

Antiepileptic Drugs for Pediatric Seizures

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Disclosure

University of Iowa Stead Family Children's Hospital

- 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

Objectives

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

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

ILAE Classification of Epilepsies 2017

University of Iowa Stead Family Children's Hospital

Seizure Type	Focal (Partial) Onset	Generalized Onset	Unknown Onset
	<p>Aware</p> <p>Impaired Awareness</p> <p>Motor Onset automatisms atonic² clonic epileptic spasms² hyperkinetic myoclonic tonic</p> <p>Nonmotor Onset autonomic behavior arrest cognitive emotional sensory</p> <p>focal to bilateral tonic-clonic</p>	<p>Motor tonic-clonic clonic tonic myoclonic myoclonic-tonic-clonic myoclonic-atonic atonic epileptic spasms</p> <p>Nonmotor (absence) typical atypical myoclonic eyelid myoclonia</p>	<p>Motor tonic-clonic epileptic spasms</p> <p>Nonmotor behavior arrest</p> <p>Unclassified³</p>

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

ILAE Classification of Epilepsies 2017

University of Iowa Stead Family Children's Hospital

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

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

Electroencephalography (EEG)

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- 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



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ILAE Classification of Epilepsies 2017

University of Iowa Stead Family Children's Hospital

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.

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Epilepsy Syndromes

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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)

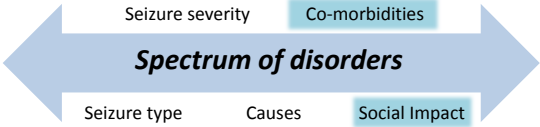
- Most common generalized epilepsy syndrome in late childhood
- Seizure types include absence, myoclonic, and generalized tonic clonic

Sidhu R, et al. *Pediatr Rev*. 2013;34(9):333-41. www.epilepsy.com. Accessed February 26, 2018.

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Pediatric Epilepsy

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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.

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Pediatric Epilepsy

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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.

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Antiepileptic Drugs: Review of the Current Options



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Antiepileptic Drugs by Primary Mechanism of Action

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Modulation of Sodium Channels	<ul style="list-style-type: none"> Carbamazepine Oxcarbazepine Phenytoin Lamotrigine 	<ul style="list-style-type: none"> Lacosamide Valproic acid Topiramate Zonisamide
Gamma-Aminobutyric Acid (GABA) Receptor Activity	<ul style="list-style-type: none"> Gabapentin Pregabalin Phenobarbital Tiagabine 	<ul style="list-style-type: none"> Vigabatrin Benzodiazepines Primidone
Other or Unknown Mechanism	<ul style="list-style-type: none"> Levetiracetam Ethosuximide Rufinamide 	<ul style="list-style-type: none"> Felbamate Perampanel Methsuximide

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Antiepileptic Drugs by Primary Mechanism of Action

University of Iowa Stead Family Children's Hospital

Modulation of Sodium Channels	<ul style="list-style-type: none"> Carbamazepine Oxcarbazepine Phenytoin Lamotrigine 	<ul style="list-style-type: none"> Lacosamide Valproic acid Topiramate Zonisamide
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Sodium Channel Modulators

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

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

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Carbamazepine (Tegretol®)

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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.

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Carbamazepine (Tegretol®)

University of Iowa Stead Family Children's Hospital

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.

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Oxcarbazepine (Trileptal®)

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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.

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Oxcarbazepine vs Carbamazepine

Carbamazepine → Oxidation → 10,11-Epoide → Hydrolysis → **Oxcarbazepine**

Carbamazepine → Reduction → MHD → Conjugation → **Active Metabolite**

- 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

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

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

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Lamotrigine (Lamictal®)

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Adverse Effects

- **Rash** – prominent interaction with concurrent valproic acid
 - 10% develop a rash with an estimated 1% of children developing SIS 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.

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Valproic Acid & Derivatives

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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 may be 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.

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Adverse Effects of Valproic Acid

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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.

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Topiramate

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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.

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Topiramate

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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.

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Zonisamide (Zonegran®)

University of Iowa Stead Family Children's Hospital

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.

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Antiepileptic Drugs by Primary Mechanism of Action

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<p>Modulation of Sodium Channels</p> <ul style="list-style-type: none"> Carbamazepine Oxcarbazepine Phenytoin Lamotrigine Lacosamide Valproic acid Topiramate Zonisamide
<p>Gamma-Aminobutyric Acid (GABA) Receptor Activity</p> <ul style="list-style-type: none"> Gabapentin Pregabalin Phenobarbital Tagabine Vigabatrin Benzodiazepines Primidone

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GABA Receptor Activity

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Potentiate GABA
↓
Chloride channel opening
↓
Decreased depolarizations

Source: Laurence L. Brunton, Randy High-Darwin, Brian C. Knutson. Goodman & Gilman's: The Pharmacological Basis of Therapeutics, Thirteenth Edition. Copyright © McGraw-Hill Education. All rights reserved.

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

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Phenobarbital

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Partial and generalized tonic-clonic seizures

- FDA approved in 1912
- Enteral and IV products

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 DL, 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.

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Vigabatrin (Sabril®)

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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

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.

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Clobazam (Onfi®)

University of Iowa Stead Family Children's Hospital

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

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.

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Clobazam & Cannabidiol

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Cannabidiol (CBD) non-psychoactive 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?

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CBD and Other AEDs

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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-desmethyloclobazam ($p < 0.01$) – 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

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Benzodiazepines for Home Rescue Therapy

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Rectal diazepam gel (Diastat®)

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

Pharmacist Instructions

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Benzodiazepines for Home Rescue Therapy

University of Iowa Stead Family Children's Hospital

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”

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Benzodiazepines for Home Rescue Therapy

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Ensure “misting” when administering

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Antiepileptic Drugs by Mechanism of Action

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Modulation of Sodium Channels	<ul style="list-style-type: none"> Carbamazepine Oxcarbazepine Phenytoin Lamotrigine 	<ul style="list-style-type: none"> Lacosamide Valproic acid Topiramate Zonisamide
Gamma-Aminobutyric Acid (GABA) Receptor Activity	<ul style="list-style-type: none"> Gabapentin Pregabalin Phenobarbital Tiagabine 	<ul style="list-style-type: none"> Vigabatrin Benzodiazepines Primidone
Other or Unknown Mechanism	<ul style="list-style-type: none"> Levetiracetam Ethosuximide Rufinamide 	<ul style="list-style-type: none"> Felbamate Perampanel Methsuximide

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Levetiracetam (Kepra®)

University of Iowa Stead Family Children's Hospital

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 QL, Shih RD. Emerg Med Clin North Am. 2013;29(1):141-50. Patsalos PN, Berry DJ, et al. Epilepsia. 2008;49(7):1239-76.

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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®) 

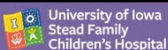
Metabolism

- 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

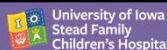
- Association between AEDs and suicidal behavior and ideation
- Incidence rate of 0.43% vs 0.24% in the placebo group
- AEDs reviewed


○ Carbamazepine	○ Pregablin
○ Felbamate	○ Tiagabine
○ Gabapentin	○ Topiramate
○ Lamotrigine	○ Valproic acid
○ Levetiracetam	○ Zonisamide
○ Oxcarbazepine	

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 



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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

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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)

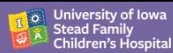
His parents have noted agitation and behavioral changes following the start of therapy resulting in disciplinary action at school.

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

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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

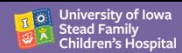
An additional agent is needed for greater seizure control.

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

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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

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Thank you!
Questions?



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