DEFINITION OF A TERATOGEN

An exposure in pregnancy that has a harmful fetal effect.
**RECOGNIZED HUMAN TERATOGENS**

1. **DRUGS:**
   - Ex. anticonvulsants
   - methimazole
   - retinoic acid (Accutane)
   - warfarin

2. **HEAVY METALS:**
   - Ex. lead
   - mercury

3. **RADIATION:** cancer therapy;
   - not diagnostic X-rays

4. **MATERNAL CONDITIONS**
   - Ex. insulin-dependent diabetes, cigarette, smoking, alcohol abuse

5. **INTRAUTERINE INFECTIONS**
   - Ex. toxoplasmosis
   - rubella
   - varicella

6. **PROCEDURES**
   - Ex. CVS
   - D & C
   - ICSI
   - amniocentesis

7. **OTHER**
   - Ex. hypotension
   - misoprostol
   - heat

**CHARACTERISTICS OF A HUMAN TERATOGEN**

1. An increase in the frequency of an abnormal fetal effect;
2. A dose-response relationship; there is a threshold below which the exposure is not teratogenic;
3. Period of greatest sensitivity;
4. Established mechanism of action, which often requires animal model;
5. The proposed teratogenicity must make sense biologically;
6. Identifying a genetically more susceptible group.
“NEW TERATOGENS”: mycophenolate mofetil (CellCept)

lamotrigine (Lamictal)

severe nausea and vomiting of pregnancy

phthalates

MYCOPHENOLATE MOFETIL


MYCOPHENOLATE MOFETIL: PHENOTYPE OF MULTIPLE ANOMALIES

microtia, severe and bilateral
cleft lip and palate
broad nasal bridge and hypertelorism
coloboma of retina
shortened digits and small nails


Selected MMF-Exposed Cases

Le Ray et al., 2004
Tjeertes et al., 2007
Perez-Aytes et al. 2008
Velinov and Zellers, 2008.
MYCOPHENOLATE MOFETIL: QUESTION

Severe microtia: mycophenolate (CellCept)

thalidomide

13-cis retinoic acid

(Accutane)

LAMOTRIGINE:

anticonvulsant drug: inhibits release of glutamate and the voltage-sensitive sodium channel

**LAMOTRIGINE (LAMICTAL):**

**LAMOTRIGINE PREGNANCY REGISTRY: GLAXOSMITHKLINE**

- lamotrigine monotherapy (n=414): 2.9% (95CI 1.6-5.1%)
- lamotrigine + valproate (n=88): 12.5% (95CI 6.7-21.7%)
- lamotrigine + other (n=182): 2.7% (95CI 1.0-6.6%)

No controls; use CDC data: 2% at birth
No study exam

Contact: Paige Churchill, Project Manager
paige.churchill@inveresk.com; Inveresk 1-800-336-2176

Cunnington M et al: Neurol 64:955-60, 2005

---

**LAMOTRIGINE, GABAPENTIN, TOPIRAMATE**

**U.K. EPILEPSY AND PREGNANCY REGISTER***

<table>
<thead>
<tr>
<th></th>
<th>Number of Women</th>
<th>Number of Malformations</th>
<th>Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>CARBAMAZEPINE</td>
<td>900</td>
<td>20</td>
<td>2.2% (1.4-3.4)</td>
</tr>
<tr>
<td>VALPROATE</td>
<td>715</td>
<td>44</td>
<td>6.2% (4.6-8.2)</td>
</tr>
<tr>
<td>LAMOTRIGINE</td>
<td>647</td>
<td>21</td>
<td>3.2% (2.1-4.9)</td>
</tr>
<tr>
<td>PHENYTOIN</td>
<td>82</td>
<td>3</td>
<td>3.7% (1.3-10.2)</td>
</tr>
<tr>
<td>GABAPENTIN</td>
<td>31</td>
<td>1</td>
<td>3.2% (0.6-16.2)</td>
</tr>
<tr>
<td>TOPIRAMATE</td>
<td>28</td>
<td>2</td>
<td>7.1% (2.2-22.6)</td>
</tr>
<tr>
<td>LEVETIRACETAM</td>
<td>22</td>
<td>0</td>
<td>0% (0-14.9)</td>
</tr>
</tbody>
</table>

AED PREGNANCY REGISTRY:
(AED = antiepileptic drugs)

• WOMEN ON ANTICONVULSANTS IN NORTH AMERICA AND CANADA
  CALL TOLL-FREE 1-888-233-2334
  (www.AEDPregnancyregistry.org)

