Epilepsy Pharmacotherapy: Epidemiology & Clinical Presentation

Barry E. Gidal, PharmD
Professor
School of Pharmacy & Dept. of Neurology
Definitions

• Seizure: the clinical manifestation of an abnormal, excessive excitation and synchronization of a population of cortical neurons

• Epilepsy: recurrent seizures (two or more) which are not provoked by systemic or acute neurologic insults
Epidemiology of Seizure / Epilepsy

- ~10% population – single seizure during lifetime
- ~4-5% population – epilepsy – two or more unprovoked seizures in lifetime
- ~1-2% population – epilepsy now
  - 30% intractable
  - 30% occasional seizures
  - 40% controlled on medications
Incidence and Prevalence of Epilepsy in the United States

Community incidence¹:
Rochester, Minn (1935–1984)

- Epilepsy affects more than 3 million people²
- 200,000 new cases of epilepsy diagnosed annually²

Risk for Epilepsy:  
**Prenatal and Perinatal Factors**

*Not statistically significant.

Adult Risk Factors for Epilepsy

- Military head injury (HI)
- Civilian HI (severe)
- Civilian HI (moderate)
- Civilian HI (mild)*
- Stroke
- Embolic risk factors
- LVH without Rx
- LVH with Rx**
- Hypertension*
- Encephalitis
- Bacterial meningitis
- Aseptic meningitis
- Alzheimer's disease
- Multiple sclerosis
- Alcohol
- Heroin
- Marijuana**
- Depression*
- Neuroleptic drugs*
- Tricyclic antidepressants*
- Electroconvulsive shock therapy*
- No risk

*Not significant; **Protective; LVH – Left ventricular hypertrophy.

Epilepsy and Other Chronic Convulsive Diseases

‘Every fit, slight or severe, is in some degree the effect of those which precede it, the cause of those that follow it.’

William Gowers, M.D., 1881
Molecular, Synaptic, and Cellular Effects of Seizures

FIG. 5. Neurologic effects of seizures. Major molecular, synaptic, and cellular processes that are induced by seizures (upper left-hand corner) are presented. Time-line is provided above; note different chronologic epochs and nonlinearity of scaling. Different "milieus" ranging from molecular to network (from top down) are given, as introduced in the text. Both functional and structural processes are surveyed. Note: points 1, 2, and 3 relate to gene expression, with 1 denoting IEG activation, 2 denoting genes activated transiently but after IEG—including those "targeted" by IEG, and 3 being a proposed permanent gene activation in the chronically epileptic brain. Point 4 (axon proliferation, growth) relates to growth factors expressed as part of 2. Point 5 relates to functional changes in constituent proteins for ligand-gated receptors, arising as a consequence of process 2.
ILAE Classification of Seizures

Seizures

Partial
- Simple Partial
- Complex Partial
- Secondarily Generalized

Generalized
- Absence
- Myoclonic
- Atonic
- Tonic
- Tonic-Clonic

ILAE – International League Against Epilepsy

American Epilepsy Society 2010
Complex Partial Seizures

- Impaired consciousness
- Clinical manifestations vary with site of origin and degree of spread
  - Presence and nature of aura
  - Automatisms
  - Other motor activity
- Duration typically < 2 minutes
Secondarily Generalized Seizures

- Begins focally, with or without focal neurological symptoms
- Variable symmetry, intensity, and duration of tonic (stiffening) and clonic (jerking) phases
- Typical duration 1-3 minutes
- Postictal confusion, somnolence, with or without transient focal deficit
ILAE Classification of Seizures

- Seizures
  - Partial
  - Generalized
    - Absence
    - Myoclonic
    - Atonic
    - Tonic
    - Tonic-Clonic

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Typical Absence Seizures

- Brief staring spells ("petit mal") with impairment of awareness
  - 3-20 seconds
  - Sudden onset and sudden resolution
  - Often provoked by hyperventilation
  - Onset typically between 4 and 14 years of age
  - Often resolve by 18 years of age
- Normal development and intelligence
- EEG: Generalized 3 Hz spike-wave discharges

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Atypical Absence Seizures

- Brief staring spells with variably reduced responsiveness
  - 5-30 seconds
  - Gradual (seconds) onset and resolution
  - Generally not provoked by hyperventilation
  - Onset typically after 6 years of age

