EPILEPSY - GETTING SEIZURES UNDER CONTROL

ACTIVITY DESCRIPTION
In the past 10 years, many new anti-elliptical drugs have become available to treat seizures and more are in the pipeline. More than 2 million people suffer from epilepsy and almost half of them continue to struggle with uncontrolled seizures. Patients with epilepsy and their health care providers continually search for a treatment option that minimizes seizures, often switching or adding an anti-seizure medication. This program will focus on the currently available and emerging treatment options and in particular those add on medications to treat seizures associated with epilepsy.

TARGET AUDIENCE
The target audience for this activity is pharmacists and pharmacy technicians in hospital, community, and retail pharmacy settings.

LEARNING OBJECTIVES
After completing this activity, the pharmacist will be able to:

- Review the epidemiology, etiology, and pathophysiology of epilepsy.
- Describe current and emerging pharmacological approaches for the management of epilepsy to include adjunctive therapy for those patients where monotherapy does not control seizures.
- Outline the pharmacist’s role in counseling epilepsy patients and caregivers on the array of challenges to daily living, seizure control, range of available resources, and non pharmacological therapy available to improve quality of life.

After completing this activity, the pharmacy technicians will be able to:

- List the symptoms of epilepsy
- List medications used to control epilepsy

ACCREDITATION

PHARMACY
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ABOUT THE AUTHOR
Jacquelyn L. Bainbridge, BSPharm, PharmD., FCCP, received her doctorate of pharmacy from the University of Colorado where she subsequently completed a specialty residency in neurology. Dr. Bainbridge currently serves as a Professor at the University of Colorado Anschutz Medical Campus in the Skaggs School of Pharmacy and Pharmaceutical Sciences, Department of Clinical Pharmacy and Department of Neurology in the School of Medicine. Dr. Bainbridge is a member of numerous professional organizations, including the Epilepsy Foundation of Colorado, the American Academy of Neurology, the American Epilepsy Society, Epilepsy Foundation of America, American College of Clinical Pharmacy, American Association of Colleges of Pharmacy, Colorado Pharmacists Society, and American Society of Health-System Pharmacists. She is a frequent lecturer on topics of neurological and pharmacological interest in the areas of restless legs syndrome, multiple sclerosis, epilepsy, migraine, neuroprotection, chronic pain disorders and movement disorders.

Research. Dr. Bainbridge is actively involved in clinical research in many areas of neurology. Currently she is working on two National Institutes of Health (NIH) trial researching prospective drugs that may be neuroprotective in Parkinson’s disease (PD). One additional clinical trial that Dr. Bainbridge is studying is comparing a newer antiepileptic drug in an advanced aging population measuring the end dose, limiting side effects and efficacy. In the past Dr. Bainbridge has completed numerous clinical trials in epilepsy, multiple sclerosis (MS), and PD.

Scholarly activity and publications. Dr. Bainbridge has published several articles in professional journals, including Epilepsia, Pharmacotherapy, and the American Journal of Health-System Pharmacy. Dr. Bainbridge has reviewed and written several book chapters on multiple sclerosis, epilepsy, migraine, chronic pain, women’s issues, and the practice of pharmacy.

Jacquelyn Bainbridge, PharmD, FCCP
Professor, University of Colorado School of Pharmacy

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**Epilepsy – “Getting Seizures Under Control”**

**Learning Objectives**

- Review the epidemiology, etiology, and pathophysiology of epilepsy
- Describe current and emerging pharmacological approaches for the management of epilepsy to include adjunctive therapy for those patients where monotherapy does not control seizures
- Outline the pharmacist’s role in counseling epilepsy patients and caregivers on the array of challenges to daily living, seizure control, range of available resources, and non-pharmacological therapy available to improve quality of life

**Epideolgy**

- Third most common neurological disorder
- 10% of the population will experience a seizure
- 1/100 adults have a diagnosis of epilepsy
- ~2% of the population
  - 40 million worldwide
  - 3 million in the USA (new estimate, The Epilepsy Foundation of America)
- Estimated annual burden on society: $12.5 billion
Age-Related Incidence

