2019 NRSP
Neurology Residents Scholar Program

The NRSP is supported through independent educational grants from:
Platinum Level & Presenting Sponsor: Greenwich Biosciences
Gold Level Sponsor: UCB
Silver Level Sponsor: Eisai
Bronze Level Sponsor: SK Life Science, Inc.

Presented by Creative Educational Concepts, Inc.
The Female with Epilepsy
*Treatment Considerations across the Lifespan*

Patricia E Penovich, MD
Minnesota Epilepsy Group PA
Adjunct Professor, Department of Neurology
University of Minnesota
St Paul, Minnesota
WOMEN
Case

Introduction to Julie

- Focal seizures at age 12 with left temporal spikes and dysplasia of insula
- Migraines + seizures responded to VPA ER
- Menstrual exacerbation
- Gained 25 lbs, irregular menses
- Age 14, re-assess treatment
  - Folate
  - AED change
Epileptogenicity

Hormonal Effects

- **Estrogen:** Most adult animal seizure models, excitability is ↑ and seizure threshold is ↓ at physiologic and pharmacologic doses of estrogen.
- **Progesterone:** ↓ neuronal firing, ↓ epileptiform discharges, ↑ seizure threshold
  - GABA<sub>A</sub> receptor, potentiates adenosine
  - ↓ excitatory dendritic spines in CA1

Epilepsy over the Menstrual Cycle

Normal Cycle

Day of Cycle

Serum Hormone Levels

E2     P

- Estradiol mcg/mL
- Progesterone ng/mL

• Response rates of progesterone and placebo vs perimenstrual (C1) catamenial level of seizure exacerbation (A)
• Significant benefit only seen in women with C1 ≥3 (RR 37.8%)
• All other outcomes were not significant; 21.4% had rate ≥1.69

# Effects of AEDs on Weight

<table>
<thead>
<tr>
<th>Weight Gain</th>
<th>Weight Loss</th>
<th>Weight Neutral</th>
</tr>
</thead>
<tbody>
<tr>
<td>VPA (40%–50%)</td>
<td>FBM (2%–75%)</td>
<td>BRV, LEV</td>
</tr>
<tr>
<td>CBZ</td>
<td>TPM (10%–20%)</td>
<td>ESLI</td>
</tr>
<tr>
<td>CLO</td>
<td>ZNS</td>
<td>LAC</td>
</tr>
<tr>
<td>GBP (15-20%)</td>
<td>CBD</td>
<td>LTG</td>
</tr>
<tr>
<td>PGB</td>
<td></td>
<td>PER</td>
</tr>
<tr>
<td></td>
<td></td>
<td>TGB</td>
</tr>
</tbody>
</table>

CBD, cannabidiol; CBZ, carbamazepine; GBP, gabapentin; FBM, felbamate; LCM, lacosamide; LTG, lamotrigine; PGB, pregabalin; TGB, tiagabine; TPM, topiramate; VPA, valproate; ZNS, zonisamide.

Polycystic Ovary Syndrome (PCOS)

- Gynecologic syndrome
  - Phenotype: hirsutism, obesity, acne
  - Infertility
  - Endocrine abnormalities: abnormal LH, increased androgens
  - Menstrual irregularities/anovulatory cycles
  - Insulin resistance
- Frequency in general population = 5%
- Frequency in WWE = 10%–20%
- Long-term health consequences
  - Diabetes
  - Cardiovascular disease (dyslipidemia)
  - Endometrial carcinoma

LH, luteinizing hormone.

Reproductive Health in WWE in Puberty

- 68 patients with epilepsy and 51 controls
  - 35 VPA, 17 CBZ, 17 OXC
  - 61% off meds
- NS Δ for patient off med and controls
- Patients on meds
  - Higher testosterone, androstenedione
- PCOS
  - On meds 38%, on VPA 63%, other meds 25%
  - Off meds 6%, controls 11%

Reproductive Dysfunction with Valproate

- Evaluation with ultrasound, menstrual cycles, hormones of 238 WWE
- 12% VPA mono, 50% CBZ, 31% other AED mono/combination, 6% untreated
- Any VPA treatment 60% with hyperandrogenism and PCO
- If VPA before age 20, 80% had PCO and hyperandrogenism
- Reversible with switch to lamotrigine: normal testosterone, menstrual cycles, and ultrasound within 2 months

<table>
<thead>
<tr>
<th></th>
<th>Menstrual abn</th>
<th>PCO</th>
</tr>
</thead>
<tbody>
<tr>
<td>VPA mono</td>
<td>45%</td>
<td>43%</td>
</tr>
<tr>
<td>Other AEDs mono/combination</td>
<td>&lt;½ rate</td>
<td>&lt;½ rate</td>
</tr>
</tbody>
</table>

Julie Matures

• Off to college and sexually active
  • BCP
  • Sexuality
• 4 years later, she is engaged
• Controlled on Lamotrigine, trough level of 10
• Planning pregnancy and being pregnant
  • Fertility
  • Seizure control
  • Teratogenesis
Sexuality and AEDs

- Enzyme-inducing drugs induce the synthesis of sex hormone binding globulin (SHBG) reducing the peripheral sex steroid hormones
- 117 patients (77 male, 40 female) + controls
- Monotherapy CBZ, LTG, LEV for >6 months
- Arizona Sexual Experience Scale (ASEX)

Results
- Women experienced significantly more sexual difficulties than men
- Patients on CBZ experienced more difficulties than those on LTG, significant only for women

Male Sexuality and Fertility

- With enzyme inducing AEDs: lower T, increased SHBG, decreased FT
- Lower sexual function and desire scores
- Higher erectile dysfunction: 37% vs 22% in general population
- Higher dysfunction in TLE than extratemporal focal epilepsy

Sexuality

Effect of Lamotrigine

• 141 patients in Spain; open, prospective using the Changes in Sexual Functioning scale (CSFQ)
• Assessment at baseline, 4 months, and 8 months
• 79 began LTG monotherapy—Group A; 62 transitioned from traditional AED to LTG—Group B

1. Significant difference in women in orgasm and arousal/excitement; in men, improved “pleasure”
2. Both increased but NS; “pleasure,” “orgasm” for men; “desire”/“frequency” for women
3. Mechanism: seizure control, primary LTG effect; improved mood; QOL changes; decreased side effects

