Managing Epilepsy – Pharmacists Help

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**Accreditation:**
- Pharmacist: 798-000-09-005-L01-P
- Pharmacy Techs: 798-000-09-005-L01-T

**CE Credits:** 1.0 contact hour

**Target Audience:** Pharmacists & Technicians

**Program Overview:**
This program is designed to assist pharmacists review the facets of the condition of epilepsy, as well as the benefits of controlling episodes with medications. Their knowledge of available options for epileptic patients will be enhanced. The program includes information on pharmacologic treatments, drug interactions, patient counseling, and a question/answer period.

**Objectives:**
- Pharmacists will identify various theories regarding the basic etiology and pathophysiology of epilepsy including risk factors, and signs and symptoms associated with this disorder.
- Pharmacists’ knowledge of current pharmacologic agents used to manage epilepsy (along with possible side effects) will be enhanced.
- Pharmacists will describe the treatment options as well as non-pharmacologic options and information needed to counsel patients with epilepsy.

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Speaker: Jacquelyn L. Bainbridge, BSPharm, PharmD., FCCP, received her doctorate of pharmacy from the University of Colorado School of Pharmacy, where she subsequently completed a specialty residency in neurology. Dr. Bainbridge currently serves as an Associate Professor at the University of Colorado Denver School of Pharmacy, Department of Clinical Pharmacy and Department of Neurology in the School of Medicine.

Speaker Disclosure: Dr. Bainbridge has no actual or potential conflicts of interest in relation to this program

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Learning Objectives

• Identify various theories regarding the basic etiology and pathophysiology of epilepsy including risk factors, and signs and symptoms associated with this disorder

• Discuss the current pharmacologic agents used to manage epilepsy including side effects and possible adverse drug reactions (1st generation vs. 2nd generation antiepileptic drugs (AEDs))

• Describe the treatment options as well as non-pharmacologic options and information needed to counsel patients with epilepsy
Why do we Need these Newer AEDs?

Common perceptions-

- Older drugs work in mostly all patients…besides, newer AEDs take too long to get to an effective dose
- Most PK problems/drug interactions are minor issues if you use AED monotherapy
- They have few adverse effects…most patients tolerate them well
- Older drugs are cheap…new drugs cost too much
Outline

- Overview of the disorder
- Pharmacokinetic differences between first generation AEDs
- First generation AED specific adverse drug reactions (ADRs)/ Patient education
- Second generation AED pharmacokinetic differences
- Second generation AED specific ADRs/ Patient education
- New AEDs
- Non-pharmacological therapies
- Generic substitution
- Broad spectrum
- Drugs on the horizon
- Summary
Epidemiology of Epilepsy

- 1/100 adults are diagnosed with epilepsy
- 1/50 children are diagnosed with epilepsy
- 200,000 new cases are diagnosed per year
- In 70% of new cases, no cause apparent
- Annual burden ~ $12.5 billion indirect and direct healthcare cost

Epilepsy Foundation: www.epilepsyfoundation.org
Incidence of Epilepsy

Incidence of Epilepsy in Rochester, Minnesota, 1935 to 1984

Adapted with permission from Hauser WA, Annegers JF, Kurland LT. *Epilepsia*. 1993;34:453–468.
Seizure Classification

• Partial onset seizures
  – Simple partial seizures
  – Complex partial seizures

• Secondarily generalized seizures

• Primary generalized seizures
  – Absence seizures
  – Atypical absence seizures
  – Myoclonic seizures
  – Atonic seizures
  – Tonic seizures
  – Clonic Seizures
  – Tonic-clonic seizures
Tonic-Clonic Seizure

Tonic phase

Clonic phase
Most Common Seizure Type
Partial onset

- Complex partial: 36%
- Simple partial: 14%
- Generalized tonic-clonic: 23%
- Other generalized: 8%
- Myoclonic: 3%
- Unclassified: 3%
- Partial unknown: 7%
- Absence: 6%

