

# Antipsychotic Use in Pregnancy

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## Introduction

There is limited data in the literature to address the use of antipsychotic medications in pregnant women. To aid practitioners, this guide was created by evaluating the available literature and it will assist practitioners as they provide treatment options and assist women to make the best decision for herself and her child.

The decision to continue or discontinue treatment should be made in collaboration with the health care team, the patient, and their supports. There are no risk-free choices in the treatment of patients with serious mental illness, but with collaborative discussion between the health care team and the patient about the known risks and benefits of medication, informed consent can be obtained.<sup>i</sup>

The outcomes of women who chose to continue medication treatment is complicated by studies that show women with schizophrenia have higher pregnancy risks (fetal distress, low birth weight, and congenital anomalies) and it is not known if these can be attributed to the medical condition itself, or if medications contribute to these outcomes<sup>i</sup>. Alternatively, for those who wish to discontinue medication treatment, the risk of relapse is also a concern for the safety of the mother and child. It has been reported that patients who stop their medication have a relapse rate of 53 percent versus 16 percent of those who remain on treatment over a 10-month period, and generally, the highest risk is found in the first 90 days<sup>i</sup>.

## Understanding Food and Drug Administration (FDA) Pregnancy Categories

There is a wide misunderstanding of the current pregnancy categories utilized by the FDA for pregnancy risk, and critics state that the categories are overly simplistic. The categories do NOT distinguish the toxicities according to severity, incidence, and type based on dose, duration, gestational timing, and other such factors.

The criteria also allow for medications with known human risk to be categorized in the same class as those with no known risk. This is especially prevalent in category C, which is assigned to two thirds of the medications approved today<sup>ii</sup>. Currently, the FDA is reviewing the pregnancy categorizations, but at this time, no changes have been set forth.

**Category A**

- Adequate and well-controlled trials have failed to demonstrate risk to the fetus in the first trimester of pregnancy and there is no evidence of risk in later trimesters.

**Category B**

- Animal reproduction studies have failed to demonstrate a risk to the fetus; AND
- There are no adequate and well-controlled studies in pregnant women.

**Category C**

- Animal reproduction studies have shown an adverse effect on the fetus; AND
- There are no adequate and well-controlled studies in humans, but potential benefits may warrant the use in pregnant woman.

**Category D**

- There is positive evidence of human fetal risk based on adverse reaction data from investigational/marketing experience or studies in humans.
- Potential benefits may warrant use of the drug in pregnant women despite potential risks.

**Category X**

- Studies in animal or humans have demonstrated fetal abnormalities; AND/OR
- There is positive evidence of human fetal risk based on adverse reactions from investigational or marketing experience; AND
- The risks involved in the use of the drug in pregnant women clearly outweigh the potential benefits.

**Pregnancy Categories for Antipsychotics<sup>iii</sup>**

<b>First Generation Antipsychotics</b>	
<b>Medication Name</b>	<b>Pregnancy Category</b>
<b>Chlorpromazine</b>	C
<b>Fluphenazine</b>	C
<b>Haloperidol</b>	C
<b>Loxapine</b>	C
<b>Perphenazine</b>	C
<b>Prochlorperazine</b>	C
<b>Pimozide</b>	C
<b>Thioridazine</b>	C
<b>Trifluoperazine</b>	C
<b>Thiothixene</b>	C

Second Generation Antipsychotics	
Medication Name	Pregnancy Category
Aripiprazole	C
Asenapine	C
Clozapine	B
Iloperidone	C
Olanzapine	C
Lurasidone	B
Paliperidone	C
Quetiapine	C
Risperidone	C
Ziprasidone	C

#### Considerations for Second Generation Antipsychotics<sup>i,iii</sup>

- Aripiprazole
  - A case report has been published that highlighted failure to lactate in one woman (potentially due to the partial agonist activity at the dopamine receptor).
- Clozapine
  - Weight gain, serum lipid abnormalities, seizure, sedation, agranulocytosis, gestational diabetes
  - Potential for neonatal convulsions and hematological toxicity should be considered, but no reports are found in the literature.
  - Clozapine is classified as a Category B medication, but treatment should only be reserved for rare cases.
- Olanzapine
  - Weight gain, serum lipid abnormalities, and gestational diabetes
- Risperidone and paliperidone
  - Hyperprolactinemia and Extrapyramidal Symptoms (EPS)
- Quetiapine
  - Very little literature
  - A few studies have published that neonates have had normal deliveries and APGAR scores.
- Ziprasidone
  - Little information in the literature
  - Neutral effects on weight
- Newer medications, including asenapine, iloperidone, and lurasidone, have very little published data.
  - These medications are weight neutral.

