Women's Issues in Epilepsy

Cleveland Clinic Epilepsy Review Course
September 2016

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Objectives

• Review key issues for women with epilepsy (WWE)
  – Interactions between epilepsy, AEDs and hormones
  – Contraception
  – Pregnancy outcomes and AEDs
  – Impact of pregnancy on seizure control and AEDs
  – Breastfeeding

I have no disclosures

Catamenial Epilepsy - Hormone Sensitive Seizures

• “katamenios” = ‘monthly’ - tendency for increased seizures related to the menstrual cycle
• Estrogen is neuroexcitatory and Progesterone (through allopregnanolone) is neuroinhibitory
• Changes in female sex steroid levels
  – Directly affect seizure threshold
  – Increase clearance of some AEDs
Establishing Relationship between Seizures and Hormones

- Self-reports not reliable
- Seizure/Menstrual diary
- Documentation of ovulation
  - Regular periods, premenstrual symptoms, dysmenorrhea and rise in BBT temperature by 0.7°F
  - Positive urinary LH
  - Midluteal progesterone >3-5 ng/mL
  - >90% decrease in dominant follicle on transvaginal US
  - Secretory phase endometrium on endometrial biopsy
- ILP cycles suspected by
  - BBT rise of <11 days
  - Midluteal progesterone level <5ng/mL
  - Out-of-phase endometrial biopsy of >2 days

Management Strategies for Catamenial Epilepsy

- Conventional medical/surgical therapy
- Acetazolamide
- Benzodiazepines, cyclical
- Hormonal therapy
  - Oral contraceptives
  - Medroxyprogesterone acetate
  - Natural progesterone – only evidence based therapy
  - Antiestrogens
  - Gonadotropin analogues
  - Neuroactive steroids

Feely M. JNPP 1984;47:1279-1282; Lim LL. Epilepsia 2001;42:740-749;

Progesterone vs. Placebo RCT Results

294 WWE randomized to P 200 mg tid days 14-28 vs. placebo

While primary outcomes not significant, C1 level predicted response;
26-71% seizure reduction Progesterone vs. 25-26% placebo


Herzog A. Neurology 2012;78:1959-1966

Contraception in Women with Epilepsy:
Impact of Enzyme Inducing AEDs on Sex Steroid Metabolism

<table>
<thead>
<tr>
<th>Inducers</th>
<th>Non-Inducers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carbamazepine</td>
<td>Clonazepam</td>
</tr>
<tr>
<td>Clonazepam</td>
<td>Carbamazepine</td>
</tr>
<tr>
<td>Eslicarbazepine*</td>
<td>Ethosuximide</td>
</tr>
<tr>
<td>Felbamate*</td>
<td>Gabapentin</td>
</tr>
<tr>
<td>Lamotrigine*</td>
<td>Lacosamide</td>
</tr>
<tr>
<td>Oxcarbazepine</td>
<td>Levetiracetam</td>
</tr>
<tr>
<td>Perampanel*</td>
<td>Pregabalin</td>
</tr>
<tr>
<td>Phenobarbital</td>
<td>Tiagabine</td>
</tr>
<tr>
<td>Phenytoin</td>
<td>Valproate</td>
</tr>
<tr>
<td>Primidone</td>
<td>Vigabatrin</td>
</tr>
<tr>
<td>Rufinamide*</td>
<td>Zonisamide</td>
</tr>
<tr>
<td>Topiramate*</td>
<td></td>
</tr>
</tbody>
</table>

*Weak inducers

CYP3A 4 inducers accelerate metabolism of sex steroids increasing risk of ovulation and contraceptive failure
Hormonal Contraceptives Increase Clearance of Some AEDs Potentially Compromising Seizure Control

- Combined OC and LTG 300 mg/d
- Significantly lower LTG levels (52% for AUC; 39% for Cmax)
- Gradual increase in LTG concentrations during pill-free week
- LTG dose adjustment may be necessary when introducing or withdrawing OC/HRT

Contraceptive Methods without AED Interactions

- Long-acting reversible contraceptives (LARC)- preferred
  - Intrauterine devices
  - Progestin implant
  - Depot medroxyprogesterone acetate (MPA)
- Barrier methods
- Fertility awareness-based methods
- Sterilization

Adverse Pregnancy Outcomes in Offspring of Women with Epilepsy

- Major congenital malformations – structural abnormalities interfering w/function/require major intervention
  - Cardiac abnormalities
  - Neural tube defects
  - Clefts
  - Hypoplasia
  - Gastrointestinal atresia
  - Limb reduction defects
- Minor anomalies – structural deviations not interfering w/health
- Developmental delay
- Low birth weight
- Prematurity
- Microcephaly
- Stillbirth
- Epilepsy

OC = oral contraceptive; AUC = area under the curve; Cmax = maximum concentration.
GSK. LAM10016 Data on file.

