Pharmacology and pharmacokinetics in epilepsy care

Mikiko Yamada, M.S., Pharm.D.
Clinical assistant professor
University of New Mexico
College of Pharmacy
Financial disclosure

None
Learning objectives

1. Discuss the classification of antiepileptic drugs (AEDs)
2. Discuss and compare the mechanisms of action and adverse reactions of the antiepileptic drugs
3. Review pharmacokinetics of AEDs and understand the detailed mechanism of how the serum concentration of AEDs can be altered by changes in drug formulations and concomitant medications
4. Compare two rescue benzodiazepine agents for prolonged seizures
5. Understand the use of herbal products in the United States
6. Analyze the mechanism of drug-herb interactions among epilepsy patients
7. Discuss cannabis use for epilepsy treatment
Outline

1. Overview of antiepileptic drugs (AEDs)
2. Classification of AEDs
3. Pharmacokinetics – ADME of AEDs
4. Topic discussion
   - Midazolam intranasal administration
   - Herbal medication and epilepsy
     - Drug-herb interactions
     - Hemp oil use for epilepsy
Antiepileptic drugs – overview

- More than 20 antiepileptic drugs are available in the United States
- Epilepsy treatment with antiepileptic drugs (AEDs)
  - Antiepileptic drugs
  - First treatment approach before nonpharmacotherapy (e.g., surgery, diet, VNS, DBS, RNS, etc.)
  - Long-term exposure
- Dilemma
  - Necessary for adequate seizure control but may be harmful
Antiepileptic drugs – overview

- Epilepsy treatment with AEDs
  - Ultimate treatment goal
    - Seizure free
  - Treatment goal when using AEDs
    - Seizure free with minimal adverse outcomes
Pharmacology of AEDs

- Classification of AEDs
  - Older agents vs. newer agents
  - Indications
    - Generalized seizures vs. focal onset seizures
  - Enzyme-inducing AEDs vs. nonenzyme-inducing AEDs
  - Drug class: channel or receptor functions
    - Na channel blockers
    - Ca channel blockers
    - GABA enhancers
    - K channel agonist
    - AMPA receptor antagonist
    - NMDA receptor antagonist
    - Combinations
    - Others/MOA unknown
Classification of AEDs

Older agents (before 1993)

- Phenobarbital (1912)
- Phenytoin (1938)
- Primidone (1954)
- Ethosuximide (1960)
- Carbamazepine (1974)
- Valproic acid (1978)
- Divalproex Na (1979)

Newer agents (1993 ~)

- Felbamate (1993)
- Gabapentin (1993)
- Lamotrigine (1994)
- Topiramate (1996)
- Tiagabine (1997)
- Levetiracetam (1999)
- Oxcarbazepine (2000)
- Zonisamide (2000)
- Pregabalin (2004)
Classification of AEDs

- Very new
  - Lacosamide (2008)
  - Rufinamide (2008)
  - Vigabatrin (2009)
  - Clobazam (2011)
  - Ezogabine (2011)
  - Perampanel (2012)
  - Eslicarbazepine (2013)
Classification of AEDs

- Indications of AEDs
  - Effective for both generalized and focal seizures
    - Lamotrigine, levetiracetam, topiramate, valproic acid
  - Effective only for generalized or focal seizures
    - Ethosuximide (only for absence seizure)
    - Newer/very new AEDs
Antiepileptic drugs – overview

- MOA of AEDs

![](image)

- Perampanel
- Eslicarbazepine
- Topiramate
- Levetiracetam
- Gabapentin, Pregabalin
- Ezogabine
- Phenytoin, carbamazepine, valproic acid, felbamate, rufinamide, lamotrigine, lacosamide, topiramate, zonisamide, oxcarbazepine

Antiepileptic drugs – overview

- MOA of AEDs
Pharmacology of AEDs

- MOA of AEDs
  - ↑ Inhibitory transmission
    - Increase Cl- current (inward)
      - Benzodiazepines, barbiturates, felbamate
    - Neurotransmitter: GABA
      - Vigabatrin: inhibit gamma-aminobutyric acid transaminase (GABA-T)
      - Tiagabin: binds to GABA uptake carrier (GAT1) and increases available GABA into presynaptic neurons
Pharmacology of AEDs

