtain information from registries and data from teratovigilance programs to accurately assess risks and benefits.

**Antipsychotics.** Antipsychotics are commonly used to treat bipolar disorder, frequently in addition to other agents such as lithium carbonate and anticonvulsants such as valproate or lamotrigine. Data<sup>12</sup> gathered over the last several decades support the relative safety of fetal exposure to typical antipsychotics, but such medications tend not to be used as first-line treatments, given the long-term side effects with which they are associated. Atypical antipsychotics used alone or in combination with other mood stabilizers may be more efficacious for some patients than typical antipsychotics, and several atypical antipsychotics are approved by the FDA for the treatment of certain phases of bipolar disorder. While atypical antipsychotics are widely used by reproductive-aged women who suffer from bipolar disorder, sparse data<sup>12-14</sup> exist regarding the safety of these agents during pregnancy, with postmarketing surveillance mostly limited to case reports and small series.

**Antidepressants.** Although the extent to which it is appropriate to use antidepressants to treat depression associated with bipolar illness has been a subject of considerable debate over the last several years,<sup>15-17</sup> these agents are frequently used to treat this population of patients. While the reproductive safety of older tricyclic antidepressants has been described,<sup>12</sup> extensive data have also accumulated across the last decade regarding risk associated with prenatal exposure to selective serotonin reuptake inhibitors (SSRIs). Multiple reviews<sup>18,19</sup> describe the absence of increased risk of major congenital malformations associated with first-trimester exposure to SSRIs.

However, preliminary reports<sup>20,21</sup> suggest that exposure to paroxetine during the first trimester may be associated with an increased risk of cardiac defects compared with other antidepressants. Epidemiologic data<sup>21,22</sup> from the United States and Sweden have indicated approximate 1.5-fold and 2.0-fold increased risks, respectively, of ventricular septal defect and atrial septal defect in infants exposed to paroxetine during the first trimester. The FDA has since changed the category label of paroxetine from C to D (see Table 1). However, other published studies, including 2 recent studies regarding the teratogenicity of SSRIs, do not demonstrate increased risk for congenital malformations associated with first-trimester exposure to this class of compounds<sup>18,23-28</sup> and have failed to demonstrate an association between SSRI exposure and specific cardiac malformations.

Multiple studies of fetal exposure to antidepressants<sup>29-31</sup> have reported adverse perinatal outcomes including decreased gestational age, low birth weight, and poor

neonatal adaptation. However, other studies<sup>32-34</sup> do not support this association. Particular concern has been raised regarding the potential effects of late trimester exposure to SSRIs, with one recent report<sup>35</sup> noting transient symptoms of jitteriness and tachypnea and tremulousness, and another study<sup>36</sup> reporting increased risk for persistent pulmonary hypertension of the newborn. Unfortunately, the vast majority of these reports have been limited by small sample size, nonsystematic assessment of infant outcome, and frequent use of nonblinded raters. These studies have also failed to assess the impact on perinatal well-being of maternal depression, which in and of itself may be associated with compromised perinatal outcome.<sup>37</sup> These reports have left ambiguous the relative safety of SSRIs when used during the peripartum period. The most consistently reported perinatal symptoms included jitteriness, restlessness, tremor, and hypertonia, but it is unclear whether these symptoms represented toxicity or withdrawal symptoms.

**Mood stabilizers.** Lithium has been a gold-standard treatment for bipolar disorder, and it was once thought to have a high teratogenic risk, on the basis of information derived from retrospective reports.<sup>38,39</sup> More recent research,<sup>8</sup> though, has shown the teratogenic risk to be lower than originally believed. Although first-trimester exposure to lithium does have a 10 to 20 times greater relative rate of cardiovascular malformations compared with that of the general population, the absolute risk associated with lithium exposure is low, at approximately 1 of 1000 infants.<sup>8</sup> Accordingly, clinicians must weigh the risk of maternal relapse with discontinuation of treatment against the teratogenic risk of lithium use during pregnancy.

