Epilepsy Updates

Newer Antiepileptic Drugs and Rescue Aid

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1

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.

2

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.

Fisher RS. Et al. ILAE official report: a practical clinical definition of epilepsy. Epilepsia. 2014 Apr;55(4):475-82.

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

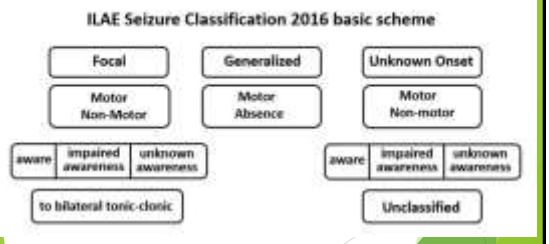
Epilepsy Foundation, available from http://epilepsyfoundation.org/aboutepilepsy/index.cfm
Epilepsia 2009 Oct;50(10):2180-5. Epub 2009 Jun 1.

4

Epilepsy – classification

- International League Against Epilepsy (ILAE) classification

Figure 1: The ILAE 2016 Operational Classification of Seizure Types: Basic and Expanded Scheme



Operational Classification of Seizure Types by the International League Against Epilepsy. Available from http://www.ilae.org/visitors/centre/documents/ClassificationSeizureILAE-2016.pdf

5

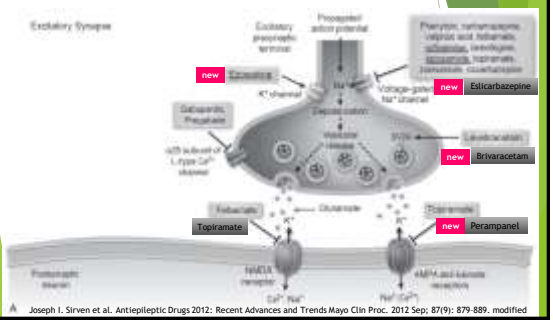
Classification of antiepileptic drugs (AEDs)

- 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

6

Pharmacology of AEDs

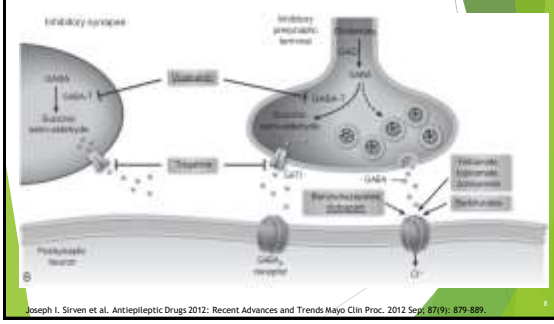
- MOA of AEDs



Joseph I. Sirven et al. Antiepileptic Drugs 2012: Recent Advances and Trends Mayo Clin Proc. 2012 Sep; 87(9): 879-889. modified

Pharmacology of AEDs

- MOA of AEDs



Joseph I. Sirven et al. Antiepileptic Drugs 2012: Recent Advances and Trends Mayo Clin Proc. 2012 Sep; 87(9): 879-889.

8

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

9

Antiepileptic drugs
Generic (abbreviation)/brand name

Newer agents (1993-2004)

- 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)

10

Antiepileptic drugs
Generic (abbreviation)/brand name

- 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)/Briviact (2016)

11

Antiepileptic drugs
Generic (abbreviation)/brand name

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

12

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://www.epilepsy.com/accelerating-new-therapies/new-therapies-pipeline
http://dij.sagepub.com/content/early/2014/12/23/2168479014537260.full.pdf

13

Epilepsy Updates
Newer Antiepileptic Drugs

14

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

15

VOTE

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

16

Question 1

Benzodiazepine – CNS depression

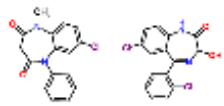
- MOA of benzodiazepine
  - Enhances $GABA_A$ receptor activity
- CNS depression
  - Drowsiness (up to 50% among adult seizure patients)
  - Drug-drug interactions
    - Other AEDs may enhance CNS depression
  - Routine checkup for excess sedation, respiratory depression, and mental condition (e.g.,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

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

17

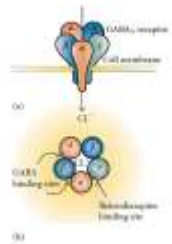
Clobazam (CLB)/Onfi

- Drug class: benzodiazepine
- MOA: enhance GABA function
  - Upregulation of GABA transporters 1 and 3
  - Less sedative



Clobazam
7-Chloro-1-methyl-5-phenyl-1H-1,5-benzodiazepine-2,4(3H,5H)-dione

Lorazepam
7-Chloro-5-(2-chlorophenyl)-3-hydroxy-1,3-dihydro-2H-1,4-benzodiazepin-2-one



