Epilepsy Overview for 3rd year medical students
Outline

• Classification
• New AED
• Epilepsy Surgery
• Drugs used for Status Epilepticus
• Conclusions
Seizures and Epilepsy

- **Seizure**: abnormal hypersynchronous electrical discharge form cerebral cortical neurons.
- **Clinical seizure**: the clinical manifestation of the electric seizure that depends on the site of onset and path of propagation.
Seizures

• Provoked seizures, also known as acute symptomatic seizures, occur with an identifiable proximate cause and are not expected to recur in the absence of that particular cause or trigger.

• Unprovoked seizures occur without an identifiable proximate cause, and epilepsy is defined as a condition of recurrent unprovoked seizures.
Epilepsy and neurotransmitters

It is classically thought to arise from an imbalance between excitation and inhibition in a localized region, multiple brain areas or the whole brain.
(GABA)

• Gamma-aminobutyric acid
• The principal inhibitory neurotransmitter in the cerebral cortex
• GABA is formed within GABAergic axon terminals and released into the synapse, where it acts at one of two types of receptor:
  – GABAA, which controls chloride entry into the cell,
  – GABAB, which increases potassium conductance, decreases calcium entry, and inhibits the presynaptic release of other transmitters.

• GABA is rapidly removed by uptake into both glia and presynaptic nerve terminals and then catabolized by GABA transaminase.

• GABA agonists suppress seizures, and GABA antagonists produce seizures

• Drugs that inhibit GABA synthesis cause seizures

• Benzodiazepines and barbiturates work by enhancing GABA-mediated inhibition.

• Drugs that increase synaptic GABA are potent anticonvulsants.

Glutamate

- Glutamate is the principal excitatory neurotransmitter in the brain and, as such, it inevitably plays a role in the initiation and spread of seizure activity.
• The release of glutamate acting on NMDA receptors can induce seizures.
• In the hippocampus; brain insults, traumatic brain injuries, or status epilepticus can cause an imbalance between the GABAergic and glutaminergic systems, while GABA has a hypoactivity action and glutamate exerts an excitotoxicity action.
Rochester Minnesota Epilepsy Study (1935-1974)
Etiology of Newly Diagnosed Epilepsy

- Cryptogenic: 61
- Vascular: 15
- Alcohol: 7
- Tumors: 6
- Post traumatic: 8
- Others: 3
<table>
<thead>
<tr>
<th>Condition</th>
<th>Relative Risk</th>
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<tbody>
<tr>
<td>control</td>
<td>1</td>
</tr>
<tr>
<td>marijuana</td>
<td>0.36</td>
</tr>
<tr>
<td>mild HI</td>
<td>1.5*</td>
</tr>
<tr>
<td>aseptic mening</td>
<td>2.3</td>
</tr>
<tr>
<td>family hx</td>
<td>2.5</td>
</tr>
<tr>
<td>heroin</td>
<td>2.6</td>
</tr>
<tr>
<td>MS</td>
<td>3.6</td>
</tr>
<tr>
<td>mod HI</td>
<td>4</td>
</tr>
<tr>
<td>bact mening</td>
<td>4.2</td>
</tr>
<tr>
<td>AD</td>
<td>10</td>
</tr>
<tr>
<td>alcohol</td>
<td>10.1</td>
</tr>
<tr>
<td>viral encph</td>
<td>16</td>
</tr>
<tr>
<td>stroke</td>
<td>22</td>
</tr>
<tr>
<td>severe civil HI</td>
<td>25</td>
</tr>
<tr>
<td>severe military HI</td>
<td>580</td>
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* Not significant

• HI = head injury
Epilepsy: Diagnosis

• History:
  – Description of the event
  – Medications and substances
  – Past medical history
• Physical examination
• EEG
• MRI
• Special testing
ILAE classification of seizures and epilepsy

- LEVEL 1: SEIZURE TYPE
- LEVEL 2: EPILEPSY BASED ON SEIZURE TYPE
- LEVEL 3: EPILEPSY SYNDROME
- LEVEL 4: EPILEPSY WITH ETIOLOGY
International classification of epileptic seizures 2017

• The classification is based on 3 key features:
  – Where seizures begin in the brain
  – Level of awareness during a seizure
  – Other features of seizures
ILAE 2017 Classification of Seizure Types Expanded Version