VA Study #428 New Onset Epilepsy in Elderly Outcome at 12 Months

LTG vs. CBZ, p = 0.00003
LTG vs. GBP, p = 0.10443
GBP vs. CBZ, p = 0.01063

57.9%
49.2%
36.6%

Target = 150mg/d
Target = 1500 mg/d
Target = 600 mg/d

<table>
<thead>
<tr>
<th>Condition</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dyslipidemia</td>
<td>80%</td>
</tr>
<tr>
<td>Hypertension</td>
<td>53.8%</td>
</tr>
<tr>
<td>Stroke</td>
<td>52.7%</td>
</tr>
<tr>
<td>Cardiac disease</td>
<td>48.1%</td>
</tr>
<tr>
<td>Diabetes</td>
<td>28.3%</td>
</tr>
<tr>
<td>Cancer</td>
<td>23.8%</td>
</tr>
<tr>
<td>Psychiatric disease</td>
<td>21.6%</td>
</tr>
<tr>
<td>Renal disease</td>
<td>12.3%</td>
</tr>
<tr>
<td>Liver disease</td>
<td>2.7%</td>
</tr>
<tr>
<td>Parkinson’s disease</td>
<td>2.7%</td>
</tr>
</tbody>
</table>

Success in AED Regimens

- Seizure free 47% Monotherapy first AED
- Seizure free 13% Monotherapy 2nd AED
- Seizure free 1% Monotherapy 3rd AED
- Seizure free 3% Polytherapy
- Not seizure free 36% All regimens attempted

### Comparative Pharmacokinetics of 1st. Generation AEDs

<table>
<thead>
<tr>
<th>Drug</th>
<th>F %</th>
<th>Binding %</th>
<th>Ci</th>
<th>t ½ (hrs)</th>
<th>Cause PK Interaction?</th>
</tr>
</thead>
<tbody>
<tr>
<td>CBZ</td>
<td>80</td>
<td>75-85</td>
<td>100% H*</td>
<td>6-15</td>
<td>yes</td>
</tr>
<tr>
<td>PB</td>
<td>100</td>
<td>50</td>
<td>75% H</td>
<td>72-124</td>
<td>yes</td>
</tr>
<tr>
<td>PHT</td>
<td>95</td>
<td>90</td>
<td>100% H**</td>
<td>12-60</td>
<td>yes</td>
</tr>
<tr>
<td>VPA</td>
<td>100</td>
<td>75-95**</td>
<td>100% H</td>
<td>6-18</td>
<td>yes</td>
</tr>
</tbody>
</table>

* autoinduction  
** non-linear  

Problems:  
Poor water solubility  
Extensive protein binding  
Extensive oxidative metabolism  
Multiple drug-drug interactions
Effect of CBZ on Serum Simvastatin and Simvastatin Acid Concentrations

# Drug-Specific Side Effects: Old Established AEDs/Patient Education

<table>
<thead>
<tr>
<th>AED</th>
<th>Drug-Specific AE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phenytoin</td>
<td>Ataxia, gingival hyperplasia</td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>Tremor, myoclonus, hyponatremia, cardiotoxicity, sexual dysfunction, visual distortion</td>
</tr>
<tr>
<td>Valproate</td>
<td>Tremor, encephalopathy, pedal edema, hair loss, weight gain</td>
</tr>
<tr>
<td>Phenobarbital</td>
<td>Connective tissue disorders*, erectile dysfunction, sedation</td>
</tr>
<tr>
<td>Primidone</td>
<td>Connective tissue disorders*, erectile dysfunction, sedation</td>
</tr>
</tbody>
</table>

* Dupuytren’s contractures, Ledderhose syndrome, Peyronie’s disease, frozen shoulder

Ramsay, Rowan & Pryor.
AED Adverse Effects

What we can see.....
Gingival Hyperplasia Induced by Phenytoin

After Withdrawal of Phenytoin

Stevens-Johnson Syndrome

Bone Health

• Gradual decline in bone mass and bone mineral density (BMD) with advancing age

• Increased risk of osteoporosis and fractures with some AEDs by interfering with Vitamin D metabolism

• PHT, PB, CBZ and possibly VPA increase risk for osteopenia/osteoporosis

• Limited data with newer AEDs
Trabecular Bone
(http://www.merck.com)
Sexual Function