Christiaan H. and CH Vinkers. Mechanisms Underlying Tolerance after Long-Term Benzodiazepine Use: A Future for Subtype-Selective GABA(A) Receptor Modulators? Advances in Pharmacological Sciences , Volume:2012
http://www.chemspider.com/Chemical-Structure.2687.html
http://www.chemspider.com/Chemical-Structure.3821.html?rid=308b8d19-5cb9-4b3b-a4f2-41c945d2529d

18

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

http://online.lexi.com/lco/action/doc/retrieve/docid/patch_f/6631

19

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

http://online.lexi.com/lco/action/doc/retrieve/docid/patch_f/6631

Geffrey AL. et al. Drug-drug interaction between clobazam and cannabidiol in children with refractory epilepsy.Epilepsia. 2015 Aug;56(8):1246-51.

20

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

21

Question 2

Ophthalmologic adverse reactions

- Which of the following antiepileptic drugs cause vision-related adverse reactions?

I. Ezogabine – Retinal abnormalities
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IV. Vigabatrin – Visual field loss

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

22

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

http://online.lexi.com/lco/action/doc/retrieve/docid/patch_f/3469462

23

Ezogabine (EZG)/Potiga

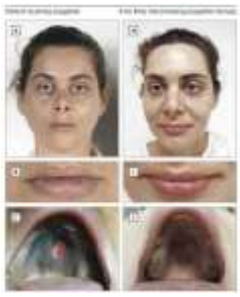
- Tips: dose adjustment and adverse reactions
  - Dosing
    - Renal impairment
    - Hepatic impairment
  - Adverse reactions
    - Dermatologic effects: Skin discoloration
    - Ocular complications
      - [U.S. boxed warning]: Retinal abnormalities

http://online.lexi.com/lco/action/doc/retrieve/docid/patch_f/3469462
http://www.fda.gov/Drugs/DrugSafety/ucm349538.htm
http://www.fda.gov/aboutfda/centersoffices/officeofmedicalproductsandtobacco/cder/ucm387805.htm

24

Ezogabine (EZG)/Potiga

- Adverse reactions
  - Skin discoloration



http://www.fda.gov/Drugs/DrugSafety/ucm349538.htm
Garin Shkolnik T et al. Blue-gray mucocutaneous discoloration: a new adverse effect of ezogabine. JAMA Dermatol. 2014 Sep;150(9):984-9.

25

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

26

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

27

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

http://online.lexi.com/lco/action/doc/retrieve/docid/patch_f/4005002

28

Perampanel (PRP)/Fycompa

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

http://online.lexi.com/lco/action/doc/retrieve/docid/patch_f/4005002

29

Perampanel (PRP)/Fycompa

- 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

http://online.lexi.com/lco/action/doc/retrieve/docid/patch_f/4005002

30

Question 4

Hyponatremia

- Which of the following AEDs cause hyponatremia most frequently?
  a. Carbamazepine
  b. Oxcarbazepine
  c. Eslicarbazepine

31

Question 4

Hyponatremia

- Which of the following AEDs cause hyponatremia most frequently?
  a. Carbamazepine
  b. Oxcarbazepine
  c. Eslicarbazepine

32

Question 4

- Hyponatremia
  - Enhances antidiuretic hormone (ADH) effect
    - ADH = arginine vasopression (AVP)
  - 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

Isoja¨rvi, JIT et al. Epilepsia, 42(6):741-745, 2001, Dong X, Leppik IE, White J, Rarick J. Neurology. 2005 Dec 27;65(12):1976-8, Himmerkus N. et al. Nephrol Dial Transplant (2012) 27: 3790-3798, Sachdeo RC et al. Ann Neurol. 2002 May;51(5):613-20.

33

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

http://online.lexi.com/lco/action/doc/retrieve/docid/patch_f/4825442

34

Eslicarbazepine (ECBZ)/Aptiom

- 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)

http://online.lexi.com/lco/action/doc/retrieve/docid/patch_f/4825442, Bialer M, Soares-da-Silva P. Pharmacokinetics and drug interactions of eslicarbazepine acetate. Epilepsia. 2012 Jun;53(6):935-46. Ortenzi A, Paggi A, Foschi N, Sabbatini D, Pistoli E. Oxcarbazepine and adverse events: impact of age, dosage, metabolite serum concentrations and concomitant antiepileptic therapy. Funct Neurol. 2008;23:97-100.

