



The North American Antiepileptic Drug Pregnancy Registry

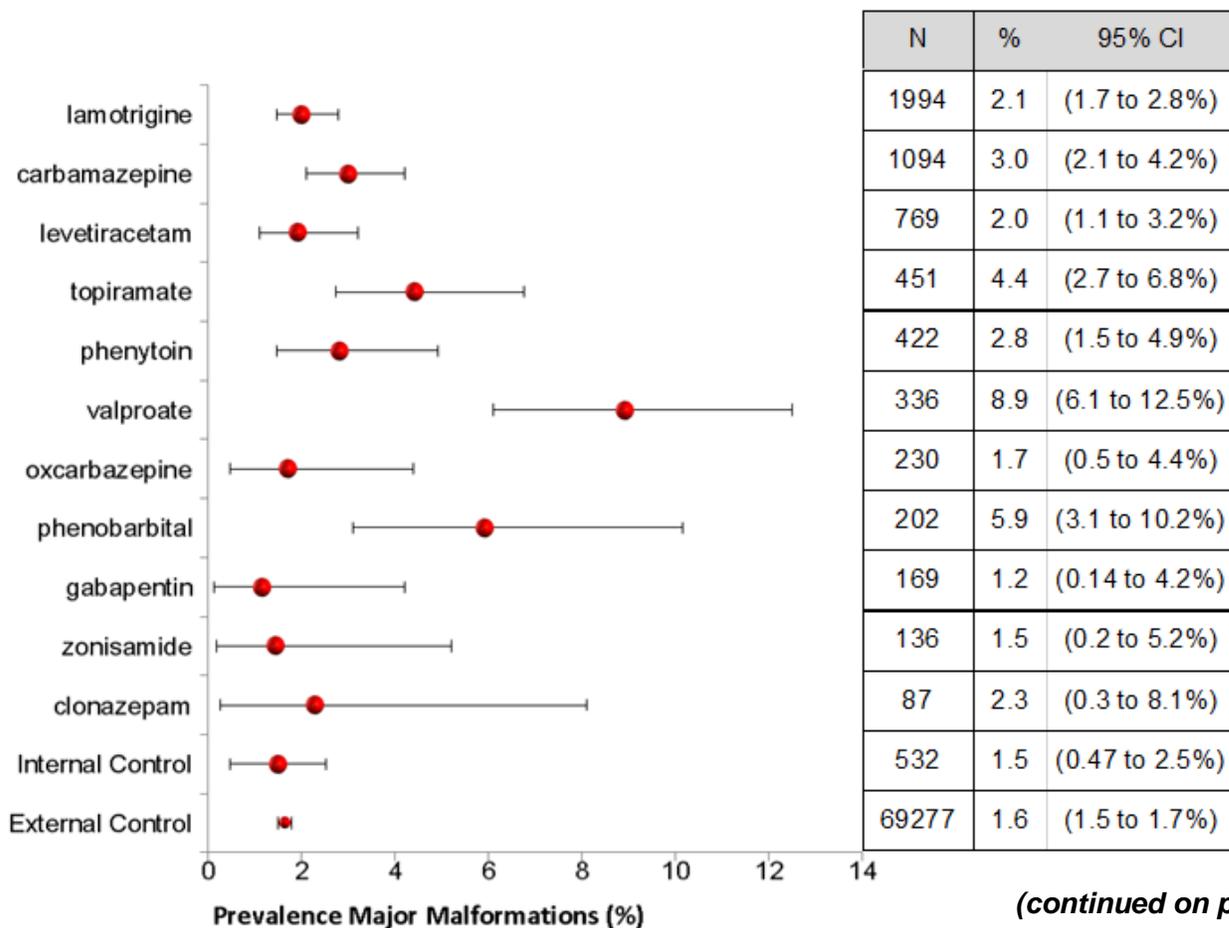
Update on monotherapy findings:

Comparative safety of 11 antiepileptic drugs used during pregnancy

The North American AED (Antiepileptic Drug) Pregnancy Registry announces updated results based on a 2012 study on the comparative safety of AED monotherapy during pregnancy. These results continue to indicate that the prenatal use of traditional antiepileptic medications, such as valproate (Depakote[®]), phenobarbital, and carbamazepine (Tegretol[®]), is associated with a higher risk of major malformations than use of the newer generation AEDs such as lamotrigine (Lamictal[®]) and levetiracetam (Keppra[®]). However, there is also an increased risk of malformations among infants exposed to topiramate (Topamax[®]), another newer generation AED.