Oral Contraceptives

- **Estrogen**
  - Control of bleeding
  - Need 20–25 mcg

- **Progesterone**
  - Prevents ovulation and controls uterine environment and implantation
  - Need 1 mg

- **Hepatic inducing AEDs result in about 50%–60% decrease in levels of hormones**
Birth Control Failure

- Induction of estrogen metabolism: Cytochrome P450 3A4 aromatic hydroxylation at C2 or C4 or ring hydroxylation at C6
- Increase production of sex hormone binding globulin: \( \uparrow \) bound progesterone, \( \downarrow \) free progesterone, less reliable
- Affects oral, injectable, and implantable modes
- Mid-cycle breakthrough bleeding **not** reliable sign of contraceptive failure
- OCP failure rate 6% in WWE cf general population 1%
- Solutions
  - Double methods
  - Increase the hormonal content—it is actually metabolized to lower
# Effects of Various AEDs on Hormonal Contraception

<table>
<thead>
<tr>
<th>Decreased Hormone Concentration</th>
<th>No Effect or Increased Hormone Concentration</th>
</tr>
</thead>
<tbody>
<tr>
<td>CBZ</td>
<td>BRI</td>
</tr>
<tr>
<td>PB</td>
<td>ETX</td>
</tr>
<tr>
<td>TPM‡</td>
<td>EZG</td>
</tr>
<tr>
<td>CLB</td>
<td>GBP</td>
</tr>
<tr>
<td>PHT</td>
<td>LCM</td>
</tr>
<tr>
<td>ESLI</td>
<td>PER</td>
</tr>
<tr>
<td>OXC†</td>
<td>LEV</td>
</tr>
<tr>
<td>PRM</td>
<td>LTG*</td>
</tr>
<tr>
<td>FBM</td>
<td>TGB</td>
</tr>
<tr>
<td>PGB</td>
<td>RUF</td>
</tr>
<tr>
<td>VGB</td>
<td>ZNS</td>
</tr>
<tr>
<td>VPA</td>
<td></td>
</tr>
</tbody>
</table>

*Level decreased by 50% with OCP use
†Dose >1,200 mg
‡Doses >200 mg

## Contraception

All hormonal agents and preparations are affected by P450-inducing AEDs

<table>
<thead>
<tr>
<th>Method</th>
<th>Efficacy</th>
<th>Reversible</th>
<th>Menstrual Bleeding</th>
<th>Duration of Use</th>
<th>Mechanism</th>
<th>Complications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral CP</td>
<td>88%–94%</td>
<td>Immediate</td>
<td>Decreased, regular</td>
<td>Daily</td>
<td>Inhibit ovulation</td>
<td>Thrombosis, weight, inducible</td>
</tr>
<tr>
<td>Transderm patch</td>
<td>88%–94%</td>
<td>Immediate</td>
<td>Decreased, Regular</td>
<td>Weekly</td>
<td>Inhibit ovulation, Progestin</td>
<td>Irritation</td>
</tr>
<tr>
<td>Vaginal Ring</td>
<td>88%–94%</td>
<td>Immediate</td>
<td>Decreased, Regular</td>
<td>Monthly</td>
<td>Inhibit ovulation</td>
<td></td>
</tr>
<tr>
<td>DMPA</td>
<td>88%–94%</td>
<td>Delayed</td>
<td>Irregular, Amenorrhea</td>
<td>Q 3 month</td>
<td>Inhibit ovulation</td>
<td>↓ Bone density</td>
</tr>
<tr>
<td>Subdermal implant</td>
<td>&gt;99%</td>
<td>Immediate</td>
<td>Decreased, irregular</td>
<td>3 years</td>
<td>Inhibit ovulation</td>
<td>Removal Positive: Bone neutral</td>
</tr>
<tr>
<td>(etonogestrel)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Levo-IUD</td>
<td>&gt;99%</td>
<td>Immediate</td>
<td>Decreased and irregular, amenorrhea</td>
<td>5 years</td>
<td>Interfere with sperm</td>
<td></td>
</tr>
<tr>
<td>Cu IUD</td>
<td>&gt;99%</td>
<td>Immediate</td>
<td>Increased, regular</td>
<td>10 years</td>
<td>Interfere with sperm</td>
<td>Cramp</td>
</tr>
</tbody>
</table>

Contraceptive Use in WWE

<table>
<thead>
<tr>
<th>Method</th>
<th>Prevalence % (WWE)</th>
<th>PRAMS %—WWE/WWoE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hormonal contraception</td>
<td>37.6</td>
<td>33.7/31.7</td>
</tr>
<tr>
<td>Barrier Methods</td>
<td>23.1</td>
<td>70.3/49.4</td>
</tr>
<tr>
<td>Intrauterine device</td>
<td>30.6</td>
<td>0/2.2</td>
</tr>
<tr>
<td>Withdrawal</td>
<td>4.3</td>
<td>38.5/42.6</td>
</tr>
<tr>
<td>Tubal/vasectomy</td>
<td>2.2</td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>2.2</td>
<td></td>
</tr>
</tbody>
</table>

- 131 used highly effective methods with 7% using hormonal contraception in combination with enzyme inducing AEDs
  - More likely with higher income and insurance
- 55%–65% pregnancies in WWE are unplanned cf ~48%–50% in general population

Ovulatory Failure in Epilepsy Resulting in Infertility

- Anovulatory cycle by type of epilepsy
  - Control: 10.9%
  - IGE: 27.1%
  - LRE: 14.3%

- Anovulatory cycle if
  - Taken VPA w/in 3 years: 38.1%
  - Discontinued VPA >3 years ago: 10.7%

- Predictors of anovulatory cycle: IGE, VPA w/in 3 years, high testosterone, decreased LH pulses

IGE, idiopathic generalized epilepsy; LRE, localization-related epilepsy.