International Seizure Classification

- Partial Seizures
  - Simple (SPS) – awareness, mentation not impaired
  - Complex (CPS) – awareness, mentation impaired
  - Secondary Generalization

- Generalized Seizures

- Epilepsy Syndromes
  - Juvenile Myoclonic Epilepsy (JME)
  - Lennox-Gastaut Syndrome (LGS)

Common AEDs: Traditional

- Phenobarbital (Luminal) (PB) - 1912
- Primidone (Mysoline) (PRM) – 1938
- Phenytoin (Dilantin) (PHT) – 1938
- Ethosuximide (Zarontin) (ESX) - 1960
- Carbamazepine (Tegretol, Carbatrol) (CBZ) – 1974
- Valproate (Depakote, Depakene) (VPA) – 1978
Common AEDs: New

- Felbamate (Felbatol) (FBM) 1993
- Lamotrigine (Lamictal) (LTG) 1993
- Gabapentin (Neurontin) (GBP) 1994
- Topiramate (Topamax) (TPM) 1996
- Tegretol (Gabitril) (TGB) 1997
- Oxcarbazepine (Trileptal) (OXC) 1999
- Levetiracetam (Keppra) (LEV) 1999
- Zonisamide (Zonegran) (ZNS) 2000
- Pregabalin (Lyrica) (PGB) 2006
- Vigabatrin (Sabril) (VGB) 2009
- Lacosamide (Vimpat) (LCM) 2009
- Rufinamide (Banzel) (RFN) 2009
- Ezogabine (Potiga) (EZG) 2011
- Clobazam (Onfi) (CLB) 2011
- Perampanel (Pycompo) 2011
- Elicarbazeptine (Apitram) 2013

Despite Treatment, Many Patients Have Not Achieved Seizure Control

- Despite initial therapy, > 1 million patients with epilepsy in the US continue to have seizures
- > 900,000 patients on ≥ 2 agents continue to experience seizures
- Quality of Life data indicates that the most important outcome that patients want in terms of their epilepsy is seizure freedom

Success in AED Regimens

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

What is the Reality?

- First AED monotherapy fails in ~50% of patients with epilepsy
- Chance of seizure freedom with substitution monotherapy after failure of initial AED is low (~13%)
  - Many patients with epilepsy will require adjunctive therapy
  - The rate of seizure freedom is ~26% with adjunctive therapy
- Adjunctive AED therapy may be more effective when initiated immediately after failure of first AED
- Better efficacy and safety profiles of newer AEDs may translate into combination therapy that improves seizure control without increased toxicity
Pharmacokinetics of Traditional AEDs

<table>
<thead>
<tr>
<th>Drug</th>
<th>F %</th>
<th>Binding %</th>
<th>CI</th>
<th>t 1/2 (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>6-13</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>

Problems: Poor water solubility, Extensive protein binding, Extensive oxidative metabolism, Multiple drug-drug interactions

