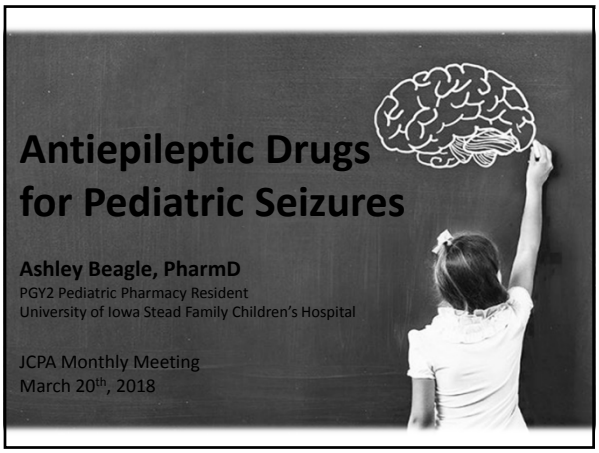


Disclosure

- Ashley Beagle reports that she has no actual or potential conflicts of interest in relation to this presentation
- Off label use of medications will be discussed during this presentation

2

Objectives

1. Identify common antiepileptic drugs (AEDs) used for pediatric epilepsy
2. Distinguish between antiepileptic drug adverse effect profiles and monitoring parameters
3. Describe drug metabolism and drug-drug interactions between agents used to maintain seizure control
4. Apply knowledge on antiepileptic drug properties to patient a case

3

Seizure

Transient occurrence of signs and symptoms due to *abnormal excessive* or *synchronous* neuronal activity in the brain

Pediatric Epilepsy

Defined as *two or more* unprovoked afebrile seizures

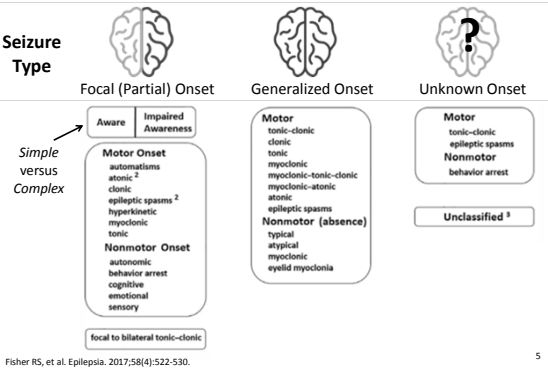
6 per 1000

of those 0 to 17 years

Scheffer IE, et al. Epilepsia. 2017;58(4):512-521.
Zack MM, Kobau R. MMWR Morb Mortal Wkly Rep. 2017;66(31):821-825.

4

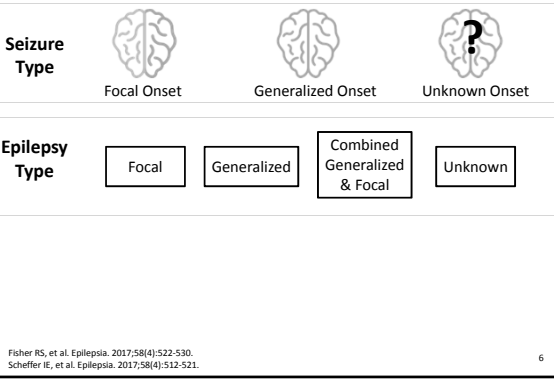
ILAE Classification of Epilepsies 2017



Fisher RS, et al. Epilepsia. 2017;58(4):522-530.

5

ILAE Classification of Epilepsies 2017

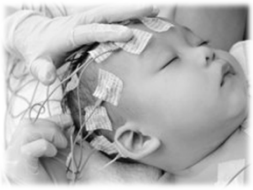


Fisher RS, et al. Epilepsia. 2017;58(4):522-530.
Scheffer IE, et al. Epilepsia. 2017;58(4):512-521.

6

Electroencephalography (EEG)

- Tracks and records brain waves to determine electrical activity of the brain
- Epileptiform activity can be seen on an EEG to help with diagnosis or monitoring of seizures



7

ILAE Classification of Epilepsies 2017

Seizure Type	Focal Onset	Generalized Onset	Unknown Onset
Epilepsy Type	Focal	Generalized	Combined Generalized & Focal	Unknown
Epilepsy Syndrome	Epilepsy Syndromes		

Fisher RS, et al. Epilepsia. 2017;58(4):522-530.
Scheffer IE, et al. Epilepsia. 2017;58(4):512-521.

