

Are Psychotropic Drugs Safe to Use During Pregnancy?

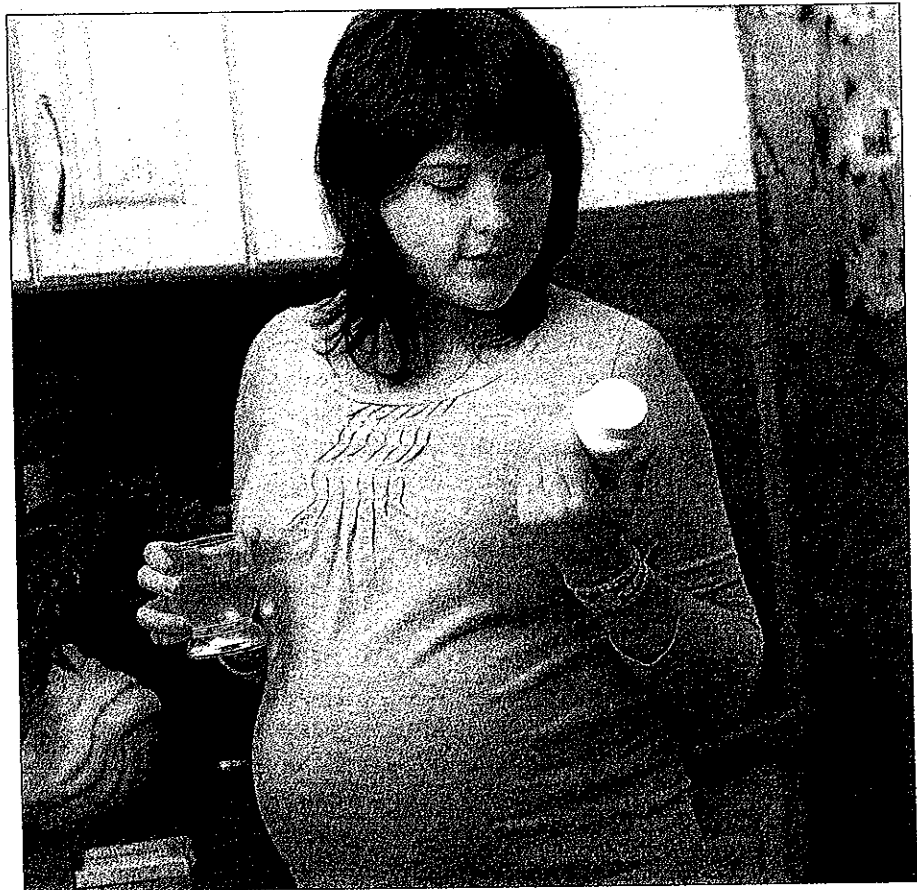
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ABSTRACT

Most psychotropics are currently given a US Food and Drug Administration (FDA) drug rating of category C, meaning there is evidence of potential risk to a fetus. Some psychotropics, however, have a higher degree of risk to the fetus than others, and this article discusses the use of those psychotropics for which caution is warranted based on currently available evidence and clinical opinion. The psychotropics that will be highlighted here include paroxetine, monoamine oxidase inhibitors, lithium, valproate, carbamazepine, and benzodiazepines. We suggest caution with regards to their routine use or as a first-line treatment in pregnancy. Five benzodiazepines are category X according to the FDA and are therefore contraindicated in pregnancy. For all these medications it is important not to overlook the benefits of psychiatric stability from continued treatment and the harms of discontinuation, which include increased risk of relapse of the illness. [*Psychiatr Ann.* 2015;45(2):71-76.]

The teratogenic risk in human pregnancy has not been adequately determined for the majority of approved medications by the US Food and Drug Administration (FDA). Adam et al.¹ reported that the teratogenic risk in human pregnancy was “undetermined” for 97.7% of medications approved between 2000 and 2010. Psychotropic medications are no exceptions in this regard. Robust, prospective trials have not been conducted for obvious ethical reasons, and most of the data comes from case reports, data base studies, and prospective figures from teratology centers—all of which fail to control for many of the confounding factors and have significant limitations. The 12-month prevalence of psychiatric disorders in past-year pregnant and postpartum women is approximately 25%,² and it has been estimated that one-third of all pregnant women are exposed to a psychotropic medication at some point during pregnancy.³ The FDA has a system of categorizing medications according to available evidence of risk to the fetus, although these categories have significant limitations and can be deceptive for clinical guidance at face value. Proposals are underway to revise and update these risk categories.⁴