Between February 1997 and December 2015, the Registry enrolled a total of 9,294 pregnant women who were taking AEDs for any reason. Of these enrolled participants, 5,962 were taking an AED as monotherapy (only one drug) in the first trimester of pregnancy and were eligible for analysis.

This figure below shows our findings for eleven different AEDs. The red dots indicate prevalence of major malformations for each drug as a percentage, while the endpoints of the lines indicate the 95% confidence intervals. The malformations were defined as structural abnormalities with surgical, medical, or cosmetic importance detected between birth and 5 days of age. The numerical value of each of these variables, as well as the sample size of each drug ("N") is indicated in the columns to the right of the figure.



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Update on monotherapy findings (continued from Page 1)

The prevalence of malformations for these AEDs can be compared to external and internal control groups, both comprised of women not exposed to any AED during their pregnancy, shown at the bottom of the figure on page 1. The external control group includes women from the Active Malformations Surveillance Program at Brigham and Women's Hospital in Boston (N=69,277), while the internal control group includes friends and family members of participants in the AED Pregnancy Registry (N=532).

The overall risk of major malformations associated with first-trimester AED monotherapy use ranges from 9.0% for valproate to 2.0% for lamotrigine. While the low malformation rates for zonisamide, clonazepam, and gabapentin are reassuring, the findings are based on a small number of monotherapy-exposed pregnancies, thus producing wide confidence intervals. Increased sample sizes are needed to confirm these preliminary results.

As reported in spring 2012, the Registry's results suggest that the risks of malformations for "newer generation" AEDs (lamotrigine, levetiracetam and oxcarbazepine) in monotherapy are lower than the risks of malformations for other traditional AEDs (valproate, phenobarbital, phenytoin, and carbamazepine).

As we continue to study the safety of these drugs, the frequency and accuracy of our findings remain contingent upon the largest possible sample size. We want to thank all of the participants who have contributed to this important research. We appreciate your support in our continued endeavors to maximize the health of newborns and to answer the difficult questions facing pregnant women who are taking antiepileptic medications. We encourage any pregnant woman who is taking an AED to call us at 1-888-233-2334 to enroll.

¹ Hernandez-Diaz et al. Comparative safety of antiepileptic drugs during pregnancy. Neurology 78:1692-1699, 2012.

Taking Antiepileptic Drugs While Pregnant: How to Weigh the Pros and Con:

According to Dr. Lewis Holmes, here are some things to think about when deciding whether to take your AEDs during pregnancy

- If you are taking an AED, you most likely rely on this medication to treat serious symptoms related to epilepsy, mood disorders, migraine headaches and chronic pain. These drugs are vital to keeping the mother feeling her best both mentally and physically so be sure to talk to your health care provider about them if pregnant or planning a pregnancy.

- There are a few AEDs developed within the last 12 years that are showing some promising results for being less risky to take during pregnancy. Talk to your doctor about the possibility of switching prescriptions to reduce the chance of birth defects.

Breastfeeding While on AEDs

For most women with epilepsy, breastfeeding is a safe and strongly recommended option. However, for women with epilepsy there are some additional factors and concerns to take into consideration. While breastfeeding is good for both you and your baby, it will create more demands for the mother, especially at night with loss of sleep. If there is a concern that loss of sleep may trigger your seizures, breast milk can be pumped in advance and used for nighttime feedings by your partner/spouse or another family member.

The infant, whose mother has taken an antiepileptic drug (AED) during pregnancy, should be monitored for excessive sleepiness, irritability, and weight loss. If any of these symptoms occur, contact your pediatrician or other healthcare provider about whether these symptoms could be related to the medication in the mother's milk. Some women also have the option to decrease the dose(s) of their AEDs. Depending on the baby's symptoms, a combination of breastfeeding and a supplement with a formula is another option.

In evaluating the safety of medications used while nursing, calculating the Relative Infant Dose (RID) can be a helpful guide. RID is calculated by dividing the infant's dose through breast milk by the maternal dose in mg/kg/day. This will determine the proportion of the mother's level of drug that the infant is ingesting. Researchers agree that RID levels less than 10% of the maternal dose do not pose a high risk for the infant.

Based on side effects in the infants and RID, use of some AEDs are of more concern during breastfeeding than others. If the mother is taking phenobarbital, topiramate or ethosuximide, you should discuss with your pediatrician whether this is safe, since these medications have been measured at high levels in breast milk. Other AEDs like phenytoin, valproate, carbamazepine, gabapentin, clonazepam and levetiracetam have RID's in the less than 10% range. The RID for lamotrigine is 9.2-18.3% which makes it moderately safe, but to be used with caution. More information is needed on the RID for women taking felbamate, pregabalin and oxcarbazepine.