8

Epilepsy Syndromes

Lennox-Gastaut Syndrome (LGS)
- Common seizure types include tonic, atypical absence, and atonic seizures
- Accounts for 2 to 5% of all childhood epilepsies
- **Often require 2+ AEDs for seizure control**

Infantile Spasms (IS) & West's Syndrome
- "Flexor spasms", arching back with drop in head, mimics a startled response
- Present at 3 to 8 months of age
- **High-dose steroids** or corticotropin (ACTH) for initial treatment
  - Steroid regimen - Week 1: 40 mg/day, Week 2: 60 mg/day

Juvenile Myoclonic Epilepsy (JME)
- Most common generalized epilepsy syndrome in late childhood
- Seizure types include absence, myoclonic, and generalized tonic clonic

Sidhu R, et al. Pediatr Rev. 2013;34(8):333-41.
www.epilepsy.com. Accessed February 26, 2018.

9

Pediatric Epilepsy

Seizure severity Co-morbidities

Spectrum of disorders

Seizure type Causes Social Impact

Children and Youth with Epilepsy (CYE)
- One of the fastest growing groups of epilepsy

Comorbidities
- Poor quality of life
- Social stigmas
- Mental health disorders
- Negative cognitive effects
- Depression
- Autism

IOM (US) Committee on the Public Health Dimensions of the Epilepsies; England MJ, Liverman CT, Schultz AM, et al., editors. National Academies Press (US); 2012.

10

Pediatric Epilepsy

SUDEP "*Sudden Unexpected Death in Epilepsy*"
- Cause of death 1 in 4,500 children with epilepsy
- Leading cause of death in people with uncontrolled seizures

AEDs
- 70% have seizure control with AED monotherapy
- 30% will require additional agents
  - Pharmacoresistant epilepsy – failure of 2 appropriately chosen and dosed AEDs

26+ AEDs for pediatric seizures

Maximize quality of life through seizure control
Minimize adverse effects

Kwan P et al. Epilepsia. 2010;51(6):1069-77.

11

Antiepileptic Drugs: Review of the Current Options

12

Antiepileptic Drugs by Primary Mechanism of Action

Modulation of Sodium Channels	• **Carbamazepine** • **Oxcarbazepine** • **Phenytoin** • **Lamotrigine**	• Lacosamide • **Valproic acid** • **Topiramate** • **Zonisamide**
Gamma-Aminobutyric Acid (GABA) Receptor Activity	• Gabapentin • Pregablin • **Phenobarbital** • Tiagabine	• **Vigabatrin** • **Benzodiazepines** • Primidone
Other or Unknown Mechanism	• **Levetiracetam** • **Ethosuximide** • Rufinamide	• **Felbamate** • Perampanel • Methsuximide

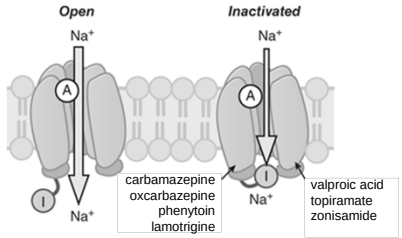
13

Antiepileptic Drugs by Primary Mechanism of Action

Modulation of Sodium Channels	• **Carbamazepine** • **Oxcarbazepine** • **Phenytoin** • **Lamotrigine**	• Lacosamide • **Valproic acid** • **Topiramate** • **Zonisamide**

14

Sodium Channel Modulators



Source: Laurence L. Brunton, Randa Hilal-Dandan, Björn C. Knollmann: Goodman & Gilman's: The Pharmacological Basis of Therapeutics, Thirteenth Edition: Copyright © McGraw-Hill Education. All rights reserved.

