Drug Safety during Pregnancy
Methods and Application:
The Topiramate experience

Safety, Value and Innovation Seminar
Center for Drug Safety and Effectiveness
Johns Hopkins Bloomberg School of Public Health

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Disclosure

- The following personal or financial relationships relevant to this presentation existed during the past 12 months:
  - SHD consulted for Boehringer-Ingelheim, UCB and Teva
  - She worked with the AED pregnancy registry, which is funded by multiple companies.
  - The Pharmacoepidemiology Program at the Harvard T.H. Chan School of Public Health is partially supported by training grants from Pfizer, Takeda, Bayer, and Asisa.
Once upon a time there was a drug…
…drug of choice to help pregnant women"

“completely safe for pregnant women”

No studies in pregnant women (or animals) had been conducted.

“Practically nothing was known about the drug at the time of its marketing"
Thalidomide

- First afflicted child
  - Girl born Dec. 25, 1956

- Thalidomide Embryopathy
  - Limb deformities (phocomelia)
  - Absence of ears
  - Others
Lesson: Need active surveillance

- December 1961, McBride letter in The Lancet:
  - Prevalence after exposure: 20% to 50%, around half of the cases included limb defects
  - Baseline prevalence of congenital malformations: 3%
- No formal epidemiologic studies were necessary to demonstrate causality
- However, the lack of a formal surveillance system had a cost....
Lesson: Need active surveillance

- Recognition of epidemic of rare defects took almost 4 more years
- Around 10,000 infants were born with deformities worldwide; only about 5,000 survived beyond childhood
Lesson: Need to focus on etiologically relevant period

- Critical period 6th and 7th week of pregnancy (35-50 days after LMP)

- Implications for
  - Public Health
<table>
<thead>
<tr>
<th>Period of Dividing</th>
<th>Age of Embryo (in weeks)</th>
<th>Fetal Period (in weeks)</th>
<th>Full Term</th>
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<tr>
<td>Zygote, Implantation &amp; Bilaminar Embryo</td>
<td>1</td>
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<td>C.N.S.</td>
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<td>External Genitalia</td>
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<td>Brain</td>
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<td>20-36</td>
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<td></td>
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<tr>
<td>38</td>
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</tr>
</tbody>
</table>

**Central Nervous System**

- Heart
- Upper Limbs
- Lower Limbs
- Eyes
- Teeth
- Palate
- External Genitalia
- Ear

**Major Congenital Anomalies (Red)**

- Prenatal Death

**Functional Defects & Minor Congenital Anomalies (Yellow)**
Lesson: Need to focus on etiologically relevant period

- Critical period 6th and 7th week of pregnancy (35-50 days after LMP)

- Implications for
  - Research
Example. Trimethoprim exposure (%) according to lunar months in cases and controls.

Lesson: No explanation

- The mechanism of thalidomide-induced malformations is still unknown.
  - “We have no idea how these cases could have been caused by Contergan.” “The claims are merely a response to the sensationalism.”
Lesson: Need to consider specific birth defects

- **Specific malformations, not all malformations**
  - **Major Malformations**, 3-4 per 100
  - **Specific Major Malformations**, 1 per 1,000
Lesson: Specific drugs

- **Exposure**
  - Members of a given drug class do not necessarily have the same teratogenic (or non-teratogenic) activity. The Fallacy of “Class Action” Teratogenesis
  - Need to consider drug-specific effects.
thalidomide
(phthalimidoglutarimide)

glutethimide
(phenylglutarimide)
Post-T-Lesson: Not everything is thalidomide

- Observation “1 every five malformed infants delivered has been exposed to Bendectin“
  - (used by 10 to 25% of pregnant women in the US)
Was there enough evidence to withdraw bendectin?

- In 1983, production was discontinued because of litigation.

- FDA: “Bendectin was withdrawn by its maker, and not for reasons of safety and efficacy.”
Drug Safety During Pregnancy

Thalidomide

Bendectin
Drug Safety During Pregnancy
Is this still a problem today?
Do pregnant women use drugs?
Are they safe?

- Most women take medications during their pregnancy
Most commonly used drugs

- Apart from vitamins and minerals, the most commonly used drugs during pregnancy are:
  - Analgesics
  - Cough/cold medications
  - Allergy/asthma
  - Antibiotics/anti-infectives

- Most commonly used drugs are non-prescription.

- Most commonly used drugs change over time (exposure to opioids, psychotropics and vaccines has increased).
Where can we identify teratogens?

