



Antiepileptic Drug Pregnancy Registry

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An update about the "new" AEDs

Several antiepileptic drug (AED) pregnancy registries have been established around the world during the past decade. Their major goal was to determine the safety of each AED when taken by pregnant women for any medical condition including epilepsy, mood disorders, migraine, and pain disorders. This approach was developed to speed up the process of identifying the anticonvulsant drugs that are most harmful. The speed of this investigation has varied greatly in regards to the "new" versus "old" AEDs.

Pregnancy registries can best identify increases in the frequency of major malformations. The baseline major malformation rate at birth in unexposed newborn infants is about 2%¹. The first finding released by the North American AED Pregnancy Registry showed that the rate was 6.5% in infants exposed to phenobarbital². The second finding demonstrated a rate of 10.7% in infants exposed to the anticonvulsant drug valproate³. Another registry, the U.K. (United Kingdom) Epilepsy and Pregnancy Register, reported recently that 6.2% of infants exposed to valproate during pregnancy had major malformations⁴.

However, these findings are for "old" drugs. Phenobarbital has been on the market since 1912, and valproate has been marketed since 1978. There are many "new" AEDs that have been introduced to the market in recent years. What about the risks for these "new" AEDs? The pregnancy registries *(continued on Page 2)*

You could win a \$400 American Express Gift Card!

As you may already know, the Registry is currently recruiting women to participate in our control group. The response from Registry participants has been wonderful! Our sincere appreciation and thanks to those of you who have already referred controls to the Registry. **But we still need your help!** If you know someone who could serve as a control, please ask her to call us TOLL FREE: 1-888-233-2334. In order to participate as a control, a woman must currently be pregnant and **not** taking any antiepileptic medication of any kind.

As a token of our appreciation, for every friend or family member you refer who enrolls as a control with the Registry, you will be entered in a drawing to win a **\$400 American Express Gift Card!** In addition, each control group participant will also be entered into a *separate* drawing to win a \$400 American Express gift card. You *both* get a chance to win! Don't forget, you get one raffle entry for *each* woman you refer who becomes part of our control group. Even if you have already referred one friend, you can refer another! The more controls you refer, the better your chances are of winning the great prize! If you have any questions about the control group, please call us TOLL FREE at 1-888-233-2334. Thank you!

The Registry Staff

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An update about the "new" AEDs (continued from Page 1)

hope to answer that important question. Only a limited amount of information about the new AEDs is available at this time. We summarize the major findings here:

- 2.9% of 414 pregnancies exposed to **lamotrigine** had major malformations. These women had enrolled in the International Lamotrigine Registry⁵. In the U.K. Epilepsy and Pregnancy Register, the rate among 647 lamotrigine-exposed infants was 3.2%⁴.
- For **gabapentin**, the rate of malformations was 3.2% among the infants born to 31 women who were enrolled in the U.K. Epilepsy and Pregnancy Register⁴.
- One registry reported that none of the infants born to 35 women who took **oxcarbazepine** as monotherapy had a malformation⁶.
- In Holland, none of the infants born to 11 women who took **levetiracetam** (both monotherapy and polytherapy cases) had a malformation⁷.
- One of 43 infants exposed to **clonazepam** had a major malformation⁸.

It is disappointing that so few clear answers are currently available, particularly for the new anticonvulsants. One reason for the delay is that as many as 500 infants must be evaluated to determine that an individual drug is relatively safe. It takes a long time for any pregnancy registry to enroll 500 women and collect all required consent, data and medical record information about those women and their infants. As a result, all registries are publicizing their work and are encouraging women to enroll. The larger the number of women who enroll in registries, the faster the better estimates of risks about these drugs can be released.

REFERENCES: ¹ Holmes L.B., et al. The teratogenicity of anticonvulsant drugs. *N Engl J Med*, 2001; 344:1132-1138. ²Holmes L.B. et al. North American Antiepileptic Drug Pregnancy Registry. *Epilepsia* 2004; 45(11):1465. ³Wyszynski D.F., et al. Increased rate of major malformations in offspring exposed to valproate during pregnancy. *Neurol* 2005; 64:961-965. ⁴ Morrow J., et al. Malformation risks of antiepileptic drugs in pregnancy: a prospective study from the UK Epilepsy Register. *J Neurol Neurosurg Psychiatry* 2006; 77:193-198. ⁵Cunnington M, et al. Lamotrigine and the risk of malformations in pregnancy. *Neurol* 2005; 64:955-60. ⁶ Meischenguiser R, et al. Oxcarbazepine in pregnancy: Clinical experience in Argentina. *Epilepsy & Behavior*, 2004; 5:163-167. ⁷ ten Berg K. et al. Levetiracetam use and pregnancy outcome. *Reproductive Toxicology*, 2005; 20:175-178. ⁸ Lin A.E., et al. Birth Def Res (part A) *Clin Mol Terat* 70: 534-536, 2004.