**Anticonvulsants.** Anticonvulsants are common in the treatment of bipolar disorder—several are approved by the FDA for the treatment of the disorder, and some anticonvulsants are better tolerated than other medications used to treat bipolar illness. In addition, mixed states, which are more common among women than among men,<sup>40</sup> may respond preferentially to anticonvulsants,<sup>41</sup> which in turn may increase their use in women.

The widely used anticonvulsant valproate is a known teratogen; data from the North American Antiepileptic Drug Registry suggest that the medication is associated with a 7% to 10% risk of neural tube defects, including spina bifida, and that cardiac defects are associated with first-trimester exposure.<sup>42,43</sup> Prenatal exposure to valproate has also been associated with craniofacial anomalies,<sup>44</sup> and there may also be an increased risk of behavioral teratogenicity associated with fetal exposure to valproate. For example, Adab and colleagues<sup>45</sup> found a higher risk of additional educational needs among school-aged children who had been exposed to valproate in utero compared with those who were exposed to carbamazepine in utero and those who were not exposed to anticonvulsants.

Lamotrigine is approved for the treatment of bipolar disorder. Data from the International Lamotrigine Pregnancy Registry<sup>46,47</sup> revealed no increased overall risk of major malformations associated with first-trimester exposure to lamotrigine compared with rates of malformations among unexposed children. However, polytherapy with other anticonvulsants may increase the risk of teratogenicity.<sup>47</sup> Additionally, a recent report from the North American Antiepileptic Drug Registry has recently suggested an increased risk for oral clefts associated with first trimester exposure to lamotrigine.<sup>48,49</sup>

Other anticonvulsants commonly used in bipolar disorder include carbamazepine, one formulation of which is FDA approved for bipolar disorder, and oxcarbazepine, which is not approved for the treatment of bipolar disorder. First-trimester exposure to carbamazepine has been associated with an approximate 1.0% risk of spina bifida.<sup>50,51</sup> Maternal use of carbamazepine also carries some risk of craniofacial anomalies and microcephaly in newborns.<sup>52</sup> Currently, there are insufficient data on maternal use of oxcarbazepine to make determinations about its reproductive safety.

**Alternative interventions.** Because of the risks associated with many psychotropic agents used to treat bipolar disorder, it is only natural that clinicians and patients would be interested in finding safe alternative treatments. Some commonly used alternative treatments include calcium-channel blockers and omega-3 fatty acids. However, such alternatives need to be efficacious as well as safe, and few data support the efficacy of these agents.<sup>53</sup> Switching a euthymic patient from an effective psychotropic medication to an alternative treatment with sparse efficacy and reproductive safety data is a strategy unsupported by evidence and may be detrimental to both maternal and fetal health.

## CLINICAL GUIDELINES FOR TREATING WOMEN WITH BIPOLAR DISORDER DURING PREGNANCY

When treating women with bipolar disorder during pregnancy, clinicians must remember that no clinical decision is risk-free and that patients who receive the same information about the risks and benefits of certain treatment strategies may make very different decisions. Guidelines for treatment vary with the severity of illness.

### Mild-to-Moderate Bipolar Disorder

For patients with mild-to-moderate bipolar disorder, where there has been a very protracted period of euthymia without intervening subsyndromal illness or evidence of frank recurrence, the clinician may decide to gradually taper and discontinue antimanic prophylactic treatment in patients who are attempting to conceive. Unfortunately, even among women with histories of sustained euthymia, discontinuation of antimanic prophylaxis may lead to a re-

lapse. Unplanned pregnancies prevent clinicians and patients from preemptively discontinuing treatment, which is particularly problematic for women on maintenance treatment with valproate. The teratogenic effect of valproate occurs early in gestation, between weeks 4 and 5, often before the patients know they are pregnant, and so any potential teratogenic insult from valproate may have already occurred by the time the patient discovers her pregnancy. Some women who discontinue treatment during the first trimester may decide collaboratively with a physician to reintroduce treatment with mood stabilizer during the second and third trimester to attenuate the risk of relapse associated with removing the protective effects of maintenance antimanic therapy. However, given the evolving data suggesting behavioral teratogenic effects of valproate that may be exerted across the various trimesters of pregnancy, this can be problematic for women who had been previously maintained on treatment with this agent.