# Male Infertility

<table>
<thead>
<tr>
<th></th>
<th>Sperm Counts</th>
<th>Morphology</th>
<th>Motility</th>
<th>Testicular volume</th>
</tr>
</thead>
<tbody>
<tr>
<td>CBZ</td>
<td>↓ ABN</td>
<td>↓</td>
<td>↓ NL</td>
<td></td>
</tr>
<tr>
<td>OXC</td>
<td>↑ ABN</td>
<td>↓</td>
<td>↑ NL</td>
<td></td>
</tr>
<tr>
<td>PHT</td>
<td>↓ ABN</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>VPA</td>
<td>↑ ABN</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
</tr>
</tbody>
</table>

**FINLAND: 40% lower fertility than men w/o epilepsy**

WEPOD Findings at 2016 AAN Contradict Conventional Wisdom

- Multicenter observational study (The Women with Epilepsy: Pregnancy Outcomes and Deliveries “WEPOD”)
  - Women ages 18–41 seeking pregnancy and <6 months removed from contraception were enrolled from 2010 to 2015
  - Electronic diaries captured AED use, seizures, sexual activity, and menstrual cycles
- Results

<table>
<thead>
<tr>
<th></th>
<th>WWE (N=88)</th>
<th>Controls (N=109)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Achieved pregnancy</td>
<td>61.4%</td>
<td>60.6%</td>
<td>NS</td>
</tr>
<tr>
<td>Median time to pregnancy</td>
<td>6.03 mo</td>
<td>9.05 mo</td>
<td>NS*</td>
</tr>
<tr>
<td>Pregnancy result: live birth</td>
<td>80%</td>
<td>80.3%</td>
<td>NS</td>
</tr>
<tr>
<td>Pregnancy result: miscarriage</td>
<td>12.9%</td>
<td>19.7%</td>
<td>NS</td>
</tr>
</tbody>
</table>

- Conclusions: WWE seeking pregnancy had comparable likelihood of achieving pregnancy, time to achieve pregnancy, and pregnancy outcomes compared to a group of healthy peers

WWE, women with epilepsy.
*After controlling for age, BMI, parity and race

A 26-year-old female takes valproic acid for juvenile myoclonic epilepsy. She has been seizure-free for 5 years. She discovers she is 5 weeks pregnant.
More than 50% of all pregnancies are unplanned

90% of women with epilepsy have normal, healthy children
Folate

• Dietary supplementation recommended
  • 0.4 mg/day for general population beginning at age of menses (child-bearing age)
  • Inducing AEDs: 2–5 mg/day
  • VPA: 4–5 mg/day

Is it protective?
Seizure Frequency during Pregnancy

- Seizure freedom 9 months prior associated with 84%–92% freedom in pregnancy\(^1\)–\(^4\) and 87.8 postpartum\(^5\)
- MONEAD: Increased monthly seizure rate and days with seizures during 2nd trimester cf nonpregnant WWE\(^4\)
- Of those women who have an increase
  - 30% partial, 40% primary generalized in first trimester
  - Sleep, stress, AED metabolism
- Unpredictable between pregnancies
- AEDs
  - Total levels ↓ over pregnancy: LTG, LEV, TPM, OXC
  - Free levels change: CBZ, PB, PHT, VPA

Pregnancy and Delivery Risk

• MONEAD Study—Prospective pregnancy study, long-term follow up
• Viinikainen\(^1\): Retro registry review, population controlled, Norway, 1998–2005
  • Mild preeclampsia and gestational hypertension
  • Late vaginal bleeding
  • Delivery before 34 weeks
  • No difference placenta previa, PROM, eclampsia
• Borthen\(^2,3\): Prospective data, retro review, controls, Finland 1989–2000, 1995–2000
  • Higher rate of small for gestational age and smaller head circumference
  • No difference preeclampsia, pre-term labor, C-section, perinatal mortality, low birth weight
  • Increased rates induction, C-section, postpartum hemorrhage
  • Increased Apgar score of <7

## Meta-analysis of Birth Registries
### Pregnancy Outcomes: Incidence (%)

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Mother without epilepsy</th>
<th>Mother with epilepsy</th>
<th>Monotherapy</th>
<th>Polytherapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Healthy birth</td>
<td>99</td>
<td>93.4</td>
<td>94.0</td>
<td>90.6</td>
</tr>
<tr>
<td>Stillbirth</td>
<td>0.8</td>
<td>1.3</td>
<td>4.2</td>
<td>—</td>
</tr>
<tr>
<td>Spontaneous abortion</td>
<td>13.2</td>
<td>7.1</td>
<td>0.6</td>
<td>0.0</td>
</tr>
<tr>
<td>Elective abortion</td>
<td>4.0</td>
<td>4.5</td>
<td>0.5</td>
<td>1.1</td>
</tr>
<tr>
<td>With malformation</td>
<td>1.9</td>
<td>4.1</td>
<td>5.1</td>
<td>8.5</td>
</tr>
<tr>
<td>Perinatal death</td>
<td>0.6</td>
<td>1.5</td>
<td>2.4</td>
<td>2.1</td>
</tr>
</tbody>
</table>

# MONEAD Pregnancy Outcomes

## Miscarriages

<table>
<thead>
<tr>
<th></th>
<th>PWWE</th>
<th>PWWoE</th>
</tr>
</thead>
<tbody>
<tr>
<td>GA at entry (weeks)</td>
<td>13.37</td>
<td>15.4</td>
</tr>
<tr>
<td>Monotherapy %</td>
<td>74</td>
<td></td>
</tr>
<tr>
<td>Polytherapy %</td>
<td>22</td>
<td></td>
</tr>
<tr>
<td>No therapy %</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Miscarriages</td>
<td>3.3</td>
<td>0</td>
</tr>
<tr>
<td>Malformations in miscarriages (N)</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>

# Delivery Risks

<table>
<thead>
<tr>
<th>Complication</th>
<th>Risk Comparison</th>
</tr>
</thead>
<tbody>
<tr>
<td>C-section</td>
<td>OR 1.04–17.8 uncertain</td>
</tr>
<tr>
<td>Preeclampsia</td>
<td>OR 1.24–1.4 no risk</td>
</tr>
<tr>
<td>Late pregnancy bleeding</td>
<td>OR 1.18</td>
</tr>
<tr>
<td>Premature contraction, labor, delivery</td>
<td>NS cf controls</td>
</tr>
<tr>
<td>Spontaneous abortion</td>
<td>Decreased but no control data</td>
</tr>
<tr>
<td>Status epilepticus</td>
<td>1%–1.8%</td>
</tr>
<tr>
<td>Seizure frequency unchanged or better</td>
<td>45%–86%</td>
</tr>
<tr>
<td>Seizure free prior and during pregnancy</td>
<td>74%–94%</td>
</tr>
</tbody>
</table>