**Focal Onset**
- **Aware**
  - Motor Onset
    - automatisms
    - atonic
    - clonic
    - epileptic spasms
    - hyperkinetic
    - myoclonic
    - tonic
  - Non-Motor Onset
    - autonomic
    - behavior arrest
    - cognitive
    - emotional
    - sensory
  - focal to bilateral tonic-clonic

- **Impaired Awareness**

**Generalized Onset**
- **Motor**
  - tonic-clonic
  - clonic
  - tonic
  - myoclonic
  - myoclonic-tonic-clonic
  - myoclonic-atonic
  - atonic
  - epileptic spasms
  - **Non-Motor (absence)**
    - typical
    - atypical
    - myoclonic
    - eyelid myoclonia

**Unknown Onset**
- **Motor**
  - tonic-clonic
  - epileptic spasms
  - **Non-Motor**
    - behavior arrest

**Unclassified**

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1. Definitions, other seizure types and descriptors are listed in the accompanying paper and glossary of terms
2. Degree of awareness usually is not specified
3. Due to inadequate information or inability to place in other categories
EPILEPSY BASED ON SEIZURE TYPE

- Generalized epilepsy
- Focal epilepsy
- Generalized and focal epilepsy
- Unknown if generalized or focal epilepsy
EPILEPSY SYNDROME

• An epilepsy syndrome represents a complex of clinical features, signs and symptoms that together define a distinctive, recognizable clinical seizure disorder.
EPILEPSY WITH ETIOLOGY

- Diagnosis at this level requires that the primary etiology of the epilepsy has been determined.
- Advances in neuroimaging and genetics, as well as improved understanding of the role of specific autoantibodies, have allowed greater accuracy in diagnosis for many people with epilepsy.
Differential diagnosis of seizures in adults

- Vasovagal syncope
- Cardiogenic syncope
- Migraine
- TIA
- Psychogenic pseudosizures
- Panic attacks
- Rage attacks
# Differences Between Syncope and Seizures

<table>
<thead>
<tr>
<th>Feature</th>
<th>Syncope</th>
<th>Seizures</th>
</tr>
</thead>
<tbody>
<tr>
<td>Posture</td>
<td>Upright</td>
<td>Any posture</td>
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<tr>
<td>Pallor and Sweating</td>
<td>Invariable</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Onset</td>
<td>Gradual</td>
<td>Sudden/ Aura</td>
</tr>
<tr>
<td>Injury</td>
<td>Rare</td>
<td>Not Uncommon</td>
</tr>
<tr>
<td>Convulsive Jerks</td>
<td>Rare</td>
<td>Common</td>
</tr>
<tr>
<td>Incontinence</td>
<td>Rare</td>
<td>Common</td>
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<tr>
<td>Unconsciousness</td>
<td></td>
<td>Minutes</td>
</tr>
<tr>
<td>Recovery</td>
<td>Rapid</td>
<td>Often Slow</td>
</tr>
<tr>
<td>Post Ictal Confusion</td>
<td>Rare</td>
<td>Common</td>
</tr>
<tr>
<td>Frequency</td>
<td>Infrequent</td>
<td>May Be Frequent</td>
</tr>
<tr>
<td>Precipitating Factors</td>
<td>Crowded Places, Lack of Food, Unpleasant Conditions</td>
<td>Rare</td>
</tr>
</tbody>
</table>

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**Note:**
- Syncope: A transient loss of consciousness due to a reduction in cerebral blood flow, usually without any injury.
- Seizures: A sudden, uncontrolled discharge of electrical activity in the brain, typically characterized by convulsive movements.

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**Definitions:**
- **Syncope:** A condition characterized by a sudden loss of consciousness due to a temporary reduction in blood flow to the brain.
- **Seizures:** A sudden, uncontrolled discharge of electrical activity in the brain, leading to convulsive movements.