- MOA of AEDs
  - ↓ Excitatory transmission
    - Decrease Na, Ca currents (inward)
      - Na channel blockers
        - Phenytoin, carbamazepine, oxcarbazepine, valproic acid, felbamate, rufinamide, lamotrigine, lacosamide, topiramate, zonisamide
      - Ca channel blockers
        - Gabapentin, pregabalin (nothing to do with GABA)
    - Increase M currents (inhibit epileptic-form activity)
      - K channel agonist
        - Ezogabine
    - Neurotransmitter: glutamate
      - NMDA receptor antagonists: felbamate, topiramate
      - AMPA receptor antagonists: perampanel, topiramate
Complications with AEDs

• Adverse reactions
  • Common
    • Sedation, drowsiness, nausea, GI discomfort, incoordination, vertigo, headache, dizziness, blurred vision, ataxia
  • Drug specific:
    • Phenytoin: nystagmus, gingival hyperplasia
    • Valproic acid: tremor
    • Levetiracetam: psych-related issues – e.g., agitation
    • Acetazolamide, topiramate, zonisamide: kidney stones
    • Carbamazepine and oxcarbazepine: hyponatremia
      • Frequency: oxcarbazepine > carbamazepine
Complications with AEDs

- Adverse reactions
  - Serious
    - Hypersensitivity reactions
      - Lamotrigine, clobazam: rash (SJS/TEN) – slow titration
      - Carbamazepine: rash – HLA-B*1502
    - Hepatotoxicity
      - Felbamate: fulminant hepatitis and aplastic anemia (BW)
      - Valproic acid: hepatotoxicity (BW)
  - Vision
    - Vigabatrin: permanent vision loss
  - Suicidal ideation
    - All AEDs increase risk of suicidal thoughts/behavior
    - Incidence rate: 0.43% treated patients vs. 0.24% of patients receiving placebo
Complications with AEDs

- **Adverse reactions: others**
  - **Hematologic effects**
    - Thrombocytopenia (valproic acid), aplastic anemia (felbamate), leukopenia (carbamazepine)
  - **Endocrinologic effects**
    - Metabolic disorders:
      - Weight gain (valproic acid, gabapentin, pregabalin)
      - Weight loss (topiramate, zonisamide)
      - Risk of osteoporosis/osteopenia (almost all AEDs)
  - **Teratogenicity**
    - Pregnancy category: C or D
Complications with AEDs

- Monitoring parameters
  - Medication compliance
    - Poor compliance exacerbates seizure disorder
    - Know the reasons for noncompliance/poor adherence
  - Efficacy
    - Seizure frequency
      - Increased, same, decreased
    - Seizure symptoms
      - New symptoms?
    - Duration of seizure
      - Prolonged, same, shorter
  - Safety
    - Adverse reactions
      - Monitor lab values
    - TDM – therapeutic drug monitoring
      - Therapeutic range, consistent with previous level, acute toxicity
Complications with AEDs

- Monitoring parameters
  - Labs
    - CBC, chemistry, LFTs, ammonia levels, vitamin D
  - TDM
    - Drug levels
  - Physical and cognitive functions
  - Drug interactions
  - Mental status
    - Depression, suicidal thoughts and/or ideation
Pharmacokinetics of AEDs

- ADME
  - Absorption
  - Distribution
  - Metabolism
  - Excretion
Pharmacokinetics of AEDs

Absorption of AEDs

- Routes
  - PO, IV, IM, intranasal (IN), PR
- Selection of formulations (IR, DR, ER)
  - Alter absorption process
  - May improve medication compliance
    - e.g., lamotrigine IR (twice daily) vs. ER (once daily)
Pharmacy question

✓ Sprinkles?
✓ Delayed release?
✓ Extended release?

✓ Interchangeable?
Formulations

- Sprinkles? Delayed release? Extended release?
  - Interchangeable?
    - No
      - When switching from IR to ER, may increase 8% to 20% of daily dose to maintain similar level

<table>
<thead>
<tr>
<th>Product(s)/strength</th>
<th>Formulation</th>
<th>FDA approval date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Depakote 250 mg, 500 mg</td>
<td>Enteric-coated delayed-release</td>
<td>1983</td>
</tr>
<tr>
<td>Depakote 125 mg</td>
<td>Enteric-coated delayed-release</td>
<td>1984</td>
</tr>
<tr>
<td>Depakote 125 mg</td>
<td>Sprinkle delayed-release</td>
<td>1989</td>
</tr>
<tr>
<td>Depakote ER 250 mg, 500 mg</td>
<td>Enteric-coated extended-release</td>
<td>2002</td>
</tr>
</tbody>
</table>

Formulations

- Delayed release versus extended release
Case 1

- A 13-year-old Hispanic male was diagnosed at age 5 with generalized epilepsy. He has been on valproic acid for about two months, and his seizures are well controlled. However, his mother mentioned that the boy feels dizzy and sleepy at about noon, which significantly makes it difficult for him to concentrate on his classes.

