Pediatric Pharmacotherapy 101: CNS Symptom Management

Melissa Hunt, PharmD
Pediatric Clinical Pharmacist
Optum Hospice Pharmacy Services

Disclosure

- I have no relevant financial relationships with manufacturers of any commercial products and/or providers of commercial services discussed in this presentation
- This discussion will include the use of medications for off-label indications

Objectives

- Identify potential causes of pediatric seizures and common seizure types
- Evaluate treatment options as patients approach end-of-life

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Patient Case: Smiley

12 month old with intractable seizures

- 12 month old with intractable seizures
- Weight: 8.6 kg
- Lives at home with parents and siblings
- Bedfast
- Gastrostomy tube
- PMH:
  - Hypoxic ischemic injury
  - Renal dysfunction
  - Seizures
    - Stiffening & rhythmic extremity jerking
    - Eye blinking & facial grimacing
    - Myoclonic jerks of the extremities

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Patient Case: Smiley

12 month old with intractable seizures

Medication	Directions
cloBAZam (Onfi®)	5 mg GT bid
diazepam (Diastat®)	5 mg PR daily prn seizure >5 minutes
levETIRAcetam (Keppra®)	80 mg GT q12h
levocarnitine (Carnitor®)	50 mg GT q8h
lorazepam (Ativan®)	1.2 mg GT q8h
midazolam (Versed®)	2.5 mg IN q6h prn seizures >3 min
valproate sodium (Depakene®)	150 mg GT q6h

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Seizures

- Brief, excessive surge of electrical activity in the brain
- Changes in sensations, perceptions, behaviors
- May be followed by a postictal state

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Prevalence

- Not well documented in hospice
- Often seen in patients with:
  - Primary neurologic illness
  - Brain tumors
  - Metastases
  - Stroke
  - Hypoxia

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Seizure Classification

Focal	Generalized
• Localized region of brain • Formerly partial seizures	• Widespread • Involves both sides of brain • Loss of consciousness

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Seizure Classification: Focal

- Occurs at any age
- Formally referred to as partial seizures
- Abnormal electrical discharge restricted to one part of brain
- With or without impairment of consciousness
- Usually last <2 minutes
- Types include: motor, sensory, autonomic, & psychic

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Seizure Classification: Focal

Benign Rolandic

- Most common in patients 3 – 11 years of age
- Rhythmic twitching of the mouth
- Predominantly occurs during sleep
- No serious underlying structural brain disorder
- Withdraw medications after 1-2 years of control
- Most have spontaneous remission by 18 years of age
- Most common focal seizure

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Seizure Classification: Generalized

Tonic-Clonic Seizures

- Occurs at any age
- Tonic: continuous stiffening of the extremities
- Clonic: rhythmic alternating contraction and relaxation of the muscles
- **Continuous tonic stiffening; followed by rhythmic jerks**
- Air forced past the vocal cords causes a cry or groan
- Loss of consciousness & bladder control
- Followed by postictal phase

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Seizure Classification: Generalized

Absence Seizures

- Most commonly occurs in patients 4-14 years of age
- Brief staring spell (3-30 seconds), with cessation of activity
- May include eye fluttering, mild lip movements, or twitches
- May or may not include loss of body tone
- No postictal phase
- Types include: typical, atypical, & special features (myoclonic, eyelid)
- 50% spontaneous remission; 50% to juvenile myoclonic

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Seizure Classification: Generalized

Myoclonic Seizures

- Occur most commonly in patients 7 – 18 years of age
- Sudden, brief (lasting only a few seconds) muscle jerks occurring on both sides of the body
- Typically occur in the morning
- Triggers: alcohol, lights, sleep deprivation, menstruation
- Types: myoclonic, myoclonic atonic, & myoclonic tonic
- Require lifelong treatment

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Seizure Classification: Generalized

Lennox-Gastaut

- Peak onset: 3 – 5 years of age
- Syndrome involving multiple seizure types
- Usually multiple seizures daily
- Distinctive brain-wave pattern on EEG
- Mental deficiency
- Difficult management, involving multiple medications
- Remission is rare

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Seizure Classification: Generalized

Ohtahara Syndrome

- Occurs most commonly in infants
- Sydrome including multiple seizures types
  - Tonic seizures
  - Partial seizures
  - Myoclonic seizures
- "Burst suppression" pattern on EEG
- Caused by metabolic disorders or structural brain damage
- Severely progressive