The risks to the fetus after medication exposure include teratogenicity, obstetrical complications, neonatal toxicity and withdrawal, and long-term neurodevelopmental sequelae. Most psychotropics are currently in category C, and there is some evidence of potential risk to the fetus for most of them, although the degree of risk is not high enough to preclude their use for pregnant women in conditions for which these medications are warranted.³ Some medications, however, have a higher degree of risk to the fetus than other psychotropics, and these psychotropics require a more thorough consideration of weighing risks and benefits.

Literature on the psychiatric treatment of pregnant women often tends to overlook the benefits of psychiatric stability from continued treatment and the harms of discontinuation, which include increased risk of relapse of the illness, and resulting substance use, fetal neglect, suicide/self-harm risk,

The 12-month prevalence of psychiatric disorders in past-year pregnant and postpartum women is approximately 25%.

and requiring higher doses of multiple medications for clinical stabilization. All of these things have to be considered, and it may be the case that the potential harms of discontinuation outweigh the potential harms of continuation in a majority of the patients. There are no absolute rules for prescribing in pregnancy, and there are no easy, straight answers. Risks and benefits have to be weighed in the case of each individual patient.

**PAROXETINE
FDA Pregnancy Drug Rating: D**

Prior to 2005, paroxetine was category C like all other selective serotonin reuptake inhibitors (SSRIs). However, in December 2005, a public health advisory⁵ was issued by the FDA highlighting the concerns that paroxetine use in the first trimester may increase the risk of congenital malformations, in particular cardiac defects, more so than other SSRIs. In the light of this heightened risk, its pregnancy risk category was changed from C to D. The FDA cited data from two epidemiological studies (which were unpublished at that point).

The first study⁶ was based on data from the Swedish National Registry showing that infants born to mothers exposed to paroxetine in early pregnancy

had an approximately 2-fold increase in the risk of cardiac defects compared to the rest of population. The second study⁵ used a United States insurance claims database (United Healthcare data) and reported that infants exposed to paroxetine in the first trimester had a 1.5-fold increase in cardiac malformations and a 1.8-fold increase in all congenital malformations compared to infants exposed to other antidepressants. Reanalysis of the preliminary findings published in 2007 reported an adjusted odds ratio (OR) of 1.46 for cardiovascular malformations associated with paroxetine monotherapy, however with a 95% confidence interval (CI) of 0.72-2.88, reflecting lack of statistical significance.⁷ The majority of cardiac defects reported in these studies were atrial and ventricular septal defects. The FDA recommended to the physicians: “Paroxetine should generally not be initiated in women who are in their first trimester of pregnancy or in women who plan to become pregnant in the near future.”⁵

The prescribing information label for paroxetine⁸ in addition cites two large case-control studies (the National Birth Defects Prevention Study⁹ and the Sloane Epidemiologic Center Birth Defects Study¹⁰) that reported a 2- to 3-fold increased risk of right ventricular outflow tract obstructions in infants of women who used paroxetine during the first trimester of pregnancy.

Other studies, however, have not detected any association of paroxetine with congenital abnormalities. A cohort study from Denmark¹¹ found no association of paroxetine with septal defects. Bar-Oz et al.¹² reported that pregnant women using antidepressants undergo ultrasound in pregnancy at a 30% higher rate, which means that a detection bias may be contributing to the increased risk of reported cardiac defects with paroxetine.

A study by Einarson et al.¹³ specifically investigated the association of paroxetine with cardiovascular defects.

They studied more than 3,000 documented exposures to paroxetine during the first trimester of pregnancy. No difference in the rates of cardiac defects was found between the paroxetine group and the unexposed group. The authors concluded that paroxetine is not associated with an increased risk of cardiovascular defects after use in early pregnancy, as the risk is comparable to population incidence of approximately 1%. The sample size was large enough to rule out a 2-fold increased risk.

