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

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
Patient Case: Smiley
12 month old with Intractable Seizures

- Medications:
  - 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

Seizures

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

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

Seizure Classification

- **Focal**
  - Localized region of brain
  - Formerly partial seizures

- **Generalized**
  - Widespread
  - Involves both sides of brain
  - Loss of consciousness
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

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
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

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
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

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
Seizure Classification: Generalized Ohtahara Syndrome

- Occurs most commonly in infants
- Syndrome 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

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
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)

Patient Case: Smiley
12 month old with Intractable Seizures

How would you classify Smiley’s seizures?
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

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

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
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

**take note**

- During an acute illness, patients may need:
  - Increased dose
  - Additional anti-epileptic drugs (AEDs)
What are potential causes of seizures in Smiley?

• Potential causes
  – Hypoxic ischemic injury
  – Renal dysfunction
  – Medications
  – Infection
Assessment

- Airway
- Breathing
- Circulation
- Glucose
- Electrolytes

Acute Assessment

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

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

Patient Case: Smiley
12 month old with Intractable Seizures

What components should be focused on during assessment of Smiley?
Patient Case: Smiley
12 month old with Intractable Seizures

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

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

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
Patient Case: Smiley
12 month old with Intractable Seizures

What non-pharmacological interventions should be discussed with Smiley?

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

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
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

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
Benzodiazepine Side Effects

- Hypotension
- Bradycardia
- Confusion
- Combativeness
- Nausea/vomiting
- Headache
- Myoclonic jerking (especially in neonates)
- Drowsiness

Benzodiazepines Comparison

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

**take note**

- **Rectal**
  - clonazePAM (KlonoPIN®), diazepam (Diastat®), LORazepam (Ativan®), midazolam (Versed®)
- **Sublingual/buccal**
  - clonazePAM (KlonoPIN®), diazepam (Diastat®), LORazepam (Ativan®), midazolam (Versed®)
- **Intranasal**
  - LORazepam (Ativan®), midazolam (Versed®)

Second-Line Acute Treatment Options

- levETIRAcetam (Keppra®)
- PHENobarbital
- phenytoin (Dilantin®)
- valproic acid (Depakene®, Depacon®)
Patient Case: Smiley
12 month old with Intractable Seizures

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

• 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®)
Maintenance Seizure Management

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

Myoclonic Seizures

First Line
• valproic acid (Depakene®)
• levETIRacetam (Keppra®)

Second Line
• topiramate (Topamax®)
• zonisamide (Zonegran®)
• acetazOLAMIDE (Diamox®)
• lamotRIGine (LaMICtal®)

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

Treatment Options
ONLY Recommended ORALLY

• ethosuximide (Zarontin®)
• felbamate (Felbatol®)
• gabapentin (Trileptal®)
• OXcarbazepine (Trileptal®)
• phenytoin (Dilantin®)
• pregabalin (Lyrica®)

• primidone (Mysoline®)
• rufinamide (Banzel®)
• tiaGABine (Gabatri®)
• vigabatrin (Sabril®)
• zonisamide (Zonegran®)
Treatment Options
When Oral Route No Longer Appropriate

<table>
<thead>
<tr>
<th>Rectal</th>
<th>Sublingual/Buccal</th>
<th>Parenteral</th>
</tr>
</thead>
<tbody>
<tr>
<td>carBAMazepine (TEGretol®)</td>
<td>lamotRilgine (LaMICtal®)</td>
<td>FOSphenytoin (Cerebyx®)</td>
</tr>
<tr>
<td>lamotRilgine (LaMICtal®)</td>
<td>Clonazepam (KlonoPIN®)</td>
<td>Lacosamide (Vimpat®)</td>
</tr>
<tr>
<td>levETIRAcetam (Keppra®)</td>
<td>diazepam (Valium®)</td>
<td>levETIRAcetam (Keppra®)</td>
</tr>
<tr>
<td>PHENobarbital</td>
<td>lorazepam (Ativan®)</td>
<td>PHENobarbital</td>
</tr>
<tr>
<td>topirimate (Topamax®)</td>
<td>midazolam (Versed®)</td>
<td>valproic acid (Depakene®)</td>
</tr>
<tr>
<td>valproic acid (Depakene®)</td>
<td>dexamethasone (Decadron®)</td>
<td>diazepam (Valium®)</td>
</tr>
<tr>
<td>clonazepam (KlonoPIN®)</td>
<td>lorazepam (Ativan®)</td>
<td>midazolam (Versed®)</td>
</tr>
<tr>
<td>diazepam (Diastat®)</td>
<td>lorazepam (Ativan®)</td>
<td>dexamethasone (Decadron®)</td>
</tr>
<tr>
<td>dexamethasone (Decadron®)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Seizure Management at End-of-Life

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

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

**take note**

**phenytoin** (Dilantin®)
- Acute & maintenance treatment
- 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
Maintenance Seizure Management

**take note**

**phenytoin** (Dilantin®)
- 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

---

**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
Maintenance Seizure Management

*Take note*

levETIRAcetam (Keppra®)
- Excellent safety profile
  - Minimal adverse effects
- Broad-spectrum antiepileptic activity
- Lacks significant drug interactions
- Favorable pharmacokinetic profile

---

**Valproic Acid (Depakote®, Depakene®)**

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

take note

valproic acid (Depakote®, Depakene®)
• Effective for all seizure types
• Black Box Warning
  – Hepatotoxicity
    • Increased risk in patients <2 years
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

Patient Case: Smiley
12 month old with Intractable Seizures

• Medications:
  – 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 q8h prn seizures >3 min
  – valproate sodium (Depakene®) 150 mg GT q8h
What recommendations would you make for managing Smiley's seizures?

- 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
Patient Case: Smiley
12 month old with Intractable Seizures

• New Medication Regimen
  – cloBAZam (Onfi®) weaning off
    • 2.5 mg GT bid x1 week, then 2.5 mg daily x1 week, then D/C
  – diazepam (Diastat®) 5 mg PR daily prn seizure >5 minutes
    • Do not reorder when supply in the home 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

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
References

- Wilfong A. Overview of the classification, etiology, and clinical features of pediatric seizures and epilepsy. In: UpToDate, Nordli DR (Ed), UpToDate, Waltham, MA, 2012. [cited 2012 July 30]

References

• Rossetti AO, Bromfield EB. Determinants of success in the use of oral levetiracetam in status epilepticus. Epilepsy Behav 2006;8:651-4.

References

• Maynard GA, Jones KM, Guidry JR. Phenytoin absorption from tube feedings. Arch Intern Med 1987; 147(10); 1821.
Questions?

Melissa Hunt, Pharm.D.
Pediatric Clinical Pharmacist
Optum Hospice Pharmacy Services
mhunt@hospiscript.com