Medications

- Valproic acid delayed-release 500 mg po bid
  - Takes 7 a.m. and 7 p.m.
  - Latest serum valproic acid level: 125 (four hours after the dose)
    - Valproic acid: 50-100 mcg/mL
Case 1

- Pharmacokinetics of valproic acid
  - Delayed release versus extended release

![Graph showing Comparison of DR and ER](image)

- Intervention
  - Switching to extended release
    - Less fluctuation of serum concentration of valproic acid
Pharmacokinetics of AEDs

- Distribution of AEDs
  - Distribution: protein binding

![Diagram showing the distribution of AEDs]

- Blood vessel
- Blood
- Bound drug ↔ Unbound drug
- Site of action
- Peripheral sites
- Metabolism or elimination

Blood vessel
Pharmacokinetics of AEDs

- Distribution: protein binding (cont’d)
  - High protein binding AEDs
    - Phenytoin
      - e.g., warfarin: protein binding-99%, phenytoin-90%
        - Increase PT and INR
    - Valproic acid
  - Altered due to
    - Age
      - Neonates and elderly – lower protein binding
    - Nutrition
    - Liver/renal disease
    - Pregnancy – lower protein binding
Does drug distribution affect serum concentration of AED?
Pharmacokinetics of AEDs

- Drug distribution and protein binding (cont’d)
- Example:

<table>
<thead>
<tr>
<th></th>
<th>Patient A</th>
<th>Patient B</th>
</tr>
</thead>
<tbody>
<tr>
<td>Condition</td>
<td>Otherwise healthy</td>
<td>Third degree burn</td>
</tr>
<tr>
<td>Alb</td>
<td>4.4 g/dL</td>
<td>2.2 g/dL</td>
</tr>
<tr>
<td>Total PHT level</td>
<td>10 mg/L</td>
<td>10 mg/L</td>
</tr>
<tr>
<td>Adjusted PHT level</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Free PHT</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Albumin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bound PHT</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adjusted PHT level</td>
<td>?</td>
<td>?</td>
</tr>
<tr>
<td>Estimated free PHT level</td>
<td>?</td>
<td>?</td>
</tr>
</tbody>
</table>
### Pharmacokinetics of AEDs

- **Drug distribution and protein binding (cont’d)**

<table>
<thead>
<tr>
<th></th>
<th>Patient A</th>
<th>Patient B</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Condition</strong></td>
<td>Otherwise healthy</td>
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</tr>
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<td>2.2 g/dL</td>
</tr>
<tr>
<td><strong>Total PHT level</strong></td>
<td>10 mg/L</td>
<td>10 mg/L</td>
</tr>
<tr>
<td><strong>Adjusted PHT level</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Free PHT</td>
<td><img src="image1.png" alt="Diagram" /></td>
<td><img src="image2.png" alt="Diagram" /></td>
</tr>
<tr>
<td>Albumin</td>
<td><img src="image3.png" alt="Diagram" /></td>
<td><img src="image4.png" alt="Diagram" /></td>
</tr>
<tr>
<td>Bound PHT</td>
<td><img src="image5.png" alt="Diagram" /></td>
<td><img src="image6.png" alt="Diagram" /></td>
</tr>
<tr>
<td><strong>Adjusted PHT level</strong></td>
<td><img src="image7.png" alt="Diagram" /></td>
<td><img src="image8.png" alt="Diagram" /></td>
</tr>
</tbody>
</table>
| \[
\frac{10 \text{ mg/L}}{(0.9 \times \frac{4.4 \text{ g/dL}}{4.4 \text{ g/dL}}) + 0.1} = 10 \text{ mg/L}
\] | \[
\frac{10 \text{ mg/L}}{(0.9 \times \frac{2.2 \text{ g/dL}}{4.4 \text{ g/dL}}) + 0.1} = 18.2 \text{ mg/L}
\] |
| **Estimated free PHT level** | 1 mg/L                           | 1.8 mg/L                             |
Pharmacokinetics of AEDs

