

Benefits and Risks of Psychiatric Medications During Pregnancy

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Traditionally, psychiatric medications were withheld during pregnancy because of fear of teratogenic and other effects. The emergence of evidence of the safety of most commonly used psychiatric medications, the availability of this information in the form of online databases, and the documentation of the adverse effects of untreated maternal mental illness have all increased the comfort of physicians and patients with respect to the use of psychiatric medications during pregnancy. The tricyclic antidepressants and fluoxetine (Prozac) appear to be free of teratogenic effects, and emerging data support similar safety profiles for the other selective serotonin reuptake inhibitors. The mood stabilizers appear to be teratogenic. With the exception of the known risk for depression to worsen in the postpartum period, there is little consistent evidence of the effects of pregnancy on the natural history of mental illness. Decisions regarding the use of psychiatric medications should be individualized, and the most important factor is usually the patient's level of functioning in the past when she was not taking medications. (Am Fam Physician 2002;66:629-36,639. Copyright© 2002 American Academy of Family Physicians.)

📄 A patient information handout on the use of mental health medicines in pregnancy, written by the authors of this article, is provided on page 639.

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Psychiatric disorders are common in women of reproductive age.¹ Despite the morbidity associated with these disorders, there has been a tendency to avoid prescribing psychiatric medications during pregnancy. An expanding body of knowledge about the risks and benefits of these medications has made it possible to make more rational decisions about their use.^{2,3} Growing evidence suggests that many of these agents are safe; however, there are some that clearly should be avoided.

This article reviews the risks and benefits of commonly used psychiatric medications. The use of these medications in lactation is the subject of a recent *American Family Physician* review.⁴

Risks of Psychiatric Medications

Psychiatric symptoms can affect pregnancy because of their effect on the mother's emotional state, functional status, ability to obtain proper prenatal care, and potential to engage in dangerous behavior.² After the birth of a child, untreated maternal mental illness may have an effect on the infant's development and well-being.^{2,3,5}

All currently available psychopharmacologic agents and their metabolites cross the placenta, principally by simple diffusion.⁶ The specific fetal serum levels are unknown, but they may be higher than maternal levels.⁶ Medications can potentially affect the fetus in several ways: structural teratogenesis (birth defects), behavioral teratogenesis, and perinatal syndromes.^{2,6}

STRUCTURAL TERATOGENESIS

The timing of exposure to chemical agents during development affects the risk for malformations.⁷ The second through the eighth weeks postfertilization, during which time the development of major organ systems occurs, is the critical period of risk for structural teratogenesis.⁷

BEHAVIORAL TERATOGENESIS

Behavioral teratogenicity is the occurrence of behavior or neuropsychiatric symptoms in offspring after in utero exposure to a drug or toxin.³ Subsequent prospective human studies have not shown convincing evidence for such an effect, perhaps because of the difficulty of separating the behavioral teratogenicity of maternal mental illness from drug effects.^{3,5}

TABLE 1

Perinatal Syndromes Reported with Classes of Psychiatric Medications

<i>Medication class</i>	<i>Reported infant effects</i>	<i>Comments</i>
Tricyclic antidepressants	Jitteriness, irritability, seizures, tachypnea, tachycardia, sweating, functional bowel obstruction, urinary retention	Data consist of case reports
Selective serotonin reuptake inhibitors	Agitation, tachycardia	Data come from a case report; animal studies showed no evidence of perinatal syndromes; one limited study showed an increased risk of prematurity and other problems with fluoxetine (Prozac), but this has not been confirmed by other studies
Lithium	Hypotonicity, cyanosis	Data come from several case reports; one observational study did not confirm this problem
Benzodiazepines	Impaired temperature regulation, apnea, low Apgar scores, hypotonicity, feeding difficulties	Data consist of case reports, mainly of intrapartum exposures; a small case series of women treated on a chronic basis did not substantiate neonatal toxicity or withdrawal
Antipsychotics	Motor restlessness, tremor, feeding difficulties, hypertonicity, dystonic movements, parkinsonian movements	Data consist of case reports, and symptoms have been of short duration

Information from references 3, and 8 through 10.

PERINATAL SYNDROMES

Administration of psychiatric medications proximate to delivery can cause what are termed perinatal syndromes (*Table 1*)^{3,8-10} of drug intoxication or withdrawal. In some cases, these effects are reasonably well established and pharmacologically plausible, such as the somnolence and hypotonia of infants exposed to intrapartum benzodiazepines.² In most cases, the evidence is limited to case reports in which nonspecific neonatal effects (e.g., poor feeding and irritability) have been interpreted as possible evidence of exposure to, or withdrawal from, certain antidepressants.⁸ The limited data are best viewed as potential class effects, and it is not possible to draw conclusions about specific agents within classes.

