ANTI-EPILEPTIC DRUGS

Mr. Smrutiranjan Dash
Assistant Professor (Pharmacology)

B-Pharm 4th Semester Pharmacology-I

EPILEPSY

- Epilepsy is the group of chronic disorders characterized by recurrent seizures.
- Seizure are sudden, transitory, and uncontrolled episodes of brain dysfunction resulting from abnormal discharge of neuronal cells with associated motor, sensory, or behavioral changes.

TYPES OF SEIZURES

1. **Partial seizures**
    a. Simple (consciousness normal)
    b. Complex (consciousness altered – no memory)
2. **Generalized**
    a. Tonic-Clonic (Grand mal)
    b. Absence (Petite mal)
    c. Myoclonic
    d. Infantile spasm
    e. Status epilepticus

1. PARTIAL SEIZURES

- It involves typically the part of one lobe of the hemisphere.
- The symptoms depends on neuronal discharge from the neurons.

Simple partial seizures

- Simple partial seizures may occur at any age.
- It caused by hyperactivity of neuron that exhibit abnormal electrical impulses, which are blocked to a single locus in the brain.
- No alteration of consciousness because the electrical discharge does not spread.
- Confined to a single limb or muscle group.

Complex partial seizures (Temporal lobe epilepsy or psychomotor seizures)

- It exhibit complex sensory hallucination mental confusion, inappropriate or dazed behavior.
- Consciousness is impaired or lost.

2. GENERALIZED SEIZURES

Tonic-Clonic (Grand mal)

i. **Tonic Phase**
    - Sustain powerful muscle contraction, which arrest ventilation.
    - EEG: Rhythmic high frequency, high voltage discharge with cortical neurons undergoing sustain depolarizing with protected trains of action potentials.

ii. **Clonic Phase**
    - Rapid contraction and relaxation, causing a reciprocating movement which could be bilaterally symmetrical or running movement.
    - EEG: characterized by group of spike on the EEG and periodic neuronal depolarization with cluster of action potentials.

Absence seizures (Petite mal)

- Brief and abrupt (sudden) loss of consciousness.

ANTI-EPILEPTIC DRUGS

Mr. Smrutiranjan Dash
Assistant Professor (Pharmacology)

- It occurs in patients at 3 to 5 years of age and last until puberty.
- The patient stakes and exhibits rapid eye-blinking, which lasts for 3 to 5 secs.
- **EEG:** bilaterally synchronous, high voltage 3 per second and wave discharge pattern.
- Spike phase – neurons generate short duration depolarization and a burst of action potentials. No sustained depolarization or repetitive firing.

Myoclonic seizures

- This seizure consist of short episodes of muscle contraction that may recur for several minutes.
- It exhibit as brief jerks of the limbs.
- Occurs at any age, mainly at puberty.

Infantile spasm

- May be idiopathic (Unknown case) or symptomatic, example: Tuberous, Sclerosis.
- Occurs usually at 4-8 month of age.
- Characterized by brief symmetric contractions of the neck, trunk, and extremities occurring in clusters of seizures persisting for minutes with brief interval between each spasm.
- **EEG:** Shows chaotic pattern of high voltage, bilaterally asynchronous, slow wave activity called **hypsarrhythmia status epilepticus**.

Status epilepticus

- Continuous seizure lasting greater than 30 minutes.
- Two or more sequential seizure without recovery of full consciousness lasting > 30 minutes.