Premarketing Approaches:

- Pharmacologic or toxicologic studies - poor predictors
- Animal studies - poor predictors
- Clinical trials - exclude pregnant women
Where can we identify teratogens?

Postmarketing Approaches:

- Case reports - clues; false alarms
- Ecological studies - clues; false alarms
Where can we identify teratogens?

Postmarketing Approaches:

- Case reports - clues; false alarms
- Ecological studies - clues; false alarms
- Experimental studies - too small
- Non-experimental (epidemiologic) studies
  - Cohort
  - Case-Control
Where can we identify teratogens?

**Designed for Birth Defects Research**

- **Cohorts, wide range of exposures** - Collaborative Perinatal Project
- **Cohorts, specific exposures** — Exposure Pregnancy Registries
- **Case control studies** — Case Control Surveillance

**Designed for Other Purposes**

- **Health care databases** — Claims & Electronic Medical Records
Surveillance strategy

- **Exposure pregnancy registries**
  - To identify drugs with dramatic fetal risks (e.g., thalidomide)
  - *E.g., new drugs required by some pregnant women*

- **Health care databases**
  - To identify drugs with intermediate fetal risk
  - *E.g., commonly used prescription drugs*

- **Case control surveillance**
  - To identify drugs with moderate fetal risk
  - *For example, suspected specific malformation*
Methodologic aspects: Sources of data

Rx drugs
- Prescriber
- Pharmacy
- Insurance
- Drug used by subject

OTC drugs
- Super-market Medicines cabinet
- Interview

- Medical Record
- Dispensing Records
- Pharmacy Claims
- Interview
Information Bias - Exposure

- **Misclassification**
  - False positives (adherence / compliance, stop after conception)
    - More than a quarter of new prescriptions are unfilled, especially when the drugs are for symptomless conditions
  - False negatives (OTC, sharing, missing data, recall)
    - 36.5% of women of reproductive age reported prescription medication borrowing or sharing

Information Bias - Exposure

- Differential misclassification
  - Recall bias (retrospective interviews)
  - Differential ascertainment (more info for cases)
Information Bias - Exposure

- Etiologically relevant period
  - Timing of Exposure: Induction time, carry over, prescription-use
  - Timing of Gestation:
    - Last Menstrual Period (LMP) – Conception
      - Maternal recall vs. early ultrasound
Information Bias – Outcome

- Misclassification (e.g. ICD9 codes, maternal report)
- Differential misclassification
  - Diagnostic bias (ultrasounds and minor defects)
  - Comparable “major malformation” definition
    - Period of diagnosis (prenatal, birth, life)
    - Inclusion / exclusion criteria
Selection Bias

- Censoring of person-time “at risk”
  - Start of follow up (left-censoring)
    - What would you expect to find if exposed subjects are enrolled during first trimester and unexposed are enrolled later in pregnancy?
Selection Bias

Pregnancies
Selection Bias

Pregnancies
Selection Bias

- Censoring of person-time “at risk”
  - Start of follow up (left-censoring)
  - End of follow up (right-censoring)
    - Incidence versus prevalence at birth (birth defects)
    - Intrauterine survival and elective abortions
      - *What would you expect to find in an analysis of teratogenicity if exposure to drug XX causes early pregnancy losses?*
Selection Bias

Pregnancies
Selection Bias

Pregnancies
Confounding

- SES, smoking, illegal drugs, BMI, etc.
- Indication (e.g. depression, asthma)
Surveillance strategy

- Exposure pregnancy registries

North American Anti-Epileptic Drugs (AED) Pregnancy Registry

Topiramate
Pregnancy Registry

Observational prospective cohort of women receiving a biopharmaceutical product(s) of interest as part of their routine clinical care who are enrolled voluntarily during gestation, before outcome can be known. Participants are followed until the end of pregnancy or longer to systematically collect information on specific pregnancy outcomes and evaluate their frequency relative to a scientifically valid reference population(s).

Introduction: FDA’s guidelines

- **Good drug candidates:**
  - Likely to be used in pregnancy, or
  - Likely to be used by women of childbearing age, or
  - Pose special risks, such as live vaccines

- **Recommended timing of enrollment:**
  - After exposure but before outcome of pregnancy is known
  - However, it is expected that retrospective cases will arise
  - Analyses should be conducted separately in these groups

Introduction: FDA’s guidelines

- Analysis: comparison groups
  - Internal
    - Exposed to comparator drugs
    - Unexposed
  - External
    - surveillance systems
    - background rates
    - other pregnancy registries

Introduction: FDA’s guidelines

- In 2005, similar guidelines were published by the EMA.
- In 2007, the Food and Drug Amendments Act (FDAAA) provided the authority under Title IX to require pregnancy registries as a post marketing requirement (PMR)

List of Pregnancy Exposure Registries

A pregnancy exposure registry is a study that collects health information from women who take medicines or vaccines when they are pregnant. The FDA does not run pregnancy studies, but it keeps registries that are going on now.