Prolonged inactivation

Reduced frequency of firing

Goodman and Gilman's The Pharmacological Basis of Therapeutics, 13th Edition. 2017

15

Carbamazepine (Tegretol®)

Partial seizures
- Products: oral suspension, chewable tablets, ER & IR tablets and capsules
- Dosing divided twice daily to three times daily
- Max dosing:
  - < 6 years - 35 mg/kg/day
  - ≥ 6 years - 1,000 mg/day

Metabolism
- **Autoinducer** and **Inducer** of CYP2C9 and CYP3A4
  - Valproic acid is decreased
  - Decreased oral contraceptive (OCP) serum concentrations
- ILAE Therapeutic Drug Monitoring (TDM): 4 – 12 mg/L (trough)

Hung OL, Shih RD. Emerg Med Clin North Am. 2011;29(1):141-50.
Perucca E. Br J Clin Pharmacol. 2006;61(3):246-55.
Patsalos PN, Berry DJ, et al. Epilepsia. 2008;49(7):1239-76.

16

Carbamazepine (Tegretol®)

Adverse effects
- Ataxia, blurred vision, syndrome of inappropriate antidiuretic hormone (SIADH)
- Decreased folic acid levels – recommended to supplement in adolescent girls
- Aplastic anemia & agranulocytosis
- Serious dermatologic reactions including **Stevens-Johnson Syndrome (SJS) and Toxic Epidermal Necrolysis (NEC)**
  - HLA-B*1502 protein positive

Hung OL, Shih RD. Emerg Med Clin North Am. 2011;29(1):141-50.
Harden CL, et al. Neurology. 2009;73(2):126-32.

17

Oxcarbazepine (Trileptal®)

FDA approved as adjunct for partial seizures, but may be used as monotherapy
- Products: oral suspension, IR and ER tablets
- Maintenance dose: 20 to 50 mg/kg/day divided two to three times daily

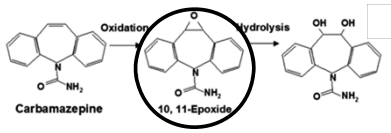
Liu X et al, 2017
- Trends in AED prescribing in a pediatric population from 1999 to 2009
- Carbamazepine decreased from 37.1% to 10.2%
- Oxcarbazepine increased from 1.3% to 19.1%

Oxcarbazepine versus Carbamazepine?

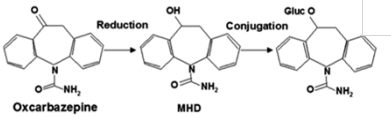
Hung OL, Shih RD. Emerg Med Clin North Am. 2011;29(1):141-50.

18

Oxcarbazepine vs Carbamazepine



- Autoinduction
- **Significant drug interactions**



- No autoinduction
- **Fewer drug interactions**

Monohydroxy Derivative
Active Metabolite

Schmidt D, Elger CE. Epilepsy Behav. 2004;5(5):627-35.

19

Oxcarbazepine (Trileptal®)

Metabolism
- Metabolized to MHD and **no autoinduction**
- Decrease concentrations of OCPs
- ILAE TDM: 3 – 35 mg/L of MHD
  - Adverse effects more likely > 30 mg/L; toxic > 40 mg/L

Adverse effects
- Drowsiness, blood dyscrasias
- **SIADH – more prominent with oxcarbazepine**
  - **Check sodium with any reports of altered mental status**
- HLA-B*1502 protein positive have risk of SJS or TEN

Patsalos PN, Berry DJ, et al. Epilepsia. 2008;49(7):1239-76.
Perucca E. Br J Clin Pharmacol. 2006;61(3):246-55.

20

Dermatologic Reactions with Carbamazepine & Oxcarbazepine

SJS and TEN
- Severe and often fatal dermatologic reaction
- Associated with HLA-B*1502 genotypes
  - Predominantly in those of Asian descent
- Latent reaction that occurs within first 3 months of therapy

Carbamazepine
- Greater risk than oxcarbazepine
- If HLA-B*1502 positive and naïve to therapy **avoid use**

Oxcarbazepine
- Does not carry Black Box Warning
- If HLA-B*1502 positive and naïve to therapy **avoid use**

Phillips EJ, et al. Clin Pharmacol Ther. accepted 20 December 2017; advance online publication 00 Month 2018.

