Newer Antiepileptic Drugs

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Learning objectives

- Pharmacists
  - To review pharmacology and pharmacokinetics of antiepileptic drugs (AEDs) and to detect possible adverse reactions at early stage.
  - To review pharmacology and pharmacokinetics of newer AEDs and to explain the differences and similarities of newer AEDs.
  - To select appropriate AED for patients with epilepsy and to monitor adequate labs for patient safety.

- Pharmacy technicians
  - To review pharmacology and pharmacokinetics of antiepileptic drugs (AEDs).
  - To update drug information on the newer AEDs.
  - To identify major adverse reactions from AEDs for patient safety.

Epilepsy - definition

- Seizure
  - Clinical manifestation of abnormal and excessive activity of cortical neurons

- Epilepsy
  - Brain disorder characterized
    - By an enduring predisposition to generate epileptic seizures and...
    - By the neurobiologic, cognitive, psychological, and social consequences of the condition.
  - Definition requires occurrence of at least one epileptic seizure.


Epilepsy - epidemiology

- Approximately 3 million Americans (3% of population) and 50 million people worldwide suffer from epilepsy
- Epilepsy affects more than 1.1 million women of childbearing age in the United States
- Crude prevalence on the Navajo reservation: 13.5 per 1,000
- Epilepsy prevalence in the U.S.: 5-10 per 1,000


Epilepsy - classification

- International League Against Epilepsy (ILAE) classification

Classification of antiepileptic drugs (AEDs)

- Drug class: channel or receptor functions
  - Na channel blockers
  - Ca channel blockers
  - GABA enhancers
  - K channel agonists
  - AMPA receptor antagonists
  - NMDA receptor antagonists
  - Carbonic anhydrase inhibitors
  - Combinations
  - Others/Mode unknown
  - Older agents vs. newer agents
  - Enzyme-inducing AEDs vs. nonenzyme-inducing AEDs
Pharmacology of AEDs

- MOA of AEDs

Antiepileptic drugs

Generic (abbreviation)/brand name

Older agents (Before 1993)
- Phenobarbital (PB)
- Phenytoin (PHT)/Dilantin
- Primidone (PRM)/Mysoline
- Ethosuximide (ETX)/Zarontin
- Carbamazepine (CBZ)/Tegretol, Carbatrol
- Valproic acid and derivative (VPA)/Depakene, Depakote

- Felbamate (FBM)/Felbatol (1993)
- Gabapentin (GBP)/Neurontin (1993)
- Topiramate (TPM)/Topamax (1997)
- Lamotrigine (LTG)/Lamictal (1999)
- Levetiracetam (LEV)/Keppra (1999)
- Oxcarbazepine (OXC)/Trileptal (2000)
- Zonisamide (ZNS)/Zonegran (2000)
- Pregabalin (PGB)/Lyrica (2004)

Very new
- Tiagabine (TGB)/Gabitril (2005)
- Lacosamide (LAC)/Vimpat (2008)
- Rufinamide (RUF)/Banzel (2008)
- Vigabatrin (VGT)/Sabril (2009)
- Clobazam (CLB)/Onfi (2011)
- Ezogabine (EZG)/Potiga (2011)
- Perampanel (PRP)/Fycompa (2012)
- Eslicarbazepine (ECBZ)/Aptiom (2013)
- Brivaracetam (BRV)/Brivact (2016)

Relatively new and different formulation
- Oxtellar XR (oxcarbazepine extended release) (2012)
- Trokendi XR (topiramate) (2013)
- Qudexy XR (topiramate) (2014)
Antiepileptic drugs
New therapies pipeline

- Benzodiazepines for prolonged seizures
  - Diazepam, Intranasal (2015) - Orphan drug designation
  - Midazolam, oromucosal solution
  - Midazolam, intranasal spray

http://dij.sagepub.com/content/early/2014/12/23/2168479014537260.full.pdf

Question 1
Benzodiazepine

- AB is a 14-year-old female who suffers from generalized tonic clonic seizures. At her last visit, her neurologist prescribed clonazepam, and since then, her seizures have been well controlled. Her mother said that add-on clonazepam significantly decreased seizure frequency. However, AB complains about severe daytime sleepiness.

