

# Mood Stabilizers and Their Use in Pregnancy

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## Introduction

There are limited data in the literature to address the use of traditional mood stabilizers in pregnant women. To aid practitioners, this guide was created by evaluating the available literature; it assists practitioners as they provide treatment options and provide to aid women in making the best decision for herself and her child.

The decision to continue or discontinue treatment should be made in collaboration with the healthcare 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 healthcare team and the patient about the known risks and benefits of medication, informed consent can be obtained. Pregnancies in women with bipolar disorder have been linked to a slight increase in the risk of pre-term birth and giving birth to small for gestational age infants, but no studies have evaluated if the risk is due to the illness itself, medications, or other lifestyle behaviors<sup>i</sup>.

It was once believed that pregnancy provided protection from mood disorders but, with newer clinical information, this belief is now refuted<sup>ii</sup>. If a woman wishes to discontinue medications during pregnancy, some prefer to restart these medications only at the first sign of symptom reoccurrence, while others consider treatment after the first trimester to avoid the largest risks of congenital malformation<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>iii</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 a 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 women.

**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 Mood Stabilizers<sup>iv</sup>**

Generic Ingredient	Brand Name	Pregnancy Category
<b>Carbamazepine</b>	Carbatrol <sup>®</sup> , Epitol <sup>®</sup> , Equetro <sup>®</sup> , Tegretol <sup>®</sup> , Tegretol XR <sup>®</sup>	D
<b>Divalproex sodium, Valproic Acid</b>	Depakote <sup>®</sup> , Depakote ER <sup>®</sup> , Depakene <sup>®</sup> , Stavzor <sup>®</sup>	D/X*
<b>Gabapentin<sup>§</sup></b>	Gralise <sup>®</sup> , Horizant <sup>®</sup> , Neurontin <sup>®</sup>	C
<b>Lamotrigine</b>	Lamictal <sup>®</sup> , Lamictal XR <sup>®</sup>	C
<b>Levetiracetam</b>	Keppra <sup>®</sup> , Keppra XR <sup>®</sup>	C
<b>Lithium</b>	Eskalith <sup>®</sup> , Eskalith CR <sup>®</sup> , Lithobid <sup>®</sup> , Lithium Citrate	D
<b>Oxcarbazepine<sup>‡</sup></b>	Oxtellar XR <sup>®</sup> , Trileptal <sup>®</sup>	C
<b>Tiagabine<sup>§</sup></b>	Gabitril <sup>®</sup>	C
<b>Topiramate<sup>§</sup></b>	Topamax <sup>®</sup> , Topiragan <sup>®</sup> , Qsymia <sup>®</sup> (includes phentermine)	D
<b>Zonisamide<sup>§</sup></b>	Zonegran <sup>®</sup>	C

\* Category X for migraine prophylaxis only, but it remains category D for acute mania and seizures.

§ Generally not recommend for treatment of bipolar disorder.

≠ In 2009, the Canadian Network for Mood and Anxiety Treatments (CANMAT) moved oxcarbazepine from a second-line treatment option to third line, stating that recent clinical trials showed no significant improvement in manic symptoms compared to placebo.

### Considerations for Treatment Recommendations

- Carbamazepine (CBZ)
  - ❑ Preferred by some as the anticonvulsant treatment of choice, along with low dose lamotrigine for treatment of epilepsy in pregnant women<sup>v</sup>
  - ❑ Increase risk of spina bifida (1 percent) compared to the general population (0.1 percent)<sup>vi</sup>
  - ❑ Associated with unique facial features and underdevelopment of fingers, toes, and nails
- Divalproex/Valproic Acid (VPA)
  - ❑ Generally, not the preferred agent for use in pregnancy or women of childbearing age.
  - ❑ Fetal valproate syndrome<sup>vi</sup>
    - ❖ Slow growth
    - ❖ Small head circumference
    - ❖ Characteristic facial features
    - ❖ Cleft lip
    - ❖ Limb anomalies
  - ❑ Recent literature has shown developmental issues (e.g., decreased Intelligence Quotient (IQ), developmental delay, behavior problems) for children born to mothers taking divalproex or valproic acid products<sup>vi</sup>.
  - ❑ Both CBZ and VPA have been associated with an increased risk of neural tube defects<sup>vi</sup>.
  - ❑ In May 2013, the FDA changed the pregnancy category for divalproex use in migraine prevention from category D to category X. It remains category D for the treatment of manic episodes associated with bipolar disorder and epilepsy.
  - ❑ If the benefits of continuing this medication outweigh the risk, doses should not exceed 1,000mg/day in divided doses.
- Lamotrigine
  - ❑ Preferred by some as the anticonvulsant treatment of choice, along with carbamazepine for treatment of epilepsy in pregnant women<sup>vi</sup>.
  - ❑ Recent studies have shown there could be an increased risk of cleft palate (9/1,000)<sup>ii</sup>.
  - ❑ Dose-related teratogenesis has been reported with doses over 200 mg/day<sup>vii</sup>.
- Lithium
  - ❑ Despite some conflicting data regarding the congenital malformations, mainly Ebstein's anomaly, some consider the use of lithium as the drug of choice for bipolar disorder in pregnancy, while other resources state to avoid administration, particularly in the first trimester<sup>ii, viii</sup>.
    - ❖ Ebstein's anomaly is a rare heart defect in which parts of the tricuspid valve are abnormal and this malformation results in tricuspid regurgitation at varying levels.

