Anticonvulsant or Antiepileptic Drugs

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February, 2019
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**Epilepsy:** a disease characterized by recurrent attacks of convulsions.

**Convulsion (Fit):** the attack itself.

**Seizure:** an abnormal electrical activity, not necessarily to result in a convulsion.
Neuronal Mechanisms involved in Seizures

- Suppression of Inhibition--------Onset
- Post-tetanic Potentiation--------Spread and Maintenance
- Reinstitution of Inhibition---Termination
Pathophysiological Conditions Enhancing Convulsions

- Low PO2
- High pH
- Increased Intracranial Pressure
- Low Ca++
- Low Glucose
- Overhydration
- Fatigue
- Emotional State
Causes of Convulsions

- Poisons
- Trauma
- Infection
- Space Occupying Lesions
- Fever
- Drugs
- Idiopathic, Epilepsies
Seizure Classification

Partial
(seizure activity originates in one part of the brain)

Simple

Complex

Generalised
(seizure activity involved entire brain)

Absence
Myoclonic
Tonic clonic
Tonic
Atonic
Classification of Epilepsies

Grand Mal or Major Epilepsy or Tonic-Clonic Epilepsy:

- Aura
- Cry - Loss of consciousness
- Tonic Phase: Rigid violent muscle contraction with limbs fixed.
- Clonic Phase: Repetitive muscle jerks
- Post-ictal depression and incontinence
GENERALIZED TONIC- CLONIC SEIZURE

A. Tonic phase
- Epileptic cry
- Cervical
- Incontinence
- Generalized stiffening of body and limbs, back arched

B. Clonic phase
- Salivary drooling
- Cervical
- Clonic jerks of limbs, body and head

C. Post-ictal confusional fatigue
- Eyes blinking
- Limbs and body limp
Classification of Epilepsies

Petit Mal or Minor Epilepsy or Absence States:

Psychomotor Epilepsy:

- Automatic movements
- Clouded dreamy feeling
- Aggressiveness
Classification of Epilepsies

- Status Epilepticus
- Parietal Lobe Epilepsy
- Infantile Myospasm
- etc.......
### TABLE 32.1 Major Seizure Types

<table>
<thead>
<tr>
<th>Clinical Seizure Type</th>
<th>Key Ictal EEG Manifestations</th>
<th>Major Clinical Manifestations</th>
</tr>
</thead>
<tbody>
<tr>
<td>I. Partial (focal, local) seizures</td>
<td>Local contralateral discharge</td>
<td>Seizures may be limited to a single limb or muscle group; may show sequential involvement of body parts (epileptic march); consciousness usually preserved; may be somatosensory (hallucinations, tingling, gustatory sensations); may have autonomic symptoms or signs such as epigastric sensations, sweating, papillary dilation</td>
</tr>
<tr>
<td>A. Simple partial seizures</td>
<td>Unilateral or bilateral asynchronous focus, most often in temporal region</td>
<td>Impairment of consciousness, may have automatisms, flash-back (déjà vu, terror); autonomic activity such as pupil dilation, flushing, pilocerection</td>
</tr>
<tr>
<td>B. Complex partial seizures (psychomotor epilepsy, temporal lobe epilepsy)</td>
<td></td>
<td>May generalize to tonic, clonic, or tonic-clonic</td>
</tr>
<tr>
<td>C. Partial seizures evolving to secondary generalized seizures</td>
<td>3-Hz polyspike and wave</td>
<td>Brief loss of consciousness with or without motor involvement; occurs in childhood with a tendency to disappear following adolescence</td>
</tr>
<tr>
<td>II. Generalized seizures</td>
<td></td>
<td>Sudden, brief, shocklike contractions of musculature (myoclonic jerks)</td>
</tr>
<tr>
<td>A. Absence seizures (petit mal epilepsy)</td>
<td>Fast activity (10 Hz or more; slow waves)</td>
<td>Repetitive muscle jerks</td>
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<tr>
<td>B. Myoclonic seizures</td>
<td>Low-voltage, fast activity</td>
<td>Rigid, violent muscular contraction with limbs fixed</td>
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<tr>
<td>C. Clonic seizures</td>
<td>Fast activity (10 Hz or more) increasing in amplitude during tonic phase; interrupted by slow waves during clonic phase</td>
<td>Loss of consciousness; sudden sharp tonic contractions of muscles, falling to ground, followed by clonic convulsive movements; often postictal depression and incontinence</td>
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<tr>
<td>D. Tonic seizures</td>
<td>Polyspikes and wave</td>
<td>Sudden diminution in muscle tone affecting isolated muscle groups or loss of all muscle tone; may have extremely brief loss of consciousness</td>
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<tr>
<td>E. Tonic-clonic seizures (grand mal epilepsy)</td>
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<td></td>
</tr>
</tbody>
</table>
Provocative Procedures