35

Eslicarbazepine (ECBZ)/Aptiom

- 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 (-nib)
      - Oxcarbazepine
      - etc.
    - Risk D
      - CYP3A4 substrates (e.g., contraceptives, clarithromycin, etc.)
      - CYP2C19 substrate (e.g., clopidogrel, etc.) - decreased serum concentration of the substrates

http://online.lexi.com/lco/action/doc/retrieve/docid/patch_f/4825442

36

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.

37

VOTE

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

38

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%

Helmstaedter C. et al. Epilepsia. 2013 Jan;54(1):36-44.

39

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

http://online.lexi.com/lco/action/doc/retrieve/docid/patch_f/5983000

40

Brivaracetam (BRV)/Briviact

- 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)

http://online.lexi.com/lco/action/doc/retrieve/docid/patch_f/5983000

41

Epilepsy Updates

Rescue Agents

42

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

10 mg (for 5 mg, 7.5 mg, and 10 mg)

http://www.sec.gov/Archives/edgar/data/946840/000119312512399193/d414342dex991.htm
http://online.lexi.com.libproxy.unm.edu/lco/action/home

43

Rescue agents – overview

- Benzodiazepines for a prolonged seizure
  - FDA-approved medications among benzodiazepines

Benzodiazepine	FDA approved for status epilepticus	FDA approved for treatment of seizures
Clonazepam	No - off-label use	Yes
Diazepam	Yes (rectal gel)	Yes
Lorazepam	Yes; parenteral only	No - off-label use (complex partial seizures)
Midazolam	No - off-label use	No - only for sedation

http://online.lexi.com.libproxy.unm.edu/lco/action/home

44

Midazolam

- IN administration

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

45

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

46

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

47

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

48

Midazolam - IV vs. IN

- Veldhorst-Janssen et al. (2011)

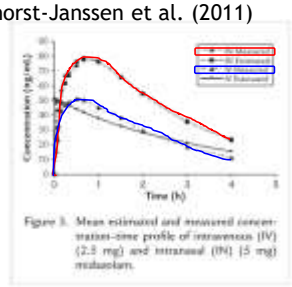


Figure 1. Mean estimated and measured concentration–time profile of intravenous (IV) (2.5 mg) and intranasal (IN) (5 mg) midazolam.

Veldhorst-Janssen NM et al. Clin Ther. 2011 Dec;33(12):2022-8.

49

Midazolam

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

50

IN midazolam

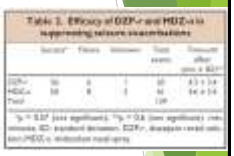
- Clinical study
  - Primary outcome: comparisons between diazepam (rectal) and midazolam (intranasal) in efficacy, safety, and preference
- Study population
  - Adults (N = 21) – patients with epilepsy
    - Male: 13 (61.9%) and female 8 (38.1%)
- Dose
  - Diazepam (DZP): 10 mg
  - Midazolam (MDZ): 2.5 mg

de Haan GJ, van der Geest P, Doelman G, Bertram E, Edelbroek P. A comparison of midazolam nasal spray and diazepam rectal solution for the residential treatment of seizure exacerbations. Epilepsia. 2010 Mar;51(3):478-82.

51

IN midazolam

- 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)



de Haan GJ, van der Geest P, Doelman G, Bertram E, Edelbroek P. A comparison of midazolam nasal spray and diazepam rectal solution for the residential treatment of seizure exacerbations. Epilepsia. 2010 Mar;51(3):478-82.

52

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."

https://www.ismp.org/newsletters/acutecare/showarticle.aspx?id=117

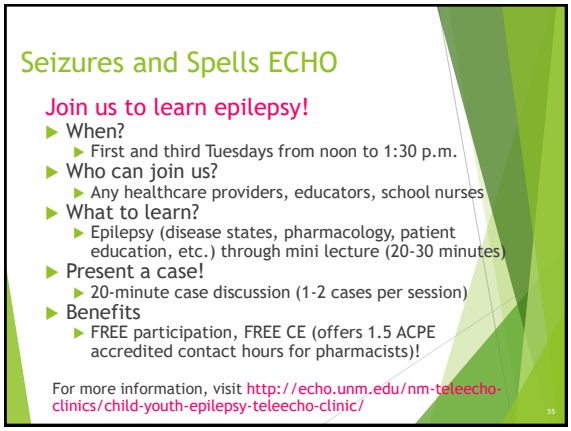
53

Midazolam

- 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.

Anderson C, MacKay M. Stability of Fentanyl Citrate, Hydromorphone hydrochloride, Ketamine hydrochloride, Midazolam, morphine Sulfate, and Pentobarbital sodium in polypropylene syringes. Pharmacy. 2015;3(4):379-385. doi:10.3390/pharmacy3040379. http://www.mdpi.com/2226-4787/3/4/379/htm. Accessed November 6, 2016.

54


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/
55