CBZ: carbamazepine, PB: phenobarbital, PHT: phenytoin, VPA: valproate

Pharmacokinetics of Newer AEDs

<table>
<thead>
<tr>
<th>Drug</th>
<th>Absorption</th>
<th>Binding</th>
<th>Elimination*</th>
<th>t 1/2 (hrs)</th>
<th>Interactions</th>
</tr>
</thead>
<tbody>
<tr>
<td>CBZ</td>
<td>40%</td>
<td>50%</td>
<td>100% renal</td>
<td>5-9</td>
<td>No</td>
</tr>
<tr>
<td>PB</td>
<td>90%</td>
<td>0%</td>
<td>95% renal</td>
<td>6</td>
<td>No</td>
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<tr>
<td>LGT</td>
<td>100%</td>
<td>55%</td>
<td>100% hepatic</td>
<td>18-30</td>
<td>No</td>
</tr>
<tr>
<td>LEV</td>
<td>&lt;10%</td>
<td>&lt;10%</td>
<td>68% renal</td>
<td>4.8</td>
<td>No</td>
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<tr>
<td>TGB</td>
<td>&lt;10%</td>
<td>&lt;10%</td>
<td>100% hepatic</td>
<td>5-13</td>
<td>No</td>
</tr>
<tr>
<td>TPM</td>
<td>&gt;90%</td>
<td>&gt;10%</td>
<td>50-70% renal</td>
<td>18-30</td>
<td>Yes/No</td>
</tr>
<tr>
<td>ZNS</td>
<td>80-100%</td>
<td>50-70%</td>
<td>50-70% hepatic</td>
<td>50-60</td>
<td>No</td>
</tr>
<tr>
<td>CBZ/P/MPD</td>
<td>100%</td>
<td>40%</td>
<td>100% hepatic</td>
<td>5-11</td>
<td>No</td>
</tr>
<tr>
<td>VGB</td>
<td>50%</td>
<td>None</td>
<td>5%-20% renal</td>
<td>5-7</td>
<td>Yes</td>
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<tr>
<td>LCM</td>
<td>100%</td>
<td>&gt;15%</td>
<td>95% renal</td>
<td>13</td>
<td>No</td>
</tr>
<tr>
<td>RFN</td>
<td>80%</td>
<td>34%</td>
<td>85% renal</td>
<td>6-10</td>
<td>Yes</td>
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<tr>
<td>EZG</td>
<td>80%</td>
<td>80%</td>
<td>85% renal</td>
<td>7-11</td>
<td>No</td>
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<tr>
<td>CLB</td>
<td>87%</td>
<td>80-90%</td>
<td>82% renal</td>
<td>28-42</td>
<td>Yes</td>
</tr>
<tr>
<td>FMP</td>
<td>&lt;10%</td>
<td>95-98%</td>
<td>12% renal</td>
<td>105</td>
<td>No</td>
</tr>
<tr>
<td>ESL</td>
<td>&gt;90%</td>
<td>&gt;40%</td>
<td>90% renal</td>
<td>13-20</td>
<td>Yes</td>
</tr>
</tbody>
</table>

AED: Effects on Drug Metabolism

Older Agents
- Potent Enzyme Inducers (CYP1A2, 2C, 3A4, UGTs)
  - CBZ
  - PHT
  - PB/PRM
- Potent Enzyme Inhibitor
  - VPA (CYP2C19, UGT, EH)
- Potent P-gp Inducers
  - CBZ
  - PHT

Newer Agents
- No effects on CYP:
  - LEV
  - LGT
  - MBT
  - ZNS
  - GBB
  - Oxidation
  - VGB
  - TPM
  - Active
  - RUF

Problems: Poor water solubility, Extensive protein binding, Extensive oxidative metabolism, Multiple drug-drug interactions

Issues with enzyme-inducing AEDs

- Drug-drug interactions
  - Antidepressants & antipsychotics
  - Immunosuppressive therapy
  - Antiretroviral therapy
  - Chemotherapeutic agents
- Reproductive hormones, sexual function, OC in women
- Sexual function & fertility in men
- Bone health
- Vascular risk

*Summary: Adapted from "Fellows"
AEDs: Pharmacodynamic Interactions

- Lacosamide (Vimpat)/ Na+ blockers
  - Concomitant sodium channel blockers: increase risk of neurotoxicity (dizziness, drowsiness, diplopia)
  - Reducing dose of concomitant sodium channel blockers may reduce CNS-related side effects
- Topiramate (Topamax)/ Valproic acid (Depakene)
  - Increase risk of valproic acid-induced encephalopathy
- Potential anticonvulsant synergism
  - Valproic acid (Depakene) / Lamotrigine (Lamictal)
  - Topiramate (Topamax) / Lamotrigine (Lamictal)

Lacosamide (Vimpat®)

- MOA: Sodium channel blockade (slow and selective)
- Indication: Adjunct, substitution monotherapy or monotherapy for partial-onset seizures in patients with epilepsy in patients ≥ 17 years old
- Pharmacokinetics:
  - Not affected by food
  - Renally eliminated; 300mg/day max for CrCl<30ml/min and mild-moderate liver disease
  - IV formulation: pH 3.5-5 (possible interface at y-site)