21

Phenytoin Sodium (Dilantin®)

Partial and tonic-clonic seizures
- Intravenous and enteral products
  - IV formulation contains **propylene glycol & ethanol** – rate related hypotension & cardiac arrhythmias

Metabolism
- Micheaelis-Menten pharmacokinetics
- **Inducer of CYP2C9, CYP2C19, CYP3A4**
- Decrease concentrations of OCPs
- ILAE TDM: 10 – 20 mg/L; free phenytoin: 1 – 2.5 mg/L

Source: Larry A. Bauer: Applied Clinical Pharmacokinetics, 3rd Edition
www.accesspharmacy.com

Adverse Effects
- Dose-related
  - Nystagmus, ataxia, **cognitive impairment**, decreased folic acid levels
- Not dose-related
  - **Gingival hyperplasia**, hirsutism, acne

Hung OL, Shih RD. Emerg Med Clin North Am. 2011;29(1):141-50.
Applied Clinical Pharmacokinetics. McGraw Hill Professional; 2007.
Perucca E. Br J Clin Pharmacol. 2006;61(3):246-55.

22

Lamotrigine (Lamictal®)

LGS, primary generalized tonic-clonic seizures, partial seizures, adjunct agent
- Enteral products only
- Weight based dosing **titrating every 1 to 2 weeks** to maintenance dose
  - Dose adjusted based on drug-drug interactions

Metabolism
- ↑ with inducers; ↓ with inhibitors; auto-induction during first 2 weeks
- Decreased concentrations of OCPs
- ILAE TDM: not common to monitor; adverse effects at > 15 mg/L

Hung OL, Shih RD. Emerg Med Clin North Am. 2011;29(1):141-50.
Patsalos PN, Berry DJ, et al. Epilepsia. 2008;49(7):1239-76.

23

Lamotrigine Titration Schedule

8 yo M (weight 60 kg) with LGS receiving valproic acid and starting lamotrigine

	Weight based dosing	Dose
Week 1 & 2	0.15 mg/kg/day	9 mg daily
Week 3 & 4	0.3 mg/kg/day	18 mg daily
Week 5 & 6	0.6 mg/kg/day	36 mg daily
Week 7	0.9 mg/kg/day	54 mg daily*

*25 mg tablets available → consider 25 mg twice daily or 50 mg daily

Titration schedule variations
- ***Inducers* – Starting dose increased**
  - Carbamazepine, phenytoin, phenobarbital
- ***Inhibitors* – Starting dose decreased**

Titrate to effect with dose adjustments every 1 to 2 weeks

24

Lamotrigine (Lamictal®)

Adverse Effects
- **Rash** – prominent interaction with concurrent valproic acid
  - 10% develop a rash with an estimated 1% of children developing SJS or TEN
- **Nausea and vomiting**

Slow titration is utilized to prevent severe dermatologic reactions!

Hung OL, Shih RD. Emerg Med Clin North Am. 2011;29(1):141-50.
Perucca E. Br J Clin Pharmacol. 2006;61(3):246-55.
Patsalos PN, Berry DJ, et al. Epilepsia. 2008;49(7):1239-76.

25

Valproic Acid & Derivatives

Partial and tonic-clonic seizures, LGS, JME, absence seizures (broad spectrum)
- Additional mechanisms
  - Stimulates GABA synthesis and inhibits GABA degradation enzymes
- IV and enteral products
  - Valproic acid (VPA) (capsules)
  - Divalproex sodium (IR, sprinkle capsules)
  - Valproate sodium (IV and oral solution)
- Max dose: 40 mg/kg/day

Metabolism
- Predominantly hepatic metabolism, **enzyme inhibitor**
- ILAE TDM: 50 – 100 mcg/mL
- Valproic acid increases concentrations of:
  - Carbamazepine, phenytoin, phenobarbital, **lamotrigine**, **rufinamide**
- Valproic acid concentrations by may decreased by:
  - Carbamazepine, phenytoin, ethosuximide

bold = dose reduction recommended

Hung OL, Shih RD. Emerg Med Clin North Am. 2011;29(1):141-50.
Patsalos PN, Berry DJ, et al. Epilepsia. 2008;49(7):1239-76.

26

Adverse Effects of Valproic Acid

Hepatic
- Hepatotoxicity (increased risk in those < 2 years), increased LFTs, elevated ammonia

Gastrointestinal
- Nausea, vomiting

Endocrine
- **Weight gain** – occurs in 30 to 50%, pancreatitis

Dermatologic
- Delayed hair loss (females > males) – recommended to start a multivitamin with biotin, selenium, and zinc

Hematologic
- Thrombocytopenia (dose related)

Hung OL, Shih RD. Emerg Med Clin North Am. 2011;29(1):141-50.
Valproic Acid and derivatives. Pediatric & Neonatal Lexi-Drugs. Accessed February 25, 2018.