- AEDs
  - Levetiracetam 1,000 mg po twice daily (50 mg/kg/day)
  - Clonazepam 0.5 mg po three times daily

VOTE
A. MOA-related adverse reaction
B. Non-MOA-related adverse reaction/unclear

Question 1
Benzodiazepine - CNS depression

- MOA of benzodiazepine
  - Enhances GABA receptor activity

- CNS depression
  - Drowsiness (up to 50% among adult seizure patients)
  - Drug-drug interactions
  - Other AEDs may enhance CNS depression
  - Routine checkup for excess sedation, respiratory depression, and mental condition (e.g., suicidality) in addition to laboratory tests (CBC, chemistry, LFTs)

Clobazam (CLB)/Onfi

- Drug class: benzodiazepine
- MOA: enhance GABA function
- Indications
  - Lennox-Gastaut syndrome (adjunctive)
  - For adults/children
- Formulation
  - Tablet (10 and 20 mg), suspension (2.5 mg/mL)
- Maintenance dose (adult)
  - 10-20 mg twice daily

http://online.lexi.com/lco/action/doc/retrieve/docid/patch_f/6631
http://online.lexi.com/lco/action/doc/retrieve/docid/patch_f/6642#f_adverse-reactions

Clobazam (CLB)/Onfi

- Tips: metabolism
  - Metabolized by CYP2C19 (major), 2B6 (minor), CYP3A4 (minor)
  - For poor metabolizer of CYP2C19, use the lowest recommended dose, slower titration
  - Off-label use: catamenial epilepsy
  - 20-30 mg daily for 10 days during the perimenstrual period

http://online.lexi.com/lco/action/doc/retrieve/docid/patch_f/6631
Which of the following antiepileptic drugs cause vision-related adverse reactions?

I. Ezogabine - retinal abnormalities
II. Oxcarbazepine - diplopia, blurred vision
III. Phenytoin - Nystagmus, impaired color perception
IV. Vigabatrin - Visual field loss

a. I only
b. II only
c. II and III
d. All of the above

Ezogabine (EZG)/Potiga

- Drug class: potassium channel opener
- MOA
  - Binds the KCNQ (Kv7.2-7.5) voltage-gated potassium channels, enhance GABA function
- Indications
  - Partial-onset seizures (adjunct)
  - For adults only
- Formulation
  - Tablet (10, 200, 300, and 400 mg)
  - Maintenance dose (adult) 200-400 mg three times daily

Question 3

Topiramate

MJ is a 12-year-old Hispanic male (height 150 cm; weight 37.5 kg) who has generalized intractable epilepsy of undetermined etiology. He was diagnosed with epilepsy at the age of 10. He has been taking topiramate 100 mg by mouth every morning and 200 mg every evening. His parents complain of his loss of memory and bad performance at school (average grade: B). Before MJ had seizures, his performance at school was great, and he received As.
Question 3

**Topiramate - cognitive impairment**

- MOA of topiramate
  - Blocks Na channels
  - Enhances GABA(A) activity
  - Antagonizes AMPA/kainate glutamate receptors
  - Antagonizes NMDA receptors
  - Inhibits carbonic anhydrase
- Cognitive impairment
  - Risk factors: rapid dose titration, high dose, polytherapy
  - Results from previous studies: decreased frontal lobe-associated neuropsychological functions
  - Verbal fluency and working memory


Question 4

**Oxcarbazepine**

- AS is a 54-year-old Asian female who was diagnosed with complex partial seizures at the age of 17. She moved to the United States about a year ago. She had been treated with valproic acid. However, her neurologist in the United States decided to switch her AED to oxcarbazepine, because her liver function tests were higher than normal. After three months of treatment with oxcarbazepine 900 mg by mouth twice daily, her sodium level dropped to 127 mEq/L.