- Pentylene tetrazole "Metrazole"
- Hyperventilation
- Photic stimulation - Flicker Fusion
Principles of Epilepsy Treatment

✓ Seizures are self-limiting.
✓ Use one drug at a time (Monotherapy):
  - Lower incidence of adverse reactions.
  - Avoidance of drug interactions.
  - Improved patient compliance.
  - Lower medication cost.
✓ Start with a small dose.
✓ Monitor serum level.
# Table 32.2 Categorization of Anticonvulsants by Their Proposed Mechanism

<table>
<thead>
<tr>
<th>Class</th>
<th>Description</th>
<th>Drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type I</td>
<td>Block SRF by enhancing sodium channel inactivation</td>
<td>Phenytoin</td>
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<tr>
<td></td>
<td></td>
<td>Carbamazepine</td>
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<tr>
<td></td>
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<td>Oxcarbazepine</td>
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<td></td>
<td></td>
<td>Lamotrigine</td>
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<td></td>
<td></td>
<td>Felbamate&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Type II</td>
<td>Multiple actions: enhance GABAergic inhibition, reduce T-calcium currents, and possibly block SRF</td>
<td>Valproic acid</td>
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<td></td>
<td></td>
<td>Benzodiazepines</td>
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<tr>
<td></td>
<td></td>
<td>Phenobarbital</td>
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<tr>
<td></td>
<td></td>
<td>Primidone</td>
</tr>
<tr>
<td>Type III</td>
<td>Block T-calcium currents only</td>
<td>Ethosuximide</td>
</tr>
<tr>
<td>Type IV</td>
<td>Only enhances GABAergic inhibition</td>
<td>Trimethadione</td>
</tr>
<tr>
<td>Noncategorized</td>
<td>Has no known effect on SRF, GABAergic inhibition, or T-calcium currents</td>
<td>Vigabatrin&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Gabapentin&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
</tbody>
</table>


<sup>a</sup>Felbamate probably possesses other actions.

<sup>b</sup>The mechanisms of action of gabapentin are unknown.

SRF: sustained high-frequency repetitive firing.
Voltage-Gated Sodium Channel

(a) Closed but capable of opening
- At resting potential (-70 mV)

(b) Open (activated)
- From threshold to peak potential (-50 mV to +30 mV)

(c) Closed and not capable of opening (inactivated)
- From peak to resting potential (+30 mV to -70 mV)

Extracellular fluid (ECF)
Intracellular fluid (ICF)
Plasma membrane
Barbiturates

✔ Phenobarbital
✔ Mephobarbital
✔ Methabarbital
✔ Primidone
Barbiturates

- Oldest but still used.
- Relatively safe, but sedating.
- Effective in Grand mal and partial seizures.
- Might worsen patients with other types.
- Bind to GABA receptor, to prolong opening of Cl- channels.
- Also, at high doses, block Na+ and Ca++ channels (L and N type).
- Also block Glutamate receptors.
Barbiturates

Adverse Effects:

- Sedation
- Allergies
- Anemia
- Drug Interactions
- Enzyme Induction ----- Withdrawal!!
- Additive to CNS depressants.
Phenytoin (1938) (Diphenyl Hydantoin DPH)

- Generalized tonic - clonic seizures
- Partial seizures with complex symptomatology
- Antipsychotic
- Antiarrhythmic
- Many others
- Revolutionary
Phenytoin

Mechanism of Action:
Acts on several physiologic systems.
Major action is sodium channel blockade, arising from preferential binding to and prolongation of the inactivated state of the Na\(^+\) channel.
Also, inhibits Ca\(^++\) influx, membrane potential, as well as, the concentrations of amino acids, NE, ACh, and GABA.
Blocks sustained high-frequency repetitive firing of action potentials(SRF).
Phenytoin

Pharmacokinetics:

- Slow absorption
- 90% bound to proteins.
- Metabolized:
  
  Zero order in high doses used in epilepsy, so, no SSL achieved.

- Interactions:

  Protein binding.
  Enzyme induction.
Phenytoin

Adverse Effects:

- Skin rashes, fever
- Blood: megaloblastic anemia, agranulocytosis, lymphadenopathy.
- Gingival hyperplasia (50%)
- Hirsutism
- "Hydantoin Facies"
- Peripheral neuropathy
- Cerebellar degeneration
- Teratogenic ------- Folate Deficiency
Phenytoin

Overdose:

✓ Nystagmus,
✓ Ataxia,
✓ Vertigo,
✓ Diplopia
✓ Loss of consciousness.
Carbamazepine

✓ Partial seizures
✓ Generalized tonic - clonic
✓ Like phenytoin and barbiturates, it is not useful for petit mal
✓ Initially marketed for Trigeminal Neuralgia.
✓ Bipolar mood disorders, it is a tricyclic compound.
✓ Peripheral Neuropathy
✓ Migraine --------- etc
Carbamazepine

Mechanism of Action:
Like phenytoin, blocks Na+ channels.
Carbamazepine

- Slow and erratic absorption
- $T_{1/2}$ 12-60 hr.
- Induces liver enzymes = Autoinduction.
- Interactions.
- Blood monitoring is necessary.
Carbamazepine

Adverse Effects:

- Vertigo, Ataxia, Diplopia appear early.
- Drowsiness, nausea, headache, dizziness.
- Tolerance develops to the above effects.
- Skin rashes, fever, hepatosplenomegaly, lymphadenopathy.
- **Blood dyscrasias:** leukopenia, aplastic anemia, and agranulocytosis.
Oxacarbazepine.

- Less capacity to induce enzymes.
- $T^{1/2}$ 1-2hr.
- May be safer.
Vigabatrin

✓ GABA-Transaminase irreversible inhibitor, which breaks down GABA in the brain.

✓ Renal elimination.

✓ Partial seizures ____ Not for absence or myoclonic

✓ Well tolerated: drowsiness, dizziness, weight gain, visual field defects.
Lamotrigine

- Inhibits Na+ and Ca++ channels, also decreases release of glutamate.
- Partial and generalized seizures.
- Completely absorbed.
- Glucoronidated, so will not induce or inhibit enzymes.

**Side Effects:**

- Similar to carbamazepine.
- Skin rashes
- Cerebellovestibular symptoms.
Gabapentin and Pregabalin

- GABA analogs, but work indirectly to increase GABA levels in the brain.
- Partial Seizures.
- Good PK Properties.
- Effective when combined with others.
- Safe: somnolence, dizziness, ataxia.
Benzodiazepines

- GABA mechanism, and,
- Na+ channel inhibition in doses used in status epilepticus.
Benzodiazepines

- Diazepam ---------- Status epilepticus
- Lorazepam ---------- Longer acting
- Clonazepam ---------- Petit mal, but causes sedation and drooling
- Nitrazepam ---------- Infantile Spasms
Valproic Acid

✓ Increases GABA levels by enhancing synthesis and inhibiting transaminase.