FDA Risk Categories

*Table 2*¹¹ shows the five U.S. Food and Drug Administration (FDA) categories for drug use in pregnancy. These ratings have a number of limitations, including a lack of internal consistency within classes of medications; attempts to aggregate diverse information, such as risks,

into a single rating; poor discrimination between different medications within a class; and lack of agreement with the findings of other credible sources. While physicians should be familiar with these ratings, they are likely to find a variety of online and print resources to be more useful.^{7,12-16}

Risks of Specific Agents**ANTIDEPRESSANTS**

The results of numerous studies that included thousands of pooled patients taking tricyclic antidepressants (TCAs) and the selective serotonin reuptake inhibitor (SSRI) fluoxetine (Prozac) support the relative safety of these medications for use throughout pregnancy.^{8,17,18} Neither the TCAs nor fluoxetine has been associated with major teratogenic effects.^{8,17,18} In addition, a well-designed follow-up study revealed no evidence of behavioral teratogenicity with these agents after up to seven years of follow-up.¹⁹ There have been case reports of perinatal syndromes relating to all of these agents, but the effects appear to be mild, transient, and of questionable causation (*Table 1*).^{3,8-10}

TABLE 2

FDA Ratings of Drugs Used in Pregnancy

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Fewer data are available about other widely used SSRIs.^{18,20} Paroxetine (Paxil), sertraline (Zoloft), and citalopram (Celexa) have been studied prospectively in a few hundred women exposed at various times during pregnancy; these agents do not appear to increase the risk of teratogenesis.^{18,20} Even fewer data are available about novel agents such as venlafaxine (Effexor), nefazodone (Serzone), or bupropion (Wellbutrin).³ Limited data on the use of monoamine oxidase inhibitors are not reassuring, and use of these agents is not recommended during pregnancy.³

BENZODIAZEPINES

The potential teratogenicity of benzodiazepines remains controversial, but a recent meta-analysis suggested a twofold increase, at most, in the risk of orofacial clefts.²¹ Although benzodiazepines are often used as primary pharmacotherapy in anxiety disorders, there are generally more effective and safer treatments, such as cognitive behavior therapy and SSRIs.²² Perinatal use of benzodiazepines has been associated with hypotonia, apnea, hypo-

thermia, and feeding difficulties, and it should be discouraged.¹³ There is little data on behavioral teratogenesis, with a few reports suggesting developmental delay.² There are almost no data on the nonbenzodiazepine anxiolytic buspirone (BuSpar) during pregnancy.¹³

MOOD STABILIZING AGENTS

Lithium, valproic acid (Depakene), and carbamazepine (Tegretol) are commonly used in the treatment of bipolar disorder. Unfortunately, all of these agents are known teratogens.²³ Exposure to lithium in the first trimester is associated with a tenfold increase in Ebstein's anomaly, a condition of hypoplasia of the right ventricle and tricuspid valve abnormalities, from a baseline risk of one in 20,000 to, at most, one in 1,000.²³ There have been reports of a perinatal syndrome of cyanosis and hypotonic-

Mood stabilizing agents such as lithium, valproic acid, and carbamazepine are known teratogens.

The use of psychiatric medications during pregnancy should be individualized; an important consideration is the patient's prior functional level when off medication.

ity (*Table 1*)^{3,8-10}; one follow-up study did not find evidence of behavioral teratogenicity after lithium exposure.⁹

Valproic acid and carbamazepine have been associated with a marked (tenfold) increase in neural tube defects with first-trimester exposure, with incidences of 1 to 5 percent and 0.5 to 1.0 percent, respectively.²³ Oral clefts have also been associated with first-trimester exposure.²³ Data on neurobehavioral effects are conflicting, but no major effects have been identified.²

ANTIPSYCHOTIC AGENTS

Antipsychotic agents can generally be grouped into three classes: high-potency agents such as haloperidol (Haldol); low-potency agents such as chlorpromazine (Thorazine); and the newer agents such as risperidone (Risperdal), clozapine (Clozaril), and olanzapine (Zyprexa). A small but statistically significant increased risk for nonspecific teratogenic effects has been associated with first-trimester exposure to low-potency agents.¹⁰ Among the high-potency agents, haloperidol has been the subject of the most study. It has been shown to be free of congenital malformations with first-trimester exposure and is a preferred agent during pregnancy.¹⁰ There are insufficient data on the newer agents to allow any conclusions to be drawn about their safety profile.¹⁰ Reports of transient perinatal effects have been described (*Table 1*).^{3,8-10} There are limited data on behavioral teratogenesis.¹⁰

Individualizing Treatment Decisions

In individualizing treatment decisions, several general considerations must be addressed. The most important consideration is the patient's past level of function when not taking medication. An assessment of the level of

function should include a history of previous psychiatric hospitalization (generally considered evidence of significant dysfunction); suicidality or similar self-destructive thoughts or behaviors; and an assessment of the patient's ability to meet home, educational, and occupational responsibilities. The natural history of symptoms and dysfunction during previous pregnancies and deliveries, if known, is also important, especially in patients with depressive and bipolar disorders.