- Iloperidone has a high incidence of initial orthostatic hypotension, so syncope and tachycardia should be monitored.

#### Recommendations for Patients Who Are Already Pregnant

- Work with the patient to evaluate the risk and benefits of medication continuation or discontinuation and acquire informed consent.
  - Inform the women that the risk of fetal malformations in the general population is 2–4%<sup>iv</sup>.
  - Published risks estimates are based on population data and are used to measure individual risk, but does not provide information about the women herself.
  - It is often helpful to present data in frequencies (2 out of 100) rather than percentages.

#### Recommendations for Patients Trying to Become Pregnant

- Work with the patient to identify risks and benefits of medication continuation versus discontinuation.
- Consider switching to a first generation antipsychotic because more data are available and the data show minimal risk.
  - Chlorpromazine has the most information about safety in published literature.
- It should be noted that prolactin level elevations, due to dopamine receptor blockade, may reduce the chance of conception.

#### Recommendations for All Patients

- Encourage women to enroll in the Massachusetts General Hospital National Pregnancy Registry for Atypical Antipsychotics by calling 1-866-961-2388. At this time, medical practitioners cannot enroll pregnant women into this study, but the success of this study will largely be based on patient referrals.
  - This participation will be crucial for gathering information to further understand the benefits and risks of anticonvulsant medications in pregnancy.**
- Monotherapy is preferred over polypharmacy to limit the exposure to multiple medications during fetal development.
- Consider using the lowest effective antipsychotic dose that addresses target symptoms.
- Anticholinergic medications should not be routinely prescribed for extrapyramidal symptoms for long durations; consider dosage adjustment or altering the administration time of the antipsychotic.
- Encourage a healthy lifestyle, including physical activity, healthy diet, elimination of alcohol, and smoking cessation (optimal) or reduction.
- Evaluate folate intake and obtain serum folate and B12 levels
  - Deficiencies in folate and B12 have been linked with neural tube defects.
  - Encourage administration of a prenatal vitamin and extra folic acid supplementation, if required.
- Monitor gestational weight and work with obstetrician to monitor for gestational diabetes.

**Postnatal Period**

- Neonate
  - ❑ Extrapyramidal Symptoms (EPS)<sup>i</sup>
    - ❖ Some case reports are found in the literature.
    - ❖ These symptoms include motor restlessness, tremor, hypertonicity, dystonia, and parkinsonism.
    - ❖ These symptoms are usually brief, but one case of hypertonicity lasted up to 10 months.
      - Subsequent motor development in that case was normal.
  - ❑ Biphasic Syndrome
    - ❖ Initial neonatal depression
      - Symptoms include diminished spontaneous movement, minimal crying, vasomotor instability, and difficulty with oral feeding.
    - ❖ Followed by agitated phase (lasting up to 1–7 months)
      - Excessive crying, hyperreflexia, tremor, and sucking with increased intake
- Mother
  - ❑ Community supports and groups should be offered to deal with the stress of motherhood.
  - ❑ Support services for irritable or unsettled babies, breast or bottle feeding concerns, and mother’s physical recovery
  - ❑ Closely monitor for an increase in behavioral symptoms, especially for those at risk for postpartum depression or psychosis

**Breastfeeding<sup>v</sup>**

- There are many published benefits of breastfeeding, but it is important for the mother to understand the benefits and risks associated with breastfeeding her child while taking antipsychotic medications.
- Very limited published literature is available for breastfeeding while taking an antipsychotic.
- The available evidence suggests that these medications are all passed through breast milk, but the use of antipsychotics is relatively safe.

First Generation Antipsychotics <sup>vi</sup>	
Medication Name	Summary
<b>Chlorpromazine</b>	Levels appear detectable in milk, but do not appear to correspond with a mother’s serum level. Sedation has occurred, so it is recommended to monitor the infant for sedation and milestone development.
<b>Fluphenazine</b>	No published literature, so alternates should be considered. <ul style="list-style-type: none"> <li>▪ Alternates: haloperidol, risperidone</li> </ul>
<b>Haloperidol</b>	Limited information show doses up to 10 mg/day produce low levels in milk and do not appear to affect the infant. Monitor the infant for sedation and milestone development.
<b>Loxapine</b>	No published literature, so alternates should be considered. <ul style="list-style-type: none"> <li>▪ Alternates: haloperidol, olanzapine</li> </ul>