- Often in children with global cognitive impairment

- EEG: Generalized slow spike-wave complexes (<2.5 Hz)

- Patients often also have Atonic and Tonic seizures

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Myoclonic Seizures

Epileptic Myoclonus

- Brief, shock-like jerk of a muscle or group of muscles
- Differentiate from benign, nonepileptic myoclonus (e.g., while falling asleep)
- EEG: Generalized 4-6 Hz polyspike-wave discharges

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Tonic and Atonic Seizures

**Tonic seizures**
Symmetric, tonic muscle contraction of extremities with tonic flexion of waist and neck

Duration - 2-20 seconds.

EEG – Sudden attenuation with generalized, low-voltage fast activity (most common) or generalized polyspike-wave.

**Atonic seizures**
Sudden loss of postural tone
- When severe often results in falls
- When milder produces head nods or jaw drops.

Consciousness usually impaired

Duration - usually seconds, rarely more than 1 minute

EEG – sudden diffuse attenuation or generalized polyspike-wave
Generalized Tonic-Clonic Seizures

- Associated with loss of consciousness and post-ictal confusion/lethargy
- Duration 30-120 seconds
- Tonic phase
  - Stiffening and fall
  - Often associated with ictal cry
- Clonic Phase
  - Rhythmic extremity jerking
- EEG – generalized polyspikes

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Seizure Precipitants

- Metabolic and Electrolyte Imbalance
- Stimulant/other proconvulsant intoxication
- Sedative or ethanol withdrawal
- Sleep deprivation
- Antiepileptic medication reduction or inadequate AED treatment
- Hormonal variations
- Stress
- Fever or systemic infection
- Concussion and/or closed head injury
Seizure Precipitants (cont.)

Metabolic and Electrolyte Imbalance

- Low blood glucose
  (or high glucose, esp. w/ hyperosmolar state)
- Low sodium
- Low calcium
- Low magnesium
Seizure Precipitants (cont.)

Stimulants/Other Pro-convulsant Intoxication

- IV drug use
- Cocaine
- Ephedrine
- Other herbal remedies
- Medication reduction
Medications that can lower seizure threshold

♦ Antidepressants:
  - Bupropion
  - Tricyclics

♦ Neuroleptics
  - Phenothiazines
    - Clozapine
  - Theophylline

♦ Isoniazid
♦ Penicillins
♦ Cyclosporin
♦ Meperidine
Choosing an Antiepileptic Drug (AED)

- Seizure type
- Epilepsy syndrome
- Drug Mechanism of Action (MOA)
- Pharmacokinetics
  - Drug interactions
  - formulation
- Concomitant medical/psychiatric conditions
- Adverse effects
- Cost
## Currently Available AEDs:

### Generic Names & Trade Names

<table>
<thead>
<tr>
<th>Generic</th>
<th>Trade</th>
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<tbody>
<tr>
<td>Carbamazepine (CBZ)</td>
<td>Carbatrol, Tegretol</td>
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<tr>
<td>Eslicarbazepine (ESL)</td>
<td>Aptoim</td>
</tr>
<tr>
<td>Ezogabine (EZG)</td>
<td>Potiga</td>
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<td>Ethosuximide (ETH)</td>
<td>Zarontin</td>
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<td>Felbamate (FBM)</td>
<td>Felbatol</td>
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<td>Fosphenytoin (FOS)</td>
<td>Cerebyx</td>
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<td>Gabapentin (GBP)</td>
<td>Neurontin</td>
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<td>Lamotrigine (LTG)</td>
<td>Lamictal</td>
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<tr>
<td>Levetiracetam (LEV)</td>
<td>Keppra</td>
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<tr>
<td>Oxcarbazepine (OXC)</td>
<td>Trileptal</td>
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<tr>
<td>Generic</td>
<td>Trade</td>
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<tr>
<td>Perampanel (PER)</td>
<td>Fycompa</td>
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<td>Phenobarbital (PB)</td>
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<td>Phenytoin (PHT)</td>
<td>Dilantin</td>
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<tr>
<td>Pregabalin (PGB)</td>
<td>Lyrica</td>
</tr>
<tr>
<td>Primidone (PRM)</td>
<td>Mysoline</td>
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<tr>
<td>Tiagabine (TGB)</td>
<td>Gabitril</td>
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<td>Topiramate (TPM)</td>
<td>Topamax</td>
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<td>Valproate (VPA)</td>
<td>Depakote</td>
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<td>Vigabatin (VGB)</td>
<td>Sabril</td>
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<tr>
<td>Zonisamide (ZNS)</td>
<td>Zonegran</td>
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<tr>
<td>Lacosamide (LCM)</td>
<td>Vimpat</td>
</tr>
<tr>
<td>Vigabatin (VGB)</td>
<td>Sabril</td>
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</tbody>
</table>
AED Options

