Communicating Risk in an Environment of Uncertainty

Michael F. Greene M.D.
Massachusetts General Hospital
Harvard Medical School
March 5, 2018

Michael F. Greene Disclosures

- Associate Editor: New England Journal of Medicine
- Section Editor: UpToDate
- Editor: Creasy & Resnik's Maternal Fetal Medicine
- Editor: deSwiet's Medical Disorders in Obstetric Practice

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- What is your counseling approach in the face of lack of safety data or conflicting / uncertain human safety data.
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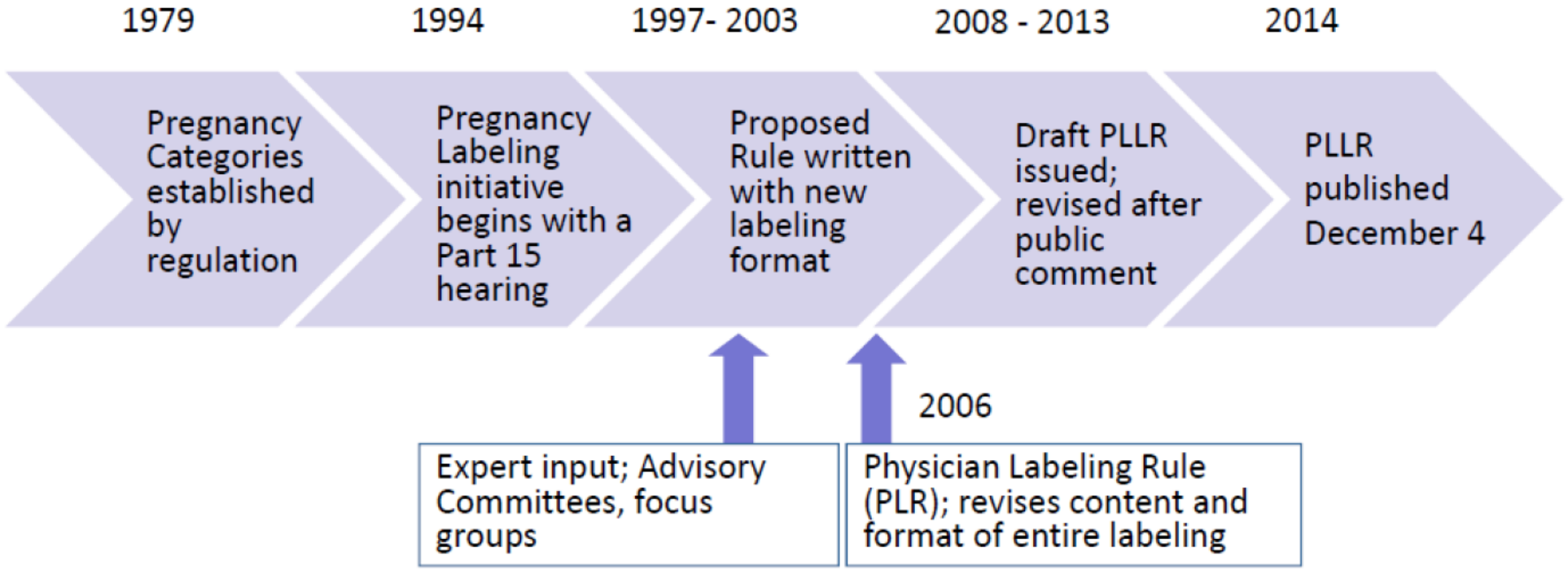
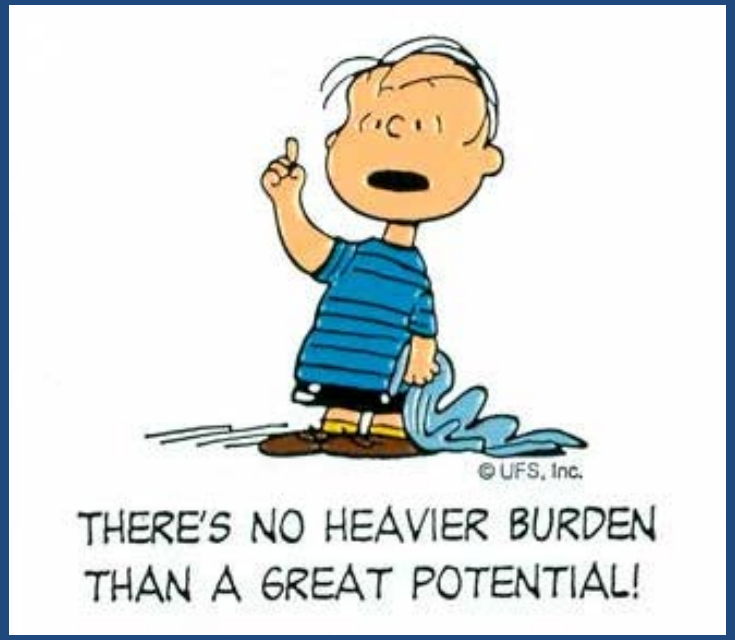
Figure 1: Development Timeline of the Pregnancy and Lactation Labeling Rule



Rear Admiral
Sandra Kweder
M.D.
Deputy Director
Office of New
Drugs FDA

1998 Pregnancy Labeling Taskforce



Three Major Tasks

1. Examine current regulations
2. Recommend changes
3. Consider bigger picture of related needs

Meeting Clinical Needs: Drugs & Pregnancy

Sandra Kweder, MD

Deputy Director, Office of New Drugs

U.S. Food & Drug Administration

Obstetrical Society of Boston

Boston, MA

2/2005

“One comment suggested that depression should not be treated pharmacologically during pregnancy, whereas a separate comment suggested that FDA ban the use of all drugs and vaccines during pregnancy.”

