Epilepsy Updates
Newer Antiepileptic Drugs and Rescue Aid

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Leaning 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 United States: 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 agonist
  - AMPA receptor antagonist
  - NMDA receptor antagonist
  - Carbonic anhydrase inhibitor
  - Combinations
  - Others/MOA 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 (prior to 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)
- Topiramat (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)
- Estilcarbazepine (ECBZ)/Aptiom (2013)
- Brivaracetam (BRV)/Briviact (2016)

Relatively new and different formulation
- Oxtellar XR (oxcarbazepine extended release) (2012)
- Trokendi XR (topiramate) (2013)
- Qudexy XR (topiramate) (2014)

Antiepileptic drugs

Generic (abbreviation)/brand name

Modified
- Brivaracetam

New
- Perampanel
- Eslicarbazepine
- Brivaracetam
- Tiagabine
- Lacosamide
- Rufinamide
- Vigabatrin
- Clobazam
- Ezogabine
- Perampanel
- Estilcarbazepine
- Brivaracetam
Antiepileptic drugs
New therapies pipeline
- Benzodiazepines for prolonged seizures
  - Common benzodiazepine formulation
    - Diazepam, rectal
  - New formulation
    - Diazepam, Intranasal (2015) - Orphan drug designation
    - Midazolam, oromucosal solution (European countries)
    - Midazolam, intranasal spray

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

Epilepsy Updates
Newer Antiepileptic Drugs

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

Clobazam (CLB)/Onfi
- Drug class: benzodiazepine
- MOA: enhance GABA function
  - Upregulation of GABA transporters 1 and 3
  - Less sedative

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

http://www.chemspider.com/Chemical-Structure.2687.html
http://www.chemspider.com/Chemical-Structure.3821.html?rid=308b8d19-5cb9-4b3b-a4f2-41c945d2529d

Benzodiazepine - CNS depression
- MOA of benzodiazepine
  - Enhances GABA_A 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

- 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

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
- Effect of cannabis on clobazam
  - Cannabis inhibits the metabolism of clobazam
  - Higher serum concentration of clobazam and its metabolites

Question 2

Ophthalmologic adverse reactions
- 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, enhances 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

Tips: dose adjustment and adverse reactions
- Dosing
  - Renal impairment
  - Hepatic impairment
- Adverse reactions
  - Dermatologic effects: Skin discoloration
  - Ocular complications
    - [U.S. boxed warning]: Retinal abnormalities
Ezogabine (EZG)/Potiga
► Adverse reactions
  ▶ Skin discoloration

Question 3
Control substance in antiepileptic drugs
► Which of the following antiepileptic drugs is (are) a controlled substance, schedule 3(III) drug(s)?
  I. Ezogabine
  II. Clobazam
  III. Perampanel
  IV. Pregabalin
  a. I only
  b. II only
  c. II and III
  d. All of the above

Question 3
Control substance among antiepileptic drugs
► Which of the following antiepileptic drugs is (are) a controlled substance, schedule 3(III) drug(s)?
  I. Ezogabine (C-V)
  II. Clobazam (C-IV)
  III. Perampanel (C-III)
  IV. Pregabalin (C-V)
  a. I only
  b. II only
  c. III only
  d. II and III
  e. All of the above

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 threats, hostility, and irritability
    ▶ May occur around 6 weeks after initiation
    ▶ Regardless of history of psychiatric diseases
  ▶ Monitor behavior and mood change

Control substance in antiepileptic drugs
► Which of the following antiepileptic drugs is (are) a controlled substance, schedule 3(III) drug(s)?
  I. Ezogabine
  II. Clobazam
  III. Perampanel
  IV. Pregabalin
  a. I only
  b. II only
  c. II and III
  d. All of the above
Hyponatremia

Which of the following AEDs cause hyponatremia most frequently?

