EPILEPSY
PATHOPHYSIOLOGY & PRINCIPLES OF DRUG THERAPY

SEIZURES
- **Electrical disturbance** in brain: abnormal, excessive, synchronous discharges of cortical neurons
- **Cellular events**: prolonged depolarization → recruitment → rapid firing → synchronized discharge of abnormally linked neurons → localized or generalized spread
- **Neurochemical causes**: imbalance between excitation & inhibition in CNS
  - Abnormal voltage/ligand gated ion channels
  - Ionic micro-environment changes
  - ↓GABA (inhibitory)
  - ↑Glutamate (excitatory)
- **Clinical manifestations**: changes in motor activity, sensation, autonomic function, consciousness

EPILEPSY
- ≥2 seizures (unpredictable, intermittent) without known or provoked cause
- **Epidemiology**: most frequently precipitated in young children (<5) and the elderly (>65)
- **Etiology**
  - Mostly idiopathic, with genetic influences
  - Pediatric: congenital malformations, developmental disorders, metabolic defects, injury, infection
  - Adult: trauma, tumors, infection, AV malformations
  - Elderly: CVD, CNS degeneration, tumors
- **Diagnosis**
  - Confirm diagnosis & identify seizure type, epilepsy syndrome, and cause
  - History: med hx, family hx, seizure description
  - Physical/neurological exam
  - Lab testing: rule out other metabolic disorders
  - EEG: findings alone not sufficient to confirm/deny diagnosis
    - Absence: 3 Hz spike & wave complex
    - Minor motor seizures (tonic, atonic, atypical absence): slow spike & wave complex
    - Infantile spasms: hypsarrhythmia
    - Myoclonic: polyspike & wave complex
  - Neuroimaging studies: MRI, CT scan

SEIZURE TYPES
- **Partial**: localized involvement of brain
  - Two main types of partial seizures:
    - **Simple**: maintain consciousness
    - **Complex**: impaired consciousness
  - Partial seizures can spread
    - Simple partial → complex partial
    - Simple/complex partial → secondarily generalized tonic clonic
  - Can’t always tell if started out as partial
- **Generalized**: whole brain involved
  - **Absence**: brief interruption of consciousness
  - **Myoclonic**: brief, jerky
  - **Tonic clonic**: rigid muscle contractions → tongue biting, incontinence, absence of breathing → rhythmic muscle contractions
  - **Clonic**: regularly repeating jerks
  - **Atonic**: lose all muscle tone, drop attacks
- **Epilepsy syndromes**: classified based on seizure type, etiology, age, etc.; useful to classify epilepsy syndrome (vs. just seizure type) particularly in children
AED THERAPY

- Important! Need to classify epilepsy syndrome or seizure type correctly
- Balance between seizure control and side effect profile
- Avoid AED therapy if: reversible cause, 1st unprovoked seizure, benign epilepsies (febrile seizures, rolandic)
- Monitoring: seizures, drug interactions, side effects, compliance
- Avoid precipitating factors: alcohol, sleep deprivation, stress, poor diet, fever, flickering lights
- Selecting the appropriate AED
  - 1st principle: seizure type (for children, use epilepsy syndrome instead)
  - 2nd principle: dose optimization & individualization
    - Start low, go slow! Until seizures controlled or SE are too much to handle

<table>
<thead>
<tr>
<th>Well tolerated</th>
<th>Can start now</th>
<th>Gabapentin, levetiracetam, phenytoin, pregabaline, vigabatrin</th>
</tr>
</thead>
<tbody>
<tr>
<td>CNS &amp; GI effects</td>
<td>Taper up</td>
<td>Carbamazepine, ethosuximide, lamotrigine, oxcarbazepine, primidone, topiramate, valproate, zonisamide</td>
</tr>
<tr>
<td>Skin rash</td>
<td>Don’t go too fast</td>
<td>Carbamazepine, lamotrigine</td>
</tr>
</tbody>
</table>

- Select initial target dose → titrate to target dose → determine optimal maintenance dose
- Initial target dose: usually low end of therapeutic range
- Pharmacokinetic/pharmacodynamics considerations
  - Weight: mg/kg dosing needed
  - Age: mg/kg dose higher in children, dose lower in elderly
  - Concurrent drug therapy: may alter absorption, or may inhibit/induce metabolism
  - Other diseases: particularly hepatic disease or impaired renal function
- Allow time to assess response: time for Csp to be reached, time to assess seizure frequency
- Dose adjustment: based on clinical response, plasma concentrations, PK
  - 3rd principle: look at other options when treatment fails
    - Monotherapy > polytherapy
    - Polytherapy (if failed 2-3 mono), surgery, vagal nerve stimulation, ketogenic diet
  - 4th principle: monitoring AED therapy
    - Level of control: frequency, change in type, time of occurrence
    - SE: type, severity, impact on life, time of occurrence
    - Changes in concurrent therapy
    - AED plasma concentration
    - Compliance, education
    - Can stop therapy if seizure free for 2-5 years!

**Drugs of Choice**

<table>
<thead>
<tr>
<th>Seizure Type</th>
<th>First-Line Drugs</th>
<th>Second-Line Drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Simple or Complex Partial</td>
<td>Carbamazepine Lamotrigine Levetiracetam</td>
<td>Gabapentin Phenytoin Valproic Acid Oxcarbazepine Topiramate Zonisamide</td>
</tr>
<tr>
<td>Generalized Tonic-Clonic (primary or secondary)</td>
<td>Carbamazepine Lamotrigine Valproic Acid</td>
<td>Gabapentin Levetiracetam Oxcarbazepine Topiramate</td>
</tr>
<tr>
<td>Absence</td>
<td>Ethosuximide Valproic Acid</td>
<td>Lamotrigine Levetiracetam</td>
</tr>
<tr>
<td>Atypical absence, atonic, myoclonic</td>
<td>Valproic Acid Lamotrigine Topiramate (not myoclonic)</td>
<td>Clonazepam Levetiracetam Zonisamide</td>
</tr>
</tbody>
</table>

- Well tolerated
- Can start now
- Gabapentin, levetiracetam, phenytoin, pregabaline, vigabatrin
- CNS & GI effects
  - Taper up
  - Carbamazepine, ethosuximide, lamotrigine, oxcarbazepine, primidone, topiramate, valproate, zonisamide
- Skin rash
  - Don’t go too fast
  - Carbamazepine, lamotrigine

- Select initial target dose → titrate to target dose → determine optimal maintenance dose
- Initial target dose: usually low end of therapeutic range
- Pharmacokinetic/pharmacodynamics considerations
  - Weight: mg/kg dosing needed
  - Age: mg/kg dose higher in children, dose lower in elderly
  - Concurrent drug therapy: may alter absorption, or may inhibit/induce metabolism
  - Other diseases: particularly hepatic disease or impaired renal function
- Allow time to assess response: time for Csp to be reached, time to assess seizure frequency
- Dose adjustment: based on clinical response, plasma concentrations, PK
  - 3rd principle: look at other options when treatment fails
    - Monotherapy > polytherapy
    - Polytherapy (if failed 2-3 mono), surgery, vagal nerve stimulation, ketogenic diet
  - 4th principle: monitoring AED therapy
    - Level of control: frequency, change in type, time of occurrence
    - SE: type, severity, impact on life, time of occurrence
    - Changes in concurrent therapy
    - AED plasma concentration
    - Compliance, education
    - Can stop therapy if seizure free for 2-5 years!