- Metabolism
  - Phases of drug metabolism

  - Phase I
  - Metabolite
  - Phase II
  - Elimination
Pharmacokinetics of AEDs

- Metabolism
  - Phases of drug metabolism
    - Phase I
      - Primary enzyme system is Cytochrome P450 (CYP)
      - Often produces active metabolites
    - Phase II
      - Makes drug molecules water soluble for elimination in urine
      - Most studied enzyme is UDP-glucuronosyltransferases (UDP/UGT)
Pharmacokinetics of AEDs

- Metabolism
  - Enzyme systems
    - Substrates, inducers, inhibitors
  - Drug interactions
    - Enzyme-inducing AEDs
      - Phenytoin: CYP2C9, CYP2C19
      - Carbamazepine: CYP3A4, CYP2C8, CYP1A2
      - Lamotrigine: UGT1A4 (weak)
      - Phenobarbital (primidone): CYP3A4
Pharmacy question

✓ Enzyme-inducing AEDs?
✓ Substrate? Inducer? Inhibitor?
Metabolism of AEDs

Drug interactions

- Substrate? Inducer? Inhibitor?
  - Substrate: a drug metabolized by specific enzyme
  - Inhibitor: a drug that inhibits specific enzyme activity
  - Inducer: a drug that induces specific enzyme activity

<table>
<thead>
<tr>
<th>Drug A</th>
<th>Drug B</th>
<th>Mechanism</th>
<th>Serum concentration of Drug A</th>
</tr>
</thead>
<tbody>
<tr>
<td>Substrate of CYP3A4</td>
<td>Inhibitor of CYP3A4</td>
<td>Drug B decreases the metabolism of Drug A</td>
<td>Increased</td>
</tr>
<tr>
<td>Substrate of CYP3A4</td>
<td>Inducer of CYP3A4</td>
<td>Drug B increases the metabolism of Drug A</td>
<td>Decreased</td>
</tr>
</tbody>
</table>
Metabolism of AEDs

- **Drug interactions**
  - Example: co-administration of carbamazepine and oral contraceptives (OC)
  - OC: substrate of CYP3A4
  - Carbamazepine: *inducer* of CYP3A4
    - What would the serum concentration of OC be?
      - Decreased
Pharmacokinetics of AEDs

- **Metabolism**
- **Drug interactions**
  - Interactions between AEDs and other medications
    - e.g., induction: warfarin and CBZ
  - Interactions between AEDs
    - e.g., valproic acid and lamotrigine
      - Increase lamotrigine concentration (UGT)
Pharmacokinetics of AEDs

- **Metabolism**
  - **Autoinduction**
    - Induces its own drug metabolism
      - e.g., CBZ
    - Metabolism of CBZ typically increases after first month of therapy
Pharmacokinetics of AEDs

- **Excretion/elimination**
  - **Drug elimination routes**
    - Hepatic elimination
    - Renal elimination
    - Others: sweat, saliva, breast milk, etc.
      - Total clearance = hepatic clearance + renal clearance + others
  - **Disease states may alter AED clearance**
    - e.g., CHF patient with gabapentin/pregabalin
More pharmacokinetics

- Relationship between
  1. Dose and serum concentration
  2. Dose and clearance
Dose and serum concentration

Figure 1. Effects of dose on the steady-state concentrations of classic AEDs. PHT = phenytoin; PB = phenobarbital; VPA = valproic acid; CBZ = carbamazepine.

Dose and clearance

- Zero-order elimination
  - Rate of elimination
    - Constant
  - Serum concentration
    - Decreases linearly with time
  - Elimination half-life
    - $t_{1/2} = \frac{A_0}{2kz}$
• **First-order elimination**

• **Rate of elimination**
  - Proportional to drug concentration

• **Serum concentration**
  - Decreases exponentially with time

• **Elimination half-life**
  - \[ t_{\frac{1}{2}} = \frac{0.693}{k_f} \]
Pharmacy question

✓ Why does serum concentration of phenytoin increase rapidly?
Zero-order elimination

Example

- A 45-year-old male patient with moderate renal insufficiency (CrCL = 40 mg/L) was transferred to neuro ICU. He had an MVA and required brain surgery.
- Phenytoin was given for the prophylaxis of seizures due to post traumatic brain injury.
- Today is Day 3 at neuro ICU, and his PHT levels are creeping up.
- His nutrition status is nothing by mouth for four days.
PHT is eliminated by the same rate constantly.

The kidneys are not able to eliminate PHT due to renal insufficiency.

PHT will accumulate in the body.