- ❑ Neonatal toxicity, even with therapeutic doses, at the time of delivery has been seen. These include cyanosis, muscle flaccidity, hypotonia, poor sucking and grasp reflexes, and lethargy that may take up to 10 days to resolve.
- ❑ If it is determined clinically appropriate to continue lithium throughout the pregnancy, some dosing recommendations have been set forth.
  - ❖ In most cases, plasma levels should remain between 0.7 and 1.2 mEq/L.
  - ❖ Single doses greater than 300mg should be avoided to minimize peak plasma spikes<sup>viii</sup>.

During the last week of gestation, decreasing the lithium dose by 50 percent and completely stopping administration at the onset of labor is recommended. The pre-pregnancy dose can be resumed after fluid homeostasis is re-established, usually within 3 days<sup>viii</sup>.

#### 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 percent<sup>vii</sup>.
  - ❑ Published risk estimates are based on population data and are used to measure individual risk but do not provide information about the women herself.
  - ❑ It is often helpful to present data in frequencies (e.g., 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 discontinuing VPA products and stabilize the patient on an alternative mood stabilizer
  - ❑ If continuation of VPA is preferred, dosing should not exceed 1,000mg/day and smaller doses should be administered throughout the day rather than larger once-daily dosing to avoid large peaks in plasma levels.
- Consider supplementation with high dose folic acid supplementation (4–5 mg/day) one month prior to conception and throughout the first trimester to decrease the risk of neural tube defects<sup>vii,viii</sup>.

#### Recommendations for All Patients

- Work with the patient to evaluate the risk and benefits of medication continuation or discontinuation and acquire informed consent
  - ❑ Published risk estimates are based on population data and are used to measure individual risk, but do not provide information about the women herself
  - ❑ It is often helpful to present data in frequencies (e.g., 2 out of 100) rather than percentages.
  - ❑ Remind the woman that the risk of major congenital malformations in the general population is 2–3 percent
    - ❖ The risk in women who take anticonvulsant medications is 4–6 percent<sup>i</sup>.

- Encourage pregnant women to enroll in the Antiepileptic Drug Treatment Registry by calling 1-888-233-2334
  - ❑ **At this time, medical practitioners cannot enroll pregnant women into this study, but 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.
  - ❑ Infants exposed to polypharmacy have a significantly higher risk of birth defects versus monotherapy (9.84 percent versus 5.3 percent)<sup>vii</sup>.
- Consider supplementation with folic acid 4 or 5 mg/day one month prior to conception and through the first trimester to decrease the risk of neural tube defects
- Enzyme-inducing anticonvulsants can lead to vitamin K deficiency and increased bleeding. It is recommended that women in the last month of pregnancy take 10mg/day oral vitamin K and infants should be given the standard 1 mg vitamin K dose IM or IV soon after birth<sup>vi</sup>.
- Encourage a healthy lifestyle, including physical activity, healthy diet, elimination of alcohol, and smoking cessation (optimal) or reduction
- Monitor gestational weight and work with obstetrician to monitor for gestational diabetes
- Changes in volume of distribution, plasma proteins, and kidney/liver function may require dosage adjustments throughout the pregnancy and postpartum. These pharmacodynamic changes may not cause as many dose adjustments compared to the use for seizure prophylaxis.
- The importance of monitoring early symptoms should be discussed with the patient.
  - ❑ After symptom reoccurrence, the consensus is to treat symptoms very early and aggressively to minimize complications and stop or slow the advance of the disease<sup>viii</sup>.
  - ❑ The data suggest that those women who remain well throughout their pregnancy have a lower risk of postpartum relapse compared to those who become ill during their pregnancy<sup>i</sup>.