Dosage forms:
- Tablet: 50, 100, 150, and 200mg
- Solution: 10mg/ml
- IV solution: 200mg/20ml single-use vial
- Oral: 50mg twice daily, increase weekly by 100mg/day in two divided doses up to 200 to 400mg/day
- Oral monotherapy: 100 mg twice daily, increase weekly by 100 mg/day in two divided doses up to 300 to 400 mg/day
- Oral substitution monotherapy: after 3 days of adjunctive therapy withdrawal previous antiepileptic drug
- IV: Same as oral, infuse over 30 to 60 minutes
- Loading dose: IV or Oral: 200 mg followed by 100 mg in 12 hours then continue twice daily - medical supervision (9/1/2014)
- Controlled substance: Schedule V
- Side effects/counseling points: Headache, nausea, diplopia, PR interval increase [minimal]

Rufinamide (Banzel®)

- MOA: Prolongation of the inactive state of sodium channels
- Indications: Adjunct treatment of seizures associated with LGS in adults and children ≥4 years old
- Pharmacokinetics:
  - Food increases bioavailability
  - Protein bound: 34%
  - Metabolized via enzymatic hydrolysis (not CYP450 dependent)
  - Elimination is 85% renal
  - Plasma half-life is 6-10 hours
Rufinamide (Banzel®)

- Dosage forms: 100, 200, and 400mg tablets
- Dosage:
  - Children: 10mg/kg/day 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 in two equally divided doses. Increase by 400-800mg every other day to a target dose of 3200mg/day in two equally divided doses
  - Should be taken with food
  - Dose adjustment not necessary for CrCl < 30ml/min
- Side effects/ counseling points:
  - Shortened QT interval, headache, somnolence

Ezogabine (Potiga®)

- MOA: Activates voltage-gated potassium channels
- Indication: Adjunct therapy for partial-onset seizures in adults (≥18 years) who have responded inadequately to several alternative treatments and benefits outweigh the risk of retinal abnormalities and potential decline in visual acuity
- Pharmacokinetics:
  - Not affected by food
  - Renally eliminated; 600mg/day max for CrCl < 50ml/min
  - Moderate liver disease (Child-Pugh 7-9) max 750mg/day
  - Severe liver disease (Child-Pugh >9) max 600mg/day

Ezogabine (Potiga®)

- Dosage forms: 50, 200, 300, and 400mg tablet
- Dosage: 100mg TID, increase by max of 150mg/day every week until at maintenance dose of 200-400 TID
- Side effects/ counseling points:
  - Somnolence, dizziness, confusion
  - Rare: Urinary retention, prolonged QT interval
- Black box warning:
  - Retinal abnormalities
  - Retinal pigment dystrophies
  - Baseline and every 6 month eye exam

Clobazam (Onfi®)

- MOA: a 1,5-benzodiazepine, Enhances GABA via enhanced Cl⁻ conductance through GABA-A receptors
- Indication: Adjunct therapy LGS in age ≥ 2 years
- Pharmacokinetics:
  - Food does not affect absorption
  - Highly protein bound (80-90%)
  - Substrate of 2C19, oxidative metabolism and sequential glucuronidation, inducer 3A4, inhibitor 2D6
  - 82% eliminated by kidney, and 11% by feces
  - Active metabolite: N-desmethylclobazam (norclobazam)
  - T1/2: clobazam: 36 to 42 hours, N-desmethyliclobazam: 71 to 82 hours
**Clobazam (Onfi®)**

- Dosage form: 5, 10, 20mg tablet, 2.5 mg/ml oral suspension
- Dosage:
  - <30kg: 2.5 twice daily, increase to 5mg twice daily in one week, then 10mg twice daily at week two
  - >30kg: 5mg twice daily, increase to 10mg twice daily in one week, then 20mg twice daily at week two
- Dose Adjustments:
  - Hepatic impairment (Child-Pugh 5 to 9), Geriatric, CYP2C19 poor metabolizers: initial 5 mg once daily, titrated no faster than every 7 days to 10 to 20 mg/day in 2 divided doses; max dose of 20 to 40 mg per day on day 21
  - Concomitant use with CYP2C19 inhibitors; may require clobazam dose reduction
- Side effects/counseling points: Somnolence (perhaps less than other benzos), fever, drooling, lethargy, constipation