Pregnancy Outcomes over Recent Decades in 283 Women with Epilepsy

<table>
<thead>
<tr>
<th></th>
<th>1970s</th>
<th>1980s</th>
<th>1990s</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major malformations</td>
<td>19.5</td>
<td>9.6</td>
<td>3.5</td>
</tr>
<tr>
<td>Monotherapy</td>
<td>34.2</td>
<td>63.5</td>
<td>74.4</td>
</tr>
<tr>
<td>Folic acid (TM1)</td>
<td>27.8</td>
<td>43.2</td>
<td>82.7</td>
</tr>
</tbody>
</table>


FDA Pregnancy Categories of Antiepileptic Drugs

**Category C**
- Clobazam
- Eslicarbazepine
- Ethosuximide
- Ezogabine
- Felbamate
- Gabapentin
- Lacosamide
- Lamotrigine
- Levetiracetam
- Oxcarbazepine
- Perampanel
- Pregabalin
- Rufinamide
- Tiagabine
- Vigabatrin

**Category D**
- Carbamazepine
- Clonazepam
- Phenytoin
- Primidone
- Topiramate
- Valproate

In 2013, FDA changed VPA category from “D” to “X” when used for migraine prevention as risks outweigh benefits

North American AED Pregnancy Registry

- Launched in 1997 in US and Canada
- Patient initiated
- Follow-up at 7 months gestation, postpartum
- Comparison groups
  - External comparison group base rate: 1.6% at 5 d among 69,277 enrolled
  - LTG TM1 monoRx
  - Unexposed (without epilepsy, not taking AEDs)
- 10,2000 enrollees
  - >6000 monoRx exposures
  - >600 untreated

888-233-2334

May 2016

1st Trimester Monotherapy Cases

<table>
<thead>
<tr>
<th>AED</th>
<th>Total MCM</th>
<th>Enrolled</th>
<th>MCM %</th>
<th>95%CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lamotrigine</td>
<td>31</td>
<td>1562</td>
<td>2.0</td>
<td>1.4-2.8</td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>31</td>
<td>1033</td>
<td>3.0</td>
<td>2.1-4.2</td>
</tr>
<tr>
<td>Phenytoin</td>
<td>12</td>
<td>416</td>
<td>2.9</td>
<td>1.5-5.0</td>
</tr>
<tr>
<td>Levetiracetam</td>
<td>11</td>
<td>450</td>
<td>2.4</td>
<td>1.2-4.3</td>
</tr>
<tr>
<td>Topiramate</td>
<td>15</td>
<td>359</td>
<td>4.2</td>
<td>2.4-6.8</td>
</tr>
<tr>
<td>Valproate</td>
<td>30</td>
<td>323</td>
<td>9.3</td>
<td>6.4-13.0</td>
</tr>
<tr>
<td>Phenytoin</td>
<td>11</td>
<td>199</td>
<td>5.5</td>
<td>2.8-9.7</td>
</tr>
<tr>
<td>Oxcarbazepine</td>
<td>4</td>
<td>182</td>
<td>2.2</td>
<td>0.6-5.5</td>
</tr>
<tr>
<td>Gabapentin</td>
<td>1</td>
<td>145</td>
<td>0.7</td>
<td>0.02-3.8</td>
</tr>
<tr>
<td>Zonisamide</td>
<td>0</td>
<td>90</td>
<td>0</td>
<td>0.0-3.3</td>
</tr>
<tr>
<td>Clonazepam</td>
<td>2</td>
<td>64</td>
<td>3.1</td>
<td>0.4-10.8</td>
</tr>
<tr>
<td>Unexposed</td>
<td>5</td>
<td>442</td>
<td>1.1</td>
<td>0.37-2.6</td>
</tr>
</tbody>
</table>


EURAP Registry

- Launched in 1999
- 42 countries worldwide
- Physician initiated
- Follow-up each TM, birth and 1 yr postpartum on-line
- 22,244 enrolled; 12,256 prospective, >80% monoRx
- Most common AEDs: LTG, CBZ, VPA
- MCM rate overall was 5.1%; monoRx 4.7%; polyRx 7.1%
- 10% detected perinatally, 62% at birth, 28% in 1st yr