“FDA received 16 comments from physicians, pharmacists, pharmacy associations, nurses, manufacturers, drug safety consultants and individual consumers, requesting that FDA either retain the pregnancy category system, or replace the pregnancy category system with another standardized schema.”

(Response) “Through experience and stakeholder feedback, FDA learned that the pregnancy categories were heavily relied upon by clinicians but misinterpreted, misunderstood, and erroneously used as a grading system where fetal risk increased from A to X.”

Pregnancy and **L**actation **L**abeling **R**ule

Updates: "[w]hen new human data concerning the use of a drug during pregnancy becomes available, if that information is clinically relevant, FDA believes that it is necessary for the safe and effective use of the drug and, therefore, the pregnancy subsection of the labeling must be updated to include that information."

Pregnancy and Lactation Labeling Rule

FDA believes that it is necessary for the safe and effective use of the drug and, therefore, the pregnancy subsection of the labeling must be updated to include that information. Failure to include clinically relevant new information about the use of a drug during pregnancy could cause the drug's labeling to become inaccurate, false, or misleading"

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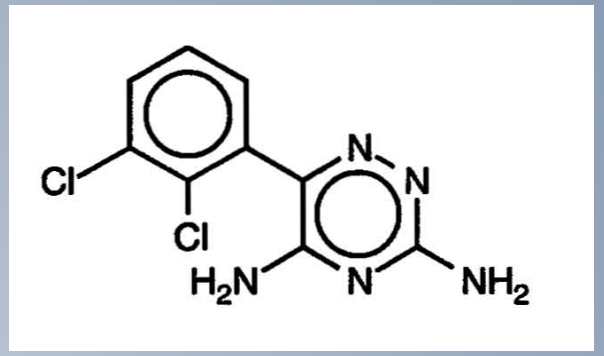
The example of Lamotrigine
Original approval 12/27/1994
Indications as of 2015



---------- **INDICATIONS AND USAGE**----------

LAMICTAL is indicated for:

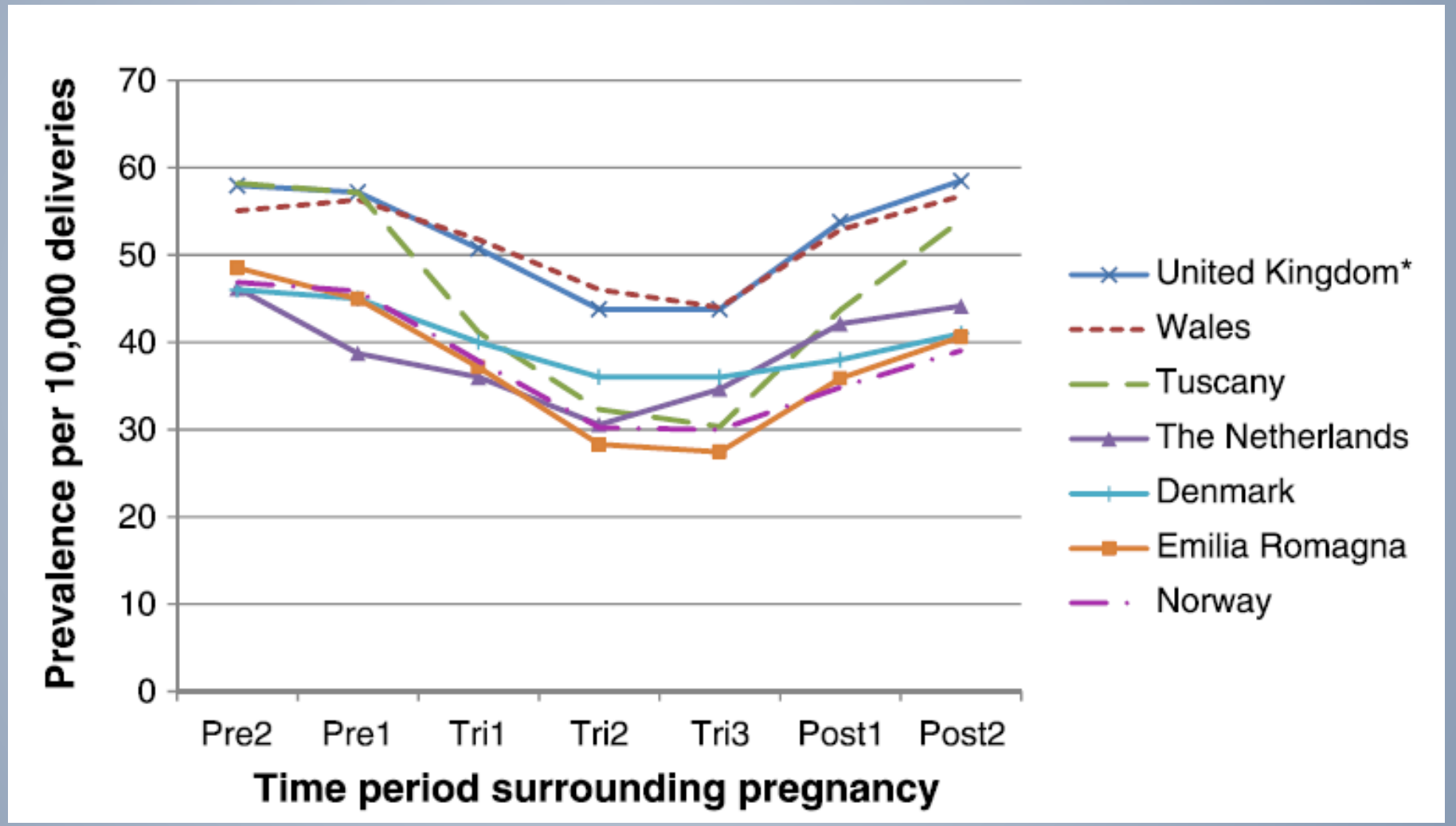
Epilepsy—adjunctive therapy in patients aged 2 years and older:

- partial-onset seizures.
- primary generalized tonic-clonic seizures.
- generalized seizures of Lennox-Gastaut syndrome. (1.1)

Epilepsy—monotherapy in patients aged 16 years and older: Conversion to monotherapy in patients with partial-onset seizures who are receiving treatment with carbamazepine, phenytoin, phenobarbital, primidone, or valproate as the single AED. (1.1)

Bipolar disorder in patients aged 18 years and older: Maintenance treatment of bipolar I disorder to delay the time to occurrence of mood episodes in patients treated for acute mood episodes with standard therapy. (1.2)

AED use in Europe 2004-2010, n ≈ 11,000
Charlton Pharmacoepi Drug Safety 2015;24:1144



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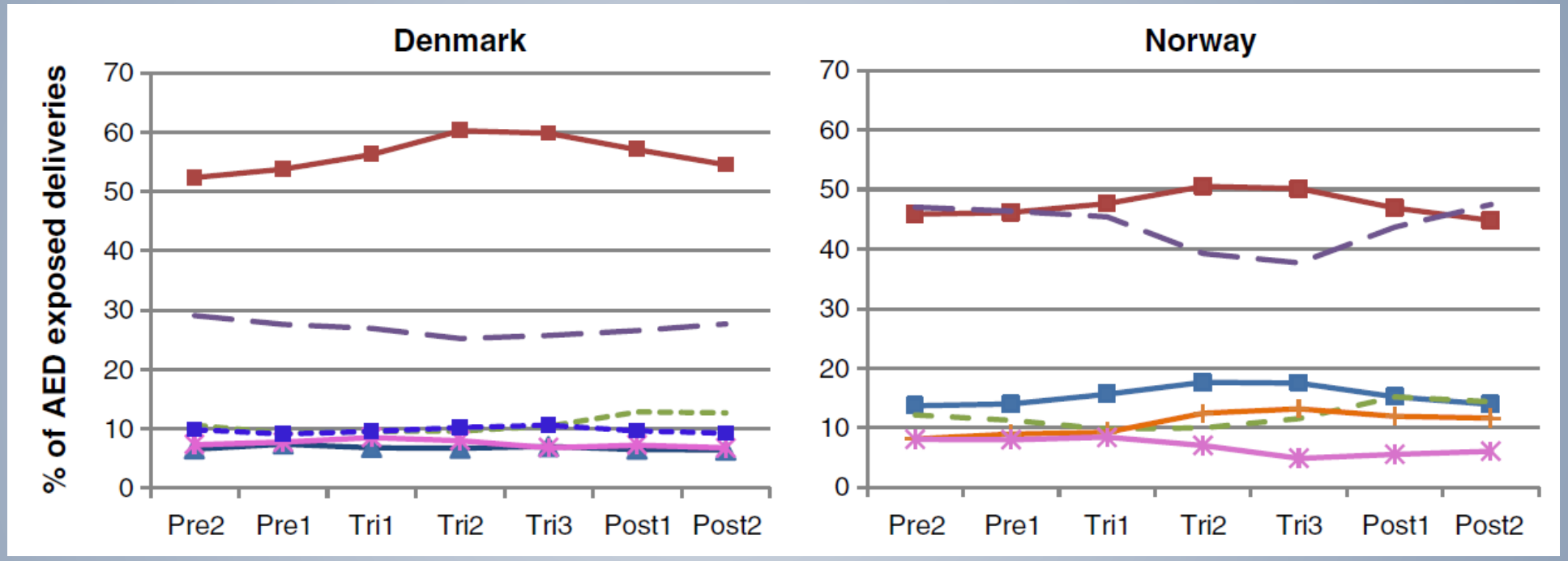

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List of Pregnancy Exposure Registries

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Pregnancy exposure registries are studies that collect health information on exposure to medical products such as drugs and vaccines during pregnancy. FDA does not conduct any pregnancy registries. The registries on this page are posted based on a sponsor or investigator's request to list their registry. FDA does not endorse any registry and is not responsible for the content of registries listed on this webpage. This webpage may not represent a comprehensive list of pregnancy exposure registries. If you would like your registry added to this list, please email FDA at Registries@fda.hhs.gov. This webpage is intended for informational purposes only.