**Perampanel (Fycompa®)**

- MOA: Non-competitive antagonist of AMPA on postsynaptic neurons
- Indication: Adjunct therapy for PS w/o w/ secondary generalized seizures
- Pharmacokinetics:
  - Effects of food: unchanged AUC; decreased Cmax 28 to 40%; delayed Tmax 2 to 3 hours
  - Liver metabolism: extensive CYP3A4/5
  - Excretion: Fecal 48%, Renal 22%
  - T1/2: 105 hours hepatic impairment 305 hours (mild); 295 hours (moderate impairment)
  - Mild liver disease: 2 mg once daily at bedtime, may increase dose by 2 mg/day every 2 weeks to a max of 6 mg/day
  - Moderate liver disease: 2 mg once at bedtime, may increase dose by 2 mg/day every 2 weeks to a max of 4 mg/day; severe impairment, use not recommended
  - Renal: mild/ moderate impairment no dosage adjustment just monitor, severe impairment use not recommended

**Eslicarbazepine Acetate (Aptiom®)**

- MOA: Unknown, but thought to involve sodium channel blockade
- Indication: Adjunct treatment of partial-onset seizures
- Pharmacokinetics:
  - Prodrug metabolized to eslicarbazepine
  - Not affected by food
  - Metabolized liver 91% via hydrolytic 1′ pass metabolism, intestinal wall
  - Eslicarbazepine (major) active, (R)-carbazepine and oxcarbazepine (minor) active
  - Moderate inhibitor of CYP2C19, inducer of CYP3A4
  - Renal elimination > 90% as eslicarbazepine and glucuronide metabolites
  - t1/2: 13-20 hours
Eslicarbazepine (Aptiom®)

- Dosage forms: 200, 400, 600, 800mg tablets
- Dosage:
  - 400mg QD, increase to 800mg after one week. Max dose of 1200mg
  - Moderate to severe renal impairment: 200mg QD. Increase to 400mg after two weeks. Max dose of 600mg.
  - Hepatic impairment: mild to moderate no change, severe not recommended
  - Not recommended with oxcarbazepine (Trileptal)
  - Eslicarbazepine is inducible
- Side effects/counseling points:
  - Dizziness, somnolence, N/V, headache, diplopia, fatigue, vertigo, ataxia, blurred vision, tremor
  - Suicidal behavior/ideation, dermatologic reactions (SJIS)

Carbamazepine, Oxcarbazepine, Eslicarbazepine

![Chemical structures of carbamazepine, oxcarbazepine, and eslicarbazepine acetate.]

Comorbidity in Epilepsy

- People with epilepsy are overall 11.1 times more likely to die prematurely than unaffected persons. 5.5 times more likely to die from non-vehicle accidents, and 3.7 times more likely to die from suicide. Among persons with epilepsy who die from an external cause, three-quarters of the cases involve a psychiatric diagnosis
  - Heart disease
  - Hypertension
  - Stroke
  - Diabetes mellitus
  - Asthma
  - Attention Deficit Hyperactivity Disorder (18.4%)
  - Anxiety
  - Depression
  - Cognitive impairment
  - Migraine
  - Unemployed

Treatment Options for Epilepsy

- Pharmacologic
- Non-pharmacologic
  - Surgical intervention
  - Vagus nerve stimulation (VNS)
  - Ketogenic diet
  - Responsive neurostimulator system (NEUROPACE)

How do you choose therapy?
Pharmacists Role in Counseling

- Educate the patient on generic substitution and potential risk of increased adverse effects or loss of seizure control
- Write important information down for the patient or caregiver
- Encourage the patient or caregiver to report a change in seizure pattern or new side effect
- For females of childbearing potential it is essential to discuss a pregnancy plan or contraception use
- Discuss the importance of adherence

Useful Resources

- Epilepsy
  - Epilepsy.com
  - AESNET.org
  - EpilepsyFoundation.org

Summary

- Epilepsy is common and treatable
- Treatment is with AEDs and other non-pharmacological modalities
- When monotherapy fails immediate adjunctive therapy should be attempted
- Patients and caregivers should be counseled on all treatment options
- Pharmacists play an important role in AED selection and treatment counseling