Check to see if there is a registry for the medicine you are taking. Look for your medicine condition on one of the lists on this page. Then use the phone number or website shown organization that runs the pregnancy registry.

- View a list by the medical condition - Check here if you have cancer, epilepsy, seizures, autoimmune or a transplant.
- View a list by the name of the drug or vaccine - Check here if you know the name of your medicine.

What if I do not see my medicine on the list? There may not be a pregnancy registry for that medicine added to the list as information becomes available. You may find other information about your medicine.

Vaccines and Medications in Pregnancy Surveillance System (VAMPSS)

The Vaccines and Medications in Pregnancy Surveillance System ("VAMPSS")

A Collaboration of
American Academy of Allergy Asthma and Immunology
Organization of Teratology Information Specialists
Stone Epidemiology Center at Boston University

What is VAMPSS?

VAMPSS is a new nationwide post-marketing survey that monitors the use and safety of vaccines and medications during pregnancy. It is a collaboration between the American Academy of Allergy Asthma and Immunology, the Organization of Teratology Information Specialists, and the Stone Epidemiology Center at Boston University.

Pregnancy Registry

Since there are no adequate and well-controlled studies of GILENYA in pregnant women, a pregnancy registry has been established to collect information about the effects of GILENYA during pregnancy. Physicians are encouraged to register patients who become pregnant while exposed to GILENYA or within 3 months after stopping therapy.

Cymbalta® duloxetine HCl Pregnancy Registry

20MG, 30MG, 60MG DELAYED RELEASE CAPSULES

http://www.fda.gov/ScienceResearch/SpecialTopics/WomensHealthResearch/ucm134848.htm
<table>
<thead>
<tr>
<th>Medical Condition</th>
<th>Registry Name</th>
<th>Registry Contact Information</th>
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<tbody>
<tr>
<td>Autoimmune Diseases</td>
<td>OTIS Autoimmune Diseases Study</td>
<td>Organization of Teratology Information Specialists (OTIS) Phone: 1-877-311-8972</td>
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<td></td>
<td></td>
<td>OTIS-Autoimmune Disease in Pregnancy Study</td>
</tr>
<tr>
<td>Asthma Medications:</td>
<td>OTIS Pregnancy Outcomes and Asthma</td>
<td>Organization of Teratology Information Specialists (OTIS) Phone: 1-877-311-8972</td>
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<td>specifically long-acting</td>
<td>Medications in Pregnancy Study</td>
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<tr>
<td>beta agonist and short-acting beta agonist producta</td>
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<tr>
<td>Cancer</td>
<td>Cancer and Childbirth Registry</td>
<td>Cooper Health</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Phone: 1-877-635-4499</td>
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<tr>
<td></td>
<td></td>
<td><a href="http://www.cooperhealth.org/content/pregnancyandcancer.html">www.cooperhealth.org/content/pregnancyandcancer.html</a></td>
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<td>Epilepsy</td>
<td>AED (Antiepileptic Drug) Pregnancy</td>
<td>Genetics and Teratology Unit, Massachusetts General Hospital</td>
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<tr>
<td></td>
<td>Registry</td>
<td>Phone: 1-888-223-2334</td>
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<td>Antiretroviral Pregnancy Registry</td>
<td>Kendle International</td>
</tr>
<tr>
<td></td>
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<td>Phone: 1-800-259-1923</td>
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**ANTIEPILEPTIC DRUG PREGNANCY REGISTRY**

**NEWS:** The North American AED Pregnancy Registry publishes "Comparative Safety of Antiepileptic Drugs during Pregnancy" in the May 3, 2012, online issue of Neurology®, the medical journal of the American Academy of Neurology. Click here for more information.