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Seizure Classification: Unknown

Epileptic Spasms

- Infantile spasms also referred to as West Syndrome
- Occurs most commonly in patients 2 – 12 months
- Clustered bouts of 3-6 myoclonic jerks with momentary loss of tone,
- Clusters of forceful extension or flexion of the head, legs, and trunk
- Overproduction of corticotropin releasing hormone
- EEG finding of hypsarrhythmia

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Seizure Classification: Unknown

Febrile Seizures

- Occurs most often in children 6 months – 6 years
- Convulsion triggered by fever
- Loss of consciousness, but eyes typically remain open
- Most are simple (lasting < 5 minutes)

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Patient Case: Smiley

12 month old with intractable seizures

How would you classify Smiley's seizures?

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Patient Case: Smiley

12 month old with intractable seizures

- Seizure classification
  - Description
    - Stiffening & rhythmic extremity jerking
    - Eye blinking & facial grimacing
    - Myoclonic jerks of the extremities
  - Classification
    - Tonic-clonic seizures
    - Possibly absence component
    - Occasional myoclonic jerks

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Causes of Seizures

Conditions That Can Mimic Seizures

- Anxiety
- Behavioral events
  - Tantrums
  - Daydreaming
- Complicated migraine
- Conversion disorders
- Delirium
- Gastroesophageal reflux
- Syncope
  - Breath holding
  - Vasovagal syncope
  - Arrhythmias
- Tics or dyskinesia
- Transient ischemic attacks
- Stroke

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Causes of Seizures at End-of-Life

- Primary neurologic illness
- Overwhelming systemic illness or infection
- Disease progression
- Metabolic derangement
  - Hypoglycemia (<36 mg/dL)
  - Hyponatremia (<125 mEq/L)
  - Hypocalcemia (<8 mg/dL)
  - Hypomagnesemia (<1 mEq/L)
  - Uremia
  - Multi-system organ failure
- Hypoxic injury

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Causes of Increased Seizure Activity

- Medications
  - Changes
  - Interactions
  - Inappropriate levels
  - ↓ seizure threshold
- Fever
- Hepatic failure
- Hypoxia
- ↑ intracranial pressure
- Infection
- Renal failure
- Sleep deprivation
- Stroke
- Withdrawal
  - Alcohol
  - Medications

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Causes of Increased Seizure Activity

take note

- During an acute illness, patients may need:
  - Increased dose
  - Additional anti-epileptic drugs (AEDs)

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Patient Case: Smiley

12 month old with intractable seizures

What are potential causes of seizures in Smiley?

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Patient Case: Smiley

12 month old with intractable seizures

- Potential causes
  - Hypoxic ischemic injury
  - Renal dysfunction
  - Medications
  - Infection

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Assessment

Acute Assessment

- Airway
- Breathing
- Circulation
- Glucose
- Electrolytes

- Confirm seizure activity
- Injury
  - Trauma causing seizure
  - Seizure causing trauma

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General Assessment

- Electroencephalography (EEG)
- Characteristics
- Frequency
- Impact
- Medication history
  - Changes
  - Interactions
  - Decrease threshold

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Patient Case: Smiley

12 month old with intractable seizures

What components should be focused on during assessment of Smiley?

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Patient Case: Smiley

12 month old with intractable seizures

- Assessment
  - EEG
  - Medication review
  - Laboratory evaluation
    - valproic acid serum levels
    - Renal function
    - Hepatic function

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Non-Pharmacological Options

Non-Pharmacological Seizure Management

- Gently move patient to a stable position
  - Lying down to prevent fall and injury
  - On one side to minimize the risk of aspiration
- *Do not insert anything into the patient's mouth*
- Assess airway, breathing, and circulation
  - Jaw thrust maneuver may help open the airway
  - Brief period of apnea and asystole possible at peak

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Non-Pharmacological Options for Seizures

- Assess for potential underlying causes
  - Hypoglycemia
  - Electrolyte abnormalities
- Ensure seizure resolves into a post-ictal phase
- Educate regarding seizure precautions
  - What to expect
  - How to manage seizures if they recur
  - Ways to minimize seizures if underlying cause

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Patient Case: Smiley

12 month old with intractable seizures

What non-pharmacological interventions should be discussed with Smiley?