CLASSIFICATION

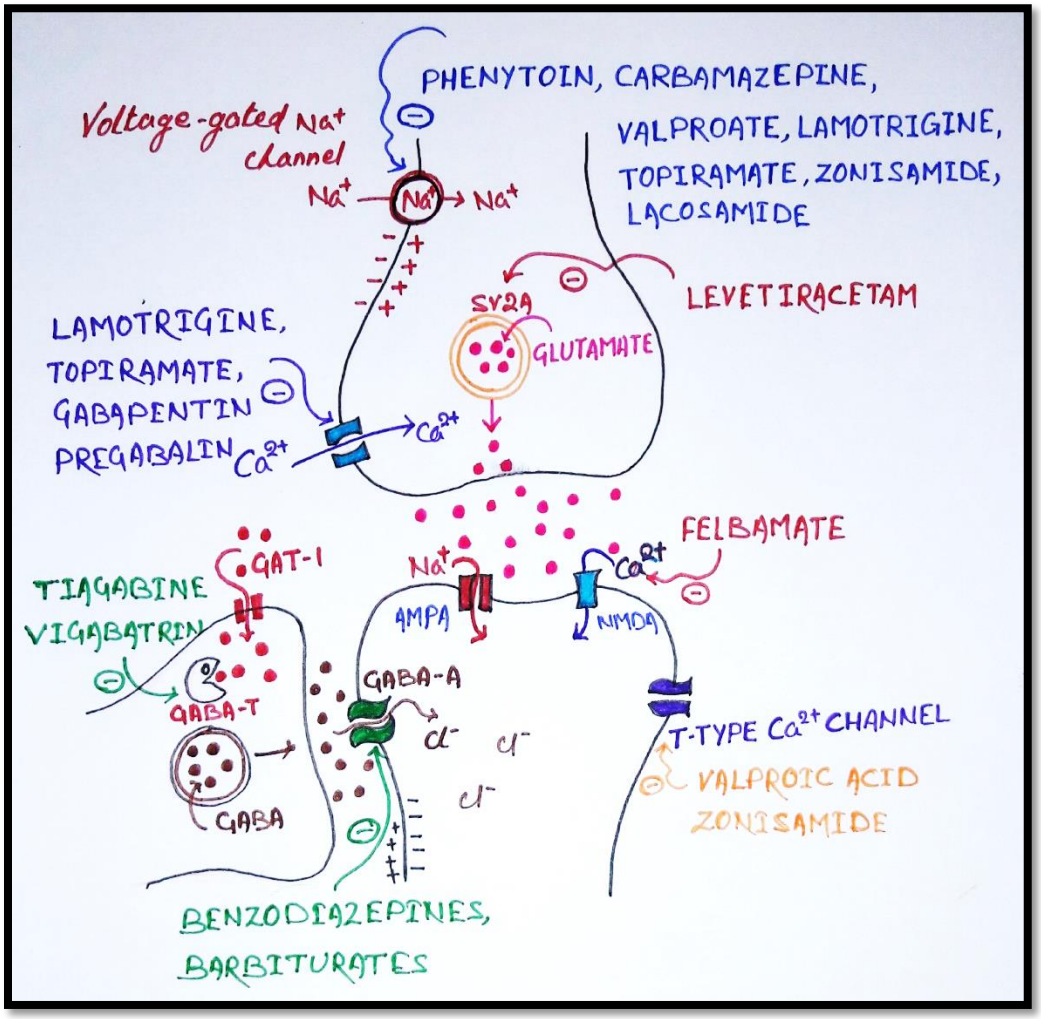
1.	**Barbiturates**	:	Phenobarbitone
2.	**Deoxybarbiturate**	:	Primidone
3.	**Hydantoin**	:	Phenytoin
			Fosphenytoin
4.	**Iminostilbene**	:	Carbamazepine
			Oxcarbazepine
5.	**Succinimide**	:	Ethosuximide
6.	**Aliphatic carboxylic acid**	:	Valproic acid (Sodium valproate), Divalproex
7.	**Benzodiazepine**	:	Clonazepam
			Diazepam
			Lorazepam
			Clobazam
8.	**Phenyltriazine**	:	Lamotrigine
9.	**Cyclic GABA analogues**	:	Gabapentin
			Pregabalin
10.	**Newer Drugs**	:	Topiramide
			Zonisamide
			Levetiracetam
			Vigabatrin
			Tiagabine
			Lacosamide

ANTI-EPILEPTIC DRUGS

Mr. Smrutiranjan Dash
Assistant Professor (Pharmacology)