• Sexual dysfunction described in 30-60% of men and women with epilepsy

• Older AEDs (phenytoin, carbamazepine, phenobarbital & primidone) induce hepatic drug metabolism

• CytochromeP450 isozymes participate in metabolism of estradiol and testosterone

• Increased hepatic synthesis of sex hormone binding globulin (SHBG) → ↓ concentrations of bioactive androgen
### Pharmacokinetics of Newer AEDs

<table>
<thead>
<tr>
<th>Drug</th>
<th>Absorption</th>
<th>Binding</th>
<th>Elimination&lt;sup&gt;a,b&lt;/sup&gt;</th>
<th>T ½ (hrs)</th>
<th>Cause Interactions?</th>
</tr>
</thead>
<tbody>
<tr>
<td>GBP</td>
<td>≤ 60%c</td>
<td>0%</td>
<td>100% renal</td>
<td>5-9</td>
<td>No</td>
</tr>
<tr>
<td>LTG</td>
<td>100%</td>
<td>55%</td>
<td>100% hepatic</td>
<td>18-30</td>
<td>No</td>
</tr>
<tr>
<td>LEV</td>
<td>~100%</td>
<td>&lt;10%</td>
<td>66% renal</td>
<td>4-8</td>
<td>No</td>
</tr>
<tr>
<td>TGB</td>
<td>~100%</td>
<td>96%</td>
<td>100% hepatic</td>
<td>5-13</td>
<td>No</td>
</tr>
<tr>
<td>TPM</td>
<td>≥80%</td>
<td>15%</td>
<td>30-55% renal</td>
<td>20-30</td>
<td>Yes/No</td>
</tr>
<tr>
<td>ZNS</td>
<td>80-100%</td>
<td>40-60%</td>
<td>50-70% hepatic</td>
<td>50-80</td>
<td>No</td>
</tr>
<tr>
<td>OXC/MHD&lt;sup&gt;d&lt;/sup&gt;</td>
<td>100%</td>
<td>40%</td>
<td>100% hepatic</td>
<td>5-11</td>
<td>Yes/No</td>
</tr>
<tr>
<td>VGB</td>
<td>50%</td>
<td>None</td>
<td>~70% renal</td>
<td>5-7</td>
<td>Yes</td>
</tr>
<tr>
<td>LCM</td>
<td>100%</td>
<td>&lt;15%</td>
<td>95% renal</td>
<td>13</td>
<td>No</td>
</tr>
<tr>
<td>RFN</td>
<td>85%</td>
<td>34%</td>
<td>85% renal</td>
<td>6-10</td>
<td>Yes</td>
</tr>
</tbody>
</table>

**Potential Advantages:**
- Improved water solubility...predictable bioavailability
- Negligible protein binding...no need to worry about hypoalbuminemia
- Less reliance on CYP metabolism...perhaps less variability over time
# AED Effects on Drug Metabolizing Isozymes

<table>
<thead>
<tr>
<th>Older</th>
<th>Newer</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Enzyme inducers (CYP1A2, 2C, 3A, UGTs)</td>
<td>• No effects on CYP:</td>
</tr>
<tr>
<td>– CBZ</td>
<td>– LEV</td>
</tr>
<tr>
<td>– PHT</td>
<td>– LTG</td>
</tr>
<tr>
<td>– PB/PRM</td>
<td>– ZNS</td>
</tr>
<tr>
<td>• Inhibitor</td>
<td>– TIA</td>
</tr>
<tr>
<td>– VPA (CYP2C19, UGT, EH)</td>
<td>– GBP</td>
</tr>
<tr>
<td></td>
<td>– PGB</td>
</tr>
<tr>
<td></td>
<td>– LCM</td>
</tr>
<tr>
<td></td>
<td>• Modest inducer</td>
</tr>
<tr>
<td></td>
<td>– OXC, TPM (CYP3A), VGB</td>
</tr>
<tr>
<td></td>
<td>• Inhibitors</td>
</tr>
<tr>
<td></td>
<td>– TPM, OXC (CYP2C19), VGB</td>
</tr>
</tbody>
</table>
## Drug-Specific Side Effects: Newer AEDs/Patient Education