27

Topiramate

Partial and tonic-clonic seizures, LGS, JME
- Available products
  - Immediate release tablets and sprinkle capsules (Topamax®)
    - Twice daily dosing
    - Sprinkle capsules can be added to small amount of soft food
    - Tablets may be crushed and mixed with water
  - Extended release sprinkle capsules (Quedexy XR®)
    - Doses should be rounded to the nearest capsule size
    - Sprinkled on small amount of soft food
  - Extended release capsule (Trokendi XR®)
- Dosing: 1 to 5 mg/kg/day divided twice daily
- Max dose: 10 mg/kg/day

Hung OL, Shih RD. Emerg Med Clin North Am. 2011;29(1):141-50.
Topiramate. Pediatric & Neonatal Lexi-Drugs. Accessed February 26, 2018.

28

Topiramate

Metabolism
- Serum concentrations reduced by approximately 50% with inducers
  - Phenytoin, phenobarbital
- Decreased concentrations of OCPs (> 200 mg/day)
- ILAE TDM: not common to monitor

Adverse Effects
- Metabolic acidosis (mild carbonic anhydrase inhibitor), **decreased sweating**, kidney stones
- **Weight loss**, **difficulty concentrating or remembering words**

Hung OL, Shih RD. Emerg Med Clin North Am. 2011;29(1):141-50.
Perucca E. Br J Clin Pharmacol. 2006;61(3):246-55.
Patsalos PN, Berry DJ, et al. Epilepsia. 2008;49(7):1239-76.

29

Zonisamide (Zonegran®)

Partial seizures (primary and adjunct)
- Enteral products only
- Maintenance dosing: 4 to 8 mg/kg/day divided twice daily
- Max dose in children: 12 mg/kg/day

Metabolism
- **CYP3A4 substrate**
  - Significant reduction in half-life when given with carbamazepine, phenytoin, phenobarbital
- ILAE TDM: not common to monitor

Adverse Effects
- **Decreased sweating**, kidney stones (weak carbonic anhydrase inhibitor)

Hung OL, Shih RD. Emerg Med Clin North Am. 2011;29(1):141-50.
Zonisamide. Pediatric & Neonatal Lexi-Drugs. Accessed February 26, 2018.
Patsalos PN, Berry DJ, et al. Epilepsia. 2008;49(7):1239-76.

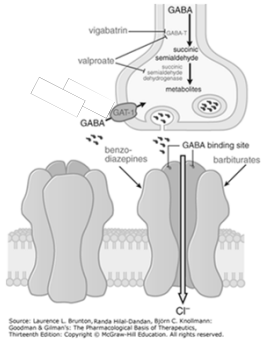
30

Antiepileptic Drugs by Primary Mechanism of Action

Modulation of Sodium Channels	• **Carbamazepine** • **Oxcarbazepine** • **Phenytoin** • **Lamotrigine**	• Lacosamide • **Valproic acid** • **Topiramate** • **Zonisamide**
Gamma-Aminobutyric Acid (GABA) Receptor Activity	• Gabapentin • Pregablin • **Phenobarbital** • Tiagabine	• **Vigabatrin** • **Benzodiazepines** • Primidone

31

GABA Receptor Activity



Source: Laurence L. Brunton, Randa Hilal-Dandan, Björn C. Knollmann: Goodman & Gilman's: The Pharmacological Basis of Therapeutics, Thirteenth Edition: Copyright © McGraw-Hill Education. All rights reserved.

Potentiate GABA

↓

Chloride channel opening

↓

Decreased depolarizations

Goodman and Gilman's The Pharmacological Basis of Therapeutics, 13th Edition. 2017

32

Phenobarbital

Partial and generalized tonic-clonic seizures
- FDA approved in 1912
- Enteral and IV products

IV

Metabolism
- Potent inducer of CYP1A2, CYP2C, CYP3C
  - **Decreases levels of carbamazepine, lamotrigine, OCPs & other CYP substrates**
- Serum concentration increased by phenytoin, oxcarbazepine, valproic acid
- ILAE TDM: 15 to 40 mg/L; long half life (60 to 180 hours)

Adverse Effects
- Sedation and CNS depression, respiratory depression (IV)
- **Cognitive impairment**, lethargy, drowsiness, low folic acid levels
- **Vitamin D deficiency** with chronic use
  - Level should be monitored and may require supplementation

Hung OL, Shih RD. Emerg Med Clin North Am. 2011;29(1):141-50.
Perucca E. Br J Clin Pharmacol. 2006;61(3):246-55.
Patsalos PN, Berry DJ, et al. Epilepsia. 2008;49(7):1239-76.