A recent study by Huybrechts et al.¹⁴ studied a cohort of 949,504 pregnant women from the nationwide Medicaid Analytic eXtract. Of that group, 64,389 women used antidepressants during the first trimester, and 11,126 used paroxetine. The study suggested no substantial increase in the risk of cardiac malformations attributable to antidepressant use during the first trimester, and found no significant association between the use of paroxetine and right ventricular outflow tract obstruction.

These recent studies cast doubt on the association of paroxetine with cardiac defects. Clinical opinion at present, however, still reflects the concerns from earlier years.

According to the 2008 practice guidelines by American College of Obstetricians and Gynecologists (ACOG),³ paroxetine use in pregnant women and women planning pregnancy should be avoided, if possible, and fetal echocardiography is recommended for women who are exposed to paroxetine in early pregnancy. However, the guidelines warned against abrupt discontinuation of paroxetine by pregnant women.

The 2010 practice guidelines for the treatment of patients with major depressive disorder (MDD) by the American Psychiatric Association state: "Because paroxetine use is classified as having a higher level of risk than other SSRIs, it should not be consid-

ered a first-line treatment when selecting a new antidepressant for a pregnant patient."¹⁵

For pregnant patients on paroxetine, the recommendation to avoid paroxetine should be weighed along with the fact that there are considerable risks to discontinuing antidepressant treatment during pregnancy. In a study by Cohen et al.,¹⁶ 68% of women who discontinued their antidepressant proximate to conception relapsed during pregnancy compared to 26% who maintained their medication throughout their pregnancy.

MONOAMINE OXIDASE INHIBITORS FDA Pregnancy Drug Rating: C

Monoamine oxidase inhibitors (MAOIs) were the first antidepressants to be discovered and have proven efficacy. However, their use in psychiatric practice has declined significantly owing to stringent dietary restrictions and significant drug interactions (such as with meperidine during labor). There are four FDA-approved MAOIs: isocarboxazid, phenelzine, tranylcypromine, and selegiline. The transdermal patch preparation of selegiline has been approved to treat MDD by the FDA for use without dietary restrictions at its lowest dose—6-mg; this may lead to more frequent clinical use of MAOIs. There is very limited human data for all of them, and in animal studies, MAOIs have been associated with an increased risk of congenital anomalies and fetal growth restriction.¹⁷⁻²⁰ Selegiline and isocarboxazid are pregnancy category C while the safety of phenelzine and tranylcypromine has not been established. In various animal studies with selegiline, fetal growth retardation, increase in malformations, postimplantation loss, and stillbirths were reported. Retarded neurobehavioral and sexual development were observed.²¹ Because of the harmful effects on fetal development in animal studies, the lack of human data, and the fact that MAOIs can lead to potentially

fatal hypertensive crisis and serotonin syndrome, it is our recommendation that MAOIs should be avoided in pregnant women.

LITHIUM

FDA Pregnancy Drug Rating: D

Lithium has been associated with teratogenic risk of cardiac malformations for many decades. In particular, Ebstein's anomaly (malformation of the tricuspid valve and right ventricle) has been most characteristically associated with lithium use. Early studies reported a 400-fold increased risk of congenital cardiac defects with fetal exposure to lithium,^{22,23} although later studies have estimated the risk ratio to be much lower—1.2-7.7 for heart malformations and 1.5-3 for all congenital defects.^{3,24} Ebstein's anomaly occurs in the general population with a risk of about 1 in 20,000 live births.²⁵ Subsequent to lithium exposure in the first trimester, the risk jumps up 20-fold to approximately 1 in 1,000²⁶ (however many authors consider this still to be low risk²⁷). Other cardiac defects include coarctation of the aorta and mitral atresia. There is expected to be no cardiac risk if lithium is used in pregnancy after 10 to 12 weeks since the fetal heart is formed by week 12. There is no evidence of long-term neurobehavioral effects in infants with lithium use in pregnancy.²⁸ Although lithium exposure during the second and third trimester is not associated with teratogenic risk, it can result in various neonatal complications, such as premature labor, polyhydramnios, cardiomegaly, hepatomegaly, nephrogenic diabetes insipidus, goiter and hypothyroidism, and gastrointestinal bleeding.^{20,27} Lithium toxicity in neonates has also been reported, and this can manifest as flaccidity, lethargy, and poor suck reflexes ("floppy infant syndrome"), low Apgar scores, shallow breathing, apnea, and other symptoms.^{3,27} Neonatal toxicity

depends on lithium levels, and occurs at levels lower than adults, which is a significant consideration given that lithium completely equilibrates across the placenta.²⁹ Newport et al.²⁹ show that lithium delivery concentrations can be significantly reduced at delivery without compromising pharmacotherapeutic efficacy by briefly withholding lithium therapy.