**HOME**

**ABOUT THE REGISTRY**

**PUBLICATIONS & PRESS**

**INFORMATION FOR WOMEN**

**INFORMATION FOR PROVIDERS**

**FREQUENTLY ASKED QUESTIONS**

**CONTACT US**

**LINKS**

http://www.fda.gov/ScienceResearch/SpecialTopics/WomensHealthResearch/ucm134848.htm
0.5 - 1% of pregnant women have epilepsy

Guidelines recommend to continue treatment during pregnancy

Older anticonvulsants increase the risk of congenital malformations

The use of newer anticonvulsants has been increasing

Topiramate is a “new” anticonvulsant
Evidence of fetal adverse effects in animal studies
Inconsistent results in post-marketing studies
Suggestion of increased risk of low birth weight
One report had suggested an increased risk of oral clefts after in utero exposure to topiramate

Hunt S et al. Topiramate in pregnancy: Preliminary experience from the UK Epilepsy and Pregnancy Register. Neurology 2008;71;272-276
Objective:

- To estimate the risk of major malformations in infants whose mothers had taken topiramate as monotherapy during the first trimester of pregnancy
Methods - Study Design:

- North American AED Pregnancy Registry
  - Established in 1997 at Mass. General Hospital, Boston
  - Enrolls pregnant women taking AEDs, and a reference group of friends and family members not taking AED
  - Women call
  - Consent is obtained verbally for interview. Written consent obtained for maternal and infant’s medical records
  - Scientific Advisors supervise and approve release of findings

1-888-233-2334 (toll-free) http://www.AEDPregnancyRegistry.org
**Methods - Data collection:**

- Three telephone interviews:
  - Enrollment (10-15 min.)
  - 7 Months GA (5 min.)
  - 2 Months postpartum (5 min.)

- Ask about
  - AEDs. For any AED data is collected on indication, dose, and start and stop dates
  - Demographic characteristics, vitamin use, smoking, etc
  - Health status of her infant and presence of malformations
Methods – Exposure definition:

- Use of specific AEDs any time during the four lunar months after the last menstrual period (LMP)
- Classified according to number of AEDs
  - Monotherapy
  - Polytherapy
Methods – Timing of first interview:

Lunar months from last menstrual period to first interview

% of population

- monthly
- cumulative
Methods – Outcome definition:

- Major malformation diagnosed before 12 weeks
  - Overall
  - Specific

- Presence of malformations determined in interviews and confirmed by medical records

- Findings in infant reviewed by teratologist (L. Holmes) blinded to exposure status
Methods – Outcomes:

- Exclusions:
  - Minor anomalies: preauricular sinus, simian crease
  - Birth marks: hemangioma, congenital mole
  - Prematurity related: undescended testes, PDA
  - Genetic disorders: Down syndrome, achondroplasia
  - Positional deformity: hip dysplasia with breech
  - Ultrasound only: unilateral renal agenesis
  - Technology induced: muscular VSDs, small ASD (<0.4 mm)

- Approximately 17-27% of identified malformations excluded
- Comparisons with external group restricted to <5 days after birth

Methods - Analysis:

- Compared the risk of malformations in users of tomiramate as monotherapy with reference groups
- Relative risk (RR) and 95% confidence interval (CI) estimated using multivariate regression
- Potential confounders: maternal age, race, education, smoking, diabetes, and periconceptional use of multivitamins
- Sensitivity analyses: e.g., restricted to prospective enrollment
Methods – Reference groups:

1. Exposed (to other AED) internal reference group
   - Lamotrigine, the most commonly reported AED.

2. Unexposed internal reference group
   - Friends and family members not taking AED enrolled in the Registry

   - 206,244 livebirths, stillbirths and elective terminations
   - Malformations identified before 5 days of age

Time trends of enrollment for specific AEDs:

North American AED Pregnancy Registry
Risk of major malformations among infants exposed to specific AED in monotherapy during the first trimester.