• INFORMED CONSENT

• 3 INTERVIEWS: ENROLLMENT
  Demographics, Confounders
  7-MONTHS GESTATION
  Change in dosage, U/S findings
  POSTPARTUM
  Health of infant

• OBTAIN WRITTEN RELEASES FOR NEUROLOGIST
  OR PSYCHIATRIST AND PEDIATRICIAN

LAMOTRIGINE (LTG) – EXPOSED:
MAJOR MALFORMATIONS

19/684 : MAJOR MALFORMATIONS
  2.8% (95 CI: 1.7-4.3)
16/684 (2.3%) : IDENTIFIED AT BIRTH (0 to 5 days of age)
  not increased significantly vs.
  unexposed controls (1.62%)

Relative Risk 1.4 (95 CI: 0.9-2.3)

(Comparison population: Brigham and Women’s Hospital:
# Lamotrigine Monotherapy-Exposed: Oral Clefts

<table>
<thead>
<tr>
<th>Study #</th>
<th>Phenotype*</th>
<th>mg First Trimester</th>
<th>Folic Acid Suppl at Conception</th>
<th>Cigarette Smoking</th>
</tr>
</thead>
<tbody>
<tr>
<td>1779</td>
<td>Cleft lip, unilateral</td>
<td>400 mg</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>2389</td>
<td>Cleft palate</td>
<td>300</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>3036</td>
<td>Cleft palate</td>
<td>500</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>4557</td>
<td>Cleft palate</td>
<td>100</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>5638</td>
<td>Cleft lip &amp; palate</td>
<td>125</td>
<td>Yes</td>
<td>No</td>
</tr>
</tbody>
</table>

* None considered syndromic; negative family history

Prevalence: 5/684 = 1:137 or 7.3/1,000

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# Lamotrigine Monotherapy-Exposed vs Unexposed Comparison Population

\[
\frac{5}{684} \quad \text{or} \quad \frac{7.3}{1,000} = 10.4 \times \text{increase (95 CI 4.3 – 24.9)}
\]

\[
\frac{0.7}{1,000}
\]

Anticonvulsant Drugs and Oral Clefts

<table>
<thead>
<tr>
<th>Drug</th>
<th>Relative Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lamotrigine (n = 952)</td>
<td>9.1</td>
</tr>
<tr>
<td>Valproate (n = 303)</td>
<td>20.1</td>
</tr>
<tr>
<td>Phenobarbital (n = 189)</td>
<td>32.4</td>
</tr>
<tr>
<td>Carbamazepine (n = 913)</td>
<td>20.9</td>
</tr>
</tbody>
</table>

Question: Common mechanism or different mechanisms?

Lamotrigine Monotherapy-Exposed: Other Sources

<table>
<thead>
<tr>
<th>Source</th>
<th>Number</th>
<th>Total Malformations</th>
<th>Oral Clefts</th>
</tr>
</thead>
<tbody>
<tr>
<td>GSK Internat. LTG Registry</td>
<td>707</td>
<td>2.7%</td>
<td>1 CP; 1 CLP</td>
</tr>
<tr>
<td>UK Epilepsy Preg. Register</td>
<td>647</td>
<td>3.2</td>
<td>1 CLP</td>
</tr>
<tr>
<td>Swedish Medical Birth Registry</td>
<td>90</td>
<td>4.4</td>
<td>1 CP</td>
</tr>
<tr>
<td>Australian Preg. Registry</td>
<td>128</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Danish Registry</td>
<td>51</td>
<td>2</td>
<td>0</td>
</tr>
</tbody>
</table>

\[
\frac{2.5}{0.7} = 3.6 \text{ RR}
\]
NUTRITIONAL DEFICIENCIES IN PREGNANCY: CASE REPORTS

PHENOTYPES: MID-FACE HYPOPLASIA (BINDER ANOMALY)
ANENCEPHALY – SPINA BIFIDA

CLINICAL STORIES:
POST-BARIATRIC SURGERY
CHRONIC DIARRHEA, MALABSORPTION, WEIGHT LOSS
HYPEREMESIS GRAVIDARUM


BILIARY LITHIASIS EARLY IN PREGNANCY
(Courtesy of Angela E. Lin, M.D.)