Search by Medicine or Medical Condition:

(Search results update automatically as you type)

Spotlight

- Pregnancy Registry Homepage
- Other Pregnancy Resources
- Report a Problem with a Medicine

Show 10 entries Export Print

Medicine	Medical Condition	Registry	How to contact	Status
Multiple Drugs	Epilepsy	AED (Antiepileptic Drug) Pregnancy Registry	Massachusetts General Hospital **Website:** http://www.aedpregnancyregistry.org/ **Phone:** 1-888-233-2334	Ongoing

Website accessed February 25, 2018

Increased frequency of isolated cleft palate in infants exposed to lamotrigine during pregnancy

	Lamotrigine-exposed: AED Pregnancy Registry (n = 684)	Comparison group BWH Hospital (n = 206,224)	Relative risk (95% CI) (isolated clefts)
Cleft palate alone			
Total	3	94	21.0 (6.8–65.1)
Isolated	3	43 (46%)	
Rate isolated	4.4/1,000	0.21/1,000	
Rate total		0.46/1,000	

Holmes Neurology 2008;70:2152

Table 4 Findings of published studies that evaluated the fetal effects of maternal exposure to lamotrigine monotherapy

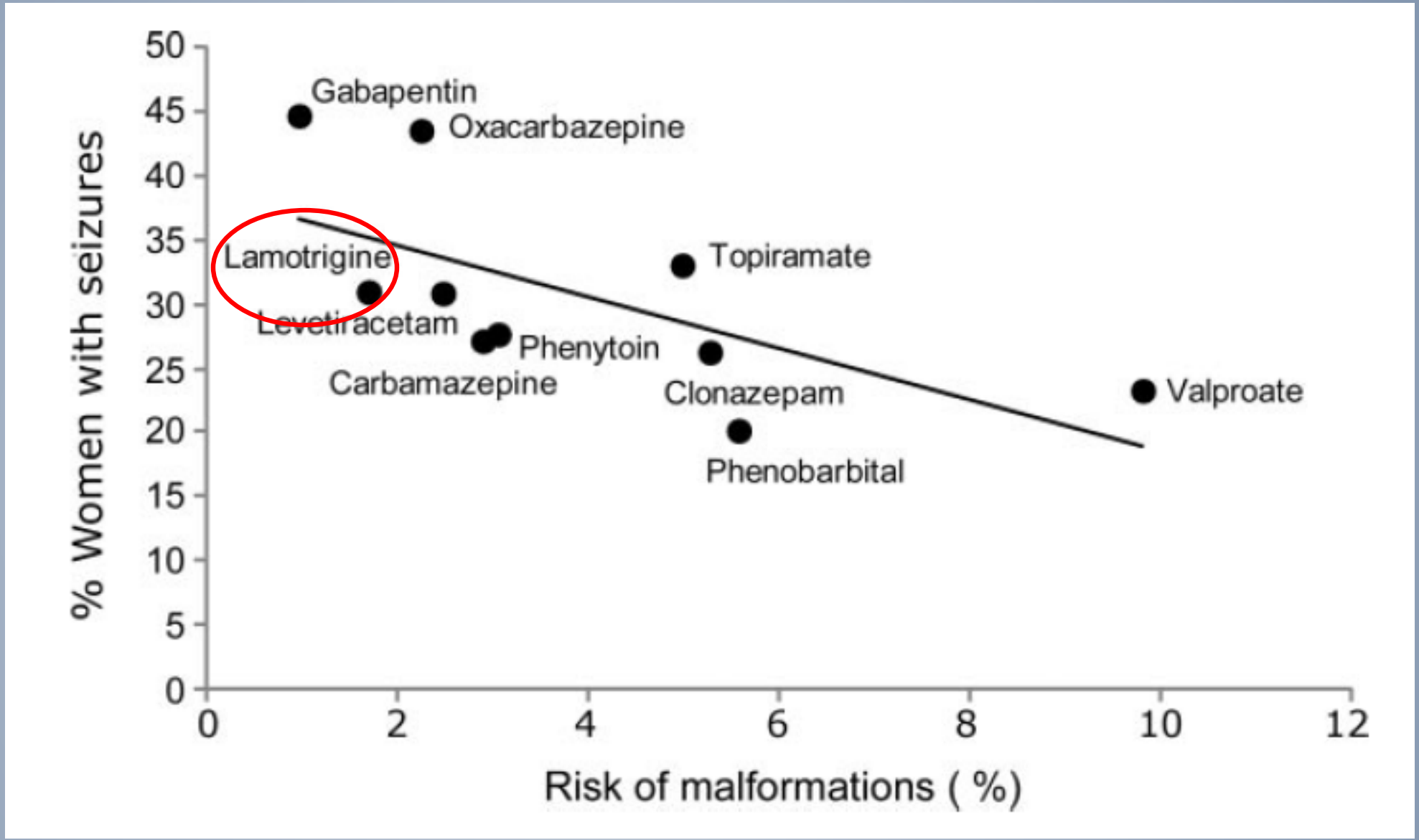
	No. of women exposed to lamotrigine monotherapy	Prevalence of all major malformations (95% CI)	Infants with oral clefts
GSK International Lamotrigine Registry[14,20*]	707	2.8% (1.6–5.1%)	1 cleft palate; 1 cleft lip and palate
UK Epilepsy and Pregnancy Register[15†]; J. Morrow, personal communication	647	3.2% (2.1–4.9%)	1 cleft lip and palate
Swedish Medical Birth Registry[21‡]; K. Wide, personal communication	90	4.4%	1 cleft palate
Australian Pregnancy Registry[22*]	128	0%	None
Danish Multicentre Registry[23*]	51	2% (0.1–10.7)	None
Total	1,623		4 (2.5/1,000)