New valproate study needs your help

Researchers at the University of Massachusetts Boston need your help in studying the language development, general learning abilities, and social-emotional responding in infants and toddlers exposed to valproate before birth. Participants are paid \$50.00 for a 1.5 to 3 hour appointment either at our lab or at a convenient location closer to your home. Women who did not take medication during their pregnancy may also be eligible to participate in our comparison group. If you would be interested in learning more about this study, please contact Dr. Jane Adams, Director of the Neurodevelopmental Toxicology Laboratory at **Jane.Adams@umb.edu** or **(617) 287-6346**.

Statistics Update

Enrollment:

4982 participants as of March 2006

Participants:

Gravidity:

1st Pregnancy: 38%
2nd Pregnancy: 30%
3rd Pregnancy: 17%
4th + Pregnancy: 16%

Ethnicity:

White: 87%
Black: 4%
Hispanic: 6%

Education:

Some high school or less: 21%
Some college: 25%
College: 33%
Post-graduate: 20%

Health Insurance

Some form of insurance: 97%

Drugs Taken:

23 different monotherapies and 197 different polytherapy combinations

A Message from the Coordinator

Thank you to everyone who has taken the time to enroll with the Registry! The information you share is vital to us in our mission to determine the fetal risks, if any, when a pregnant woman takes an AED. Any incomplete information from a woman's file means that we cannot use that woman's data in our analysis. Since we don't want that to happen, we work very hard to ensure that every woman who enrolls in the Registry has a completed file.

A completed file includes the telephone interviews and copies of your and your child's medical records. It is essential that we have your permission to obtain these records. We use the records to confirm the information you've given us and to make sure we haven't missed anything. As always, it is important that you know that none of the data provided about you is accessible to anybody outside of the Registry staff.

To make it easier for each woman to have a complete file, there are new links on our website. You can now go to www.aedpregnancyregistry.org and click on "Information for Women." Then you'll find a link for "FORMS." Print out the forms with instructions and fill them out. When you send them back to us, we can use those forms to make your file complete!

If you have any questions, please call us TOLL FREE at **1-888-233-2334**.

Are you moving? Have a new phone number?

If any of your contact information has changed, or will change before the birth of your baby, please let the Registry know. Keeping in touch with Registry participants is incredibly important to the success of our research. Simply call us at **1-888-233-2334** (TOLL FREE) and we can quickly update your information. Thank you!

Medications being Studied by the AED Pregnancy Registry *:

alprazolam (generic)
Ativan® (lorazepam)
Carbatrol® (carbamazepine)
Celontin® (methsuximide)
Depakene® (valproic acid)
Depakote® & Depakote ER (divalproex sodium)
Diamox® (acetazolamide)
Dilantin® (phenytoin)
Felbatol® (felbamate)
Frisium® (clobazam)
Gabitril® (tiagabine)
Keppra® (levetiracetam)
Klonopin® (clonazepam)
Lamictal® (lamotrigine)
Lyrica® (pregabalin)
Mesantoin® (mephenytoin)
Milontin® (phensuximide)
Mysoline® (primidone)
Neurontin® (gabapentin)
Paradione® (paramethadione)
Peganone® (ethotoin)
phenobarbital (generic)
Phenytek® (extended phenytoin sodium)
Sabril® (vigabatrin)
Serax® (oxazepam)
Tegretol® (carbamazepine)
Topamax® (topiramate)
Tranxene® (clorazepate dipotassium)
Tridione® (trimethadione)
Trileptal® (oxcarbazepine)
Valium® (diazepam)
Zarontin® (ethosuximide)
Zonegran® (zonisamide)

* This is **not** a complete list. Please call TOLL FREE **1-888-233-2334** to determine if the Registry is studying your specific medication.

AED Pregnancy Registry

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www.aedpregnancyregistry.org

1-888-233-2334
CALL TOLL-FREE



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The Publications of the Registry

Wyszynski D.F., Nambisan M., Surve T., Alsdorf R.M., Smith C.R., Holmes L.B. Increased rate of major malformations in offspring exposed to valproate during pregnancy. *Neurology* 2005; 64:961-965.

Holmes L.B., Wyszynski D.F., Lieberman E.S., The AED (Antiepileptic Drug) Pregnancy Registry: A 6-Year Experience. *Arch Neurol.* 2004; 61:673-678.

A North American Registry for Epilepsy and Pregnancy, a unique public/private partnership of health surveillance. *Epilepsia* 1998;39:793-798.

Who Can Participate in the Registry?

The Registry is currently enrolling pregnant women who are taking AEDs for any reason. Participating in the Registry only requires 3 telephone interviews of about 10 minutes each, and all information is kept strictly confidential. We are also recruiting controls, please see page 1 for details.

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 they have had any prenatal screening. To enroll, or get more information please call the Registry TOLL FREE at **1-888-233-2334**.

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