*Studies typically were class II-III*
# MONEAD Pregnancy Outcomes

## Obstetric and Neonatal Outcomes

<table>
<thead>
<tr>
<th></th>
<th>PWWE (N=331)</th>
<th>PWWoE (N=102)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>C-section</strong> *</td>
<td>34.7 (25.8**)</td>
<td>28.6 (NS) (17.1**)</td>
</tr>
<tr>
<td>Preterm PROM</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Polytherapy</td>
<td>11.3</td>
<td></td>
</tr>
<tr>
<td>Monotherapy/No therapy</td>
<td>2.7</td>
<td>(P=0.010)</td>
</tr>
<tr>
<td>Premature Delivery</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Polytherapy</td>
<td>16.2</td>
<td></td>
</tr>
<tr>
<td>Monotherapy/No therapy</td>
<td>8.4</td>
<td></td>
</tr>
<tr>
<td>SGA Overall</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lamotrigine</td>
<td>4.3</td>
<td>10.3 (P=0.051)</td>
</tr>
<tr>
<td>Levetiracetam</td>
<td>0</td>
<td>(P=0.033 for monotherapies)</td>
</tr>
<tr>
<td>Other Monotherapy</td>
<td>4.3</td>
<td></td>
</tr>
<tr>
<td>NICU</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lamotrigine</td>
<td>11.4</td>
<td>(P=0.045 for monotherapies)</td>
</tr>
<tr>
<td>Levetiracetam</td>
<td>5.6</td>
<td></td>
</tr>
<tr>
<td>Other Monotherapy</td>
<td>20.9</td>
<td></td>
</tr>
<tr>
<td>All Monotherapy/No therapy</td>
<td>11.6</td>
<td>(P=0.057 mono vs poly)</td>
</tr>
<tr>
<td>Polytherapy</td>
<td>21.7</td>
<td></td>
</tr>
</tbody>
</table>

*NS for preeclampsia, placental abruption, instrument delivery, peripartum hemorrhage or other OB cx

**Includes only women with no prior C section history

Types of Birth Defects

Malformation
• Significantly compromises health and requires surgical correction
  • 2%–3% in general population
  • 4%–8% in infants of women with epilepsy

Anomaly
• Definition: a minor deviation from normal appearance
  • 5%–10% in general population
  • ~15% of infants of women with epilepsy
Anomalies
Fetal Anticonvulsant Syndrome

VPA
Critical Periods of Development
Red Denotes Highly Sensitive Periods

<table>
<thead>
<tr>
<th>Prenatal Death</th>
<th>Major Morphological Abnormalities</th>
<th>Physiological Defects &amp; Morphological Abnormalities</th>
</tr>
</thead>
</table>

**Embryonic Period (in weeks)**
- Week 1: Period of dividing zygote, implantation & bilaminar embryo
- Week 2: CNS, Heart, Eye, Ear, Arm, Leg
- Week 3: CNS
- Week 4: CNS, Ear
- Week 5: CNS, Ear
- Week 6: CNS, Ear
- Week 7: CNS
- Week 8: CNS, Ear
- Week 9: CNS
- Week 16: CNS
- Week 20+: CNS

**Fetal Period (in weeks)**
- Week 9: Brain
- Week 16: Brain
- Week 20+: Brain

**Major Morphological Abnormalities**
- Ear
- Palate

**Physiological Defects & Morphological Abnormalities**
- Ear
- Palate
- External Genitalia
- Central Nervous System
- Heart
- Arms
- Eyes
- Legs
- Teeth
- Palate
- External Genitalia
- Ear
Factors That Increase Risk of Malformations

• Polytherapy
• High treatment dose
• Folic acid deficiency
• Family history of birth defects
• AED selection
• Previous pregnancy with malformation
  - 35% if + malformation vs 3% incidence if no malformation in first pregnancy
  - Especially if VPA

Folate Use

• Prenatal vitamin/folate month before pregnancy: WWE cf to WWoE
• Factors: Older ≥30, Caucasian, ↑ income, insurance

## FDA Risk Categories

<table>
<thead>
<tr>
<th>Category C</th>
<th>Category D</th>
</tr>
</thead>
<tbody>
<tr>
<td>BRI, CLB, CLO, EZO, GBP, ESLI, FBM, LCM, LEV, LTG, PER, PGB, PRP, RUF, VGB, CBD</td>
<td>BZs, CBZ, PHT, TPM, VPA</td>
</tr>
<tr>
<td>Adverse effect in animal studies; no human studies</td>
<td>Positive human fetal risk</td>
</tr>
<tr>
<td>Risk/benefit analysis</td>
<td>Risk/benefit analysis</td>
</tr>
<tr>
<td>Category not assigned: BRV, PER</td>
<td></td>
</tr>
<tr>
<td>Cleft lip/palate in topiramate exposure: 4.1/1000 compared to 1.1/1000 in unexposed</td>
<td></td>
</tr>
</tbody>
</table>

*As of 2015, category designations will not be used. Description details in insert.*
Meta-analysis of Birth Registries
Malformations

- 59 registries reported in English between 1979–2006 that had reports of >100 patients
- Mean age: 29.1 years
- On monotherapy: 57%
- Rates of malformation: >2.5 times healthy population
- Types of malformations
  - Cardiovascular > Musculoskeletal > Ear, neck, face
- Congenital malformation rate: 7.08/100 pregnancies
  - Monotherapy: 5.1%
  - Polytherapy: 8.5%