Holmes Neurology 2008;70:2152

Comparative safety of antiepileptic drugs during pregnancy

"We published a risk of oral clefts of 7.3 per 1,000 among [684] users of lamotrigine monotherapy. With a larger sample size [1,562], the estimate is now 4.5 per 1,000 (95% CI 2.0 – 8.8). Other studies have reported lower risks of oral clefts after first-trimester lamotrigine exposure: 1–2.5 per 1,000."

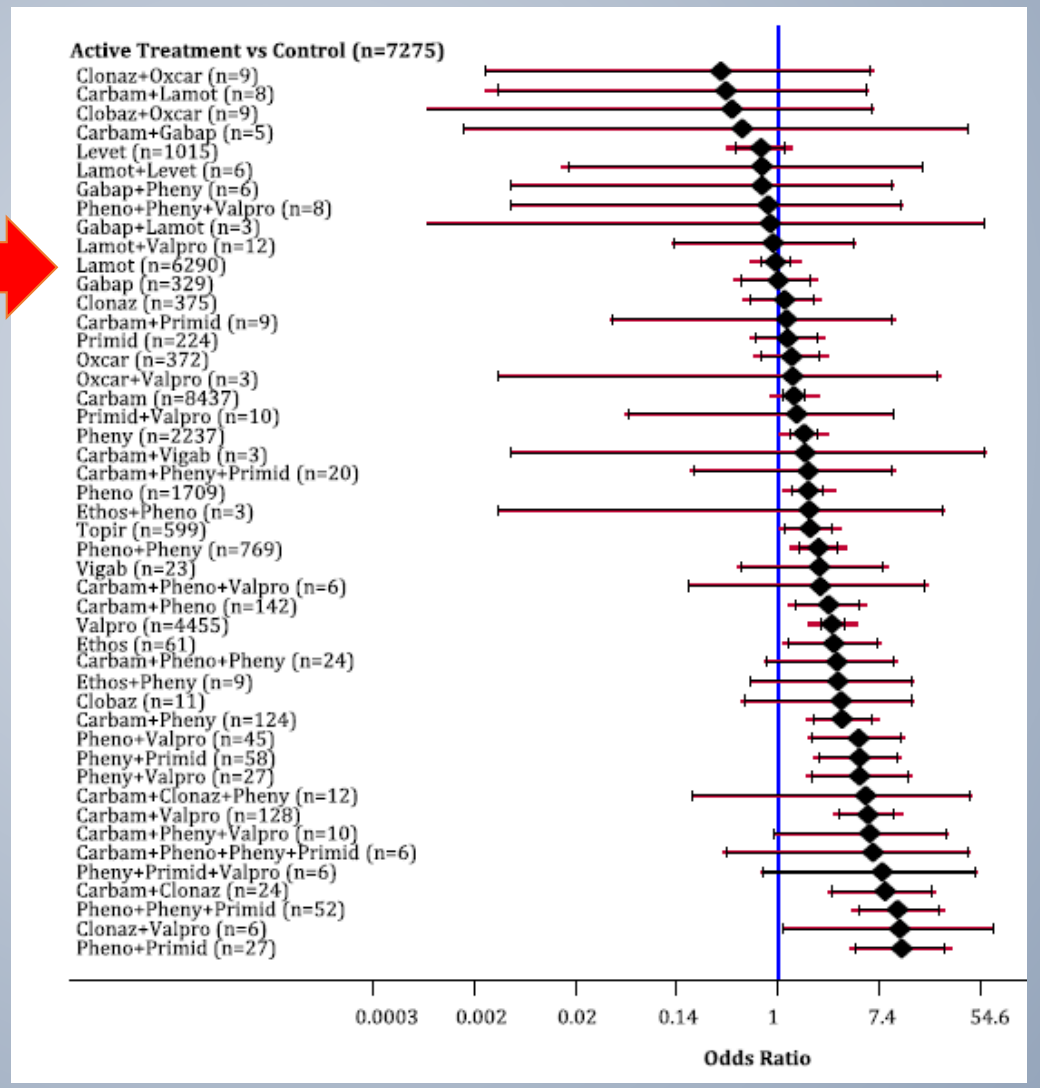
Hernandez-Diaz Neurology 2012;78:1692



Hernandez-Diaz Neurology 2012;78:1692

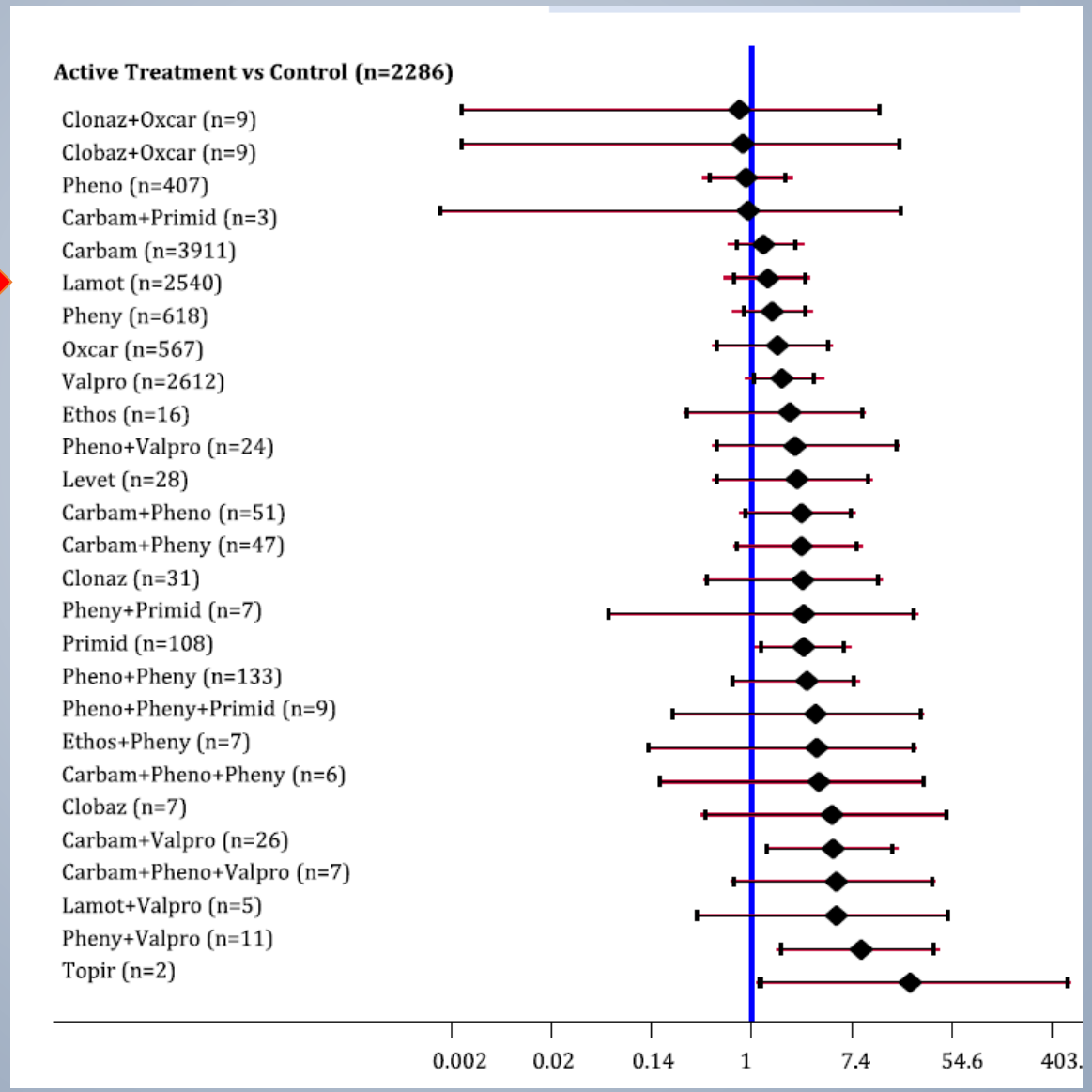
Comparative risks major congenital malformations

