Epilepsy and EEG in Clinical Practice

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Disclosures

Relevant financial relationship(s) with industry
• None

References to off-label usage(s) of pharmaceuticals or instruments
• None
The ultimate goal of epilepsy treatment is for the patient to have no seizures and no harm from the seizure treatment.

In special populations, particularly women looking to become pregnant and the elderly, achieving this goal requires additional considerations.
Epilepsy + Pregnancy

• Exposure to AED in the first trimester of pregnancy has been associated with:
  • Increased risk of birth defects
  • Lower than expected IQ
  • Behavioral problems
• Risks are drug and dose specific
Risks of In Utero AED Exposure

Major Malformations

Tomson T + Battino 2009 J Neurol; meta-analysis
Malformation Rate by AED
North American Pregnancy Registry

Ref: North American Pregnancy Registry, Fall 2014
Use of VPA in WWE

**ILAE Recommendations**

- Avoid where possible
- VPA should not be used as first line treatment for focal epilepsy
- Where VPA is the most effective treatment, risks and benefits should be considered
- Choice should be a shared decision between clinician and patient
- Women using VPA should have regular follow-up and ongoing consideration for change in treatment

Developmental Outcomes

**NEAD Study**

<table>
<thead>
<tr>
<th>Antiepileptic Drug</th>
<th>No. of Children</th>
<th>Mean IQ</th>
</tr>
</thead>
<tbody>
<tr>
<td>High dose</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>47</td>
<td>97</td>
</tr>
<tr>
<td>Lamotrigine</td>
<td>52</td>
<td>100</td>
</tr>
<tr>
<td>Phenytoin</td>
<td>28</td>
<td>98</td>
</tr>
<tr>
<td><strong>Valproate</strong></td>
<td>22</td>
<td>87</td>
</tr>
<tr>
<td>Low dose</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>46</td>
<td>100</td>
</tr>
<tr>
<td>Lamotrigine</td>
<td>48</td>
<td>102</td>
</tr>
<tr>
<td>Phenytoin</td>
<td>27</td>
<td>98</td>
</tr>
<tr>
<td>Valproate</td>
<td>39</td>
<td>97</td>
</tr>
</tbody>
</table>

**Mean IQ at Age 3 Yr (95% CI)**

Meador KJ et al, 2009 NEJM 360: 1597
Preventative Strategies

- PRIOR to conception
- Eliminate AED if feasible
- Monotherapy
- Lowest dose that will maintain reasonable seizure control
- Folic acid supplementation (minimum of 0.4 mg/day)
Seizure Control During Pregnancy

- 50-60% seizure free
- ≤ 2% with status epilepticus
- 3.5-5% with a seizure during labor/delivery
- Baseline seizure control predicts control during pregnancy

EURAP Study Group 2006 Neurology 66: 354; n=1956
Australian Pregnancy Register: Vajda et al 2008 Epilepsia 49: 172; n= 841
AAN Practice Parameter, Harden et al 2009
Seizure Control in Pregnancy

Percent with Seizures in Pregnancy

Years Seizure Free

Vajda et al. Epilepsia 2008; 49: 172
Seizure control + Malformations
North American Pregnancy Registry

Factors Contributing to Breakthrough Seizures During Pregnancy

- Medication non-compliance
- Altered AED pharmacokinetics
  - OXC, LTG
- Altered sex steroid hormone levels
- Impaired sleep

Schmidt et al, JNNP 1983; 46: 751
Pregnancy Complications in WWE

- EURAP
  - 7055 AED exposed pregnancies
  - 632 intrauterine deaths (9%)
  - Risk increased with polytherapy (12%; RR 1.38)
  - Risk not different between individual AEDs, drug dose, use of folic acid, GTCs
  - Other risk factors: maternal age, parental MCM

Pregnancy Complications in WWE

- U.S. Nationwide Inpatient Sample, 2007-11
- 69,385 WWE vs. 20,449,532 controls
- 11x Increased risk of death (80/100,000)
- 1.2 –1.5x Increased risk of pre-eclampsia, pre-term labor, stillbirth
- 1.4 x Increased risk of C-section
- 2x Increased risk of hospital stay >6 days

Birth Control and AEDs

• Enzyme inducing AEDs increase metabolism of OCPs:
  • (phenytoin, carbamazepine, phenobarbital, primidone, ethosuximide, oxcarbazepine, topirimate)
  • Serum estradiol levels decreased by 40-50% (15-30% with TPX)
  • Reported failure rate 7% vs. 0.1-3%
  • Effectiveness of “high dose” estrogen pills (50ug vs. 20-30 ug)
Birth Control and AEDs

• AEDs with no known effect on OCPs:
  • VPA, lamotrigine, zonisamide, gabapentin, pregabalin

