



The North American Antiepileptic Drug *Pregnancy Registry*

WINTER 2011

Contents:

Page 1

- Registry Releases Topiramate Findings

Page 2

- Registry Releases Findings
(continued)
- Did You Send Back Your Forms?

Page 3

- Updated Statistics
- Win a gift card!

Page 4

- Publications of the Registry
- Who Can Participate in the Registry?

Registry Releases Topiramate Findings: Increased risk for malformations and low birth weight

The North American AED Pregnancy Registry announces the release of findings on the safety of topiramate (brand name Topamax®) use during pregnancy. Our results suggest that topiramate is associated with both an increased risk of major malformations and of low birth weight (less than 5 pounds 8 ounces) in babies exposed to the drug *in utero*.

Since its inception in 1997, the Registry has enrolled 7,310 pregnant women who take anti-epileptic (AED) medications. The majority of our participants use AEDs for epilepsy control, but an increasing number of women enrolled in the Registry take them for other reasons, such as mood disorders, migraines and chronic pain.

Recently, we looked at the frequency of major malformations or birth defects in infants exposed to topiramate. We restricted our analysis to women who took topiramate as monotherapy (only one drug) in the first trimester of their pregnancy. At the time of analysis, 289 women using monotherapy topiramate had enrolled and completed participation in the study. Of these 289 pregnancies, 11 children were born with major malformations, defined as “abnormalities of structural, cosmetic or surgical significance.” This translates to a 3.8% prevalence of major birth defects in children exposed to topiramate *in utero* during the first trimester.

Of the 11 major malformations observed in the topiramate-exposed infants, four of the birth defects were cleft lips. Of these, two were isolated cleft lip, i.e., no associated cleft palate or other anomaly. The other two children, having non-isolated cleft lip, had additional associated anomalies. The frequency of all types of oral clefts, isolated and non-isolated, in the general population is 0.13%.¹

We compared this occurrence of adverse pregnancy outcomes in the exposed group with an internal reference group of 372 pregnant women who were not taking AEDs. At the time of analysis, 372 unexposed women comprised our internal reference group. The prevalence of major malformations within this unexposed group was 1.3% (5 of 372 enrolled controls).

We also compared the observed rate of major malformations for topiramate users against the two most commonly reported monotherapy AEDs in the Registry, namely, lamotrigine and carbamazepine. The relative risk (RR) for having a baby with a major birth defect with topiramate is 2.8 times higher (95% Confidence Interval, 1.0-8.1) than in the population at large. Comparatively, the RR for lamotrigine is 1.3 times higher (95% CI, 0.52 to 3.5), and the RR for carbamazepine is 2.1 times higher (95% CI, 0.82 to 5.4). This comparison of relative risks demonstrates that there is a greater probability of birth defects in topiramate-exposed children than in children exposed to either lamotrigine or carbamazepine. However, it is important to point out that the RR for topiramate is actually much lower than some of the most harmful AEDs, like valproate and phenobarbital. (*continued on page 2*)

The Registry Staff

Director:

Lewis B. Holmes, MD

Epidemiologist:

**Sonia Hernandez-Diaz, MD,
DrPH**

Senior Project Manager:

Caitlin R. Smith, MPH

Clinical Research Coordinator:

Aileen Shen

Research Assistants:

**Melanie Harkins
Mary Noonan**

Epileptologists:

**Barbara A. Dworetzky, MD
Daniel Hoch, MD, PhD**

Psychopharmacologist:

Lee Cohen, MD**The Scientific Advisory
Committee:****Janet Cragan, MD**

CDC, Atlanta

Brandy Fureman, PhD

NIH - Epilepsy Branch

W. Allen Hauser, MD

Columbia University, NY

Lewis B. Holmes, MD

Mass. General Hospital, Boston

Robert Mittendorf, MD, DrPH

Loyola University, Chicago

Mark Yerby, MD (Chairman)

Portland, OR

Sponsors:**Abbott****Eisai****Novartis****Ortho-McNeil****Pfizer****Sepracor****Topiramate Findings** (continued from Page 1)

It has long been known that one of the drug side effects in non-pregnant women who take topiramate is weight loss. Of interest, our findings also suggest that women who take topiramate during pregnancy have babies with decreased birth weight. The average weight of babies exposed to topiramate during pregnancy was 307 grams less than the birth weight of babies born to mothers from our control group. Although taking any AED during pregnancy may lead to babies having lesser birth weights than the average in the population, the loss with topiramate seems to be far greater. For example, among mothers taking lamotrigine and carbamazepine, the average birth weights for their babies were 74 and 94 grams less than the control group, respectively.

Dr. Robert Mittendorf has been on the Scientific Advisory Committee of our Registry since its founding. He is a Professor of Obstetrics and Pediatrics at Loyola University Chicago's Stritch School of Medicine, and has done previous epidemiologic research on the significance of birth weight. He puts these findings of lower birth weight in topiramate exposed infants into a context of medical consequence:

"The loss in birth weight, about 300 g, associated with the use of topiramate in pregnancy is even greater than that associated with smoking in pregnancy, which is about 200 g. In terms of the immediate health of the baby, decreased weight at birth is an important predictor of neonatal morbidity and mortality. Furthermore, low birth weight may be related to an increased risk for coronary heart disease, stroke, diabetes, and hypertension in adult life. So, low birth weight is an important health determinant."