**Perampanel (PRP)/Fycompa**

- Drug class: AMPA glutamate receptor antagonist
- MOA
  - Binds to alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) glutamate receptor on postsynaptic neurons
  - Glutamate: Neuro excitatory neurotransmitter
- Indications
  - Partial-onset seizures (adjunct) and primary generalized tonic-clonic seizures (adjunct)
  - For adults and children
  - Children ≥12 years and adolescents only

Perampanel (PRP)/Fycompa

- Formulation
  - Tablet (2, 4, 6, 8, 10, and 12 mg)
- Maintenance dose (adult)
  - 8-12 mg once daily at bedtime

Tips: psychiatric adverse reactions
- Controlled substances: C-III
  - Neuropsychiatric disorders: U.S. boxed warning
  - e.g., aggression, anger, homicidal ideation and threat, hostility, and irritability
  - May occur around 6 weeks after initiation
  - Regardless of history of psychiatric diseases
- Monitor behavior and mood change
Question 4

**Oxcarbazepine - hyponatremia**
- MOA of oxcarbazepine
  - Blocks Na channels and Ca channels
  - Enhances antidiuretic hormone (ADH) effect
    - ADH = arginine vasopression (AVP)
- Hyponatremia
  - Antidiuretic effect of oxcarbazepine
    - May enhance responsiveness to circulating AVP
    - May alter the sensitivity to AVP on the renal collecting tubules
  - Risk factors: female gender, concomitant use of diuretics, high dose, age (elderly)
  - Frequency: oxcarbazepine > carbamazepine

**Eslicarbazepine (ECBZ)/Aptiom**
- Drug class: miscellaneous
- MOA
  - Detailed mechanism is unknown
  - May bind to the sodium channel
- Indications
  - Partial-onset seizures (monotherapy/adjunct)
  - For adults only
- Formulation
  - Tablet (200, 400, 600, and 800 mg)
  - Maintenance dose (adult)
    - 800-1,600 mg once daily

**Eslicarbazepine (ECBZ)/Aptiom**
- Tips: adverse reactions and metabolism
  - **Adverse reactions**
    - Hyponatremia (serum sodium <125 mEq/L: 1% to 2%)
    - Carbamazepine: unknown
    - Frequency: oxcarbazepine > carbamazepine
  - **Metabolism**
    - Substrate of UGT2B4; CYP2C19 inhibitor (moderate), CYP3A4 inducer (moderate)

**Eslicarbazepine (ECBZ)/Aptiom**
- Metabolism
  - Substrate of UGT2B4, CYP2C19 inhibitor (moderate), CYP3A4 inducer (moderate)
- Drug interactions
  - Risk X
    - Antivirals (e.g., asunaprevir, elbasvir, grazoprevir, simeprevir, antiretroviral combination products, etc.)
  - Biological (~nib)
    - Oxcarbazepine
    - etc.
  - Risk D
    - CYP3A4 substrates (e.g., contraceptives, clarithromycin, etc.)
    - CYP2C19 substrate (e.g., clopidogrel, etc.) – decreased serum concentration of the substrates

Question 5

**Levetiracetam**
- DP is an 8-year-old male (weight: 25 kg) with juvenile myoclonic epilepsy. He was treated with 500 mg of levetiracetam by mouth twice daily. Although his seizures were well controlled, he demonstrated raging aggression. His parents reported that DP was violent to his classmates yesterday and hurt his best friend. Thus, DP was referred to a school administrator. The parents never saw DP's aggressive behavior before he started levetiracetam.

VOTE

A. MOA-related adverse reaction
B. Non-MOA-related adverse reaction/unclear
**Question 5**

**Levetiracetam - psychiatric ADRs**

- **MOA of levetiracetam**
  - Binds to synaptic vesicle glycoprotein 2A (SV2A) in the brain, which regulates neurotransmitter release
  - Inhibits voltage-dependent N-type calcium channels
  - Increases GABA-ergic inhibitory transmission

- **Psychiatric ADRs**
  - **Mechanisms unclear**
  - Symptoms: aggressive behaviors, agitation, anxiety, irritability, etc.
  - **Frequency of psychiatric ADRs: 30%**


**Question 6**

**Lamotrigine**

- **KJ is a 24-year-old Asian female diagnosed about three months ago with complex partial epilepsy. Her epileptologist decided to prescribe lamotrigine. Although KJ followed a lamotrigine titration schedule with a small dosage (initial dose: 25 mg by mouth once daily; increased by 25 mg/week, target dose: 150 mg by mouth twice daily), she experienced a rash that required a visit to the emergency room three weeks after the initiation.**