a. Carbamazepine
b. Oxcarbazepine
c. Eslicarbazepine

Tips: adverse reactions and metabolism

Adverse reactions
- Hyponatremia (serum sodium <125 mEq/L; 1% to 2%)
- Oxcarbazepine: 9.2% (Ortenzi A et al.)
- Carbamazepine: unknown
- Frequency: oxcarbazepine > carbamazepine

Metabolism
- Substrate of UGT2B4, CYP2C19 inhibitor (moderate), CYP3A4 inducer (moderate)
- Drug interactions
  - Risk X
    - Antivirals (e.g., asunaprevir, elbasvir, grazoprevir, simeprevir, antihepaciviral combination products, etc.)
  - Biological (-mib)
  - Oxcarbazepine
  - etc.
  - Risk D
    - CYP3A4 substrates (e.g., contraceptives, clarithromycin, etc.)
    - CYP2C19 substrate (e.g., clopidogrel, etc.) decreased serum concentration of the substrates
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.

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%

Brivaracetam (BRV)/Briviact

- Drug class: miscellaneous
- MOA
  - Binds to the synaptic vesicle protein 2A (SV2A)
- Indications
  - Partial-onset seizures (adjunct)
  - For adults and children
  - Adolescents ≥16 years
- 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)

Epilepsy Updates

Rescue Agents
Rescue agents - overview

- 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

Benzodiazepines for a prolonged seizure

- 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>
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</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>

Clonazepam

- FDA approved for status epilepticus
- FDA approved for treatment of seizures

Diazepam

- FDA approved for status epilepticus
- FDA approved for treatment of seizures

Lorazepam

- FDA approved for status epilepticus
- FDA approved for treatment of seizures

Midazolam

- FDA approved for status epilepticus
- FDA approved for treatment of seizures

Midazolam

- Administration route: IM or IN
- Formulation:
  - Solution for IV, IM, IN, Buccal
  - Syrup for PO
  - Buccal (UK)
- Dosing for prehospital treatment:
  - 13-40 Kg: 5 mg once
  - > 40 Kg: 10 mg once
- Cost:
  - 5 mg/mL (1 mL, preservative free): $1.56

Midazolam - Pharmacokinetics

- Onset
  - IM (adults): 15 minutes; peak plasma effect within 1 hour
  - IM (children): 5 minutes; peak plasma effect within 30 minutes
  - IN (children): 4-8 Minutes
- Duration
  - IM (adults): Two hours
  - IN (children): 18-41 minutes
- Bioavailability (adult data): 90%
- Half-life: Two to six hours

Midazolam

- Why IN administration?
  - Efficacy
    - Same as rectal diazepam
  - Convenience
    - Easy preparation
    - Easy administration
  - Cost effectiveness
    - Inexpensive compared with diazepam rectal
  - Social factor
    - Can be used in public
Midazolam - IV vs. IN

- Veldhorst-Janssen et al. (2011)

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%) and female 8 (38.1%)
  - Dose
    - Diazepam (DZP): 10 mg
    - Midazolam (MDZ): 2.5 mg

Midazolam

- Issues
  - Institute for Safe Medication Practices comment on BD syringe medication storage:
    - "These syringes were never cleared by FDA for use as a closed container storage system for drug products, and the suitability of these syringes for that purpose has not been established."

Stability

- Midazolam 5 mg/mL
- Becton-Dickinson (BD) Luer-Lok Syringe, 10 mL
- Stable for at least 100 days when stored at room temperature in polypropylene syringes
- Percent remaining at day 100: 96.5 ± 2.6
- All samples were found to be clear and colorless after 100 days of storage
- Midazolam is stable for 100 days when stored at room temperature in polypropylene syringes.

Clinical study (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)

Clinical study

- IN midazolam
  - Administration - dosing
    - 0.2-0.3 mg/kg
  - Adverse reactions
    - Irritation
      - May use preservative-free solution
  - Adverse reactions
    - May use preservative-free solution
Seizures and Spells ECHO

Join us to learn epilepsy!

- **When?**
  - First and third 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/](http://echo.unm.edu/nm-teleecho-clinics/child-youth-epilepsy-teleecho-clinic/)