In closing, we want to thank everyone who has contributed to this important research. We greatly appreciate your support and participation in our endeavors to maximize the health of newborns and to answer the difficult questions facing pregnant women who are taking anti-epileptic medications. 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 encourage any pregnant woman who is taking an AED to call us at **1-888-233-2334** in order to enroll.

¹ Holmes L.B., et al. *Neurology* 2008; 70:2152-2158

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. Any incomplete information from your file means that we cannot use your data in our analysis. After enrolling in the Registry, you received two sets of medical record release forms in the mail (printed on blue and pink paper). 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 file! **It is never too late to send in your forms!**

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

Statistics Update

Enrollment: 7,793 participants as of November 2010

Participants:

Gravidity:

1st Pregnancy: 39%
2nd Pregnancy: 29%
3rd Pregnancy: 16%
4th + Pregnancy: 16%

Education:

Some high school or less: 20%
Some college: 24%
College: 34%
Post-graduate: 21%

Ethnicity:

White: 86%
Black: 3%
Hispanic: 6%
Other: 5%

Health Insurance

Some form of insurance: 97%

Drugs Taken:

25 different monotherapies and over 150 different polytherapy combinations

Would you like to win an American Express gift card?

We are pleased to announce the winners of our most recent control group raffle drawing. The referring participant winner of the \$400 American Express Gift Card is **L. from MO**. The winner of the control group raffle, who also receives a \$400 American Express Gift Card, is **S. from New York**.

Didn't win this time? You can still win! The Registry is continuing this to recruit women to participate in our control group, and **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.

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! 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, please call us TOLL FREE at 1-888-233-2334.

Are you moving? Have a new phone number?

If your phone number or mailing address has changed or will change before the birth of your baby, please let us know. You can call us toll free at **1-888-233-2334**, or email us at info@aedpregnancyregistry.org.

It is important for us to have your updated contact information so that we can contact you to complete your file and keep you informed about the upcoming release of our latest research findings.

Medications being Studied by the AED Pregnancy Registry *:

Ativan® (lorazepam)
Banzel® (rufinamide)
Carbatrol® (carbamazepine)
Celontin® (methsuximide)
Depakene® (valproic acid)
Depakote® & Depakote ER (divalproex sodium)
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)
Tridione® (trimethadione)
Trileptal® (oxcarbazepine)
Valium® (diazepam)
Vimpat® (lacosamide)
Xanax® (alprazolam)
Zarontin® (ethosuximide)
Zonegran® (zonisamide)

* This is not a complete list. We study all antiepileptic medications marketed in the United States and Canada.

Please call TOLL FREE **1-888-233-2334** to determine if the Registry is studying your specific medication.

The North American AED Pregnancy Registry

Massachusetts General Hospital
121 Innerbelt Road, Suite 220
Somerville, MA 02143

PHONE (TOLL-FREE):

(888) 233-2334

FAX:

(617) 724-8307

E-MAIL:

info@aedpregnancyregistry.org

Visit us on the Web:

www.aedpregnancyregistry.org

1-888-233-2334

CALL TOLL-FREE



MASSACHUSETTS
GENERAL HOSPITAL



HARVARD
MEDICAL SCHOOL

Recent Publications of the Registry

Hernandez-Diaz, S., Mittendorf, R., Holmes L.B. Comparative Safety of Topiramate During Pregnancy. *Birth Defects Research (Part A)* 88:408 (2010). (Abstract)

Holmes LB. Classifying birth defects in reproductive research. *Birth Defects Research (Part A)* (Part A) 88:404, 2010. (Abstract)

Holmes, L.B., Smith, C.R., Shen, A., Mittendorf, R., Hernandez-Diaz, S. Comparative Safety of Some Anticonvulsant Polytherapies During Pregnancy. *Birth Defects Research (Part A)* 85:465 (2009). (Abstract)

Holmes L.B., Wyszynski D.F., Baldwin, E.J., Smith, C.R., Habecker, E., Glassman, L.H. Increased Frequency for Isolated Cleft Palate Among Infants Exposed To Lamotrigine During Pregnancy. *Neurology* 2008; 70:2152-2158.

Bromfield, E.B., Dworetzky, B.A., Wyszynski, D.F., Smith, C.R., Baldwin, E.J., Holmes, L.B. Valproate Teratogenicity and Epilepsy Syndrome. *Epilepsia* 2008 Jun 13 (Brief Communication).

Smith, C.R., Holmes, L.B. Recruitment of An Unexposed Control Group For A Pregnancy Registry. *Birth Defects Research (Part A)* 82:311 (2008). (Abstract)

Holmes, L.B., Smith, C.R., Hernandez-Diaz, S. Pregnancy Registries: Larger Sample Sizes Essential. *Birth Defects Research (Part A)* 82:307 (2008). (Abstract)

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. The first interview takes 20 minutes to complete and the next two take 5 minutes each. All information is kept strictly confidential. We are also recruiting controls, please see page 3 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 any prenatal screening. To enroll, or get more information please call the Registry TOLL FREE at **1-888-233-2334**.

AED Pregnancy Registry
Massachusetts General Hospital
121 Innerbelt Road, Suite 220
Somerville, MA 02143

NON-PROFIT ORG.
U.S. POSTAGE
PAID
MASSACHUSETTS
GENERAL HOSPITAL