March 2016
Major Malformation Risks Vary by AED Combination

<table>
<thead>
<tr>
<th>MCM % (95% CI)</th>
<th>Monotherapy</th>
<th>Polytherapy without VPA</th>
<th>Polytherapy with VPA</th>
</tr>
</thead>
<tbody>
<tr>
<td>LTG⁴</td>
<td>1.9 (1.3-2.8)</td>
<td>2.9 (1.6-4.8)</td>
<td>9.1 (3.4-19.0)</td>
</tr>
<tr>
<td>CBZ⁴</td>
<td>2.9 (2.0-4.0)</td>
<td>2.5 (1.1-4.6)</td>
<td>15.4 (6.5-29.3)</td>
</tr>
<tr>
<td>LTG²</td>
<td>2.2 (1.6-3.1)</td>
<td>2.8 (1.5-5.0)</td>
<td>10.7 (6.4-17.0)</td>
</tr>
</tbody>
</table>

Selected AEDs are Associated with Specific Malformations

• Valproate¹
  — Neural tube defects (OR 9.7; 95% CI, 3.4-27.5)
  — Oral clefts (OR 4.4; 95% CI, 1.6-12.2)
  — Cardiac defects (OR 2.0; 95% CI, 0.78-5.3)
  — Hypospadius (OR 2.4; 95% CI, 0.62-9.0)
• Carbamazepine²
  — Spina bifida (OR 2.6; 95% CI, 1.2, 5.3) vs. no AED

Oral Clefts Associated with 1st Trimester AED Exposure

• Increased rates vs. general population (0.11%)
  — Carbamazepine (0.48%)
  — Phenytoin (0.48%)
  — Topiramate (1.4%)
  — Valproate (1.2%)
  — Phenobarbital (2.0%)

FDA downgraded TPM to Category D in 2011 due to risk of oral clefts and low birth weight

¹Holmes HB. Arch Neurol 2011; doi:10.1001; ²Cunnington MC. Neurology 2011;76;1817-1823.
EURAP: Dose-Dependent Risk of MCMs

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>MCM % (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Carbamazepine</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;400</td>
<td>148</td>
<td>3.4 (1.1, 7.7)</td>
</tr>
<tr>
<td>≥400 - &lt;1000</td>
<td>1047</td>
<td>5.3 (4.1, 6.9)*</td>
</tr>
<tr>
<td>≥1000</td>
<td>207</td>
<td>8.7 (5.2, 13.4)*</td>
</tr>
<tr>
<td><strong>Lamotrigine</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;300</td>
<td>836</td>
<td>2.0 (1.2, 3.2)</td>
</tr>
<tr>
<td>≥300</td>
<td>444</td>
<td>4.5 (2.8, 6.9)</td>
</tr>
<tr>
<td><strong>Phenytoin</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;150</td>
<td>166</td>
<td>5.4 (2.5, 10.0)*</td>
</tr>
<tr>
<td>≥150</td>
<td>51</td>
<td>13.7 (5.7, 26.3)*</td>
</tr>
<tr>
<td><strong>Valproic acid</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;700</td>
<td>431</td>
<td>5.6 (3.6, 8.2)*</td>
</tr>
<tr>
<td>≥700 - &lt;1500</td>
<td>480</td>
<td>10.4 (7.8, 13.5)*</td>
</tr>
<tr>
<td>≥1500</td>
<td>99</td>
<td>24.2 (16.2, 33.9)*</td>
</tr>
</tbody>
</table>

Tomson T. Lancet Neurology 2011;10:609-617. *greater risk than LTG <300 mg

Neurodevelopmental Effects of AEDs (NEAD Study)

<table>
<thead>
<tr>
<th></th>
<th>CBZ  (N=92)</th>
<th>LTG  (N=99)</th>
<th>PHT  (N=52)</th>
<th>VPA  (N=60)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maternal IQ*</td>
<td>99 (95-102)</td>
<td>101 (98-104)</td>
<td>92 (88-97)</td>
<td>96 (92-100)</td>
</tr>
<tr>
<td>Maternal age, y*</td>
<td>30 (29-31)</td>
<td>30 (29-31)</td>
<td>31 (29-32)</td>
<td>28 (27-30)†</td>
</tr>
<tr>
<td>Dose, mg/d*</td>
<td>784 (697-870)</td>
<td>457 (406-507)</td>
<td>400 (354-450)</td>
<td>1032 (877-1188)</td>
</tr>
<tr>
<td>Standardized dose*</td>
<td>32 (29-36)</td>
<td>35 (31-39)</td>
<td>49 (44-54)</td>
<td>26 (22-31)†</td>
</tr>
<tr>
<td>Periconceptional folate</td>
<td>55 (59%)</td>
<td>59 (60%)</td>
<td>21 (45%)</td>
<td>39 (64%)</td>
</tr>
<tr>
<td>Epilepsy Type (%)</td>
<td>Focal</td>
<td>23</td>
<td>22</td>
<td>20†</td>
</tr>
<tr>
<td>ISD</td>
<td>11%</td>
<td>13%</td>
<td>15%</td>
<td>10%</td>
</tr>
<tr>
<td>Uncertain</td>
<td>10%</td>
<td>16%</td>
<td>8%</td>
<td>10%</td>
</tr>
</tbody>
</table>