**VOTE**

A. MOA-related adverse reaction
B. Non-MOA-related adverse reaction/unclear

**Aromatic AEDs**

- Lamotrigine
- Phenytoin
- Phenobarbital
- Carbamazepine
- Oxcarbazepine


**Question 6**

**Lamotrigine - Rash**

- **MOA of lamotrigine**
  - Blocks Na channels

- **Rash**
  - **Mechanisms unclear**
  - Drug-induced autoimmunity?
  - Death of lymphocytes?
  - **Frequency:** 5% - 10%
  - **Risk factors:** rapid titration, female gender, children, history of rash with other AEDs (cross-reactivity: aromatic AEDs - carbamazepine, oxcarbazepine, phenobarbital, phenytoin), co-administration of valproic acid

Brivaracetam (BRV)/Briviact

- Drug class: miscellaneous
- MOA:
  - Binds to the synaptic vesicle protein 2A (SV2A)
- Indications:
  - Partial-onset seizures (adjunct)
- Formulation:
  - Tablet (10, 25, 50, 75, and 100 mg)
  - Solution (10 mg/mL, 300 mL)
- Maintenance dose (adult)
  - 50-100 mg twice daily

Tips: titration schedule
- Initiation:
  - Relatively short titration period
  - 25-50 mg po twice daily
- Discontinuation:
  - Gradual titration
  - Reduce the dose by 50 mg/day on a weekly basis
(Canadian label)

Benzodiazepines for a prolonged seizure
- MOA of benzodiazepines:
  - Binds to GABA receptor and reduces excessive excitation in the brain
- Administration routes:
  - Oral, intravenous, intramuscular, rectal, intranasal, buccal

FDA-approved medications among benzodiazepines
<table>
<thead>
<tr>
<th>Benzodiazepine</th>
<th>FDA approved for status epilepticus</th>
<th>FDA approved for treatment of seizures</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clonazepam</td>
<td>No - off-label use</td>
<td>Yes</td>
</tr>
<tr>
<td>Diazepam</td>
<td>Yes (rectal gel)</td>
<td>Yes</td>
</tr>
<tr>
<td>Lorazepam</td>
<td>Yes; parenteral only</td>
<td>No - off-label use (complex partial seizures)</td>
</tr>
<tr>
<td>Midazolam</td>
<td>No - off-label use</td>
<td>No - only for sedation</td>
</tr>
</tbody>
</table>

Midazolam – IV vs. IN
- Veldhorst-Janssen et al. (2011)
Midazolam

- IN administration - dosing
  - 0.2-0.3 mg/kg
- Adverse reactions
  - Irritation
  - May use preservative-free solution

IN midazolam

- Clinical study
  - Primary outcome: comparisons between diazepam (rectal) and midazolam (intranasal) in efficacy, safety, and preference
- Study population
  - Adults (N = 21) - patients with epilepsy
    - Male: 13 (61.9%)
- Dose
  - Diazepam (DZP): 10 mg
  - Midazolam (MDZ): 2.5 mg

IN midazolam (cont.)

- Results
  - Success rate
    - DZP 89% vs. MDZ 82% (NS)
  - Time to stop seizures: NS
  - ADRs
    - No severe ADRs were observed
    - More CNS ADRs in DZP group; more local irritation in MDZ group
  - Preference (easy to use)
    - MDZ > DZP (p<0.001)

Epilepsy across the Lifespan ECHO

Join us to learn epilepsy!

- When?
  - Tuesdays from noon to 1:30 p.m.
- Who can join us?
  - Any healthcare providers, educators, school nurses
- What to learn?
  - Epilepsy (disease states, pharmacology, patient education, etc.) through mini lecture (20-30 minutes)
  - Present a case!
  - 20-minute case discussion (1-2 cases per session)
- Benefits
  - FREE participation, FREE CE (offers 1.5 ACPE accredited contact hours for pharmacists)!

For more information, visit http://echo.unm.edu/nm-teleecho-clinics/child-youth-epilepsy-teleecho-clinic/