<table>
<thead>
<tr>
<th></th>
<th>Internal Controls</th>
<th>Lamotrigine</th>
<th>Carbamazepine</th>
<th>Phenytoin</th>
<th>Levetiracetam</th>
<th>Topiramate</th>
<th>Valproate</th>
<th>Phenobarbital</th>
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<tbody>
<tr>
<td>n = 408**</td>
<td>n = 1441</td>
<td>n = 1012</td>
<td>n = 407</td>
<td>n = 378</td>
<td>n = 321</td>
<td>n = 317</td>
<td>n = 197</td>
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<tr>
<td>Child with Confirmed Major Congenital Anomaly*</td>
<td>6 (1.5%)</td>
<td>28 (1.9%)</td>
<td>29 (2.9%)</td>
<td>12 (3.0%)</td>
<td>8 (2.1%)</td>
<td>11 (3.4%)</td>
<td>30 (9.5%)</td>
<td>11 (5.6%)</td>
</tr>
<tr>
<td>(95%CI)</td>
<td>(0.5 to 3.2%)</td>
<td>(1.3 to 2.8%)</td>
<td>(1.9 to 4.1%)</td>
<td>(1.5 to 5.1%)</td>
<td>(0.9 to 4.1%)</td>
<td>(1.7 to 6.1%)</td>
<td>6.5 to 13.2%</td>
<td>(2.8 to 9.8%)</td>
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<td></td>
</tr>
<tr>
<td>Relative risk</td>
<td>reference</td>
<td>1.3</td>
<td>2.0</td>
<td>2.0</td>
<td>1.4</td>
<td>2.4</td>
<td>7.0</td>
<td>4.0</td>
</tr>
<tr>
<td>(95%CI)</td>
<td>(0.5 to 3.2)</td>
<td>(0.8 to 4.8)</td>
<td>(0.8 to 5.5)</td>
<td>(0.5 to 4.2)</td>
<td>(0.9 to 6.5)</td>
<td>(2.9 to 17.1)</td>
<td>(1.4 to 10.9)</td>
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<td>1.8</td>
<td>5.3</td>
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<tr>
<td>(95%CI)</td>
<td>(0.9 to 2.5)</td>
<td>(0.8 to 3.0)</td>
<td>(0.5 to 2.4)</td>
<td>(0.9 to 3.6)</td>
<td>(3.1 to 9.0)</td>
<td>(1.5 to 6.1)</td>
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</tr>
</tbody>
</table>

Results – Oral Clefts:

- 4 of these 11 were oral clefts (13.5/1,000)
- Frequency in the external control group: 0.7/1,000
- Conclusion: **Need to replicate**
NEW INDICATION:

- This potential teratogenic effect is of particular relevance given current consideration of FDA approval for a topiramate-containing weight loss product.
Topamax (topiramate): Label Change - Risk For Development of Cleft Lip and/or Cleft Palate in Newborns

Available as generic topiramate

AUDIENCE: Neurology, OB/GYN

ISSUE: FDA notified healthcare professionals and patients of an increased risk of development of cleft lip and/or cleft palate (oral clefts) in infants born to women treated with Topamax (topiramate) during pregnancy. Because of new human data that show an increased risk for oral clefts, topiramate is being placed in Pregnancy Category D. Pregnancy Category D means there is positive evidence of human fetal risk based on human data but the potential benefits from use of the drug in pregnant women may be acceptable in certain situations despite its risks. The patient medication guide and prescribing information for Topamax and generic topiramate will be updated with the new information.

BACKGROUND: Topiramate is an anticonvulsant medication approved for use alone or with other medications to treat patients with epilepsy who have certain types of seizures. Topiramate is also approved for use to prevent migraine headaches. The new data was from the North American Antiepileptic Drug (NAAED) Pregnancy Registry.

RECOMMENDATION: Before starting topiramate, pregnant women and women of childbearing potential should discuss other treatment options with their health care professional. Women taking topiramate should tell their health care professional immediately if they are planning to or become pregnant. Patients taking topiramate should not stop taking it unless told to do so by their health care professional. Women who become pregnant while taking topiramate should talk to their health care professional about registering with the North American Antiepileptic Drug Pregnancy Registry, a group that collects information about outcomes in infants born to women treated with antiepileptic drugs during pregnancy.
Time trends of enrollment for specific AEDs:

- lamotrigine
- carbamazepine
- phenytoin
- levetirac
- valproic
- topiramate
- phenobarb
- gabapentin
- oxcarba
- zonisamide
- pregabalin
Time trends of enrollment for specific AEDs:
Two North American birth defects case control studies

- Slone Epidemiology Center Birth Defects Study (BDS)
- Centers for Disease Control and Prevention National Birth Defects Prevention Study (NBDPS)

The two studies have many similarities:

- Study design
- Data collection methods (e.g. identification of cases and controls; a computer-assisted telephone interview)
- Case classification (i.e. by expert clinical reviewers)
- Controls are live born infants without birth defects
Replication: Topiramate

- **Exposure definition:** Topiramate monotherapy during the first trimester of pregnancy
- **Case definition:** cleft lip with or without cleft palate
- **Frequency compared between cases and non-malformed controls**