Veroniki BMC Medicine 2017;15:95



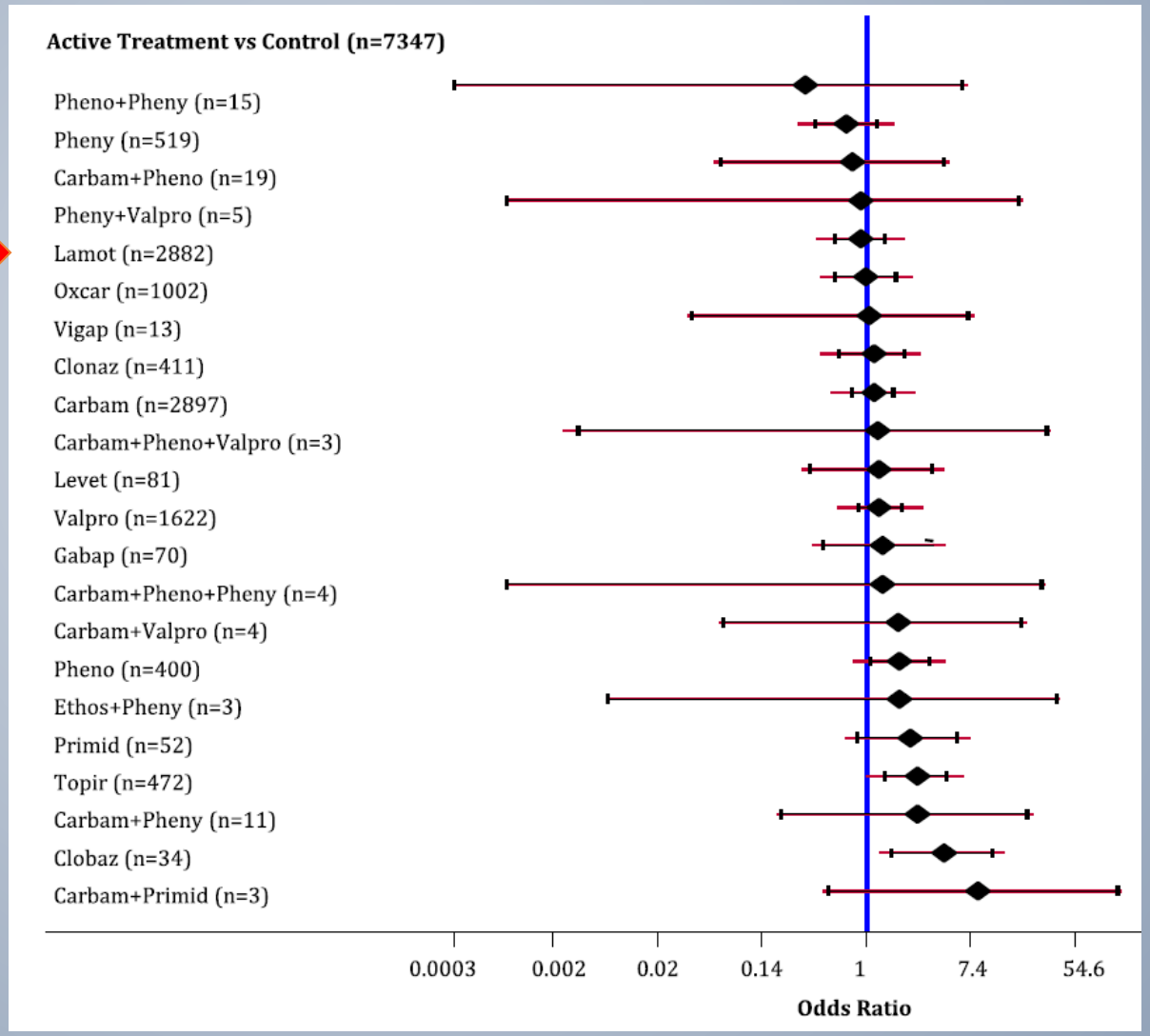
Comparative risks all cause fetal losses