<table>
<thead>
<tr>
<th>AED</th>
<th>Drug-specific AE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gabapentin</td>
<td>Myoclonus, pedal edema, weight gain</td>
</tr>
<tr>
<td>Pregabalin</td>
<td>Similar to gabapentin</td>
</tr>
<tr>
<td>Lamotrigine</td>
<td>Dose &amp; titration-dependent rash, visual distortion</td>
</tr>
<tr>
<td>Topirramate</td>
<td>Renal stones, word-finding difficulties, paresthesia, weight loss, glaucoma, metabolic acidosis</td>
</tr>
<tr>
<td>Zonisamide</td>
<td>Renal stones, paresthesia, weight loss, metabolic acidosis</td>
</tr>
</tbody>
</table>
## Drug-Specific Side Effects: Newer AEDs/Patient Education Cont’d

<table>
<thead>
<tr>
<th>AED</th>
<th>Drug-specific AE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tiagabine</td>
<td>Encephalopathy, knee-buckling</td>
</tr>
<tr>
<td>Levetiracetam</td>
<td>Sedation, behavioral changes</td>
</tr>
<tr>
<td>Oxcarbazepine</td>
<td>Hyponatremia</td>
</tr>
<tr>
<td>Vigabatrin</td>
<td>Irreversible visual field defects (25-33%), drowsiness, fatigue, hyperactivity</td>
</tr>
<tr>
<td></td>
<td>(children)</td>
</tr>
<tr>
<td>Lacosamide</td>
<td>Dizziness, HA, nausea, diplopia, PR-interval</td>
</tr>
<tr>
<td>increase (minimal)</td>
<td></td>
</tr>
<tr>
<td>Rufinamide</td>
<td>Shortened QT Interval, HA, somnolence</td>
</tr>
</tbody>
</table>
Non-pharmacological Therapies

• Ketogenic diet
• Vagal Nerve Stimulator (VNS)
• Surgery
What’s New

• Levetiracetam / myoclonic seizures in JME / IV can be used for myoclonic seizures associated with JME when oral is not feasible (adults 16 and above) / initial monotherapy indication in Europe in partial seizures / in the US adjunctive treatment of primary generalized tonic-clonic seizures

• Levetiracetam injection
• Bioavailability to oral the same
• Starting dose 500 mg IV BID
• Dilute in NS, LR, D5W in 100 ml
• Administer over 15 minutes
• No loading dose required
• Peak concentration in 15 minutes
• Compatible with Lorazepam, Diazepam, Valproate sodium
Advantages

Levetiracetam IV
- Can be used acutely
- May have synergy with benzodiazepines
- Easy to use
- Faster onset of action
- Prophylaxis in neurosurgery – SAH
- No interactions with chemotherapeutic agents, transplant drugs, or antiretroviral therapy
- Price generally between phenytoin and fosphenytoin
Levetiracetam (Keppra®) XR

- Effective starting dose 1000 mg/day (2 x 500 mg tablets)
- No titration required
- Can adjust daily dosage in increments of 1000 mg every 2 weeks to maximum 3000 mg/day
- Tablets should not be broken, chewed, crushed
- Dose missed
  - Do not double next dose
  - If only a few hours have passed, take missed dose
- IR and XR bioavailability similar
- IR Cmax = 1 hour and XR Cmax = 4 hours
Vigabatrin (Sabril®)

- MOA: GABA-transaminase inhibitor
- FDA Approved indications:
  - Adjunctive therapy for refractory complex partial seizures in adults
  - Infantile Spasm
- Dosage:
  - Seizure:
    - Adults: Starting dose 1gm/day; maintenance dose 2-4gm/day
    - Children: Starting dose 40mg/kg/day in two divided doses; maintenance dose is 80-100mg/kg/day
  - Infantile Spasm: 50-100mg/kg/day, divided twice daily
- Dosage Forms:
  - Powder: Sabril® [CAN]: 0.5 g [not available in the U.S.]
  - Tablet: Sabril® [CAN]: 500 mg [not available in the U.S.]
- Pharmacokinetics:
  - Absorption not affected by food
  - Renally eliminated (adjust dose for CrCl <60ml/min)
- Interactions: Inhibits carbamazepine (major intxn), induces phenytoin and fosphenytoin (moderate intxn)
Lacosamide (Vimpat®)