Meador K Lancet Neurol 2013;12:244-252. *Mean (95% CI) †p<0.05

http://www.neadstudy.com

Child IQ at 6 yr by AED Exposure & Periconceptual Folic Acid Status


Adjusted for maternal IQ, AED type, AED standardized dose, gestational age, periconceptual folic acid

Meador K. Lancet Neurol 2013;12:244-252. solid line: PCFA; dotted line: no PCFA
Potential Mechanisms of AED Teratogenicity

- Toxic intermediary metabolites
  - Epoxide formation: PHT, CBZ
  - Epoxide hydrolase inhibition: VPA
- Folate deficiency
- Hypoxia/Reoxygenation
  - PHT, CBZ, PB, Trimethadione
- Apoptosis
- Genetic susceptibility
  - Placental transfer, absorption, metabolism, distribution, receptor binding
  - Folate metabolism
  - Antioxidant compounds

Seizure Control in 5000 Pregnancies: EURAP & Kerala Registries

- 48-67% seizure free
- Relapse higher for:
  - Focal vs. generalized epilepsy (OR 1.6)
  - Poly vs. MonoRx (OR 2.98)
  - Seizures in prepregnancy month (OR 15)
  - LTG monoRx
  - GTCs
  - Increased drug dose

Causes of Seizures during Pregnancy in Women with Epilepsy

- Alterations in AED pharmacokinetics
  - Declining plasma proteins
  - Increased hepatic metabolism – P450, glucuronidation
  - Increased renal clearance
  - Increased volume of distribution
- Medication noncompliance
- Stress
- Sleep deprivation

Convulsive seizures -> fetal hypoxia, heart rate decelerations, miscarriage, stillbirth
Nonconvulsive seizures -> abdominal trauma
AED Clearance and Seizure Control in 115 Pregnancies

- Significant increase in peak clearance for LTG (191%) and LEV (207%)
- Marked variation within and between individuals
- Falls in AED blood levels >35% associated with worsening seizures


https://www.clinicalkey.com/#!ContentPlayerCtrl/doPlayContent/1-s2.0-S1525505013003132

Sarah 24 yr old: LTG Concentrations and Daily Dosage

![Graph showing LTG concentrations and daily dosage]

Therapeutic Drug Monitoring of AEDs in Pregnancy

- No Class 1 evidence
- Need/frequency of monitoring should be individualized
- Pronounced decline/worsening seizures expected for drugs eliminated by glucuronidation (LTG, OXC); reversion to baseline within days of delivery requires proactive strategy
- Less need for monitoring for drugs w/minor alterations in free concentration (CBZ, VPA)
- Recent evidence supporting unpredictable, potentially significant decline in LEV concentration associated w/seizures

Breastfeeding (BF) in Women with Epilepsy

• Breast milk penetration inversely proportional to protein binding
• Impaired hepatic elimination of LTG and OXC in newborn can lead to clinically relevant concentrations
• No harmful effects of BF on child IQ at 3 yr\(^1\)
• No association with adverse development at 6-36 mo; trend for more favorable outcomes with continuous BF\(^2\)
• No evidence for harmful effects\(^3\)


2009 AAN Epilepsy Physician Performance Measure #8 Counseling for Women of Childbearing Potential

• Counsel WWE (12-44 yr) about epilepsy and treatment effects on contraception/pregnancy
• Documented in EMR at least annually
• Documentation of medical reason for not counseling (e.g. sterile)
• Provide information about contraception, conception, pregnancy, breastfeeding in advance of sexual activity or pregnancy
• Discuss decreased effectiveness of OCPs in women taking EIAEDs
• Discuss risks of seizures and fetal malformations associated with AED therapy during pregnancy
• Annual review including effects of treatment on bone health, contraception, and how pregnancy/menopause affect seizures

Management Strategies for Pregnant Women with Epilepsy

• Repeated preconception counseling
• Individualized contraceptive counseling –IUDs preferred
• Use most effective AED at lowest possible dose
• Avoid unnecessary polyRx, drug changes post conception
• Individualize therapeutic monitoring during pregnancy and postpartum
• Folic acid 1-5 mg per day preconception
• Encourage breastfeeding
• No evidence for vitamin K supplementation

Resources for Women with Epilepsy

- AAN practice parameter 2009 update
  www.aan.com/go/practice/guidelines
- North American AED Pregnancy Registry
  www.aedpregnancyregistry.org
- EFA Women & Epilepsy Initiative
  www.efa.org
- EURAP
  www.eurap.org