Difficult to estimate PHT levels, unlike AEDs, which follow first-order elimination.

It mimics that PHT is given at higher dose.

PHT follows nonlinear pharmacokinetics.
Dose and clearance

- Phenytoin case
  - Cautious for patients with renal insufficiency, liver failure (clearance of phenytoin)
  - Cautious for patients with low albumin (distribution of phenytoin – protein binding)
  - Monitor free phenytoin levels
Dose and clearance

- Rate of elimination is proportional to drug concentration
- Serum concentration is decreased exponentially with time
- This AED follows linear pharmacokinetics
Topic discussion

- Midazolam intranasal administration
- Herbal medication and epilepsy
  - Drug-herb interactions
  - Hemp oil use for epilepsy
Case 1

- A 15-year-old female diagnosed at age 1 with generalized epilepsy has been on valproic acid for about three years. Her seizures are well controlled. Since this morning, she has had three seizures, and each seizure lasts about a minute. The interval between each seizure is 30 minutes.

Questions
- What abortive agent would you recommend if a seizure last more than three minutes?
Abortive agents – overview

- 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>
</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>
Abortive 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
Midazolam

• Administration route: IM or IN
• Formulation
  • Solution for IV, IM, IN (preservative free)*, buccal*
  • Syrup
  • Buccal (UK)
• Dose for prehospital treatment
  • 13-40 kg: 5 mg once
  • >40 kg: 10 mg once
• Cost
  • 5 mg/mL (1 mL, preservative free): $1.056

http://www.hospira.com/products_and_services/drugs/MIDAZOLAM_HYDROCHLORIDE
http://online.lexi.com.libproxy.unm.edu/lco/action/doc/retrieve/docid/patch_f/7296
Midazolam

- Buccal
  - Formulation: solution (in European countries)

http://www.mims.co.uk/news/1106012/Buccolam-licensed-buccal-midazolam-product/
http://ascomed.sharepoint.com/Pages/VIROPHARMA.aspx
http://www.sec.gov/Archives/edgar/data/946840/000119312512399193/d414342dex991.htm
Midazolam

- Onset (adult data)
  - IM (adults): rapid; peak plasma effect in one hour
  - IN (children): rapid; onset four to eight minutes

- Duration
  - IM (adults): two hours
  - IN (children): 18-41 minutes

- Bioavailability (adult data): > 90%

- Half-life
  - Two to six hours
Midazolam

- IN administration

Full Nasal Kit - Store in one place

http://intranasal.net/Treatmentprotocols/default.htm

Figure. Drug delivery to the CNS from nasal formulations. CNS, Central Nervous System; BBB, Blood Brain Barrier
Midazolam

- Veldhorst-Janssen et al. (2011)

![Graph showing concentration-time profile of midazolam](image)

**Figure 3.** Mean estimated and measured concentration-time profile of intravenous (IV) (2.5 mg) and intranasal (IN) (5 mg) midazolam.

### Midazolam

- **IN administration – dosing**
  - **0.2–0.3 mg/kg**

#### MIDAZOLAM (Versed) 5 mg/ml Pediatric Dose Chart

(For Indicated Seizures Only)

<table>
<thead>
<tr>
<th>WEIGHT</th>
<th>GREY</th>
<th>PINK</th>
<th>RED</th>
<th>PURPLE</th>
<th>YELLOW</th>
<th>WHITE</th>
<th>BLUE</th>
<th>RED</th>
<th>GREEN</th>
<th>OTHER</th>
<th>OTHER</th>
</tr>
</thead>
</table>

**INTRAVENOUS / INTRAOSSEOUS / INTRAMUSCULAR**

<table>
<thead>
<tr>
<th>Dose</th>
<th>0.1 mg/kg</th>
<th>0.1 mg/kg</th>
<th>0.1 mg/kg</th>
</tr>
</thead>
<tbody>
<tr>
<td>IV/IO/IM</td>
<td>0.4 mg</td>
<td>0.65 mg</td>
<td>0.85 mg</td>
</tr>
<tr>
<td>Volume</td>
<td>0.08 ml</td>
<td>0.13 ml</td>
<td>0.17 ml</td>
</tr>
<tr>
<td></td>
<td>0.25 ml</td>
<td>0.35 ml</td>
<td>0.4 ml</td>
</tr>
<tr>
<td></td>
<td>0.5 ml</td>
<td>0.65 ml</td>
<td>0.8 ml</td>
</tr>
<tr>
<td></td>
<td>0.9 ml</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**INTRANASAL**