## Polytherapy Risk

<table>
<thead>
<tr>
<th></th>
<th>North American(^1)</th>
<th>UK(^2)</th>
<th>International LTG(^3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>1.6</td>
<td>3.1</td>
<td>3.1</td>
</tr>
<tr>
<td>Lamotrigine</td>
<td>1.2</td>
<td>2.8</td>
<td>2.1</td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>2.5</td>
<td>2.4</td>
<td>—</td>
</tr>
<tr>
<td>Valproate</td>
<td>10.7</td>
<td>6.3</td>
<td>—</td>
</tr>
<tr>
<td>LTG + CBZ</td>
<td>3.2</td>
<td>0</td>
<td>—</td>
</tr>
<tr>
<td>LTG + VPA</td>
<td>10.2</td>
<td>9.6</td>
<td>9.6</td>
</tr>
<tr>
<td>LTG + nonVPA</td>
<td>3.0</td>
<td>N/A</td>
<td>1.9</td>
</tr>
<tr>
<td>CBZ + VPA</td>
<td>6.9</td>
<td>8.8</td>
<td>—</td>
</tr>
</tbody>
</table>

\(^2\)Morrow J, et al. *J Neurol Neurosurg Psychiatry*. 2006;  
North American AED and Pregnancy Registry

• Prospective surveillance of AED in pregnancy since 1996
• 6000 enrolled; >1,000 prospective monotherapy
• Higher than expected risk of malformations with phenobarbital and valproate
• Cleft lip/palate 5/684 with lamotrigine (7.3/1,000 vs 0.7/1,000 in unexposed controls; RR=10.4). All were on folate and were nonsmokers. Not seen in any other registries.
• Women with epilepsy enroll by phone: Toll-free: 1-888-233-2334

<table>
<thead>
<tr>
<th>AED</th>
<th>Total Malf</th>
<th>Enrolled</th>
<th>Prevalence of Malf %</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lamotrigine</td>
<td>36</td>
<td>1,812</td>
<td>2.0</td>
<td>1.4–2.8</td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>33</td>
<td>1,078</td>
<td>3.1</td>
<td>2.1–4.3</td>
</tr>
<tr>
<td>Levetiracetam</td>
<td>14</td>
<td>648</td>
<td>2.2</td>
<td>1.2–3.6</td>
</tr>
<tr>
<td>Topiramate</td>
<td>19</td>
<td>425</td>
<td>4.5</td>
<td>2.7–6.9</td>
</tr>
<tr>
<td>Phenytoin</td>
<td>12</td>
<td>420</td>
<td>2.9</td>
<td>1.5–5.0</td>
</tr>
<tr>
<td>Valproate</td>
<td>30</td>
<td>333</td>
<td>9.0</td>
<td>6.2–12.6</td>
</tr>
<tr>
<td>Oxcarbazepine</td>
<td>4</td>
<td>211</td>
<td>1.9</td>
<td>0.5–4.8</td>
</tr>
<tr>
<td>Phenobarbital</td>
<td>12</td>
<td>201</td>
<td>6.0</td>
<td>3.1–10.2</td>
</tr>
<tr>
<td>Gabapentin</td>
<td>2</td>
<td>163</td>
<td>1.2</td>
<td>0.02–4.4</td>
</tr>
<tr>
<td>Zonisamide</td>
<td>0</td>
<td>119</td>
<td>0</td>
<td>0.0–3.3</td>
</tr>
<tr>
<td>Clonazepam</td>
<td>2</td>
<td>80</td>
<td>2.5</td>
<td>0.3–8.7</td>
</tr>
<tr>
<td>Unexposed</td>
<td>6</td>
<td>495</td>
<td>1.2</td>
<td>0.46–2.7</td>
</tr>
</tbody>
</table>

MONEAD

Prescribing Patterns

- Monotherapy: 74%
- Polytherapy: 22%
- None: 4%

MONEAD
AEDs Used during Pregnancy

Monotherapy

- LEV: 39%
- LTG: 43%
- ZNS: 5%
- CBZ: 5%
- OXC: 3%
- TPM: 3%

Polytherapy

- LTG/LEV: 43%
- LTG/ZNS: 5%
- LAC/LEV: 7%
- OTHER: 45%

Cognitive Development in Children Exposed to AEDs

- VPA significantly decreased early development < age 2
- VPA and polytherapy: ↑ children with extremely low or borderline full scale IQ on Wechsler, ↓ verbal comprehension and working memory with perceived perceptual reasoning and processing speed
- VPA exposed showed decreased originality and decreased fluency
- LEV exposed children achieved > VPA exposed children and equivalent to unexposed controls

NEAD Study
Cognitive Testing—6 Year Olds

- Higher IQ
  - Higher maternal IQ
  - Older gestational age
  - Periconceptual folate: mean 108 vs 101
- Lower IQ, verbal functioning, non-verbal index, general memory index with VPA
  - Dose dependent effects

Long-term Cognitive Development Effects on Fetus/Infant

- Phenobarbital: ↓ 7 VIQ compared to population
- Educational support: 62% VPA exposed vs 15% CBZ exposed
- Retrospective UK: School-aged children with ↑ educational needs
  - 30% VPA exposed; 3.2% carbamazepine; 6.5% other
- UK: IQ in 249 children exposed, ages 6–16
  - VPA more likely IQ<69 and memory impairment
- Finland: Children of normals and WWE
  - IQ: VPA 82, CBZ 96, controls 95
Treatment with Folate and IQ

MONEAD Study

## The Worry of Autism

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>N, Autism</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Controls</td>
<td>336</td>
<td>3</td>
<td>0.9</td>
</tr>
<tr>
<td>No AED exposure</td>
<td>47</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>On AED</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>VPA</td>
<td>64</td>
<td>4</td>
<td>6.3</td>
</tr>
<tr>
<td>VPA+LTG</td>
<td>51</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>LTG</td>
<td>44</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>CBZ</td>
<td>76</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>PHT</td>
<td>9</td>
<td>1</td>
<td>11</td>
</tr>
</tbody>
</table>
## Autism Worry—2

<table>
<thead>
<tr>
<th>Treatment</th>
<th>CARS&gt;30 Autistic Range (%)</th>
<th>CARS 27–29 Autistic Risk (%)</th>
<th>Total (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>VPA mono</td>
<td>1/26 (3.8)</td>
<td>1/26 (3.8)</td>
<td>2/26 (7.7)</td>
</tr>
<tr>
<td>VPA poly</td>
<td>6/15 (40.0)</td>
<td>1/15 (6.7)</td>
<td>7/15 (46.7)</td>
</tr>
<tr>
<td>CBZ mono</td>
<td>1/34 (2.9)</td>
<td>1/34 (2.9)</td>
<td>2/34 (5.9)</td>
</tr>
<tr>
<td>Other</td>
<td>0/30</td>
<td>0/30</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td>8/105 (7.6)</td>
<td>3/105 (2.9)</td>
<td>11/105 (10.5)</td>
</tr>
</tbody>
</table>

- 105 Australian children from prospective entry in prenatal Australian registry, tested voluntarily
- CARS score predicted by
  - VPA dose—inverse
  - first trimester folic acid use—protective
  - marijuana use—inverse

Autism Worry—3

Norway Prospective Study: Suggests that risk may be mitigated by periconceptional folic acid and folate status.