First Generation Antipsychotics <sup>vi</sup>	
Medication Name	Summary
<b>Perphenazine</b>	Limited information show doses up to 24 mg/day produce low levels in milk and do not appear to affect the infant. Monitor the infant for sedation and milestone development.
<b>Pimozide</b>	No published literature, so alternates should be considered. <ul style="list-style-type: none"> <li>▪ Alternates: haloperidol</li> </ul>
<b>Prochlorperazine</b>	Minimal excretion in milk and the use for the treatment of short-term nausea poses little risk.
<b>Thioridazine</b>	No published literature, so alternates should be considered. <ul style="list-style-type: none"> <li>▪ Alternates: haloperidol, olanzapine</li> </ul>
<b>Trifluoperazine</b>	Limited information show doses up to 10 mg/day produce low levels in milk and do not appear to affect the infant. Monitor the infant for sedation and milestone development.
<b>Thiothixene</b>	No published literature, so alternates should be considered. <ul style="list-style-type: none"> <li>▪ Alternates: haloperidol, olanzapine, risperidone</li> </ul>

Second Generation Antipsychotics <sup>vii</sup>	
Medication Name	Summary
<b>Aripiprazole</b>	Limited data show doses up to 15 mg/day produce low levels in milk, but until more data are available, an alternate medication may be preferred. <ul style="list-style-type: none"> <li>▪ Alternates: haloperidol, olanzapine</li> </ul>
<b>Asenapine</b>	No published literature, so alternates should be considered. <ul style="list-style-type: none"> <li>▪ Alternates: haloperidol, olanzapine, risperidone</li> </ul>
<b>Clozapine</b>	Other agents preferred due to published risks of sedation and adverse hematological effect. <ul style="list-style-type: none"> <li>▪ Alternates: haloperidol, olanzapine, risperidone</li> </ul>
<b>Iloperidone</b>	No published literature, so alternates should be considered. <ul style="list-style-type: none"> <li>▪ Alternates: haloperidol, olanzapine, risperidone</li> </ul>
<b>Olanzapine</b>	Limited information show doses up to 20 mg/day produce low levels in milk. Most cases do not report short-term side effects, but sedation has occurred. Monitor the infant for sedation and milestone development.
<b>Lurasidone</b>	There is no published literature, so alternates should be considered. <ul style="list-style-type: none"> <li>▪ Alternates: haloperidol, olanzapine, risperidone</li> </ul>
<b>Paliperidone</b>	Limited data are published on this metabolite of risperidone, so other agents may be preferred. <ul style="list-style-type: none"> <li>▪ Alternates: haloperidol, olanzapine</li> </ul>
<b>Quetiapine</b>	Limited data show doses up to 400mg/day produce low levels in milk, but there are limited long-term data. Other agents may be preferred. <ul style="list-style-type: none"> <li>▪ Alternates: haloperidol, olanzapine, risperidone</li> </ul>
<b>Risperidone</b>	Limited data show doses up to 6mg/day produce low levels in milk, but there are limited long-term data. Other agents may be preferred. <ul style="list-style-type: none"> <li>▪ Alternates: haloperidol, olanzapine</li> </ul>
<b>Ziprasidone</b>	No published literature, so alternates should be considered.

▪ Alternates: haloperidol, olanzapine, risperidone
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<sup>i</sup> Wisner, K., Sit D., Moses-Kolko E. (2007). Antipsychotic Treatment During Pregnancy: A Model for Decision Making. *Advances in Schizophrenia and Clinical Psychiatry*. Vol 3(2), 47–55.

<sup>ii</sup> Aschenbrenner D. (2008). Drug Watch: The FDA Proposes Revisions to Pregnancy Information in Drug Labeling. *American Journal of Nursing*. Vol 108(11), 32–34.

<sup>iii</sup> Clinical Pharmacology (2013). Retrieved from <http://www.clinicalpharmacology-ip.com/default.aspx>. Accessed 05/15/2013.

<sup>iv</sup> National Institute for Health and Clinical Excellence (2007). Antenatal and Postnatal Mental Health-Clinical Management and Service Guidance. NICE Clinical Guideline. Available at: <http://www.nice.org.uk/nicemedia/live/11004/30433/30433.pdf>. Accessed 05/15/2013.

<sup>v</sup> Briggs G., Freeman R., Yaffee S. (2011). *Drugs in Pregnancy and Lactation*-ninth edition. Wolters Kluwer.

<sup>vi</sup> Drugs and Lactation Database-LactMed (2013). Retrieved May 15, 2013. Available at: <http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?LACT>.

<sup>vii</sup> Drugs and Lactation Database-LactMed (2013). Retrieved May 15, 2013. Available at: <http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?LACT>.