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**Key Differences:**
- **Posture:** Syncope occurs in an upright position, while seizures can occur in any posture.
- **Pallor and Sweating:** Syncope is invariable, whereas seizures are uncommon.
- **Onset:** Syncope onset is gradual, whereas seizures are sudden or accompanied by aura.
- **Injury:** Syncope is rare, whereas seizures are not uncommon.
- **Convulsive Jerks:** Syncope is rare, whereas seizures are common.
- **Incontinence:** Syncope is rare, whereas seizures are common.
- **Unconsciousness:** Syncope lasts seconds, whereas seizures last minutes.
- **Recovery:** Syncope recovery is rapid, whereas seizures may be followed by slow recovery.
- **Post Ictal Confusion:** Syncope is rare, whereas seizures are common.
- **Frequency:** Syncope is infrequent, whereas seizures may be frequent.
- **Precipitating Factors:** Syncope is triggered by crowded places, lack of food, and unpleasant conditions, whereas seizures are rare.
## Differences Between Seizures and Pseudoseizures

<table>
<thead>
<tr>
<th>Feature</th>
<th>Epileptic Sz</th>
<th>Pseudo Sz</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Onset</strong></td>
<td>Sudden</td>
<td>May Be Gradual</td>
</tr>
<tr>
<td><strong>Retained Consciousness</strong></td>
<td>Very Rare</td>
<td>Common</td>
</tr>
<tr>
<td>In Prolonged Seizures.</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Flailing, Thrashing, Asynchronous Limb Movements</strong></td>
<td>Rare</td>
<td>Common</td>
</tr>
<tr>
<td><strong>Pelvic Thrusting</strong></td>
<td>Rare</td>
<td>Common</td>
</tr>
<tr>
<td><strong>Rolling Movements</strong></td>
<td>Rare</td>
<td>Common</td>
</tr>
<tr>
<td><strong>Movements Waxing &amp; Waining</strong></td>
<td>Rare</td>
<td>Common</td>
</tr>
<tr>
<td><strong>Cyanosis</strong></td>
<td>Common</td>
<td>Unusual</td>
</tr>
<tr>
<td><strong>Tongue Biting and Other Injury</strong></td>
<td>Common</td>
<td>Less Common</td>
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</tbody>
</table>
## Differences Between Seizures and Pseudoseizures

<table>
<thead>
<tr>
<th>Feature</th>
<th>Epileptic Sz</th>
<th>Pseudod SZ</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stereotypical Attacks</td>
<td>Usual</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Duration</td>
<td>Seconds, Minutes</td>
<td>Often Prolonged</td>
</tr>
<tr>
<td>Resistance to Passive Limb Movement or Eye Opening</td>
<td>Unusual</td>
<td>Common</td>
</tr>
<tr>
<td>Prevention of Hand Falling On Face</td>
<td>Unusual</td>
<td>Common</td>
</tr>
<tr>
<td>Induced by Suggestion</td>
<td>Rarely</td>
<td>Often</td>
</tr>
<tr>
<td>Postictal Drowsiness or Confusion</td>
<td>Usual</td>
<td>Often Absent</td>
</tr>
<tr>
<td>Ictal EEG Abnormality</td>
<td>Almost Always</td>
<td>Almost Never</td>
</tr>
<tr>
<td>Postictal EEG Abnormality</td>
<td>Usually</td>
<td>Rare</td>
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ADVERSE PROGNOSTIC FACTORS IN EPILEPSY

- Symptomatic etiology.
- Partial onset seizures.
- Atonic seizures.
- Late onset or first year epilepsy
- Additional mental or motor handicap.
- Long duration prior to therapy.
- Poor initial response to therapy.
RIGHT ANTERIOR TEMPORAL SHARPS.
INTERICTAL GENERALIZED 3 HTZ SPIKE-WAVE DISCHARGE
Intractable Epilepsy

• Impairment of quality of life due to Seizures &/ or Drugs
• 20-30% of epileptics are intractable
• Patients failing 2 drugs are likely to be intractable
• 30-40% newly diagnosed partial epilepsy will not attain a seizure remission with pharmacotherapy.
Intractable Epilepsy

- Treatment options
  - New AED
  - surgery
  - Vagus nerve stimulation
  - special diets in children
New Anti Epileptic Drugs
Potential benefits of AED related seizure control

• Reduced social stigma
• Reduced negative cognitive effects from frequent seizures.
• Reduced risk of status epilepticus (if compliant)
• Reduced risk of physical injury
• Improve employment likelihood
• Helps maintain driving privileges
Risks of AED related adverse effects

- Behavioral problems
- Cognitive impairment
- Idiosyncratic reactions
- Systemic toxicity
- Teratogenicity
- Expense
Ideal Antiepileptic Drug

- Antiepileptogenic
- Complete Seizure Suppression
- Minimal Side Effects
FACTS:

• 50% of patients fail to achieve the goal of treatment. (1985) NEJM

• 1/3 of patients treated 1984-1997 failed to become seizure free in the first year of treatment. (2000) NEJM
## History of AED

<table>
<thead>
<tr>
<th>Year Introduced</th>
<th>Generic Name</th>
<th>Trade Name</th>
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</thead>
<tbody>
<tr>
<td>1857</td>
<td>Bromide</td>
<td>Bromide</td>
</tr>
<tr>
<td>1912</td>
<td><strong>Phenobarbital</strong></td>
<td><strong>Luminal</strong></td>
</tr>
<tr>
<td>1935</td>
<td>Mephobarbital</td>
<td>Meberal</td>
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<tr>
<td>1938</td>
<td><strong>Phenytoin</strong></td>
<td><strong>Dilantin</strong></td>
</tr>
<tr>
<td>1946</td>
<td>Trimethadione</td>
<td>Tridione</td>
</tr>
<tr>
<td>1947</td>
<td>Mephenytoin</td>
<td>Mesantoin</td>
</tr>
<tr>
<td>1949</td>
<td>Paramethadione</td>
<td>Paradione</td>
</tr>
<tr>
<td>1951</td>
<td>Phenacemide</td>
<td>Phenurone</td>
</tr>
<tr>
<td>1952</td>
<td>Metharbital</td>
<td>Gemonil</td>
</tr>
<tr>
<td>Year Introduced</td>
<td>Generic Name</td>
<td>Trade Name</td>
</tr>
<tr>
<td>-----------------</td>
<td>-------------------</td>
<td>-------------</td>
</tr>
<tr>
<td>1953</td>
<td>Phensuxamide</td>
<td>Milontin</td>
</tr>
<tr>
<td><strong>1954</strong></td>
<td><strong>Primidone</strong></td>
<td><strong>Mysoline</strong></td>
</tr>
<tr>
<td>1957</td>
<td>Methsuxamidem</td>
<td>Celontin</td>
</tr>
<tr>
<td>1957</td>
<td>Ethitoin</td>
<td>Peganone</td>
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<tr>
<td>1960</td>
<td>Ethuxusamidem</td>
<td>Zarontin</td>
</tr>
<tr>
<td>1968</td>
<td>Diazepam</td>
<td>Valium</td>
</tr>
<tr>
<td>1974</td>
<td>Carbamezapine</td>
<td>Tegretol</td>
</tr>
<tr>
<td><strong>1975</strong></td>
<td><strong>Clonazepam</strong></td>
<td><strong>Clonopin</strong></td>
</tr>
<tr>
<td>1978</td>
<td>Valproate</td>
<td>Depakene</td>
</tr>
<tr>
<td>1981</td>
<td>Clorazapate</td>
<td>Tranxene</td>
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# History of New AED

<table>
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<tbody>
<tr>
<td>1993</td>
<td>Felbamate</td>
<td>Felbatol</td>
</tr>
<tr>
<td>1993</td>
<td>Gapabentin</td>
<td>Neurontin</td>
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<tr>
<td>1994</td>
<td>Lamotrigine</td>
<td>Lamictal</td>
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<tr>
<td>1996</td>
<td>Topiramate</td>
<td>Topamax</td>
</tr>
<tr>
<td>1997</td>
<td>Tiagabine</td>
<td>Gabatril</td>
</tr>
<tr>
<td></td>
<td>Vigabatrin</td>
<td>Sabril</td>
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<tr>
<td>1999</td>
<td>Levetracetam</td>
<td>Keppra</td>
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<tr>
<td>2000</td>
<td>Oxycarbazine</td>
<td>Trileptal</td>
</tr>
<tr>
<td>2000</td>
<td>Zonisamide</td>
<td>Zonergan</td>
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Possible Advantages of New AED

• More effective
• Better tolerated
• Safer
• Better for women
• Less interaction
• Broader spectrum
New AED: common concern

- High cost
- Dose related toxicity
- Pharmacodynamic interactions
- Drug levels of limited use
New AED: how they compare

• Similar in:
  Responder rate \( \approx 40\% \)
  Seizure free rate < 10%

• Differ in:
  Adverse effects
  Pharmacokinetic profile
  Efficacy for seizure type(s)
AED: Future Development