<table>
<thead>
<tr>
<th>Dose</th>
<th>0.2 mg/kg</th>
</tr>
</thead>
<tbody>
<tr>
<td>IN Dose</td>
<td>0.75 mg</td>
</tr>
<tr>
<td>IN Volume</td>
<td>0.15 ml</td>
</tr>
</tbody>
</table>

**Dose Chart Notes**

- Use a 1 ml syringe for midazolam administration to pediatric patients.
Midazolam

- Gerrit-Jan de Haan et al. (2010)
  - 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

Midazolam

- Gerrit-Jan de Haan et al. (2010)

- 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 ($p<0.001$)

---

Table 2. Efficacy of DZP-r and MDZ-n in suppressing seizure exacerbations

<table>
<thead>
<tr>
<th></th>
<th>Success*</th>
<th>Failure</th>
<th>Unknown</th>
<th>Total events</th>
<th>Time until effect (min ± SD)**</th>
</tr>
</thead>
<tbody>
<tr>
<td>DZP-r</td>
<td>56</td>
<td>6</td>
<td>1</td>
<td>63</td>
<td>4.3 ± 3.4</td>
</tr>
<tr>
<td>MDZ-n</td>
<td>50</td>
<td>8</td>
<td>3</td>
<td>61</td>
<td>4.6 ± 3.4</td>
</tr>
<tr>
<td>Total</td>
<td>106</td>
<td>14</td>
<td>4</td>
<td>124</td>
<td></td>
</tr>
</tbody>
</table>

*p = 0.57 (not significant); **p = 0.6 (not significant). min, minutes; SD, standard deviation. DZP-r, diazepam rectal solution; MDZ-n, midazolam nasal spray.

Case 1

- A 15-year-old female diagnosed at age 1 with generalized epilepsy has been on valproic acid for about three years. Her seizures are well controlled. Since this morning, she has had three seizures, and each seizure lasts about a minute. The interval between each seizure is 30 minutes.

Questions
- What abortive agent would you recommend if a seizure lasts more than three minutes?
Case 1

- Suggested rational use:
  - What abortive agent would you recommend if a seizure lasts more than three minutes? **Intranasal midazolam**
  - Appropriate for older children and adults
    - May not be effective for cluster seizures due to shorter half-life
Pharmacy question

✓ Cost of atomizer?
✓ Buccal administration?
✓ Where to send a prescription for midazolam intranasal?
Rx of midazolam

- Cost of atomizer
  - Range: $13.40 to $20/device at a pharmacy
  - Reusable if washed

- Other devices available?
  - Laryngo-tracheal mucosal atomization device

- Pharmacy
  - Compounding pharmacy

Case 2

- A 16-year-old male with generalized epilepsy showed a significant drop of serum valproic acid level. After ruling out other possible causalities (e.g., lifestyle changes, OTC medication use, timing of administration, medication compliance or adherence, weight changes, etc.), the parents of the patient said they gave their son a special energy drink twice daily. The energy drink contains multiple herbal products.
Herbal medicine – Herbal medicine facts

Approximately 40% of U.S. adult population uses CAM
- 50% of American Indians and Alaska Natives
- 43% of Whites
- 40% of Asian
- 26% of African Americans
- 28% of Hispanics

Approximately 12% of U.S. child population uses CAM
- Children whose parents are regular users of CAM are more likely to use CAM (24%) compared to children whose parents are not regular users of CAM (5%)

CAM use in the United States

- Akins et al. survey data
  - CAM use among pediatric patients with neurological disorders (autism: ASD; developmental disabilities: DD)
    - Age: 2-5 years old
    - Methods: interview – self-reported
  - Results
    - Final sample size: 453
    - CAM use: 39% of ASD patients; 30% of DD patients

Herbal medicine

- Possible issues of herbal medicine use among epilepsy patients
  - Poor medication compliance – rely on “natural” remedy
    - Need education
  - Unexpected drug-herb interaction
    - e.g., changes in metabolism – fluctuation in serum concentration of AED
    - e.g., increase risk of adverse outcomes – e.g., bleeding risk
  - Breakthrough seizures – e.g., stimulant-type herbs
  - Other serious adverse reactions
    - e.g., allergic reactions, abnormal liver/renal functions
CAM use in epilepsy - herb

- Herbal medicine
  - Pharmacist can provide evidence-based article analysis (if possible)
    - Assess safety and toxicity information on herb
    - Summary of an article with recommendations on therapeutic change
    - Education on herbal supplement use for caregiver/patient
CAM use in epilepsy - herb

- Medications for other disease states
  - Considerations
    - Safety
      - Drug-drug interactions? Alter seizure threshold?
    - Efficacy
A 16-year-old boy with generalized epilepsy showed a significant drop of serum valproic acid level. After ruling out other possible causalities (e.g., lifestyle changes, OTC medication use, timing of administration, medication compliance or adherence, weight changes, etc.), the parents of the patient said they gave their son a special energy drink twice daily. The energy drink contains multiple herbal products.