MATERNAL VITAMIN K DEFICIENCY: Additional reports

“Drumstick-like distal phalanges”

Jaillet et al., 2005
NEW PATIENT (1) MOTHER

BWH: 22 yo healthy African American G2

7 wks: Severe hyperemesis gravidarum, Compazine
185/200 lbs → 169 (16% loss) (→ 193)
Admitted after 4th visit (10 wks): Haldol, IVF, chewable vitamins

Admitted after 7th visit (15 wks): Haldol, IVF, Mg supplement
   Profuse epistaxis, required packing, cautery.
   Labs: Bleeding disorder
      ↓ K, Mg, II, VII, IX, X.
      Prolonged PT, APTT.
   Treatment:
      TPN, IV hydration, electrolyte replacement
      Vitamin K 10 mg subcutaneous/day x3 days
      Coagulopathy normalized over 10 days
   Coagulopathy secondary to Vit K deficiency in hyperemesis

MATERNAL VITAMIN K DEFICIENCY
Hyperemesis gravidarum
MATERNAL VITAMIN K DEFICIENCY

Hyperemesis gravidarum
**PHTHALATES:** plasticizers, ? endocrine disruptor

   Effect on anogenital (AG) distance in humans

   Increases levels in urine of mothers; decreases AG distance


**Developmental effects of phthalates**

- Disrupts fetal testis testosterone biosynthesis
  - Decreased gene expression and protein levels
    - Lipid transport (Scarb1 and Star)
    - Steroidogenic pathway (CYP11A1, HSDB1, CYP17A1)

- Decreased insulin-like factor 3 gene expression

**Manifestations:**
- Cryptorchidism and Hypospadias
- Reduced anogenital distance (feminization of perineum)
Measuring Anogenital Distance

This is similar to the toxicological measure
AGD is repeatable (CV = 7.2%)

HUMAN TERATOGENS: 2007 - 2008

Controversies: SSRIs, in general

Paroxetine (Paxil), in particular
SSRIs

• Celexa (citalopram)
• Lexapro (escitalopram)
• Luvox (fluvoxamine)
• Paxil (paroxetine)
• Prozac (fluoxetine)
• Zoloft (sertraline)

PAROXETINE HYDROCHLORIDE IS A SELECTIVE SEROTONIN-REUPTAKE INHIBITOR AND AN ANTIDEPRESSANT. METABOLIZED BY THE CYTOCHROME P-450 (CYP) 2D6 ISOENZYME. COMPLETELY ABSORBED FROM GI TRACT. ELIMINATION HALF-LIFE 21-24 HOURS.
SSRIs: FETAL EFFECTS

GSK RETROSPECTIVE EPIDEMIOLOGIC STUDY:

RATIONALE: Possible “signal” for heart defects, esp. ventricular outflow tract, in GSK Bupropion Pregnancy Registry spontaneous reports from health care providers.

GOAL: 1) Prevalence of heart defects in infants born to women taking bupropion.  
2) Prevalence in infants exposed to other anti-depressants, including paroxetine

INGENIX STUDY: [http://ctr.gsk.co.uk/welcome.asp](http://ctr.gsk.co.uk/welcome.asp)

<table>
<thead>
<tr>
<th>Antidepressant</th>
<th>n</th>
<th>Total</th>
<th>Preval per 1000</th>
<th>OR*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Crude (95% CI)</td>
</tr>
<tr>
<td>Amitriptyline</td>
<td>4</td>
<td>233</td>
<td>17.2</td>
<td>0.69 (0.24, 1.78)</td>
</tr>
<tr>
<td>Amitriptyline / Chlorpromazine</td>
<td>0</td>
<td>5</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Amitriptyline / Perphenazine</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Bupropion</td>
<td>15</td>
<td>463</td>
<td>32.4</td>
<td>1.32 (0.76, 2.32)</td>
</tr>
<tr>
<td>Citalopram</td>
<td>10</td>
<td>298</td>
<td>33.6</td>
<td>1.36 (0.70, 2.64)</td>
</tr>
<tr>
<td>Clomipramine</td>
<td>0</td>
<td>5</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Desipramine</td>
<td>0</td>
<td>10</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Doxepin</td>
<td>0</td>
<td>22</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Fluoxetine</td>
<td>31</td>
<td>178</td>
<td>20.3</td>
<td>1.04 (0.67, 1.61)</td>
</tr>
<tr>
<td>Fluvoxamine</td>
<td>0</td>
<td>28</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Imipramine</td>
<td>2</td>
<td>42</td>
<td>47.6</td>
<td>1.92 (0.46, 8.06)</td>
</tr>
<tr>
<td>Mirtazapine</td>
<td>0</td>
<td>23</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Nefazodone</td>
<td>1</td>
<td>75</td>
<td>13.3</td>
<td>0.91 (0.67, 1.27)</td>
</tr>
<tr>
<td>Norbupropiptyline</td>
<td>1</td>
<td>87</td>
<td>11.6</td>
<td>0.64 (0.56, 1.36)</td>
</tr>
<tr>
<td>Paroxetine</td>
<td>27</td>
<td>794</td>
<td>38.4</td>
<td>1.72 (1.59, 2.71)</td>
</tr>
<tr>
<td>Protriptyline</td>
<td>0</td>
<td>4</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Sertaline</td>
<td>12</td>
<td>705</td>
<td>17.0</td>
<td>0.61 (0.33, 1.12)</td>
</tr>
<tr>
<td>Trazodone</td>
<td>3</td>
<td>154</td>
<td>19.5</td>
<td>0.75 (0.23, 2.39)</td>
</tr>
<tr>
<td>Trimipramine</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Venlafaxine</td>
<td>5</td>
<td>215</td>
<td>27.9</td>
<td>1.10 (0.47, 2.54)</td>
</tr>
</tbody>
</table>