Phenytoin,
Carbamazepine,
eslicarbazepine,
Ezogabine,
Phenobarbital,
Gabapentin,
Tiagabine,
Oxcarbazepine,
Perampanel,
Pregabalin,
Lacosamide,
vigabatrin

Simple
Complex
Secondarily
generalized

Partial

Generalized

Tonic
Tonic-
clonic
Myoclonic
Atonic
Infantile
Spasms
Absence

Valproate, Lamotrigine, Topiramate, Felbamate,
Zonisamide, Levetiracetam, rufinamide

Vigabatrin
ACTH

Ethosuximide
Success in AED regimens

- Seizure free 47% Monotherapy first AED
- Seizure free 13% Monotherapy 2nd AED
- Seizure free 1% Monotherapy 3rd AED
- Seizure free 3% Polytherapy
- Not seizure free 36% All regimens attempted

When Monotherapy Fails……

Seizure Freedom* with Adjunctive Therapy or Substitution Monotherapy in Patients with Inadequate Seizure Control on First Well-Tolerated AED

- Adjunctive AED therapy may be more effective when initiated immediately after failure of first AED vs after failure of second AED

*Seizure freedom=no seizures of any type for $\geq$ 1 year.

Choosing an AED

• Do the pharmacokinetics match my patient?
AED Drug Interactions

- **Broad Spectrum Inducers**
  - Carbamazepine
  - Phenytoin
  - Phenobarbital

- **Selective 3A4 Inducers**
  - Felbamate
  - Topiramate
  - Oxcarbazepine

- **Inhibitors**
  - VPA (CYP 2C19, UGT)
  - Felbamate, Topiramate, Oxcarbazepine
    - (CYP 2C19)
Choosing an AED

• Adverse effects matter!
### VA Cooperative Trial I:

#### Reason for AED Failure

<table>
<thead>
<tr>
<th>Reason</th>
<th>CBZ (N=101)</th>
<th>PB (N=101)</th>
<th>PHT (N=110)</th>
<th>PRM (N=109)</th>
<th>All Patients (N=421)</th>
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<tbody>
<tr>
<td>Toxicity alone</td>
<td>12</td>
<td>19</td>
<td>18</td>
<td>36</td>
<td>85</td>
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<tr>
<td>Toxicity plus seizures</td>
<td>30</td>
<td>33</td>
<td>29</td>
<td>35</td>
<td>127</td>
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<tr>
<td>Seizures alone</td>
<td>3</td>
<td>4</td>
<td>1</td>
<td>3</td>
<td>11</td>
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<tr>
<td>Total Failures</td>
<td>45</td>
<td>56</td>
<td>48</td>
<td>74</td>
<td>233</td>
</tr>
</tbody>
</table>

Mattson et al, *NEJM*, 1985
AED Toxicity and Quality of Life

(n=200, r = -0.78, p< 0.0001)  Gilliam et al, *Neurology* 58 (suppl5): S9-19, 2002
Epilepsy Adverse Effects: Cognition and Behavior

- Most AEDs can influence cognitive function
- Monotherapy better than polypharmacy
- AEDs may amplify or ameliorate behavior
- AEDs may exacerbate certain seizure types
- Seizure frequency may significantly affect cognition/behavior transiently and permanently
- Some research shows that:
  - Intractability of the seizure disorder does not seem to be an independent risk factor for occurrence of depression*
  - There is no relationship between severity of depression and monthly seizure rate*
- Chronic disease state may significantly alter development and behavior – managing uncertainty about seizures, stigma, impact on others, managing treatments