✓ Also, blocks NMDA receptors, Na+ channels and T-Ca++ channels.

✓ 90% bound to plasma proteins.
Valproic Acid (1969)

- Petit mal and myoclonic epilepsy
- Mixed seizures.
- Bipolar disorder and migraine prophylaxis.
Valproic Acid

Toxicity:
✓ Hepatotoxic
✓ Neural tube defects
✓ Thrombocytopenia.
✓ Alopecia
✓ GI.
✓ Inhibits metabolism of many drugs.
Ethosuximide (1960s)

- Blocks transient Ca++ currents.
- Petit mal, still first choice.
- Safe.
Acetazolamide

- Diuretic, works by inhibiting Carbonic Anhydrase Enzyme, so decreases intracellular pH, causing mild acidosis.
- Helpful in all types of seizures.
- Used as an adjunct to others in refractory seizures.
- Tolerance develops.
- Special role for seizures at the time of menses.
<table>
<thead>
<tr>
<th>Agent</th>
<th>Trade name</th>
<th>Degree of protein binding (%)</th>
<th>$t_{1/2}$ (hr)</th>
<th>Therapeutic blood levels (µg/ml)</th>
<th>Most frequent adverse effect</th>
<th>Most serious adverse effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carbamazepine</td>
<td>Tegretol</td>
<td>75</td>
<td>6–12</td>
<td>6–12</td>
<td>Dizziness</td>
<td>Aplastic anemia</td>
</tr>
<tr>
<td>Clonazepam</td>
<td>Klonopin</td>
<td>85</td>
<td>25–50</td>
<td>20–80 ng/ml</td>
<td>Nausea</td>
<td>Agranulocytosis&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Ethosuximide</td>
<td>Zaronin</td>
<td>0</td>
<td>30–70</td>
<td>40–100</td>
<td>Sedation</td>
<td>Behavioral disorders</td>
</tr>
<tr>
<td>Felbamate</td>
<td>Felbatol</td>
<td>25</td>
<td>16–22</td>
<td>NE&lt;sup&gt;e&lt;/sup&gt;</td>
<td>Nausea</td>
<td>Stevens-Johnson syndrome</td>
</tr>
<tr>
<td>Gabapentin</td>
<td>Neurotonin</td>
<td>0</td>
<td>5–9</td>
<td>2–10</td>
<td>Dizziness</td>
<td>Hepatic failure</td>
</tr>
<tr>
<td>Lamotrigine</td>
<td>Lamictal</td>
<td>50</td>
<td>24</td>
<td>NE&lt;sup&gt;e&lt;/sup&gt;</td>
<td>Dizziness</td>
<td>Not established</td>
</tr>
<tr>
<td>Phenobarbital</td>
<td>Luminal</td>
<td>60</td>
<td>70–100</td>
<td>15–35</td>
<td>Sedation</td>
<td>Severe rash</td>
</tr>
<tr>
<td>Phenytoin</td>
<td>Dilantin</td>
<td>90</td>
<td>15–24&lt;sup&gt;a&lt;/sup&gt;</td>
<td>10–20</td>
<td>Gingival hyperplasia</td>
<td>Cognitive problems</td>
</tr>
<tr>
<td>Primidone</td>
<td>Mysoline</td>
<td>5</td>
<td>9–20</td>
<td>6–12&lt;sup&gt;d&lt;/sup&gt;</td>
<td>Sedation</td>
<td>Stevens-Johnson syndrome</td>
</tr>
<tr>
<td>Valproic acid</td>
<td>Depakene</td>
<td>90</td>
<td>8–10</td>
<td>50–120</td>
<td>Transient hair loss</td>
<td>Behavioral disorders</td>
</tr>
</tbody>
</table>

<sup>a</sup> Increased to 50%–70% with alcohol

<sup>b</sup> Bone marrow depression

<sup>c</sup> Femur fracture

<sup>d</sup> Includes necrotic skin ulcerations

<sup>e</sup> Not established