- Actions at NMDA receptors
- Actions at AMPA receptors
- GABA $\beta$ receptors and absence seizures
- GABA and Glutamate transporters
- Metabotropic glutamate receptors
- Serotonin
- Neurosteroids
- Genetic studies and the nicotinic acetylcholenergic system
Epilepsy Surgery
Surgical Candidates

- Medically refractory seizures
- Physically, socially disabled
- Localization-related epilepsy
- Low risk of morbidity
- Potential for rehabilitation
Response to AED in newly diagnosed epileptics. Kwan et al NEJM, 2000
Epilepsy Surgery: Types

- Medial temporal lobe epilepsy: MTS
  - Most common
  - Most successful
- Lesionectomy:
  - Tumor
  - Vascular anomaly
  - Cortical malformation
- Hemispherectomy: Rausmusen’s encephalitis
- Corpus callosotomy: LGS
- Vagal nerve stimulation: intractable, not surgical candidates
- Multiple subpial transection: eloquent areas
Vagus nerve stimulation
Status Epilepticus

- Continuous or recurrent seizures without recovery of consciousness for 30 minutes or more (tendency now to use shorter time definition like 5 minutes and more.)
**Initial assessment**
- Neurologic examination
- General evaluation with attention to respiratory and circulatory status
- O₂ ± mechanical ventilation PRN
- IV catheters inserted (at least two)
- Blood work:
  - Electrolytes, Ca, Mg, Phos, glucose, LFTs, CBC, toxicology, AED level(s)
  - Fingerstick glucose
  - Cardiac monitoring with pulse oximetry
  - Frequent vital signs
  - Consider glucose + thiamine IV

**Initial therapy**

- In first IV:
  - Lorazepam 0.1 mg/kg IV or 4 mg IV (max 2 mg/minute)
  - Alternative:
    - Diazepam 0.15 mg/kg IV up to 10 mg per dose (max 5 mg/minute)
    - Wait 1 minute for response then additional lorazepam PRN*
- If no IV access:
  - Midazolam 10 mg IM if weight > 40 kg
- In second IV:
  - Fosphenytoin 20 mg/kg PE at 100 to 150 mg PE/minute OR
  - Phenytoin 20 mg/kg at 25 to 50 mg/minute OR
  - Valproic acid 30 mg/kg at 10 mg/kg/minute OR
  - Levetiracetam 40 to 60 mg/kg (maximum 4500 mg) over 15 minutes

**Correct metabolic abnormalities if present**

**Second-line therapy**
- Repeat fosphenytoin if given previously (5 mg/kg PE) or choose among first-line drugs not already given
- Intubation, mechanical ventilation
- Continuous blood pressure, cardiac monitoring
- Prepare for continuous midazolam or propofol infusionΔ

**Refractory status epilepticus◊**

**Begin continuous EEG monitoring**

- **Midazolam**
  - Initial dose: 0.2 mg/kg IV bolus, given at 2 mg/minute
  - Continue infusion beginning at 0.1 mg/kg/hour; titrate upward to seizure freedom
  - May use infusion of up to 3 mg/kg/hour
  - If seizures stop, continue for 24 hours before tapering
  - If seizures persist after 45 to 60 minutes, change to propofol or pentobarbital
  - Use vasoressor support if necessary
  - Maintain therapeutic levels of phenytoin, phenobarbital, or both§

- **Propofol**
  - Initial dose: 5 mg/kg over 10 minutes
  - Repeat as necessary until seizures stop
  - Then, pentobarbital 1 to 5 mg/kg/hour for 24 hours of seizure freedom
  - Use vasoressor support if necessary
  - Maintain therapeutic levels of phenytoin, phenobarbital, or both§

- **Pentobarbital**
  - Initial dose: 5 mg/kg over 10 minutes
  - Repeat as necessary until seizures stop
  - Then, pentobarbital 1 to 5 mg/kg/hour for 24 hours of seizure freedom
  - Use vasoressor support if necessary
  - Maintain therapeutic levels of phenytoin, phenobarbital, or both§
CONCLUSIONS:

• Epilepsy is still a challenge
• New AED improved our treatment
• Need for more understanding of basic mechanism of epilepsy and its genesis
• Need to develop specific and target specific treatment
• Surgery is quite effective in properly selected patients but quite underused
• Intravenous benzodiazepines, phenytoin, phenobarb and valproic acid are available, effective and safe Rx for status epilepticus
THANK YOU