<table>
<thead>
<tr>
<th></th>
<th>WWE w/ AED N=335</th>
<th>WWE w/o AED N=389</th>
<th>WWoE N=104,222</th>
</tr>
</thead>
<tbody>
<tr>
<td>Crude OR @ 36 months</td>
<td>5.7 (2–16.1)</td>
<td>2 (0.4–11.2)</td>
<td>1.7 (1.6–1.9)</td>
</tr>
<tr>
<td>Folic acid 1st trimester</td>
<td>No difference</td>
<td></td>
<td>1.3/1.7</td>
</tr>
<tr>
<td>No folic acid</td>
<td></td>
<td>No difference</td>
<td></td>
</tr>
<tr>
<td>VPA w/o folic acid</td>
<td>28.6%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>VPA with folic acid</td>
<td>12.9%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Behavioral Problems in Children of WWE

Dutch collaboration with EURAP, prospective observational study, single-center registry

- Monotherapy CBZ, LTG, LEV, VPA thru pregnancy
- Children assessed 6–7 years of age
- No prematurity or chromosomal/genetic syndrome
- Child behavior checklist and social emotional questionnaire
- Adult self-report survey for parental problems

<table>
<thead>
<tr>
<th></th>
<th>VPA (26)</th>
<th>CBZ (37)</th>
<th>LTG (88)</th>
<th>LEV (30)</th>
<th>P (Chi-sq)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any Dx</td>
<td>8 (31%)</td>
<td>4 (11%)</td>
<td>10 (11%)</td>
<td>1 (3%)</td>
<td>0.015</td>
</tr>
<tr>
<td>ASD</td>
<td>3 (12%)</td>
<td>2 (5%)</td>
<td>4 (5%)</td>
<td>1 (3%)</td>
<td>0.577</td>
</tr>
<tr>
<td>ADHD</td>
<td>2 (8%)</td>
<td>2 (5%)</td>
<td>5 (6%)</td>
<td>0 (0%)</td>
<td>0.648</td>
</tr>
</tbody>
</table>

Julie is Pregnant

- She has two brief CPS at 12-weeks pregnant by dates
- She is sleeping well, exercising, and is adherent to LTG 600 mg/day
- At week 8, LTG 8 mcg/mL
- She is scheduled for high-definition ultrasound at week 18
- At week 12 she has a focal seizure, trough level is 6 mcg/mL
Fetal Heart Rate
Monitored during Maternal Seizure

Seizure

Dotted lines interpolated
### AED Changes during Pregnancy

<table>
<thead>
<tr>
<th></th>
<th>PHT</th>
<th>CBZ</th>
<th>PB</th>
<th>VPA</th>
<th>LTG</th>
<th>OXC</th>
<th>LEV</th>
<th>ESX</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Clearance</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Increased %</td>
<td>19–150</td>
<td>-11±27</td>
<td>60</td>
<td>Increased by trimesters 2 and 3</td>
<td>65–230 variable</td>
<td></td>
<td>243</td>
<td>±</td>
</tr>
<tr>
<td><strong>Decreased</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Concentration %</td>
<td>60–70</td>
<td>0–12</td>
<td>55</td>
<td>±</td>
<td>MHD and active moiety ↓ by 36–61</td>
<td>60 by Trimester 3</td>
<td>±</td>
<td></td>
</tr>
<tr>
<td><strong>Changes in Free</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AED or Metabolite</td>
<td>↓ 16-40% in trimester 3</td>
<td>NC</td>
<td>Dec 50%</td>
<td>↑ Free fraction by trimesters 2 and 3</td>
<td>89% ↑ clearance of free LTG</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Lamotrigine Kinetics in Pregnancy, Delivery, and Postpartum

Maternal Serum Clearance/Baseline Clearance

<table>
<thead>
<tr>
<th></th>
<th>1st Trimester</th>
<th>2nd Trimester</th>
<th>3rd Trimester</th>
<th>Delivery</th>
<th>Postpartum 7 days/3 weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td>N=9</td>
<td>197%</td>
<td>236%</td>
<td>248%</td>
<td>264%</td>
<td>218%/Baseline</td>
</tr>
</tbody>
</table>

Infant Exposure

<table>
<thead>
<tr>
<th></th>
<th>Umbilical cord/maternal serum concentration, N=6</th>
<th>Breast milk/maternal serum concentration, N=4</th>
<th>Infant serum post feed/maternal serum concentration, N=4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median</td>
<td>1.01</td>
<td>57%</td>
<td>26%, decreases over time after delivery</td>
</tr>
</tbody>
</table>

AEDs in Breast Milk

• 62 studies reviewed with 25 being case reports, letters, or abstracts
• Lack of information on sampling methods, number of samples in a dose interval, and few study participants

“The quality of the current literature on the transfer of anticonvulsants to breast milk is low except for lamotrigine, which makes it hard to draw conclusions about the safety of the use of anticonvulsants during the lactation period.”