### Postnatal Period

- Neonate
  - ❑ May experience withdrawal symptoms of irritability, hypertonia, exaggerated startle reflex, and tachypnoea
    - ❖ These symptoms are more common in mothers that take valproate, phenytoin, or polypharmacy during their pregnancy.
  - ❑ Some reports of hypoglycemia have been reported and infants should be monitored appropriately.
  - ❑ Enzyme inducing anticonvulsants can lead to vitamin K deficiency and increased bleeding. It is recommended that infants should be given the standard 1 mg vitamin K dose IM or IV soon after birth<sup>vi</sup>.
- 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>ix</sup>

Generic Ingredient	Brand Name	Summary
Carbamazepine	Carbatrol®, Epitol®, Equetro®, Tegretol®, Tegretol XR®	<b>Levels in breast milk are relatively high</b> , but most infants do not have any adverse reactions. Monitor for jaundice, drowsiness, weight gain, and attainment of developmental milestones.
Divalproex sodium Valproic Acid	Depakote®, Depakote ER®, Depakene®, Stavzor®	Low levels found in breast milk, and no adverse reactions have been reported. One questionable case of thrombocytopenia has been reported. Monitor for sedation, withdrawal reactions, bruising, and jaundice.
Gabapentin <sup>§</sup>	Gralise®, Horizant®, Neurontin®	Low levels found in breast milk on maternal doses up to 2.1g/day. Monitor for drowsiness, adequate weight gain, and attainment of developmental milestones.
Lamotrigine	Lamictal®, Lamictal XR®	<b>High levels reported in breast milk</b> (30–35 percent of maternal serum levels), and neonatal metabolism is limited. Monitor for apnea, rash, drowsiness, poor sucking, and consider measurement of serum levels if toxicity is suspected.
Levetiracetam	Keppra®, Keppra XR®	Low levels present in breast milk with maternal doses up to 3,500mg/day. Monitor for adequate weight gain, drowsiness, and attainment of development milestones.
Lithium	Eskalith®, Eskalith CR®, Lithobid®, Lithium Citrate®	May be used in full-term infants with the appropriate monitoring. Consider monitoring serum neonate serum levels, creatinine, Blood Urea Nitrogen (BUN), and Thyroid Stimulating Hormone (TSH) every 4 to 12 weeks.
Oxcarbazepine <sup>‡</sup>	Oxtellar XR®, Trileptal®	Limited information shows no adverse effects. Monitor for drowsiness, adequate weight gain, and attainment of developmental milestones.
Tiagabine <sup>§</sup>	Gabitril®	No published experience. Monitor for drowsiness, adequate weight gain, and attainment of developmental milestones.
Topiramate <sup>§</sup>	Topamax®, Topiragan®, Qsymia® (includes phentermine)	Low levels in breast milk with maternal doses up to 200mg/day. Monitor for diarrhea, drowsiness, adequate weight gain, and attainment of developmental milestones.

Generic Ingredient	Brand Name	Summary
Zonisamide <sup>§</sup>	Zonegran <sup>®</sup>	Low levels in breast milk with maternal doses up to 400mg/day. Monitor for drowsiness, adequate weight gain, attainment of developmental milestones, and serum level if toxicity is a concern.

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\* In 2009, the Canadian Network for Mood and Anxiety Treatments (CANMAT) removed oxcarbazepine from a second-line treatment option to third line, stating that recent clinical trials showed no significant improvement in manic symptoms compared to placebo.

<sup>i</sup> Boden R, Lundgren M, Brandt L, et al. (2012). Risks of Adverse Pregnancy and Birth Outcomes in Women Treated or Not Treated with Mood Stabilisers for Bipolar Disorder: Population Based Cohort Study. *BMJ*. Vol 345, e7085. Retrieved from: <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3493986/pdf/bmj.e7085.pdf>. Accessed 06/11/13.

<sup>ii</sup> Cohen L, Wang B, Nonacs R, et al. (2010). Treatment of Mood Disorders During Pregnancy and Postpartum. *Psychiatr Clin N Am*. Vol 33, 273-293.

<sup>iii</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>iv</sup> Clinical Pharmacology (2013). Retrieved from: <http://www.clinicalpharmacology-ip.com/default.aspx>. Accessed 06/11/13.

<sup>v</sup> The Best Practice Advocacy Centre-New Zealand (2009). Prescribing Issues Associated with Anticonvulsant Medications for Epilepsy. *The Best Practice Journal*. Vol 24. Retrieved from: [http://www.bpac.org.nz/magazine/2009/november/docs/bpj24\\_anticonvulsants\\_pages4-13\\_pf.pdf](http://www.bpac.org.nz/magazine/2009/november/docs/bpj24_anticonvulsants_pages4-13_pf.pdf) Accessed 06/11/13.

<sup>vi</sup> Kumar S, Mohanty B, Agrawal D, et al. (2012). Antiepileptics and Pregnancy: A review

<sup>vii</sup> Duke Center for Human Genetics (20). Neural Tube Defects. Retrieved from: <http://www.chg.duke.edu/diseases/ntd.html>. Accessed: 06/11/13.

<sup>viii</sup> Kerns L (2011). Treatment of Mental Disorders in Pregnancy: A Review of Neuroleptics, Antidepressants, and Lithium Carbonate. *Jefferson Journal of Psychiatry*. Retrieved from: <http://jdc.jefferson.edu/cgi/viewcontent.cgi?article=1123&context=jeffjpsychiatry>. Accessed 06/10/13.

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