Medical Management of Seizures and Epilepsy

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I have no disclosures or conflicts of interest.

Brand names of certain medications may be discussed; this is only for simplicity and clarification and does not constitute an endorsement.

Off-label use of medication may be discussed in this lecture.
Objectives

- Discuss the rational for treatment of epilepsy
- Understand the process by which physicians determine choice of antiepileptic medication therapy
- Discuss the ways in which antiepileptic medications work to both stop and prevent seizures and review currently available antiepileptic medications
The Problem

- 65 million people worldwide live with epilepsy
  - 150,000 new cases each year
    - Children and older adults are the most rapidly growing segments
    - Incidence
      - 50 in 100,000 in childhood
      - 20 in 100,000 in adolescence
  - 3 million people in the United States
    - Fourth most common neurologic disease
    - Prevalence
      - 5 in 1000 children in developed countries
- Annual direct medical cost of $12.5 billion
The Real Impacts of Epilepsy

- Development and cognition
- Psychiatric illness
- Social stigma
- Safety
- Independent living
- Employment
- SUDEP
- Status epilepticus
Which Medicine First?

- Age
- Cost
- Availability
- Administration
- Ease of dosing
- Balance of seizure control and side effects
History of Anti-Epileptic Drugs

- First generation
  - Ethosuximide
  - Ethotoin
  - Primidone
  - Phensuximide
  - Phenacemide
  - Corticosteroids/ACTH
  - Paramethadione
  - Mephenytoin
  - Trimethadione
  - Acetazolamide

- Second generation
  - Phenobarbital
  - Mephenobarbital

- Third generation
  - Bromide
  - Borax

Year of introduction:
- 1850
- 1870
- 1910
- 1930
- 1950
- 1970
- 1990
- 2010
Seizure

History, Physical Exam, Neuroimaging, EEG

Epilepsy? (Yes/No)

No Preventative AED

Onset?

Generalized

Epilepsy Syndrome (Yes/No)

Broad Spectrum AED

Yes

Syndrome Specific AED

No

Focal

Epilepsy Syndrome (Yes)

Narrow Spectrum AED

 Syndrome Specific AED
ILAE 2017 Classification of Seizure Types Basic Version

1. Definitions, other seizure types and descriptors are listed in the accompanying paper & glossary of terms

2. Due to inadequate information or inability to place in other categories
### Form, Function and Other Considerations

#### Formulations
- **Liquid**
  - Elixir
  - Suspension
  - Solution
- **Tablet**
  - Tablet
  - Chewable
  - Disintegrating
  - Extended release
- **Capsule**
  - Capsule
  - Sprinkle
  - Extended release
- **Other**
  - Nasal spray
  - Rectal gel
  - Intravenous

#### Urgency
- Loss of consciousness
- Risk of physical injury
- High seizure burden
- Active seizure
- Status epilepticus

#### Positive Effects
- **Comorbidities**
  - Trigeminal neuralgia
  - Neuropathic pain
  - Migraine
  - Essential Tremor
  - Anxiety
  - Bipolar disorder

#### Adverse Effects
- Drug interactions
- Side effects
  - Drowsiness, dizziness, rash
- Depression and suicidality
- Pregnancy impact
Mechanism of Action
Seizures and Epilepsy

- Disruption of normal balance of inhibition and excitation
  - Inhibition
    - GABA
  - Excitation
    - AMPA
    - NMDA
    - Metabotropic
      - Sodium
      - Potassium
      - Calcium

- Synchronous electrical discharges
## Categorizing Anti-Epileptics

<table>
<thead>
<tr>
<th>Spectrum</th>
<th>Specific Receptors</th>
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<tbody>
<tr>
<td><strong>Broad</strong></td>
<td><strong>Sodium Channel Blockade</strong></td>
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<tr>
<td>Levetiracetam</td>
<td>Carbamazepine</td>
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<tr>
<td>Lamotrigine</td>
<td>Oxcarbazepine</td>
</tr>
<tr>
<td>Zonisamide</td>
<td>Eslicarbazepine</td>
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<tr>
<td>Valproic acid</td>
<td>Felbamate</td>
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<td>Lacosamide</td>
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<tr>
<td>Phenobarbital</td>
<td>Phenytoin</td>
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<tr>
<td>Tiagabine</td>
<td>Rufinamide</td>
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<tr>
<td>Benzodiazepines</td>
<td>Ethosuximide</td>
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<tr>
<td>Vigabatrin</td>
<td>Ezogabine</td>
</tr>
<tr>
<td><strong>Narrow</strong></td>
<td><strong>Calcium Channel Blockade</strong></td>
</tr>
<tr>
<td>Perampanel</td>
<td>Ethosuximide</td>
</tr>
<tr>
<td>Phenytoin</td>
<td>Gabapentin</td>
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<td>Ethosuximide</td>
<td>Topiramate</td>
</tr>
</tbody>
</table>
More Receptors

- **GABA modulation**
  - Benzodiazepines
  - Phenobarbital
  - Felbamate
  - Topiramate
  - Zonisamide

- **Increase GABA**
  - Tiagabine
  - Vigabatrin

- **NMDA Receptor**
  - Perampanel
  - Topiramate

- **Synaptic Vesicle Release**
  - Levetiracetam
  - Brivaracacetam
Syndromes

- Childhood absence epilepsy
  - Ethosuximide
  - Lamotrigine
  - Valproic acid
- Juvenile Myoclonic
  - Valproate
- Infantile spasms
  - ACTH
  - Vigabatrin (TSC)
- SLC2A1 (GLUT-1)
  - Ketogenic diet
- Lennox-Gastaut
  - Clobazam
  - Rufinamide
  - Felbamate
- Dravet syndrome
  - Epidiolex
  - Stiripentol
Low And Slow

- **Minimal effective dose**
  - Suppress seizures completely with no/minimal side effects
  - Children often have long intervals between seizures
  - Therapeutic range

- **Trial and error**

- **Side effect monitoring**

- **Adherence**
Note Worthy Side effects

- Valproic acid
  - Pancreatitis
  - Liver failure
  - Weight gain
- Felbamate
  - Aplastic anemia
- Carbamazepine
  - Aplastic anemia
  - Hyponatremia
- Phenytoin
  - Liver injury
  - Aplastic anemia
- Keppra
  - Behavioral changes
- Ezogabine
  - Blue pigmentation of skin and retina
- Viagabatrin
  - Visual field changes
- Topiramate
  - Weight loss
  - Kidney Stone
- Zonisamide
  - Hyperthermia
  - Decreased sweat production
- Lamotrigine
  - Steven Johnsons Syndrome
When A Seizure Happens

- Rescue At Home
  - Clonazepam
  - Midazolam
  - Diazepam

- Ongoing seizure in the Hospital
  - 1st line
    - Lorazepam
  - 2nd line
    - Fosphenytoin
    - Valproic acid
    - Levetiracetam
  - 3rd line
    - Phenobarbital
    - Midazolam
When Seizures Stop

- Medication discontinuation
  - Two years seizure freedom
  - Prognostic factors
    - Age at onset
    - Type of seizure
    - IQ
    - Neurologic exam
    - EEG

- ILAE Definition 2014
  - Epilepsy resolved when:
    - Seizure free for at least 10 years
      - Most recent 5 years off all anti-seizure medications
    - Expected age to have outgrown epilepsy syndrome.
What If The Seizures Don’t Stop?

- Rational polytherapy
- Confirmation of diagnosis
- Ketogenic diet

- Epilepsy surgery
  - Modulating devices
  - Disconnection
  - Resection
  - Ablation