• AEDs whose level may be decreased by OCPs:
  • Lamotrigine (40-60%)
Counseling for Women with Epilepsy of Childbearing Potential

- Pre-pregnancy counseling regarding risks of AED use
- Contraceptive choice informed by potential interaction with AED
- Folic acid supplementation
- Adjustment in AED choice, dose PRIOR to conception
- Avoid VPA as possible
Epilepsy in the Elderly
Incidence/Prevalence

- Prevalence of 1% - over the age of 60
- 5% in Nursing home patients
- More prone to develop first unprovoked seizures 52-59/100,000 if <59 yrs
  - 127/100,000 if over 60 yrs
- Acute symptomatic seizures more common
- Recurrence rate - 79% at 1 yr/83% at 3 yr
Seizure Presentation In Older Adults

• Auras are less common and nonspecific
  • Often described as dizziness
  • Greater amnesia
  • Coexisting dementia may account for lack of aura

• Typical aura in TLE not often reported
  • Ramsey 2004
Etiology of Newly Diagnosed Epilepsy in Patients ≥ 60 Years Old

**VA Cooperative Study 428**

- **Cerebral Infarct**: 34.1%
- **Unknown**: 24.6%
- **Arteriosclerosis**: 14.9%
- **Head Trauma**: 6.9%
- **Other***: 18.8%
- **Hemorrhage**: 1.7%

*Includes known etiologies such as arteriovenous malformation and venous angioma.

Epilepsy in the Elderly: Special Treatment Considerations

• Pharmacokinetic changes
  • Slower drug metabolism
  • Decreased protein binding
  • Decreased renal clearance
• Reduced compliance
  • Memory loss
  • Visual impairment
• Comorbid illnesses and medications
  • Comorbid illness requiring concomitant medications
  • Drug interactions, eg, between warfarin statins and some antiepileptic drugs

AED Doses Used in Seizure-Free Older Patients with New-Onset Epilepsy

<table>
<thead>
<tr>
<th>Antiepileptic Drug</th>
<th>n</th>
<th>Median (mg)</th>
<th>Range (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carbamazepine</td>
<td>24</td>
<td>400</td>
<td>200-700</td>
</tr>
<tr>
<td>Lamotrigine</td>
<td>20</td>
<td>100</td>
<td>50-400</td>
</tr>
<tr>
<td>Sodium valproate</td>
<td>20</td>
<td>800</td>
<td>300-1500</td>
</tr>
<tr>
<td>Oxcarbazepine</td>
<td>5</td>
<td>300</td>
<td>100-600</td>
</tr>
<tr>
<td>Phenytoin</td>
<td>3</td>
<td>200</td>
<td>100-600</td>
</tr>
</tbody>
</table>

Managing AED Therapy: Elderly

• Select a drug not likely to exacerbate any pre-existing condition (tremor, ataxia, depression, dysphasia, etc)
• Start with very low doses whenever possible
• Target dose of $\frac{1}{2} - \frac{2}{3}$ that for younger adults is often sufficient for seizure control
• Consider taper and discontinue 6-12 months after stroke for early post-stroke seizures
• Monitor side effects carefully
Bone Health

- Long term use of many AEDs has been linked to increased bone turnover, decreased bone density, vitamin D deficiency
- Reported risk: benzodiazepines, *Phenytoin*, *Phenobarbital*, *Primidone*, *Carbamazepine*, *Valproate*
- Newest AEDs—risk unknown, possibly safer due to lack of hepatic enzyme induction
Prevention and Treatment of Osteoporosis in Epilepsy

• Calcium and vitamin D
• Exercise, stop smoking
• Bone density screening
• Adjustment in seizure medication can be considered
• Additional medications available to treat if osteoporosis is diagnosed
Co- Morbid Mood Disorders
Mood Disorders, Anxiety in Epilepsy

Depression:
- 20% of people with well controlled sz
- 50-60% in refractory epilepsy
- Suicide rate 25x greater than general population

Anxiety:
- 20% in refractory epilepsy

Psychosis:
- 10% of people with epilepsy
- May be more common in TLE
Mood/Anxiety Disorders in Epilepsy

Potential Contributors

• Anti-epileptic medications
• Seizures
• Psycho-social limitations associated with epilepsy
• Underlying brain disorders
Suicidality + AEDs

• 2008 FDA safety alert: increased risk of suicidal behavior/ideation with AEDs

• Meta-analysis of placebo controlled AED trials with n>30, any indication (25% epilepsy, 27% psychiatric, 48% other)

• 4 suicides/28,000 AED exposed; OR 1.8 (95% CI 1.24-2.66)

Mood/Anxiety Disorders in Epilepsy

Treatment

- Generally underdiagnosed and undertreated
- Use of validated screening tools
- Best seizure control
- Consider use of AED with mood stabilizing properties
- Conventional anti-depressants
- Therapy