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Patient Case: Smiley

12 month old with intractable seizures

- Non-pharmacological therapies
  - Education
    - Management of acute episodes
    - Positioning
    - Medication administration
      - Technique
      - Frequency

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Acute Seizure Management

Acute Management of Seizures

- Develop a written seizure plan
- Benzodiazepines first line
- Routes of administration
  - Intravenous
  - Rectal
  - Sublingual/ buccal
  - Intranasal
  - Intramuscular
  - Subcutaneous

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Rectal Medication Administration

- In syringe, combine drug & diluent
- Lubricate rectal dosage forms or devices
- Position child on his/her side with knees bent
- Gently insert catheter tip well into the rectum:
  - Infant: 1 inch
  - 2 to 4 years: 2 inches
  - 4 to 10 years: 3 inches
  - 11 years: 4 inches
- Smoothly inject medication solution

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Sublingual Medication Administration

- Wet tablets or crush and mix with 1-2 mL water
  - Avoid volumes >2 mL
- Only utilize immediate-release preparations SL
  - Do not crush enteric-coated or controlled-release tablets

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Intranasal Medication Administration

- Clear the nasal cavity
- Prepare dose
  - Max volume 0.1 mL/nare
- Position patient
  - Lateral head low
    - Atomize medication in lower nostril
- Insert applicator tip into nostril
  - Administer half the total dose in each nare
- Repeat in opposite nostril

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General Benzodiazepine Considerations

- Equal efficacy between agents
- Differences between agents
  - Pharmacokinetic profile
  - Cost
  - Patient preference
- Rarely rationale for using multiple benzodiazepines
- Provide amnesia and anxiolysis
- Monitor for potential CYP450 drug interactions
- Tolerance develops

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Benzodiazepine Side Effects

- Hypotension
- Bradycardia
- Confusion
- Combativeness
- Nausea/vomiting
- Headache
- Myoclonic jerking
  - Especially in neonates
- Drowsiness

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Benzodiazepines Comparison

Medication	Routes	Comments
cloBAZam (Onfi®)	PO	•Intermediate duration of action •Adjunct therapy for Lennox-Gastaut
clonazePAM (KlonoPIN®)	PO, SL, PR	•Long duration of action
diazepam (Diastat®)	PO, SL, PR, IV	•Short duration of action due to rapid redistribution into peripheral tissues •Tissue necrosis reported with IM
LORazepam (Ativan®)	PO, SL, IN, PR, IV, SQ, IM	•Slower onset, but longer duration in the CNS than diazepam •Better absorbed IM/SQ than diazepam
midazolam (Versed®)	PO, SL, IN, PR, IV, SQ, IM	•Quick onset •Short duration of action

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Benzodiazepine Administration

Rectal	Sublingual/ Buccal	Intranasal
• clonazePAM (KlonoPIN®) • diazepam (Diastat®) • LORazepam (Ativan®) • midazolam (Versed®)	• clonazePAM (KlonoPIN®) • diazepam (Diastat®) • LORazepam (Ativan®) • midazolam (Versed®)	• LORazepam (Ativan®) • midazolam (Versed®)

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Second-Line Acute Treatment Options

- levETIRAcetam (Keppra®)
- PHENobarbital
- phenytoin (Dilantin®)
- valproic acid (Depakene®, Depacon®)

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Patient Case: Smiley

12 month old with intractable seizures

What are possible treatment options for acute seizure management in Smiley?

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Patient Case: Smiley

12 month old with intractable seizures

- Current acute seizure plan
  - diazepam (Diastat®) 5 mg PR daily prn seizure >5 minutes
  - midazolam (Versed®) 2.5 mg IN q6h prn seizures >3 minutes
- Other options
  - PHENobarbital
    - Loading dose 172 mg PR (1.3 mL of 130 mg/mL injectable)
  - valproic acid (Depakene®)
  - levETIRAcetam (Keppra®)

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Maintenance Seizure Management

Maintenance Seizure Management

take note

- For patients with pre-existing seizure disorders
  - Continue the current antiepileptic medication
    - As long as it is effective in controlling seizures

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Maintenance Management of Seizures

- Empiric therapy based on:
  - Diagnosis
  - Seizure type
  - Age
- Initiate one first-line medication
  - Titrate gradually until either:
    - Seizure control
    - Side effects
- If seizures remain uncontrolled, add 2nd medication
  - Ideally another first-line agent

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Maintenance Management of Seizures