Prevalence per 1,000 live born infants

* Reference group for OR calculations is all other antidepressants.
** Adjusted for age, calendar year of delivery, dispensing of lithium, dispensing of carbamazepine, diagnosis of pre-eclampsia or eclampsia, and infant sex.
### SSRIs AND HEART DEFECTS


<table>
<thead>
<tr>
<th></th>
<th>Paroxetine</th>
<th>Fluoxetine</th>
<th>Sertraline</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any heart defect</td>
<td>OR 1.4</td>
<td>0.9</td>
<td>1.5</td>
</tr>
<tr>
<td></td>
<td>(0.2, 2.5)</td>
<td>(0.6, 1.5)</td>
<td>(0.9, 2.5)</td>
</tr>
<tr>
<td>Septal defects</td>
<td>0.8</td>
<td>1.2</td>
<td>2.0</td>
</tr>
<tr>
<td></td>
<td>(0.3, 2.2)</td>
<td>(0.5, 2.2)</td>
<td>(1.2, 4.0)</td>
</tr>
<tr>
<td>RVOTD</td>
<td>3.3</td>
<td>1.0</td>
<td>2.0</td>
</tr>
<tr>
<td></td>
<td>(1.3, 8.8)</td>
<td>(0.2, 3.4)</td>
<td>(0.6, 6.8)</td>
</tr>
</tbody>
</table>

No association with anencephaly, omphalocele or craniosynostosis

### SSRIs AND HEART DEFECTS


All hearts, all SSRIs – no association

Paroxetine

RVOTO: OR 2.5

(1.0, 6.0)

Positive association with anencephaly, omphalocele craniosynostosis
VENTRICULAR SEPTAL DEFECT, MUSCULAR TYPE

1,053 CONSECUTIVE NEONATES: NAHARIYA, ISRAEL
APRIL TO SEPTEMBER, 1994
COLOR DOPPLER ECHOCARDIOGRAPHY
• AGES 6 TO 170 HOURS OLD (mean 37)
56/1,053 HAD MUSCULAR VSD: 1 to 5mm
10% HAD SYSTOLIC MURMUR
89% CLOSED SPONTANEOUSLY


SSRIs: PERSISTENT PULMONARY HYPERTENSION OF THE NEWBORN (PPHN)

SLONE EPIDEMIOLOGY CENTER, BOSTON UNIVERSITY
1998-2003: 377 PPHN
836 CONTROLS

SSRI EXPOSURE: 14 PPHN
6 CONTROLS
ODDS RATIO: 6.1 (95 CI: 2.2-16.8)

SSRIs: NEONATAL WITHDRAWAL SYNDROME

MEDLINE AND PSYCINFO SEARCH: 1966-2005

LATE EXPOSURE: RISK RATIO 3.0 (95 CI:2.0-4.4)

TREATMENT: SIGNS MILD; SUPPORTIVE CARE; DISAPPEARS BY TWO WEEKS OF AGE


OTHER TOPICS: ANNUAL UPDATE, 2009

- PESTICIDES
- BISPHENOL A
- STATINS
- GENE-ENVIRONMENT INTERACTIONS
- REVISION OF DRUG CATEGORIES A, B, C, D and X
- AIRBORNE EXPOSURES
- DERMAL EXPOSURES
SPECIAL THANKS TO MARLENE ANDERKA, ANGELA LIN, RUSS HAUSER and ALLEN MITCHELL WHO PROVIDED SLIDES OR DATA TABULATIONS FOR THIS REVIEW.