AEDs in Breast Milk and Infant Exposure

- Amount secreted into milk is function of
  - Molecular weight, protein binding, lipophilicity, ionization
  - Changes over time: colostrum with high protein and less fat than mature milk, which is watery
  - Time of drug intake to breastfeeding, frequency of dosing, frequency and duration of feeding
- Infant metabolism and excretion “immature” until at least 20 months or longer, especially SGA or preemies

Klein A. Neurol Clinic. 2012.
Breastfeeding and Antiepileptic Drugs

- Infant plasma levels most often very low but may accumulate (barbs, benzos)\textsuperscript{1,2}
- Assess risks and benefits for individual patients
- May prevent withdrawal syndrome in infant exposed to some agents\textsuperscript{3,4}
- AAN, AES, and AAP encourage breastfeeding with close observation of baby and that the relative unknown does produce anxiety in WWE\textsuperscript{5–7}

Comparison of Infant and Maternal Levels in Breastfed Babies

Figure 2: Mother and Child Lamotrigine Level Comparison

*Levels between 6–12 weeks of age in 121 infants (64 LTG, 54 LEV, 9 CBZ, 7 OXC)

Use of Breastfeeding in WWE

PRAMS Study

<table>
<thead>
<tr>
<th></th>
<th>% Breastfeeding</th>
<th>Weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td>General Population</td>
<td>84.6</td>
<td>6.6</td>
</tr>
<tr>
<td>WWE</td>
<td>69.1</td>
<td>6.4</td>
</tr>
</tbody>
</table>

Comparison of Infant and Maternal LEV Levels in Breastfed Babies

*Levels between 6–12 weeks of age in 121 infants (64 LTG, 54 LEV, 9 CBZ, 7 OXC)

NEAD Study

Breastfeeding and IQ at 6 Years of Age

• Differential Ability Scales IQ
• IQ dependent on: maternal IQ, periconceptual folate use, AED type—worse for VPA by 7–13 IQ points, AED dosage (VPA dose dependent decrease)
• Verbal abilities differed between the breastfed and non-breastfed groups

### Adjusted Mean IQ

<table>
<thead>
<tr>
<th>AED</th>
<th>Breastfed¹</th>
<th>Non-breastfed</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>All AED</td>
<td>108</td>
<td>104</td>
<td>0.04*</td>
</tr>
<tr>
<td>CBZ</td>
<td>107</td>
<td>105</td>
<td>0.61</td>
</tr>
<tr>
<td>LTG</td>
<td>113</td>
<td>110</td>
<td>0.23</td>
</tr>
<tr>
<td>PHT</td>
<td>104</td>
<td>108</td>
<td>0.23</td>
</tr>
<tr>
<td>VPA</td>
<td>106</td>
<td>94</td>
<td>0.04*</td>
</tr>
</tbody>
</table>

¹Breastfed for mean of 7.2 months, 42% breastfed, monotherapy

Safety in Postpartum Period

• Risk of seizures
  • Physiological AED level changes
  • Sleep deprivation/interruption
  • Stress and lack of routine and possible decreased adherence

• Transport of infant
• Additional nighttime caregiver—daddies are a part of the family too!
• Low-to-ground diaper changing
• Supervised bathing of infant
• She has had successful pregnancies, career, and marriage
• She is active in sports, but diets frequently
• At 48, she has had no menses for 6 months, was irregular for 2 years prior
• She has had no seizures since age 25, but has had 4 focal seizures in the last year
Bone Health Issues

- Seen in healthy active ambulatory PWE and nonambulatory and/or institutionalized PWE
- High fracture risk, even outside of seizures
- Multifactorial mechanisms
  - Diet and nutrition, sun exposure, exercise
  - Induced CYP 450
  - Catabolism of vitamin D → hypocalcemia → 2nd hyperparathyroidism
  - Direct AED effect on bone cells
  - Resistance to PTH
  - Calcitonin deficiency
  - Impaired calcium absorption

Fitzpatrick LA. Epilepsy Behav. 2004.
Lumbar Osteopenia or Osteoporosis
Males and Females on Enzyme Inducing AEDs

% of Patients

- Expected
- <50 years old
- >50 years old

## Lifetime Fractures in WWE\(^1\)
### Suggestive of Neurotoxicity in 50 Women

<table>
<thead>
<tr>
<th>AED state</th>
<th>Clumsiness</th>
<th>Seizure</th>
<th>Accident</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before AED</td>
<td>2</td>
<td>0</td>
<td>7</td>
</tr>
<tr>
<td>After AED</td>
<td>10</td>
<td>8</td>
<td>2</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Fracture Site</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Skull</td>
<td>—</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>Arm</td>
<td>2</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>Lower Extremity</td>
<td>8</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Rib</td>
<td>—</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Spine</td>
<td>2</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

Rate of fracture in institutionalized non-epilepsy patients was 1/50 years; in epilepsy 1/40 years in seizure and 1/21 years other causes.\(^2\)

Effects of Lamotrigine on Bone Health
Summary of Study in Pre-menopausal WWE

- Lamotrigine was not associated with any deficits in bone mass or biochemical markers of bone health\(^1\)
  - CBZ, PHT, and VPA were associated with significant reductions in serum calcium compared to LTG
  - PHT was associated with significant elevations in BSAP compared with LTG, CBZ, and VPA
  - PHT was associated with significant reductions in IGF-1 compared to LTG
- **After 1 year of treatment**, significant bone loss was observed at the femoral neck in patients taking PHT compared to LTG, CBZ, VPA\(^2\)

BSAP, bone-specific alkaline phosphatase; IGF, insulin-like growth factor.

### Enzyme Inducers and Bone Health Compared to Maintaining PHT Treatment

<table>
<thead>
<tr>
<th>Group (N)</th>
<th>BMD at Femur</th>
<th>BMD Spine</th>
<th>Rate of change per year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Taken off AED (19)</td>
<td>Higher</td>
<td>Higher</td>
<td>Improved</td>
</tr>
<tr>
<td>Switch to LEV</td>
<td>Higher</td>
<td>Higher</td>
<td>Improved</td>
</tr>
<tr>
<td>Maintain PHT (17)</td>
<td>Lower</td>
<td>Lower</td>
<td>-0.20 and -0.23 per year</td>
</tr>
</tbody>
</table>

Also significant increases in Vit D levels for group 1 and 2.
No change in PTH, Ca\(^{+2}\), phosphate.
No group differences in means for age 33, BMI, or duration of PHT exposure.