B-Pharm 4th Semester Pharmacology-I

MECHANISM OF ACTION



- Voltage gated Na^+ channels open and allowing positively charged Na^+ ion by action potentials.
- Depolarization of membrane occurs.
- Consequently $Ca2^+$ channel open and then allow positively charged $Ca2^+$ ions.
- Ca^{2+} entry causes release of glutamate from the vesicle to synaptic cleft.
- Glutamate binds with mainly two receptor namely AMPA (α-amino-3hydroxy-5-methyl-4-isoxazolepropionic acid receptor) and NMDA (N-methyl-D-aspartate receptor).
- Glutamate bind with AMPA as well as NMDA receptor to permit Na^+ and Ca^{2+} ion.
- Also Ca^{2+} ion enter through the low voltage Ca^{2+} channel (T-type Ca^{2+} channel) and produce less depolarization of the membrane.
- If too much Glutamate binds to the receptor the neuron becomes hyper-excitable and a seizure may result.
- In this case GABA bind with the GABA-A receptor and allow the Cl^- ion into to the membrane.
- Due to higher negative concentration inside the membrane it act as inhibitory action.

ANTI-EPILEPTIC DRUGS

Mr. Smrutiranjan Dash
Assistant Professor (Pharmacology)

- If GABA dissociated from the GABA-A receptor then, it is reuptake to presynaptic membrane via GAT-1 (GABA transporter) and it is degraded by enzyme γ-aminobutyric acid aminotransferase (GABA-T).
- Hence decrease release of GABA leads to produce seizures.
- Phenytoin, Carbamazepine, Valproate, Lamotrigine, Topiramide, Zonisamide, Lacosamide inhibit the voltage gated Na^+ channel.
- Levetiracetam blocks SV2A (Synaptic vesicle membrane protein) receptor, hence prevent release of Glutamate.
- Lamotrigine, Topiramide, Gabapentin, Pregabalin inhibit high voltage Ca^{2+} channel, so that inhibit neuronal depolarization.
- Felbamate inactive NMDA receptor leads to prohibition of Ca^{2+} ion entry.
- Valproic acid and Zonisamide blocks the T-type Ca^{2+} channel.
- Benzodiazepine and Barbiturates are blocks the GABA-A receptor and inhibit the action of GABA.
- Vigabatrin and Tiagabine inhibit the enzyme GABA-T, so that degradation of GABA is prohibited.

ADVERSE EFFECT

- Sedation, fatigue, sleepiness
- Ataxia, vertigo, diplopia
- Tremor
- Slow thinking
- Insomnia
- Hyperactivity
- Depression
- Behavioral problems
- Nausea, vomiting
- Anorexia
- Increased appetite
- Headache
- Hypothermia
- Metabolic acidosis
- Reduce bone

PHENYTOIN

- It is a barbiturates analogue in 1908
- Not a CNS depressant.
- Toxic dose produce excitement and muscular rigidity.
- Action on tonic phase but no effect on clinic phase.

Pharmacokinetics

- Due to poor aqueous solubility, absorption of phenytoin by oral route is slow.
- Bioavailability may differ.
- It is widely distributed in the body and is 80–90% bound to plasma proteins.
- Metabolized by liver.
- t ½ is 12-24 hour progressively increased upto 60 hour.
- Only 5% unchanged phenytoin is excreted in urine.

ANTI-EPILEPTIC DRUGS

Mr. Smrutiranjan Dash
Assistant Professor (Pharmacology)

Interaction

- Phenobarbitone competitively inhibits phenytoin metabolism.
- Carbamazepine and phenytoin induce each other's metabolism.
- Valproate displaces protein bound phenytoin and decreases its metabolism.
- Chloramphenicol, isoniazid, cimetidine and warfarin inhibit phenytoin metabolism.
- Phenytoin competitively inhibits warfarin metabolism.
- Sucralfate binds phenytoin in g.i. tract and decreases its absorption.

Uses

- First line antiepileptic drug.
- Generalized tonic-clonic, simple and complex partial seizures. (Dose: 100 mg BD, maximum 400 mg/day; Children 5–8 mg/kg/day).
- Status epilepticus.
- Trigeminal neuralgia (second choice drug to carbamazepine).