If the patient has a psychotherapy-responsive condition, the possibility of substituting this form of therapy for medication should be considered within the context of patient preference, availability of quality psychotherapy and the patient's previous response to such therapy. Although patient preferences and values should be considered, mental illness can cause cognitive distortions that interfere with good decision-making. Ideally, preferences should be elicited when the patient is well.

DEPRESSIVE DISORDERS

In women, it is clear that the onset of major depression tends to occur in the child-bearing ages.¹ Studies have shown a similar incidence of major depressive episodes in matched gravid and nongravid women, so pregnancy appears to have neither a protective nor a detrimental effect.²⁴ In contrast, the postpartum period is one of high risk for the development of a depressive episode, particularly in women with a history of major depression (especially if it had a postpartum component), depressive symptoms during pregnancy, or bipolar disorder.^{24,25}

The management of women with depression during pregnancy is based on balancing the potential risk of the symptoms against the potential risks of pharmacotherapy.³ Antidepressant medications are among the best-studied medications in pregnancy, and the evidence of their safety is substantial.^{2,8} Guidelines for the selection of treatments for depression in pregnant women are summarized in *Table 3*.^{25,26}

BIPOLAR DISORDER

Little is known about the course of bipolar disorder during pregnancy, but the postpartum period is clearly one of high risk.^{24,27}

Postpartum relapse rates in women not treated with prophylactic mood stabilizers are 30 to 50 percent.²⁵ Initiation of treatment with a mood stabilizer before delivery or immediately postpartum markedly reduces this risk.²⁵

TABLE 3
Treatment Guidelines for Depression and Bipolar Disorders During Pregnancy and Postpartum

<i>Diagnosis</i>	<i>Risk of relapse postpartum</i>	<i>Treatment options</i>
Without history of psychiatric illness	Low	Observation
Postpartum blues	Low	Observation; consider prophylaxis with IPT*
History of subsyndromal (minor) depression	Low	Observation; consider prophylaxis with IPT*
Past history of MDD, currently euthymic without medication	Low	Observation; consider prophylaxis with IPT*
Emergence of first episode of MDD in a woman anticipating pregnancy within the next year	Low	Trial of IPT if symptoms are mild to moderate Delay pregnancy until treatment course (with medication or psychotherapy) is complete. If medication is indicated, consider fluoxetine (Prozac) as a first-line agent because of more extensive evidence of safety during pregnancy.
History of a single episode of MDD, euthymic on medication after nine months or more of adequate treatment	Low	Close observation during trial off medication; consider prophylactic IPT*
History of postpartum depression without recurrent nonpuerperal depression	Moderate	Close observation; consider prophylaxis with antidepressant†
History of cyclothymia	Moderate	Close observation; consider lithium prophylaxis‡
History of severe, recurrent MDD, euthymic following medication discontinuation	Moderate	Close observation; consider prophylaxis with antidepressant†
History of postpartum depression with recurrent MDD	High	Consider prophylactic antidepressant therapy†
History of severe, recurrent MDD, euthymic on medication during pregnancy	High	Continue antidepressant
Emergence of depression during pregnancy	Highest	Treat with antidepressant.§
History of bipolar disorder (I or II)	Highest	Lithium prophylaxis‡
History of puerperal psychosis	Highest	Lithium prophylaxis‡

IPT = interpersonal therapy; MDD = major depressive disorder.

*—*There is limited evidence that IPT may provide protection against the development of postpartum depression.*²⁵

†—*Appropriate antidepressant therapy to begin at approximately 30 weeks' gestation.*²⁵

‡—*Therapy with lithium to achieve adequate blood levels to begin at 36 weeks' gestation or within 48 hours after delivery.*²⁵

§—*Because of the better evidence of their safety during lactation, sertraline (Zoloft) or paroxetine (Paxil) would be especially appropriate choices.*²⁶

Information from Nonacs R, Cohen LS. Postpartum mood disorders: diagnosis and treatment guidelines. J Clin Psychiatry 1998;59(suppl 2):34-40, with additional information from Lewellyn A, Stowe ZN. Psychotropic medications in lactation. J Clin Psychiatry 1998;59(suppl 2):41-52.