Veroniki BMC Medicine 2017;15:95



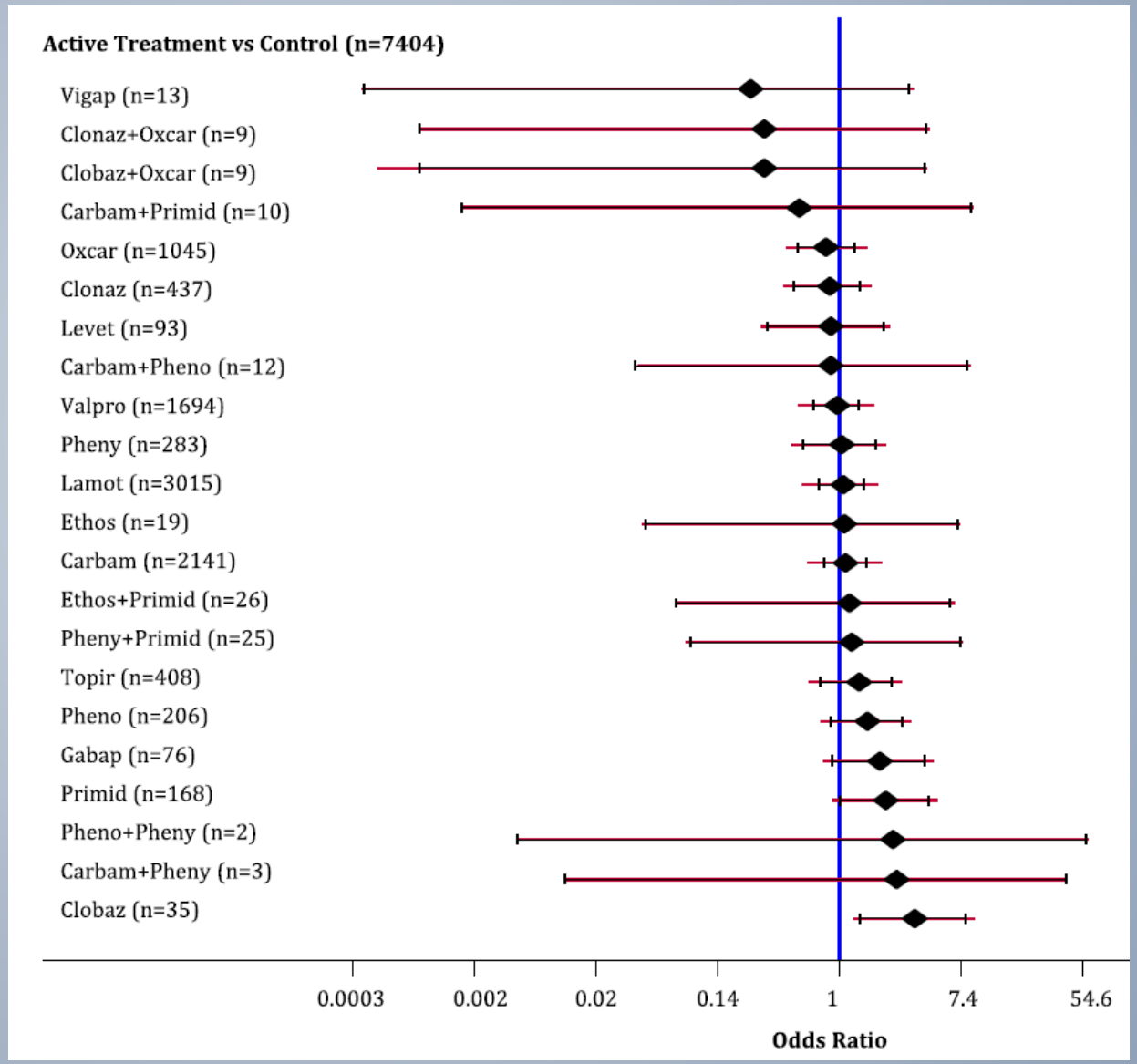
Comparative risks IUGR

Veroniki BMC Medicine 2017;15:95



Comparative risks Preterm Birth

Veroniki BMC Medicine 2017;15:95



Lamotrigine label 3/24/2015

Pregnancy Category C

There are no adequate and well-controlled studies in pregnant women. In animal studies, lamotrigine was developmentally toxic at doses lower than those administered clinically. LAMICTAL should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. When lamotrigine was administered to pregnant mice, rats, or rabbits during the

Pregnancy Registry

FDA Approved Labeling Text dated 3/24/2015

To provide information regarding the effects of in utero exposure to LAMICTAL, physicians are advised to recommend that pregnant patients taking LAMICTAL enroll in the North American Antiepileptic Drug (NAAED) Pregnancy Registry. This can be done by calling the toll-free number 1-888-233-2334 and must be done by patients themselves. Information on the registry can also be found at the website http://www.aedpregnancyregistry.org.

Principles of Counseling

- How important is the medication during pregnancy?
- If needed, could it be suspended during organogenesis?
- Individual birth defects vs. all birth defects
- Relative risks vs. absolute risks
- There are potential fetal risks of in utero drug exposure other than classic birth defects
- Discuss the quantity and quality of the data available to address the various risks especially confounding by indication

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Lamictal Meningitis & Birth Defects Lawsuits

The anticonvulsant *lamotrigine*—sold under the brand name **Lamictal**—has been identified as a potential cause of disfiguring birth defects, meningitis, and suicidal thoughts.

What Is Lamictal? When Is It Prescribed?

Lamictal is the brand name for the drug *lamotrigine*. Made and sold by British pharmaceutical giant GlaxoSmithKline, this prescription medication is used as a standalone epilepsy treatment in those aged 16 and up and as an adjunctive epilepsy and Lennox-Gastaut syndrome therapy in those aged two and up. Doctors can also prescribe it for treatment of Bipolar I Disorder. The U.S. Food and Drug Administration (FDA) first approved Lamictal in December 1994. GlaxoSmithKline sells it in oral tablets ranging from 25 mg to 200 mg *lamotrigine;* GSK sold 46 million Lamictal prescriptions between 1994 and 2009.

Website accessed February 25, 2018

Lamictal Side Effects Include Birth Defects and Meningitis

In September 2006, the FDA sent a Lamictal alert to healthcare professionals advising them that data from the North American Antiepileptic Drug Pregnancy Registry (NAAED) found a link between Lamictal use and birth defects. Specifically, women who used Lamictal in the first three months of their pregnancies were more likely to give birth to children with cleft lips and cleft palates than the general population.

The NAAED Registry found that 564 women using Lamictal gave birth to children with oral clefts, amounting to a calculated prevalence of 8.9 children with oral clefts per thousand users. By contrast, women taking neither Lamictal nor any other antiepileptic give birth to children with oral clefts at a rate of only 0.5 to 2.16 per thousand, according to other data. The FDA considered these findings merely preliminary, but in July 2011, the medical journal *The Lancet* found a correlation between high doses of antiepileptics and birth defects.

The FDA-mandated Lamictal label does not contain a "Pregnancy" entry in its "Warnings and Precautions" section. The label does indicate that Lamictal is classified as a "Pregnancy Category C" drug, however, meaning that some birth defects appeared in Lamictal studies involving animals as test subjects.

Website accessed February 25, 2018

Principles of Counseling

- Document
- Document
- Document

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What do Ob/Gyns want in labeling?

- Internet based resource
- Publicly available
- Accessible language
- Current & Reliable
- Evidence based
- Legally dominant expert opinion