Briggs et al.²⁰ recommend that lithium should be avoided during pregnancy, especially in the first trimester, if possible. In cases in which clinical condition necessitates continued lithium use, adequate screening tests such as level II ultrasound and fetal echocardiography should be performed.

Newport et al.²⁹ and UpToDate³⁰ authors recommend to withhold lithium therapy for 24-48 hours before delivery, and to restart when the patient is medically stable after delivery. Guidelines by the Royal Australian and New Zealand College of Psychiatrists recommend reducing the lithium dose by 25% just before delivery.³¹

ACOG³ recommends that for bipolar patients on lithium who plan to conceive that lithium should be gradually tapered in women with mild, infrequent episodes; should be tapered but restarted after organogenesis in patients with moderate-to-severe episodes and moderate risk of relapse in the short-term; and should be continued throughout gestation in women with especially severe and frequent manic episode. While such a recommendation offers clinical guidance to perplexed physicians and patients, there is no evidence base to suggest that patients with mild, infrequent episodes do not have a reasonable risk of relapse during pregnancy after discontinuation, and that the risk of fetal harm outweighs this risk of relapse. To bring into perspective the other side of the picture, Viguera et al.³² reported that 52% of pregnant women with bipolar disorder relapsed during the first

40 weeks after lithium discontinuation (and this was comparable to the relapse rate of 58% after discontinuing lithium in nonpregnant women). The relapse rate was significantly lower for both groups in the year before treatment was discontinued (21%). The recurrence risk was greater after rapid than after gradual discontinuation. In another study by Viguera et al.,³³ the recurrence risk was 2.3 times greater after discontinuation of mood stabilizer treatment (85.5%) than with continued treatment (37%). The subjects who discontinued the mood stabilizer spent over 40% of the pregnancy in an illness episode versus only 8.8% of who maintained the mood stabilizer.

VALPROATE

FDA Pregnancy Drug Rating: D (X for Migraine Prophylaxis)

Sodium valproate has a black box warning per FDA guidelines stating "Fetal risk, particularly neural tube defects, other major malformations, and decreased IQ."³⁴ There is sufficient evidence from human and animal studies to establish that valproate is a teratogen. Data from the North American Antiepileptic Drug Pregnancy Registry reported a 4-fold increase in congenital malformations in infants of mothers exposed to valproate monotherapy in the first trimester of pregnancy in comparison to monotherapy with all other antiepileptic drugs.³⁵ Relative to the group unexposed to antiepileptics, the relative risk of congenital malformations was 9-fold. Compared to other antiepileptic drugs, valproate was also associated with a higher risk of neural tube defects, hypospadias, cardiac defects, and oral clefts.³⁶ Approximately 1%-2% of fetuses exposed to valproate in-utero develop neural tube defects, which is a 10- to 20-fold increase in risk compared to general population.^{37,38} Apart from neural tube defects, other malformations include atrial septal defects, cleft palate, hypospadias,

polydactyly, and craniosynostosis.³⁹ The teratogenic effects of valproate are dose-dependent. Higher doses of valproate are associated with higher risk OR of 3.7 for doses less than 1,500 mg/day compared to OR of 10.9 for doses more than 1,500 mg/day.^{38,40} A characteristic pattern of facial dysmorphic features and a distinct constellation of defects (craniofacial, skeletal, urogenital and cardiovascular defects, and restricted development) have been described as well.²⁰ Folic acid supplementation before conception and during the first trimester of pregnancy decreases the risk for congenital neural tube defects in the general population, and is therefore recommended for women contemplating pregnancy and pregnant women who are taking valproate. (Use of folic acid supplementation, however, has not been shown to reduce the risk of birth defects with antiepileptic drugs.⁴¹)

When possible, valproate should be avoided during pregnancy, especially during the first trimester. Given that mood stabilizer discontinuation carries substantial risk of relapse, as discussed above, it is better to substitute an alternative mood-stabilizing agent rather than discontinue the mood stabilizer entirely. Atypical antipsychotics can be considered as alternative mood stabilizers for acute and maintenance therapy during pregnancy given their relatively better reproductive safety profile, although evidence on the benefits or harms of substitution is lacking. Prenatal testing for neural tube defects should be considered.