33

Vigabatrin (Sabril®)

Infantile spasms and adjunct for refractory complex partial seizures
- Enteral products
  - 500 mg powder packet for oral solution
  - Mix 10 mL per packet = 50 mg/mL
- Max dose: 150 mg/kg/day

VIGABATRIN REMS PROGRAM

Metabolism
- No metabolism and is excreted unchanged in the urine
- ILAE TDM: no monitoring recommended

Adverse Effects
- **Concentric bilateral visual field deficits** (28.6% ages 8 to 12 years) – REMS
  - Ophthalmologic exams: baseline, 1 month, then every 3 months
- Fatigue, somnolence, weight gain, ataxia, confusion

REMS = Risk Evaluation and Mitigation Strategies Program

Patsalos PN, Berry DJ, et al. Epilepsia. 2008;49(7):1239-76.
Vigabatrin. Pediatric & Neonatal Lexi-Drugs. Accessed February 25, 2018.

34

Clobazam (Onfi®)

LGS, partial and generalized seizures
- Common choice for drug resistant seizures
- Enteral products (suspension and scored tablet)
- Max dose:
  - < 30 kg – 20 mg/day
  - ≥ 30 kg – 40 mg/day

IV

Metabolism
- Metabolized by CYP2C19 to N-desmethylclobazam
- **Interaction with cannabidiol (CYP2C19 inhibitor)**

Adverse Effects
- **Sedation**, fatigue, irritability, somnolence, ataxia
- Abrupt discontinuation should be avoided

Patsalos PN, Berry DJ, et al. Epilepsia. 2008;49(7):1239-76.
Clobazam. Pediatric & Neonatal Lexi-Drugs. Accessed February 25, 2018.

35

Clobazam & Cannabidiol

Cannabidiol (CBD) non-pyschoctive component of cannabinoids
- Example products: Haleigh's Hope, Charlotte's Web Hemp products, hemp oil products
- **Potent CYP2C19 inhibitor**

Geffrey AL et al, 2015
- Evaluated serum concentration changes in 13 pediatric patients taking concurrent CBD oil and clobazam
- Mean increase in N-desmethylclobazam was 500 ± 300%
- **10 of 13 experienced adverse effects** associated with high clobazam doses (ex. drowsiness, ataxia) which resolved with dose decreases

Interactions with other AEDs?

36

CBD and Other AEDs

Gaston TE et al, 2017

- Retrospectively evaluated changes in AED serum concentrations with concurrent CBD
  - Included 42 subjects in the pediatric arm
- Significant changes in serum concentrations in pediatric patients:
  - Topiramate ($p < 0.01$) – metabolized by CYP2C19 and CYP2C9
  - N-desmethylclobazam ($p < 0.01$) – active metabolite of clobazam
- Association of increased LFTs with concurrent CBD and valproic acid ($p < 0.01$)
  - 4 of 14 children discontinuing valproate and CBD due to increase

37

Benzodiazepines for Home Rescue Therapy

Rectal diazepam gel (Diastat®)

- Round dose to the nearest 2.5 mg
- Must be dialed-in and locked prior to dispensing

Pharmacist Instructions

38

Benzodiazepines for Home Rescue Therapy

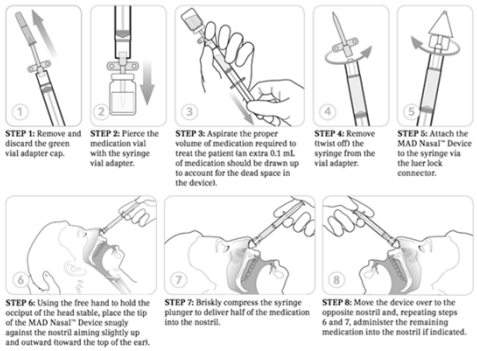
Intranasal midazolam

- Not FDA approved, but Phase III trials being conducted
- Dose: 0.2 to 0.3 mg/kg divided between each nostril
- Use of Intranasal Mucosal Atomization Device (MAD) and ensure "misting"

39

Benzodiazepines for Home Rescue Therapy

Ensure "misting" when administering



STEP 1: Remove and discard the green vial adapter cap.