Bone Health

Recommended daily dose of vitamin D = 800 IU/d

Daily Calcium Recommendation

<table>
<thead>
<tr>
<th>Condition</th>
<th>Calcium (mg/d)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;65 years</td>
<td>1,500</td>
</tr>
<tr>
<td>25–65 years</td>
<td>1,000</td>
</tr>
<tr>
<td>Menopausal on HRT</td>
<td>1,000</td>
</tr>
<tr>
<td>Menopausal w/o HRT</td>
<td>1,500</td>
</tr>
<tr>
<td>Nursing</td>
<td>1,200+</td>
</tr>
</tbody>
</table>

8 oz milk = 300 mg calcium

HRT, hormone replacement therapy.
## Recommendations

<table>
<thead>
<tr>
<th>Guidelines for Maintenance and Monitoring</th>
<th>If Abnormal</th>
<th>Treatments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ca(^{+2}) 600–1,500 mg/day</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vit D Up to 2,000 IU/day</td>
<td>2,000–5,000 IU/day</td>
<td>5000–15,000 IU/day or 50,000 per week x 8 weeks, then 2,000–5,000/day</td>
</tr>
<tr>
<td>Baseline Ca(^{+2}), Ph, Vit D, PTH, alk ptase</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline DEXA, every 2–5 years, T score &lt;-1 and &gt;-2.5</td>
<td>T &lt;- -2.5 or fracture</td>
<td>Referral for treatment</td>
</tr>
<tr>
<td>Postmenopausal</td>
<td></td>
<td>Hormonal treatment</td>
</tr>
<tr>
<td>DEXA in high-risk children</td>
<td></td>
<td>Bisphosphonates, ibandronate</td>
</tr>
</tbody>
</table>

Perimenopause and Menopause

- Premature ovarian failure (before age 40): 4.8% cf 1% in general population
- Menopause occurs earlier by 3–6 years
- Compared to normal healthy patients: 14% vs 4%
  - More often if catamenial pattern
  - Higher seizure rates
  - Enzyme inducing drugs

Epilepsy During and After Menopause

• Perimenopause
  • Seizures may worsen with significant fluctuation in ovarian steroids
  • Hormone replacement increases seizures in perimenopause

• Menopause
  • Seizures may improve, most often if prior catamenial pattern
  • HRT with unopposed estrogen may worsen seizures
  • Increased use of other medications increase risk of drug interactions
  • Risk of symptomatic bone disease

Guidelines

• International and national guidelines disseminated for 2 years and patient care evaluated retrospectively after 2 years
• No change in practices for folate supplementation, calcium and vitamin D use, or contraception advice
• Improved pregnancy care—ultrasounds, vitamin K use for inducing AEDs

## Practical Office Management

<table>
<thead>
<tr>
<th>Suggestions</th>
<th>This Conference</th>
<th>Addressed partially in AAN/AES Guidelines¹*</th>
<th>In Practice²</th>
</tr>
</thead>
<tbody>
<tr>
<td>Counsel on contraception</td>
<td>+</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Counsel on fertility</td>
<td>+</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Counsel on AED and malformation risk</td>
<td>+</td>
<td>+</td>
<td>NA</td>
</tr>
<tr>
<td>Counsel on and initiate Folic acid ≥0.4–4 mg/da</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Utilize LTG or LEV, preferable monotherapy</td>
<td>+</td>
<td>NA</td>
<td>+</td>
</tr>
<tr>
<td>Avoid VPA or at low dose/levels</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Counsel on behavioral/cognitive risks</td>
<td>+</td>
<td>+</td>
<td>NA</td>
</tr>
<tr>
<td>Counsel on seizure frequency, blood monitoring</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Counsel on breastfeeding</td>
<td>+</td>
<td>+</td>
<td>NA</td>
</tr>
<tr>
<td>Counsel on bone health, vitamin D</td>
<td>+</td>
<td>NA</td>
<td>NA</td>
</tr>
</tbody>
</table>

* New guidelines in development for 2019

The interactions of epilepsy, AEDs, and hormone status present the clinician and the patient with special treatment considerations beginning at puberty and continuing through menopause and aging.
Post-test
How confident are you with identifying seizure etiology?

A. Very confident
B. Somewhat confident
C. A little confident
D. Not at all confident
How confident are you at interpreting EEGs?

A. Very confident  
B. Somewhat confident  
C. A little confident  
D. Not at all confident
How confident are you at managing antiepileptic drug therapies?

A. Very confident
B. Somewhat confident
C. A little confident
D. Not at all confident
Which condition presents the greatest risk of developing subsequent epilepsy?

A. Febrile seizures
B. Alzheimer’s disease
C. Alcoholism
D. Military head trauma
The most common etiology of seizures in patients over age 60 is:

A. CVA/stroke
B. Head trauma
C. Alcoholism
D. Brain tumor
Which of the following EEG rhythms occurs at a frequency of greater than 13 Hz?

A. Delta rhythms  
B. Theta rhythms  
C. Alpha rhythms  
D. Beta rhythms
What is the most common cause of acquired epilepsy worldwide?

A. Primary brain tumor
B. Metastatic brain tumor
C. Mesial temporal sclerosis
D. Neurocysticercosis
Which AED may benefit generalized tonic-clonic seizures, but worsen myoclonic seizures?

A. Valproate
B. Topiramate
C. Lamotrigine
D. Clonazepam
Patients with a lifetime history of depression:

A. Are likely to have a robust response to AEDs
B. Are unlikely to respond to antidepressants
C. Are likely to develop psychosis if placed on AEDs
D. Are at greater risk of developing epilepsy
A 26-year-old female takes valproate for juvenile myoclonic epilepsy. She has been seizure-free for five years. She discovers she is 5 weeks pregnant.
What therapeutic intervention do you recommend?

A. Discontinue valproate to protect the fetus
B. Transition from valproate to lamotrigine for the remainder of the pregnancy
C. Transition from valproate to carbamazepine for remainder of the pregnancy
D. Add clonazepam to increase protection from myoclonus
E. None of the above
At 12 weeks of pregnancy, she experiences two complex focal seizures (CFS). She is adherent with the medication regimen as prescribed (lamotrigine 600 mg/day). Her lamotrigine level last month was 8 mcg/mL. Upon repeating this, her lamotrigine level today is 6 mcg/mL. She has a high-def ultrasound scheduled to be done at 18 weeks gestation.
What should be your next step?

A. Counsel regarding possible termination of pregnancy
B. Resume valproate, using extended-release 500 mg qhs
C. Increase lamotrigine dose to achieve blood level of 10 mcg/mL
D. Reschedule ultrasound to be done ASAP, no later than next week
Closing Remarks

Please be sure and return your evaluation to the Welcome Desk before you leave today.

Safe Travels Home and Thank you!