We recommend that each pregnant woman who takes an AED consult with her health care provider about breastfeeding and her medications. In addition, the following are resources that can be useful to answer questions about breastfeeding:

- **LactMed:** 'Drugs and Lactation Database' from the US National Institute of Health, updated monthly and includes information on drug levels in breast milk and infant blood, as well as adverse effects in nursing infants. <https://toxnet.nlm.nih.gov/newtoxnet/lactmed.htm>
- **www.mothersbaby.org / www.motherisk.org:** sources of evidence-based information on the safety of medications and other exposures during pregnancy and while breastfeeding (online chat, text, email or phone calls accepted for health care providers and pregnant or lactating women) MotherToBaby: 866-626-6847 (Toll-free), Motherisk: 877-439-2744 (Toll-free)
- Hale T & Rowe H. (2016). Medications and Mothers' Milk (17th ed.). New York, NY: Springer Publishing Company.
- Chandranipapongse W & Ito S. Breastfeeding and use of antiepileptics. In: Women with Epilepsy: a practical management handbook. Editors: Esther Bui and Autumn M. Klein. Cambridge University Press. 2014 July. Page 223-241.

Medications being studied by the AED Pregnancy Registry *:

Aptiom® (eslicarbazepine acetate)
 Ativan® (lorazepam)
 Banzel® (rufinamide)
 Carbatrol® (carbamazepine)
 Celontin® (methsuximide)
 Depakene® (valproic acid)
 Depakote® & Depakote ER (divalproex sodium)
 Diamox® (acetazolamide)
 Dilantin® (phenytoin)
 Epitol® (carbamazepine)
 Felbatol® (felbamate)
 Fycompa® (perampanel)
 Gabitril® (tiagabine)
 Keppra® (levetiracetam)
 Klonopin® (clonazepam)
 Lamictal® (lamotrigine)
 Lyrica® (pregabalin)
 Mebaral® (mephobarbital)
 Mysoline® (primidone)
 Neurontin® (gabapentin)
 Peganone® (ethotoin)
 phenobarbital (generic)
 Phenytek® (phenytoin)
 Potiga® (ezogabine)
 Sabril® (vigabatrin)
 Seconal® (secobarbital sodium)
 Serax® (oxazepam)
 Tegretol® (carbamazepine)
 Topamax® (topiramate)
 Tranxene® (clorazepate)
 Trileptal® (oxcarbazepine)
 Valium® (diazepam)
 Vimpat® (lacosamide)
 Xanax® (alprazolam)
 Zarontin® (ethosuximide)
 Zonegran® (zonisamide)

* We study **all** antiepileptic medications marketed in the United States and Canada.

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Pregnancy Registry

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1-888-233-2334



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Who Can Participate in the Registry?

The Registry is currently enrolling pregnant women who are taking AEDs for any reason. Participating in the Registry requires three telephone interviews. The first interview takes 20 minutes to complete and the next two take 5 to 10 minutes each. All information is kept strictly confidential. Enrollment is open to women during any stage of pregnancy, but not after the birth of the infant. Ideally, the Registry would prefer to enroll women before they reach the 16th week of pregnancy, or before any prenatal screening. To enroll, or get more information please call the Registry TOLL FREE at **1-888-233-2334**.

We need your help in recruiting controls!

In addition to our participants who take AEDs during pregnancy, we are currently recruiting for a control group in our study. Control participants are women who are pregnant but not taking any AEDs. It is very important for our analyses to have a control group to compare with the women who are taking AEDs. This internal control group allows us to determine more accurately the risks of AED use in pregnancy.

If you know of someone who can serve as a control, please ask her to call us TOLL FREE at **1-888-233-2334**. She will complete the same three telephone interviews. As a token of our appreciation, both you and the friend you refer to the Registry will receive a raffle entry for a chance at winning a \$400 **American Express Gift Card**. The more women you refer, the more chances you have to win the raffle!

Did you send back your forms?

Have you filled out and returned your medical record release forms? Returning these forms to us is necessary to complete your file. These forms give us permission to obtain medical records for you and your child. If you haven't returned them yet, please fill them out and send them to us so that we can complete your enrollment! **It is never too late to send in your forms!**

If you need a new set of forms or have any questions, please do not hesitate to call us toll-free at **1-888-233-2334**. Thank you!

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