• **MOA:**
  – Selective enhancement of sodium channel slow inactivation
  – Binds to collapsin response mediator protein 2 (CRMP-2)

• **FDA Approved Indication:**
  – Adjunctive therapy in the treatment of partial-onset seizures in patient with epilepsy aged 17 years and older.
  – Controlled substance (schedule yet to be determined)

• **Dosage:**
  – Adjunct (partial seizure)
    • Oral: Initial dose: 50 mg ORALLY twice daily; increase weekly by 100 mg/day given in 2 divided doses up to 200 to 400 mg/day
    • IV: Initial dose: 50 mg IV twice daily; increase weekly by 100 mg/day given in 2 divided doses up to 200 to 400 mg/day; infuse over 30 to 60 minutes

• **Dosage Forms:**
  – Tablet: 50 mg (pink), 100 mg (dark yellow), 150 mg (salmon), 200 mg (blue) film-coated tablets
  – IV Solution: 200 mg/20 mL single-use vial for intravenous use

• **Pharmacokinetics:**
  – Not affected by food.
  – Renally eliminated; 300mg/day max for CrCl<30ml/min/mild-moderate liver disease
  – IV formulation: pH 3.5-5 (possible interface at y-site)
Rufinamide (Banzel®)

- **MOA**: Prolongation of the inactive state of sodium channels
- **FDA Approved Indications**: Adjunctive treatment of seizures associated with Lennox-Gastaut syndrome in children 4 years and older and adults
- **Dosage**:
  - **Children**: 10mg/kg/day, given in two divided doses; increase by 10mg/kg every other day to a target dose of 45mg/kg/day given in two equally divided doses
  - **Adults**: 400-800mg/day given in two equally divided doses; dose should be increased by 400-800mg every other day to a target dose of 3200mg/day in two equally divided doses
  - Should be taken with food
  - Dosage adjustment not necessary for CrCl <30ml/min
- **Dosage Forms**: Tablet 100mg, 200mg, 400mg
- **Pharmacokinetics**:
  - Food increases bioavailability
  - Protein bound: 27% (albumin)
  - Metabolized via enzymatic hydrolysis (not CYP 450 dependent)
  - Elimination is 85% renal
  - Plasma half-life is 6-10 hrs
Benefits of Generic Antiepileptic Drugs (AEDs)

- Decrease cost
  - Patient
  - Third party payor
- Increase availability
  - Multiple manufacturing sources
- Potential better adherence
The variability between generic A and generic B may be too much for some patients and lead to loss of seizure control or adverse events.
Current Treatment Options

Partial
- Simple
- Complex
- Secondarily generalized
  - Tonic-clonic
    - PHT, CBZ, PB, GBP, PGB, OXC, TGB, VGB

Generalized
- Tonic
- Myoclonic
- Atonic
- Infantile spasms
- Absence
  - ACTH, VGB
  - ESX

- LTG
- VPA
- TPM
- LEV
- ZNS (FBM)
- LCM
What’s on the Horizon

- Lamotrigine Extended-Release
- Brivaracetam
- Ganaxolone
- Rufinamide
- Retigabine
- Carisbamate
- Many many more!!!!
Summary

• Contrary to conventional wisdom, older AEDS are not completely effective in all patients

• Older AEDs may be associated with adverse effects that can impact overall effectiveness and quality of life

• Newer AEDs may offer improved effectiveness

• Recent FDA-approved AEDs and future AEDs may be more promising because they work differently versus conventional therapies

• Unrecognized drug interactions may be participating in increased drug expense, and possibly morbidity in patients with epilepsy.

• In other words, PK interactions may be making “cheap” AEDs a very expensive treatment in some patients.