CARBAMAZEPINE

FDA Pregnancy Drug Rating: D

Exposure to carbamazepine during pregnancy has been associated with an increased incidence of teratogenic effects. These include neural tube defects such as spina bifida, craniofacial defects such as cleft palate, cardiovascular malformations, and urinary tract defects such

as hypospadias.⁴² A fetal carbamazepine syndrome has been described, consisting of facial dysmorphism, finger nail hypoplasia, and developmental delays, but the existence of this syndrome remains controversial.^{3,20} The manufacturer label warns that developmental delays have been observed; however, this could be the result of various confounding factors.⁴² Up to 1% of fetuses exposed in utero to carbamazepine develop spina bifida,⁴³ which is a 7-fold increase from that of the general population. The risk of neural tube defects from exposure to carbamazepine is less than that from exposure to valproate.³⁶ Various registries from around the world have provided rates of congenital malformations ranging from 2.2%-3.3%.^{36,44-46}

Considerations similar to valproate, as discussed above, also apply to carbamazepine. Where possible, carbamazepine should be avoided during pregnancy, especially during the first trimester. Supplementation of folic acid is recommended for women contemplating pregnancy and pregnant women who are taking carbamazepine. Consider atypical antipsychotics as alternative mood stabilizers for acute and maintenance therapy, given their relatively better reproductive safety profile, although evidence on the benefits or harms of substitution is lacking.

BENZODIAZEPINES

FDA Pregnancy Drug Rating: D

All benzodiazepines are category D, except for the following, which are category X: flurazepam, estazolam, temazepam, quazepam, and triazolam. There is uncertainty regarding the teratogenic potential of benzodiazepines. Some studies have reported that benzodiazepines are associated with an increased risk of congenital malformations, in particular oral cleft; however, other studies have not found an association.²⁷ A meta-analysis by Dolovich et al.⁴⁷ of 23 studies reported that in cohort studies fetal

exposure to benzodiazepine was not associated with major malformations or oral cleft. Analysis of case-control studies in the same meta-analysis revealed an association between benzodiazepine use in pregnancy and the development of major malformations (OR 3.01; 95% CI 1.32-6.84) and oral cleft alone (OR 1.79; 95% CI 1.13-2.82). A Swedish birth registry study reported that the rate of relatively major congenital malformations was moderately increased among infants exposed to benzodiazepines and benzodiazepine receptor agonists in early pregnancy (adjusted OR = 1.24, 95% CI 1.00-1.55).⁴⁸ Another study using data from the same Swedish birth registry did not find an association.⁴⁹ A recent study by Ban et al.⁵⁰ found no evidence for an increase in major congenital anomalies in children exposed to benzodiazepines and nonbenzodiazepine hypnotics in the first trimester of pregnancy.

The risk of oral cleft in the general population is 6 in 10,000 births. Fetal exposure to benzodiazepines can increase this risk up to 7 in 10,000⁵¹ to 11 in 10,000⁵² births. The results may be subject to recall bias and confounding factors. Nonetheless, it's a very small increase in absolute risk.

Neonatal toxicity and withdrawal syndrome secondary to benzodiazepine use in pregnancy are well established. It necessitates close monitoring of neonates in the postpartum period. Use of benzodiazepines shortly before delivery increases the risk of floppy infant syndrome, manifesting with hypothermia, lethargy, poor feeding, hypotonia, apnea, and low Apgar scores. Chronic use of benzodiazepines is associated with withdrawal symptoms in the neonate, displaying symptoms such as restlessness, hypertonia, hyperreflexia, tremulousness, apnea, diarrhea, and vomiting. These symptoms can persist up to 3 months postpartum.^{3,27}

Benzodiazepine use during pregnancy should be avoided when possible, es-

pecially in the first and late third trimester. There is no absolute contraindication to the use of benzodiazepines in pregnancy and occasional (or even chronic) use may be clinically warranted (aside from those in category X). With benzodiazepine use during pregnancy, close monitoring of neonates in the postpartum period is required to watch for neonatal toxicity and withdrawal symptoms.

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