STEP 2: Pierce the medication vial with the syringe vial adapter.

STEP 3: Aspirate the proper volume of medication required to treat the patient (an extra 0.1 mL of medication should be drawn up to account for the dead space in the device).

STEP 4: Remove (twist off) the syringe from the vial adapter.

STEP 5: Attach the MAD Nasal™ Device to the syringe via the luer lock connector.

STEP 6: Using the free hand to hold the occiput of the head stable, place the tip of the MAD Nasal™ Device snugly against the nostril aiming slightly up and outward (toward the top of the ear).

STEP 7: Briskly compress the syringe plunger to deliver half of the medication into the nostril.

STEP 8: Move the device over to the opposite nostril and, repeating steps 6 and 7, administer the remaining medication into the nostril if indicated.

40

Antiepileptic Drugs by Mechanism of Action

Modulation of Sodium Channels	• **Carbamazepine** • **Oxcarbazepine** • **Phenytoin** • **Lamotrigine**	• Lacosamide • **Valproic acid** • **Topiramate** • **Zonisamide**
Gamma-Aminobutyric Acid (GABA) Receptor Activity	• Gabapentin • Pregablin • **Phenobarbital** • Tiagabine	• **Vigabatrin** • **Benzodiazepines** • Primidone
Other or Unknown Mechanism	• **Levetiracetam** • **Ethosuximide** • Rufinamide	• **Felbamate** • Perampanel • Methsuximide

41

Levetiracetam (Keppra®)

Mechanism of Action
- Unclear – thought to interact with SV2A protein to affect neurotransmitter release and facilitate GABA transmission

Partial and tonic-clonic seizures, primary generalized seizures, myoclonic seizures
- Enteral and IV formulations (1:1 IV to PO conversion)
- **Liu X et al, 2017**
  - **Increased use from 1.8% to 32% in 2009**
- Maintenance dose: 10 to 60 mg/kg/day divided twice daily
- Max dose: 100 mg/kg/day

Metabolism
- Hydrolysis in the blood with renal excretion
- **Minimal drug-drug interactions**
- ILAE TDM: not recommended, can use to check for compliance

Hung OL, Shih RD. Emerg Med Clin North Am. 2011;29(1):141-50.
Patsalos PN, Berry DJ, et al. Epilepsia. 2008;49(7):1239-76.

42

Levetiracetam (Keppra®)

Adverse Effects
- Dizziness, somnolence, **behavioral issues, irritability, hostility**

Pyridoxine (Vitamin B6) supplementation for behavioral issues

Major et al, 2008
- 9 of 22 pediatric patients had improvement (41%)
- If no effect at starting dose within 1 week then most likely not effective

Pyridoxine (Vitamin B6)
- **Dose 25 to 100 mg/day (depending on patient weight)**
- Use over-the-counter (OTC) tablet and crush

Major P, et al. Epilepsy Behav. 2008;13(3):557-9.

43

Ethosuximide (Zarontin®)

Mechanism of Action
- Inhibits T-type calcium channels

Absence Seizures
- Enteral formulations only

Metabolism
- CYP3A4 substrate and metabolized to 3 active metabolites
- ILAE TDM: 40 to 100 mcg/mL
- Half-life: 30 hours → 4 to 5 days to reach steady state concentrations

Adverse Effects
- Dizziness, drowsiness, fatigue, **GI upset**
- DRESS, eosinophilia, leukopenia

Hung OL, Shih RD. Emerg Med Clin North Am. 2011;29(1):141-50.
Patsalos PN, Berry DJ, et al. Epilepsia. 2008;49(7):1239-76.