Facts

- The energy drink contains more than 10 herbs
- The majority of the herbs have a possibility to alter the metabolism and serum concentration of valproic acid
- Some of the herbs may increase the risk of bleeding
Recommendations

- Listen to patient and patient caregiver to understand the rationale of herbal use with respect to:
- Obtain serum AED levels of AEDs
  - Baseline and with herb
- Obtain lab values (e.g., LFTs, CBC, chemistry)
  - Baseline and with herb
- Monitor seizure frequency, description, other CAM methods
A 6-year-old girl diagnosed with Lennox-Gastaut syndrome has multiple types of seizures, including drop seizures, myoclonic seizures, and tonic-clonic seizures. She failed five AEDs and has been on valproic acid, clobazam, lamotrigine, and topiramate. Despite using four AEDs, she experiences daily seizures. Today, the patient and her mother come to your clinic and ask if cannabis could be a good treatment option for the girl.
CBD for epilepsy

- Cannabis – species
  - *Cannabis sativa*
  - *Cannabis indica*

- Cannabis – active ingredients
  - Tetrahydrocannabinol (THC)
    - Psychoactive – stimulating (e.g., hallucinations)
  - Cannabinol (CBD)
    - Nonpsychoactive – sedating

CBD for epilepsy

- What is the difference between the two?
  - Cannabis sativa: higher THC/CBD ratio
  - Cannabis indica: lower THC/CBD ratio
  - Have potential to use as epilepsy treatment

CBD for epilepsy

**Historical use of cannabis**
- China: menstrual disorders, gout, rheumatism, malaria, constipation, absent-mindedness
- Islamic countries: N/V, epilepsy, inflammation, pain, fever
- Western world (in 19th century): analgesic

**Current use of cannabis**
- Glaucoma, pain (chronic pain*, HIV-associated sensory neuropathy*), N/V (chemotherapy-induced N/V*), muscle spasms (spasms in multiple sclerosis*), insomnia, anxiety, epilepsy

* Positive evidence

CBD for epilepsy

Why CBD?

- “Multitarget” drug
  - Binds to multiple receptors
    - Inhibits neuroexcitation
    - Enhances serotonin activity
    - Acts as an antioxidant

CBD for epilepsy

Why CBD?

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CBD for epilepsy

Target population

- Epilepsy
  - Lennox-Gastaut syndrome
  - Dravet syndrome
- Neurological diseases
  - Neonatal hypoxic-ischemic encephalopathy
  - Psychosis
  - Anxiety disorders
  - Addictions

CBD for epilepsy

Issues surrounding CBD use

- Indications of CBD
- Few evidence-based analysis
- Strains of higher CBD/THC ratio
- Cost
- Pharmacokinetics of CBD

CBD for epilepsy

Indication of CBD

- Who can receive the benefits from CBD?
  - Not all types of seizures or epilepsy syndromes can be treated with CBD
  - Better evidence? – LGS and Dravet syndrome
CBD for epilepsy

- Few evidence-based analysis
  - Very few placebo-controlled studies
  - Older studies
  - Small sample size
  - Detailed study information is unclear