Myoclonic Seizures

First Line	Second Line
• valproic acid (Depakene®) • levETIRAcetam (Keppra®)	• topiramate (Topamax®) • zonisamide (Zonegran®) • acetaZOLAMIDE (Diamox®) • lamoTRIgine (LaMICtal®)

Unacceptable: carBAMazepine (TEGretol®), phenytoin (Dilantin®), felbamate (Felbatol®), OXcarbazepine (Trileptal®), pregabalin (Lyrica®), tiaGABine (Gabatril®)

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Maintenance Management of Seizures

- Consider second line agents if:
  - All first line agents have been tried
  - Other first line agents are inappropriate
    - Age restrictions, side effects, or other conditions
  - Mixed seizure type makes 2nd line agent more appropriate

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Treatment Options: ORAL

ONLY Recommended ORALLY

- ethosuximide (Zarontin®)
- felbamate (Felbatol®)
- gabapentin (Trileptal®)
- OXcarbazepine (Trileptal®)
- phenytoin (Dilantin®)
- pregabalin (Lyrica®)
- primidone (Mysoline®)
- rufinamide (Banzel®)
- tiaGABine (Gabatril®)
- vigabatrin (Sabril®)
- zonisamide (Zonegran®)

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Treatment Options

When Oral Route No Longer Appropriate

Rectal	Sublingual/ Buccal	Parenteral
• carBAMazepine (TEGretol®) • lamoTRIgine (LaMICtal®) • levETIRAcetam (Keppra®) • PHENobarbital • topirimate (Topamax®) • valproic acid (Depakene®) • clonazepam (KlonoPIN®) • diazepam (Diastat®) • lorazepam (Ativan®) • dexamethasone (Decadron®)	• lamoTRIgine (LaMICtal®) • Clonazepam (KlonoPIN®) • diazepam (Valium®) • lorazepam (Ativan®) • midazolam (Versed®) • dexamethasone (Decadron®)	• FOSphenytoin (Cerebyx®) • Lacosamide (Vimpat®) • levETIRAcetam (Keppra®) • PHENobarbital • valproic acid (Depakene®) • diazepam (Valium®) • lorazepam (Ativan®) • midazolam (Versed®) • dexamethasone (Decadron®)

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Seizure Management at End-of-Life

- Taper AEDs slowly to prevent withdrawal seizures
- Change to alternative agents if difficulty swallowing
  - Lorazepam (Ativan®)
  - PHENobarbital

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Drug Interactions

- Cytochrome P-450 enzyme interactions
  - Many antiepileptic drugs are CYP-450 enzyme inducers
  - Many antiepileptic drugs are metabolized via CYP-450 enzyme system
- Monitor for possible effects of the interaction
- Interactions may require
  - Dose adjustments
  - Increased drug level monitoring
- Antiepileptic agents may interact with feeds or adhere to tubing

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Maintenance Seizures Management

PHENobarbital

- Barbiturate
- No age restrictions
- Side effects
  - Cognitive dysfunction, sedation, hyperactivity
- Typical starting dose
  - Load: 15-20 mg/kg
  - Maintenance: 2.5 mg/kg q12h
- Routes
  - PO, PR, IV, IM, SQ
  - Elixir, tablets, injection
- Significant drug interactions
- Therapeutic serum levels: 15-40 mcg/mL

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Maintenance Seizure Management

PHENobarbital

take note

- Appropriate for maintenance & rescue therapy
- Weigh risks versus benefits

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Maintenance Seizure Management

phenytoin (Dilantin®)

- No age restrictions
- Side effects
  - Rash, gingival hyperplasia, hirsutism, nystagmus, ataxia, cognitive impairment, ↓ bone density
- Typical starting dose
  - Load: 15-20 mg/kg
  - Maintenance (initial): 2.5 mg/kg q12h
- Routes
  - PO, IV
  - Suspension, chewable tablets, capsules (IR & ER), injection
- Significant drug interactions
- Therapeutic serum levels: 10-20 mcg/mL

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Maintenance Seizure Management

phenytoin (Dilantin®)

take note

- Often difficult to administer
  - IV risk of extravasation, hypotension, & arrhythmias
    - Utilize FOSphenytoin IV
  - Poor absorption rectally
  - Suspension
    - Shake well
    - May adhere to feeding tubes
    - Separate from feeds by 1-2 hours before & after dose
  - Chewable tablets
    - May be difficult to titrate dose