44

Felbamate (Felbatol®)

Mechanism of Action
- Unknown, potential interaction with N-methyl-D-aspartate (NMDA) receptor

Partial and tonic-clonic seizures, adjunct for partial and generalized seizures, LGS
- Enteral formulations only (suspension and tablet)
- Maintenance dose: 15 mg/kg/day divided in 3 to 4 doses
- Max dose: 3,600 mg/day

Hung OL, Shih RD. Emerg Med Clin North Am. 2011;29(1):141-50.
Felbamate. Pediatric & Neonatal Lexi-Drugs. Accessed February 26, 2018.
Patsalos PN, Berry DJ, et al. Epilepsia. 2008;49(7):1239-76.

45

Felbamate (Felbatol®)

Metabolism
- **Inhibits CYP2C19 and induces CYP3A4**
  - Increases concentrations of phenytoin, phenobarbital, and valproic acid
  - Decreases concentrations of carbamazepine and OCPs
- ILAE TDM: no monitoring recommended

Adverse Effects
- Aplastic anemia
- **Hepatic failure – 67% of reported cases resulted in death**
  - "Informed consent" form required

Hung OL, Shih RD. Emerg Med Clin North Am. 2011;29(1):141-50.
Patsalos PN, Berry DJ, et al. Epilepsia. 2008;49(7):1239-76.

46

Warning for Suicidal Ideation

FDA warning released in 2008
- Association between AEDs and suicidal behavior and ideation
- Incidence rate of 0.43% vs 0.24% in the placebo group
- AEDs reviewed
  - Carbamazepine
  - Felbamate
  - Gabapentin
  - Lamotrigine
  - Levetiracetam
  - Oxcarbazepine
  - Pregablin
  - Tiagabine
  - Topiramate
  - Valproic acid
  - Zonisamide

Manufacturers required to add warning
- Monitor for suicidal thinking, behavior and depression with long-term use

Hesdorffer DC, Kanner AM. Epilepsia. 2009;50(5):978-86.

47

Patient Examples & Key Points

48

Patient Examples

16 year old female with primary generalized tonic-clonic seizures
- Weight 50 kg, BMI 18.9 (29th percentile)

Current medications
- Valproic acid 500 mg TID (30 mg/kg/day)
  - Last level 90 mcg/mL
- Loestrin 1.5/30
- Midazolam 10 mg IN PRN seizure clusters
  - Required 2 doses in the past week

She enjoys running and hiking with friends

What are some considerations for additional agents?

- ❑ Lamotrigine - drug interaction with valproic acid and interaction with OCP
- ❑ Topiramate - adverse effect of decreased sweating
- ☑ Levetiracetam - generally benign adverse effect profile with limited drug-drug interactions

49

Patient Examples

11 year old male with partial onset seizures
- Weight 50 kg, BMI 22.5 (91st percentile)

Current medication include
- Levetiracetam 1000 mg BID (40 mg/kg/day)
- Pyridoxine 100 mg QD (2 mg/kg/day)

His parents have noted agitation and behavioral changes following the start of therapy resulting in disciplinary action at school.

What are some considerations for a new agent?

- ❑ Valproic acid – weight gain occurs in ~50% (BMI 91st percentile)
- ❑ Topiramate – weight loss would potentially be beneficial however associated with memory loss and difficulty concentrating
- ☑ Oxcarbazepine – indicated for partial onset seizures with limited drug-interactions and adverse effects, monitor for rash and hyponatremia

50

Patient Examples

4 year old male with a history of hypoxic ischemic injury at birth and a new diagnosis of LGS
- Seizure types: tonic, atonic, and tonic-clonic seizures
- Weight 16 kg, BMI 15.8 (56th percentile)

Current medications
- Valproic acid 200 mg TID (37.5 mg/kg/day)
  - Last level: 95 mcg/mL

An additional agent is needed for greater seizure control.

What are some considerations for additional agents?

- ❑ Lamotrigine – drug-drug interaction, start slow titration
- ❑ Felbamate – drug-drug interaction causing increased concentrations, BBW for hepatotoxicity
- ☑ Topiramate – ok side effect profile for this patient, monitor for weight loss and nephrolithiasis

51

Key Points

- Epilepsy is the most common pediatric neurologic disorder and is associated with significant development and social issues
- AEDs are used to maintain seizure control but are associated with significant adverse drug effects and drug-drug interactions
- Goal of AEDs: maximize quality of life through seizure control while minimizing adverse effects
- **No two children with epilepsy are the same** and therapy should be tailored to seizure type, co-morbidities, and adverse effects

52

Thank you!

Questions?

53

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54

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55

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56