### Severe Bipolar Disorder

Clinicians are often faced with the challenge of managing female patients who have severe, recurrent bipolar disorder who become pregnant or who want to conceive. Such patients generally relapse or may even have some evidence of subsyndromal illness at baseline; they tend to relapse quickly if they discontinue the medication that has been used to afford relative euthymia. Efforts to sustain maternal euthymia in this population are absolutely critical for such women, and in these cases, continuation of treatment throughout the pregnancy may be warranted.

For women with severe bipolar disorder who need to continue medication throughout pregnancy, lithium alone or in combination with an antipsychotic may be a safe alternative to valproate. Many patients who are on valproate treatment may not have received an adequate trial of lithium in the past, so a lithium trial prior to pregnancy may be appropriate. For those patients who are lithium nonresponders, clinicians should consider lamotrigine monotherapy or treatment with lamotrigine and a typical antipsychotic. Patients who have had an inadequate response to typical antipsychotics may respond well to atypical antipsychotic monotherapy or atypical antipsychotic treatment in combination with lithium or lamotrigine. Given the limited data supporting the use of typical antipsychotics as monotherapy for bipolar disorder, that course of treatment should not be pursued.

### Other Clinical Issues

Planned pregnancy provides time for thoughtful treatment choices, so clinicians should encourage their female patients to plan their pregnancies to the extent possible. Since there is a narrow teratogenic window with valproate, patients who take valproate and who would like to conceive may be switched to lithium or lamotrigine.

Because of the risks of cardiac malformations with lithium exposure and spina bifida with carbamazepine exposure, prenatal screening for these conditions may be advisable.<sup>54</sup> High-resolution ultrasonography is recommended for pregnant women taking either drug, and fetal echocardiography is recommended for those taking lithium.

Another clinical issue to consider is that women with bipolar disorder are at high risk for postpartum decompensation.<sup>55</sup> Estimates of the risk of postpartum relapse are as high as 50%, which may be an underestimate. Relapse of affective disorders during pregnancy is a strong predictor of postpartum relapse. Fortunately, postpartum prophylaxis is effective.<sup>56</sup> There are several treatment options for postpartum women who suffer from bipolar disorder. For example, the reintroduction of lithium at or around the time of delivery or during the acute postpartum period (as early as 36 weeks gestation or as late as 24 to 48 hours postpartum) can attenuate the risk for relapse.<sup>56</sup> For some patients, it may be appropriate to reintroduce mood-stabilizer treatment before delivery, even as early as the second trimester, to maximize the likelihood for maintaining euthymia. In all female patients, especially those who decide against peripartum prophylactic treatment with a mood stabilizer, clinicians should maintain extreme vigilance for early signs of postpartum mood disturbance.

### CONCLUSION

Decisions regarding psychotropic treatment of pregnant women with bipolar disorder require thorough knowledge of available reproductive safety of the drugs involved, awareness of the dangers of maternal relapse, and acceptance of the fact that no decision is risk-free. Since pregnancy is not protective against bipolar disorder, it may be necessary for women who are trying to conceive or who are already pregnant to continue taking their medications. Clinicians should be familiar with the latest reproductive safety research of any medications used to treat this disorder as they assist their patients in making the best possible choices to ensure the health of both mother and child.

*Drug names:* carbamazepine (Equetro, Tegretol, and others), lamotrigine (Lamictal and others), lithium (Eskalith, Lithobid, and others), oxcarbazepine (Trileptal), paroxetine (Paxil, Pexeva, and others).

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