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Maintenance Seizure Management

levETIRAcetam (Keppra®)

- No age restrictions
- Side effects
  - Rare
  - Behavioral disturbances
- Typical starting dose
  - 10-20 mg/kg q12h
- Routes
  - PO, PR, IV
  - Suspension, tablets (IR & ER), injection, infusion
- Minimal drug interactions
- Serum levels not necessary

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Maintenance Seizure Management

levETIRAcetam (Keppra®)

take note

- Excellent safety profile
  - Minimal adverse effects
- Broad-spectrum antiepileptic activity
- Lacks significant drug interactions
- Favorable pharmacokinetic profile

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Maintenance Seizure Management

valproic acid (Depakote®, Depakene®)

- Age restrictions
  - IR: >2 years
  - ER: >10 years
- Warnings
  - Hepatotoxicity
    - Levocarnitine for liver protection
  - Pancreatitis
- Side effects
  - Headache, somnolence, dizziness, weakness, blurred vision
  - Pain, alopecia, nausea, thrombocytopenia, tremor

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Maintenance Seizure Management

valproic acid (Depakote®, Depakene®)

- Typical starting dose
  - Initial: 10-15 mg/kg divided q8-24h
  - Maintenance: 30-60 mg/kg divided q8-12h
- Routes
  - PO, PR, IV
  - Syrup, capsules, ER capsules, injection, sprinkles, EC tablets, ER tablets
- Significant drug interactions
- Therapeutic serum levels: 40-100 mcg/mL
  - Generally increases 5 mcg/mL for every mg/kg loaded

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Maintenance Seizure Management

valproic acid (Depakote®, Depakene®)

take note

- Effective for all seizure types
- Black Box Warning
  - Hepatotoxicity
    - Increased risk in patients <2 years

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Patient Case

Patient Case: Smiley

12 month old with intractable seizures

- Weight: 8.6 kg
- Lives at home with parents and siblings
- Bedfast
- Gastrostomy tube
- PMH:
  - Hypoxic ischemic injury
  - Seizures
    - Stiffening & rhythmic extremity jerking
    - Eye blinking & facial grimacing
    - Myoclonic jerks of the extremities
  - Renal dysfunction

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Patient Case: Smiley

12 month old with intractable seizures

Medications	Directions
cloBAZam (Onfi®)	5 mg GT bid
diazepam (Diastat®)	5 mg PR daily prn seizure >5 minutes
levETIRAcetam (Keppra®)	80 mg GT q12h
levocarnitine (Carnitor®)	50 mg GT q8h
lorazepam (Ativan®)	1.2 mg GT q8h
midazolam (Versed®)	2.5 mg IN q6h prn seizures >3 min
valproate sodium (Depakene®)	150 mg GT q6h

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Patient Case: Smiley

12 month old with intractable seizures

What recommendations would you make for managing Smiley's seizures?

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Patient Case: Smiley

12 month old with intractable seizures

- Recommendations:
  - Adjust valproate sodium (Depakene®) to q8h
    - Same total daily dose divided q8h
    - Monitor level and hepatic function
  - Increase levETIRAcetam (Keppra®) dose
  - Review acute seizure management plan
    - midazolam (Versed®) versus diazepam (Diastat®)
    - Medication administration
  - Discuss duplicate benzodiazepine orders
  - Monitor renal function

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Patient Case: Smiley

12 month old with intractable seizures

New Medication Regimen

Medications	Directions
cloBAZam (Onfi®) *weaning off*	2.5 mg GT bid x1 week then 2.5 mg daily x1 week, then D/C
diazepam (Diastat®) *Do not reorder*	5 mg PR daily prn seizure >5 minutes *when supply depleted*
levETIRAcetam (Keppra®)	100 mg GT q12h
levocarnitine (Carnitor®)	50 mg GT q8h
lorazepam (Ativan®)	1.2 mg GT q8h
midazolam (Versed®)	4 mg IN q6h prn seizures >3 min
valproate sodium (Depakene®)	200 mg GT q8h

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Summary

- Develop written seizure plan
- Plan ahead for end-of-life seizure management
- Continue current antiepileptic medication if effective
- Choose antiepileptic therapy based on seizure type and patient specific factors

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Questions?

Melissa Hunt, Pharm.D.
Pediatric Clinical Pharmacist
Optum Hospice Pharmacy Services
melissa.hunt@optum.com