Medical Management of Pediatric Seizures
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Disclosure
Linda D. Leary, M.D. discloses the following relationships with commercial companies:
Owns stock in Johnson & Johnson

Learning Objectives
At the end of this presentation the participant will be able to:
1. Determine appropriate antiepileptic drugs (AEDs) based on seizure type
2. Recognize current AEDs and typical adverse events

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Antiepileptic Drugs (AEDs)
- Decreases the severity and/or frequency of seizures
- Treats the symptoms of the seizures not the underlying condition
- Goal of treatment to maximize quality of life through seizure control while minimizing adverse effects

Challenges in Pediatric AED Use
- Drugs initially tested in adults
- Rare inclusion of young children in trials
- Formulation may not be child friendly
- Different susceptibility to adverse effects
- Epilepsy types different in children
- Different pharmacokinetics

History of AED Development
- 1857 - bromides
- 1912 - phenobarbital
- 1937 - phenytoin
- 1944 - trimethadione
- 1954 - primidone
- 1958 - ACTH
- 1958 - ethosuximide
- 1963 - diazepam
- 1974 - carbamazepine
- 1975 - clonazepam
- 1978 - valproate
- 1993 - felbamate
- 1995 - gabapentin
- 1995 - lamotrigine
- 1997 - topiramate
- 1999 - levetiracetam
- 2000 - oscarbazepine
- 2005 - pregabalin
- 2008 - lacosamide
- 2009 - vigabatrin
- 2011 - clozazepam
- 2012 - paravanel
- 1993 - felbamate
- 1995 - lamotrigine
- 1997 - topiramate
- 1999 - levetiracetam
- 2000 - oscarbazepine
- 2005 - pregabalin
- 2008 - lacosamide
- 2009 - vigabatrin
- 2011 - clozazepam
- 2012 - paravanel
Pediatric FDA Approved AEDs

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Cellular Basis of Seizures

**Excitation**
- Inward Na⁺ and Ca²⁺ currents
- Neurotransmitters: glutamate, aspartate

**Inhibition**
- Inward Cl⁻, outward K⁺ currents
- Neurotransmitter: GABA

Mechanisms of Action of AEDs

- Reduce excitation
  - Na⁺ channels blockers / inactivators
  - Ca²⁺ channel blockers
  - Reduce glutamate

- Increase inhibition
  - K⁺ channel modulators
  - Enhance GABA
Summary of AED Mechanisms

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<th>AED</th>
<th>Na⁺ Channel Blockade</th>
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*Adapted from White HS and Rho JM, Mechanisms of Action of AEDs, 2010.

Approach to Treatment: Absence

- Treatment of choice: ethosuximide (CAE), valproate, lamotrigine
- Alternative options: zonisamide, topiramate, levetiracetam, felbamate


Approaches to Treatment: Myoclonic / GTCS

- Treatment of choice: valproate, topiramate, zonisamide, lamotrigine
- Other options: levetiracetam, benzodiazepines, felbamate, phenobarbital

Approaches to Treatment: Partial

- Treatment of choice: Oxcarbazepine, carbamazepine, levetiracetam, lamotrigine*
- Other options: gabapentin, lacosamide, phenytoin, phenobarbital, valproate


Approach to Treatment: Lennox-Gastaut Syndrome

- Treatment of choice: valproate, topiramate, lamotrigine*
- Other options: zonisamide, levetiracetam, rufinamide, felbamate, clobazam
- Most AEDs have a place in treatment of LGS


Approach to Treatment: Newborns & Infants

- Limited data
- Transition from phenobarbital to newer agents
- Limited reports of levetiracetam, topiramate use in infants

- Infantile spasms
  - Best data for ACTH, prednisone, vigabatrin (T.S.C.)
  - Efficacy based on limited data with topiramate, zonisamide, valproate, felbamate, phenobarbital, benzodiazepines

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Types of Adverse Effects

- Acute dose-related
- Chronic
- Idiosyncratic

Acute / Dose Related AEs

- Sedation
  - Many AEDs except lamotrigine / felbamate
- Imbalance, dizziness
  - Often with Na+ channel drugs
- Nausea
- Tremor
  - Valproate / lamotrigine

Acute / Dose Related AEs (2)

- Mood issues
  - May see with any AED
  - Levetiracetam / gabapentin
- Cognitive decline
  - Phenobarbital, topiramate > zonisamide
- Paresthesias / kidney stones / oligohydrosis
  - Topiramate / zonisamide
Acute / Dose Related AEs (3)
- Diplopia
- Carbamazepine / lamotrigine
- Lab abnormalities
  - Hyponatremia
  - Oxcarbazepine>carbamazepine
  - Metabolic acidosis
    - Topiramate / zonisamide
  - Hematologic
  - Changes in AST or ALT

Acute / Dose Related AEs (4)
- Weight gain
  - Valproate
  - Gabapentin
- Weight loss
  - Topiramate
  - Zonisamide
  - Felbamate

Idiosyncratic Adverse Effects
- Rash
- Stevens-Johnson Syndrome
- Hematologic abnormalities
- Hepatotoxicity
Pharmacokinetic Factors in Pediatrics

- Neonate - often lower per kg doses
  - Low protein binding
  - Low metabolic rate
- Children - higher, more frequent doses
  - Faster metabolism

Pharmacological Differences Affect Adverse Effects

- Carbamazepine
  - Adverse reactions to metabolite
  - ↑ CBZ epoxide: CBZ ratio in children
  - More rapid CYP metabolism to epoxide > elimination
  - Especially elevated with concomitant valproate use
  - Labs aren't useful

AED Hypersensitivity Syndrome

- Characterized by rash, systemic involvement
- Cross-reactivity
  - phenytoin
  - carbamazepine
  - phenobarbital
  - oxcarbazepine
- Relative cross reactivity - lamotrigine

AED → arene oxide intermediate → non-toxic metabolite
Lamotrigine Metabolism

![Lamotrigine Metabolism Diagram]

Risk of Adverse Events

- Felbamate
  - Aplastic anemia 1 in 3,600 to 5,000 exposed patients
    - Never reported in children < 13 years
  - Fatal liver toxicity
    - 1 in 12,000 to 34,000

Valproic Acid Related Liver Toxicity

- Increased risk in children < 3 years (1:500) if
  - Taking several AEDs
  - Coexistent medical issues (IDD, metabolic syndrome)
- Children < 2 years with higher risk (1:800) for developing hepatotoxic syndrome without risk factors
- Adult risk of fatal hepatotoxicity without risk factors
  - 1:500,000

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Carnitine Use

- Bohan et al. Neurology 2001
- Evaluation of 92 patients with severe valproate-induced hepatotoxicity
  - 48% of 42 patients treated with L-carnitine survived vs. 10% of 50 patients treated with supportive care
- Dosing for carnitine 50-100 mg/kg/day

Avoid Use of VPA in Metabolic Disease

- Valproic acid alters fatty-acid metabolism, impairs beta-oxidation (a mitochondrial process), and disrupts the urea cycle
- Through several mechanisms, valproic acid depletes carnitine levels resulting in decreased transport of fatty acids and their accumulation in the cytoplasm

Chronic Adverse Effects of AEDs

- Osteomalacia or osteoporosis
- Teratogenesis
- Reproductive
- Altered connective tissue metabolism or growth
Conclusions

- Optimal AED treatment of child based on efficacy and risks
- Knowledge of age-specific toxicity important in clinician and parental decisions
- Limitations in clinical trials impair data driven decisions