## Replication: Topiramate

### Results from pooled data

<table>
<thead>
<tr>
<th></th>
<th>No AED</th>
<th>Topiramate</th>
<th>Adjusted* OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Controls</strong></td>
<td>15,367</td>
<td>6</td>
<td>Reference</td>
</tr>
<tr>
<td><strong>MCM</strong></td>
<td>33,605</td>
<td>15</td>
<td>1.01 (0.37 – 3.22)</td>
</tr>
<tr>
<td><strong>CL/P</strong></td>
<td>3,034</td>
<td>7</td>
<td>5.36 (1.49 – 20.07)</td>
</tr>
</tbody>
</table>

AED, antiepileptic drug; CI, confidence interval; CL/P, cleft lip with or without cleft palate; MCM, major congenital malformations; OR, odds ratio

* Conditional on year and region of birth, and study
Replication: Topiramate

- Medicaid Analytic eXtract (MAX) linked mother-infant cohort
Study Design:

- **Data Source**
  - 2000-2010 Medicaid Analytic eXtract (MAX)
    - Medicaid enrollment & health care utilization data
    - Woman-infant linkage

- **Cohort**
  - 1.3 M pregnancies ending in live birth in which women were enrolled in Medicaid from 3 months before the LMP through 1 month post delivery, and infants were enrolled for ≥3 months

Validation study approach

Medicaid claims data

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<tr>
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<th>Type of Code</th>
<th>Code</th>
<th>Description</th>
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<td>ICD-9 diagnosis</td>
<td>769</td>
<td>Respiratory distress syndrome</td>
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<td>12345</td>
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<td>71010</td>
<td>Radiologic examination. chest</td>
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<tr>
<td>12345</td>
<td>11/15/2005</td>
<td>ICD-9 diagnosis</td>
<td>7454</td>
<td>Ventricular septal defect</td>
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<tr>
<td>12345</td>
<td>11/16/2005</td>
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<td>Ventricular septal defect</td>
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</tbody>
</table>

Hospital medical records

## Results (under-peer-review)

<table>
<thead>
<tr>
<th></th>
<th>Unexposed</th>
<th>Lamotrigine</th>
<th>Topiramate</th>
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<tbody>
<tr>
<td>n</td>
<td>n = 1,322,955</td>
<td>n = 2796</td>
<td>n = 2425</td>
</tr>
<tr>
<td>Oral clefts</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prevalence (per 1,000)</td>
<td>1.1</td>
<td>1.5</td>
<td>4.1</td>
</tr>
<tr>
<td>Unadjusted RR (95%CI)</td>
<td>Reference</td>
<td>N/A</td>
<td>3.63 (1.95-6.76)</td>
</tr>
<tr>
<td>PS-Adjusted RR (95%CI)</td>
<td>Reference</td>
<td>2.30 (0.69-7.64)</td>
<td></td>
</tr>
</tbody>
</table>

1. This estimate was adjusted for multiple covariates including age, sex, and other confounders.

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![Oral clefts per 1000 livebirths](chart.png)
If pooled results represent the “truth”, the absolute risk of CL/P would increase from approximately 1 per 1,000 births to 5 per 1,000 births.
Registries

Advantages

- Prospective drug exposure information. No recall bias.
- Concentrating on selected drugs can increase efficiency, particularly to study uncommon drugs in relation to common events.
- Longitudinal. Can estimate risk and risk differences.
- Assess real use through maternal interview.
- Can study multiple exposures and multiple outcomes
Registries

Limitations

- Non-representative (self-referral bias, volunteers).
- Often lack control group (non-comparable external comparison groups).
- Inefficient (cost and time).
- Limited power.
- Short follow up (cannot assess late development).
- Losses to follow-up (selective under-ascertainment).
Case-Control Studies

Advantages

- Information on non-prescription drugs.
- Assess real use.
- Information on wide range of covariates.
- Statistical power to study the risk of specific (uncommon) birth defects in relation to relatively common medications.
Case-Control Studies

Limitations

- May be relatively slow to complete. Cost and time.
- Rely on volunteer participation (under-represent minorities).
- Need to identify a valid control group (e.g. malformed controls).
- Need to obtain complete and unbiased drug exposure information.
Advantages

- Prospective drug exposure information. No recall bias
- Efficient (cost and time)
- Real clinical practice, population-based
- Longitudinal. Can estimate risk and risk differences
- Can study multiple exposures and multiple outcomes
Databases

Limitations

- Limited to prescription drugs.
- Assess prescription or dispensing ≠ real use.
- Limited power. *(Future: Multi-Database studies to increase power)*
- Short follow up, inability to study long-term consequences.
- Limited information on potential confounders *(e.g. smoking)*.