Consider the use of nonpharmacologic therapies that may eliminate or reduce the need for medications, including cognitive behavior therapy for anxiety and interpersonal therapy for depression.

In addition, many patients who present with postpartum psychosis may be having an initial episode of bipolar disorder.²⁷ Again, treatment should be guided by the patient's history of previous and current mood symptoms balanced against the risks of pharmacotherapy, as detailed in *Table 3*.^{25,26} Involvement of a psychiatrist will be helpful in characterizing the risk and predicted severity of relapse. Women taking mood stabilizing agents should be offered folate supplementation and prenatal screening for cardiac and neural tube defects, as indicated.^{2,9,23}

PSYCHOTIC DISORDERS

There are few data on the impact of pregnancy on the course of schizophrenia.^{2,3} The delusions, hallucinations, and disorganized thinking and behavior present in persons with untreated schizophrenia can have a particularly devastating effect on the person's overall function and ability to comply with prenatal

care.²⁸ Chronic schizophrenia has an extremely high rate of relapse when medications are withdrawn.² Pharmacologic treatment is guided by the woman's psychiatric history, with continued maintenance treatment usually being the safest overall strategy.²

New-onset psychosis during pregnancy is a psychiatric and obstetric emergency. Careful diagnostic assessment to evaluate for psychiatric and organic disorders is necessary. Decisions regarding regular dosing or as-needed use of antipsychotics are guided by the patient's symptoms and the likely primary diagnosis. Ordinarily, these decisions are made in consultation with the patient's psychiatrist.²

ANXIETY DISORDERS

Pregnancy does not have a clear impact on the natural history of anxiety disorders, although there is an apparent risk of susceptibility in the postpartum period.²⁴ Patients on maintenance pharmacotherapy for these disorders show high rates of relapse with medication discontinuation. Cognitive behavior therapy has been shown to be an effective treatment modality in many of these disorders, and it may be a reasonable option for patients who wish to discontinue medications during pregnancy.²²

If benzodiazepines are used during pregnancy, they should be avoided in the first trimester because of possible teratogenicity and before delivery because of an apparent perinatal syndrome.^{2,19} In women receiving chronic daily benzodiazepine therapy who wish to conceive, medication should be weaned gradually (approximately 10 percent per week) and consideration given to cognitive behavior therapy or antidepressant therapy.²² The best-studied agents for use during pregnancy are alprazolam (Xanax), clonazepam (Klonopin), and diazepam (Valium).²

Guidelines

Despite the many uncertainties about the effects of psychiatric disorders and various

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medications on the mother, fetus, and infant, there are guidelines for making decisions about using pharmacologic agents during pregnancy.

- The patient's psychiatric history is the best predictor of future functioning. The patient's diagnosis, severity of previous episodes, necessity for medication, and responsiveness to medication are strong predictors of the need for medication to maintain remission. Patients with schizophrenia, bipolar disorder, severe chronic depression, and panic disorder with agoraphobia are generally at risk for a high degree of dysfunction and morbidity with relapse. Patients with disorders such as dysthymia, generalized anxiety disorder, or panic disorder without agoraphobia may experience less of an impact on their functional status.

- Nonpharmacologic therapies may eliminate or reduce the need for medications in some disorders. Cognitive behavior therapy for anxiety disorders and interpersonal psychotherapy and cognitive behavior therapy for depressive disorders have proved efficacious.

- When medications are used, those that are most appropriate for the patient's condition should be chosen. The SSRIs are usually the agents of choice in the treatment of depressive and anxiety disorders.

- When there is a choice, medications should be selected on the basis of existing data.

- Collaboration and consultation with mental health professionals is an important aspect of treatment planning. Diagnosis, risk assessment, symptom monitoring, and optimal medication management can require special expertise and can be time intensive. Patients with chronic severe depressive and anxiety disorders, psychotic disorders, and bipolar disorders are particularly in need of specialty consultation and management.

- Psychotherapy, in addition to being an appropriate primary symptomatic treatment for some depressive and anxiety disorders, should be considered as a means of helping patients deal with issues related to their psy-

Selective serotonin reuptake inhibitors are the agents of choice in the treatment of depressive and anxiety disorders.

chiatric disorder, pregnancy, and other life stresses.

- The patient should be educated about the known benefits, risks, and uncertainties of pharmacotherapy, and informed consent should be documented in the medical record.

- Contacting regional or university-based teratogenicity centers for up-to-date information on medications and as an additional source of risk counseling is another consideration.

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