# CBD for epilepsy

## Table 1. Clinical trials of cannabidiol in epilepsy

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatments (subjects per group)</th>
<th>Duration</th>
<th>Outcome</th>
<th>Toxicity</th>
<th>Limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mechoulam and Carlini, (1978)</td>
<td>TRE – CBD 200 mg/day (4) TRE – Placebo (5)</td>
<td>3 months</td>
<td>CBD: 2 seizure free; 1 partial improvement; 1 no change</td>
<td>None</td>
<td>No baseline seizure frequency, no definition of improvement; unclear if AEDs were changed; small N/limited power; not truly randomized-blinded; unknown if groups were matched</td>
</tr>
<tr>
<td>Cunha et al. (1980)</td>
<td>TRE-TLE CBD (7) TRE-TLE Placebo (8)^a,b</td>
<td>200–300 mg/day for 3–18 weeks</td>
<td>Last visit: 4 CBD, 1 placebo</td>
<td>Somnolence</td>
<td>Not clearly blinded, since one patient transferred groups and doses were adjusted in CBD, but no mention of this in placebo group and CBD group received had longer average treatment</td>
</tr>
<tr>
<td>Ames and Cridland (1986)</td>
<td>IDD-TRE CBD (16)^c IDD-TRE Placebo (16)^c × 4 weeks</td>
<td>CBD 300/day × 1 week; 200/day × 3 weeks</td>
<td>No difference between CBD v. Placebo</td>
<td>Somnolence</td>
<td>This was a letter to the editor and details are lacking</td>
</tr>
<tr>
<td>Trembly and Sherman (1990)</td>
<td>TRE (?10 or 12)^d</td>
<td>3 months baseline; 6 months placebo: Randomized to either 6 months placebo v. CBD 100 t.i.d.; then crossover for 6 months on alternative treatment</td>
<td>No change in seizure frequency or cognitive/behavioral tests</td>
<td>None</td>
<td>Only truly double blind study. Unclear why sample size differed in two reports. Data reported is incomplete</td>
</tr>
</tbody>
</table>

TRE, treatment-resistant epilepsy; TLE, temporal lobe epilepsy; IDD, intellectual/developmental disability.

^aFrequent convulsions for ≥1 year; ~1 GTCSz per week.

^bOne patient transferred from placebo to treatment after 1 month.

^c12 subjects were divided into two groups, but distribution uncertain.

^dAbstract and subsequent book chapter have different N's (10 and 12).
CBD for epilepsy

- Strains of higher CBD/THC ratio
- Standardization
  - Medical marijuana
    - Cannabis indica?
    - THC/CBD ratio?
  - Hemp oil
    - THC/CBD ratio?
CBD for epilepsy

Cost

Expensive

- Many caregivers refrain from using hemp oil due to cost
- Effective dose (adult): 200-300 mg/day
  - e.g., Commercially available hemp oil
    - 1 oz (30 mL) costs $40
    - 80 servings in 30 mL; 1 serving = 15 drops (0.375 mL)
    - 15 drops × 80 servings = 1,200 drops
    - 1.25 mg of CBD in 15 drops (0.375 mL)
    - For a 200 mg of CBD,
      1. \[ 200 \text{ mg} \times \frac{0.375 \text{ mL}}{1.25 \text{ mg}} = 60 \text{ mL/day} = $80/\text{day} \]
      2. \[ 200 \text{ mg} \times \frac{15 \text{ drops}}{1.25 \text{ mg}} \times \frac{30 \text{ mL}}{1200 \text{ drops}} = 60 \text{ mL/day} = $80/\text{day} \]

Monthly cost = $80 × 30 days = $2,400

http://dixiebotanicals.com/products/dew-drops-hemp-oil-supplement/
CBD for epilepsy

- Pharmacokinetics of CBD
  - Administration: po? inhaler?
    - PO: bad taste; bioavailability – approximately 6%
    - Inhaler: bioavailability – approximately 30%
  - Distribution
    - Highly lipophilic
      - Distributed mainly in the brain and adipose tissue
    - High protein binding (90%)

CBD for epilepsy

• Pharmacokinetics of CBD
  • Metabolism – liver
    • Substrate of CYP3A2, 3A4, 2C8, 2C9, 2C19
    • Inhibitor of CYP3A, 2C
    • Inducer of CYP2B
  • Concerns for drug interactions
    • e.g., carbamazepine and phenytoin may reduce serum concentration of CBD

• Elimination
  • Mainly in feces; less in urine

Summary

1. AEDs are classified based on year of drug availability, mechanism of action, indications, and metabolism
2. Various mechanisms and adverse reactions of AEDs are known, and new AEDs are on the market
3. Understanding zero-order and first-order elimination is important to understand how serum concentration of AEDs is altered by changes in physical condition. Other pharmacokinetics factors, such as protein binding and drug metabolism, significantly affect efficacy and adverse reactions of AEDs
4. Intranasal and buccal administration are effective to treat prolonged seizures
5. Herbal products are frequently used in the United States, and analysis of drug-herb interaction is helpful to avoid serious adverse outcomes
6. Cannabis use for epilepsy is a hot topic; however, not all epilepsy patients will benefit from CBD