

EPILEPSY

(Pathophysiology & Drugs Pharmacology)

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Contents of the Lecture:

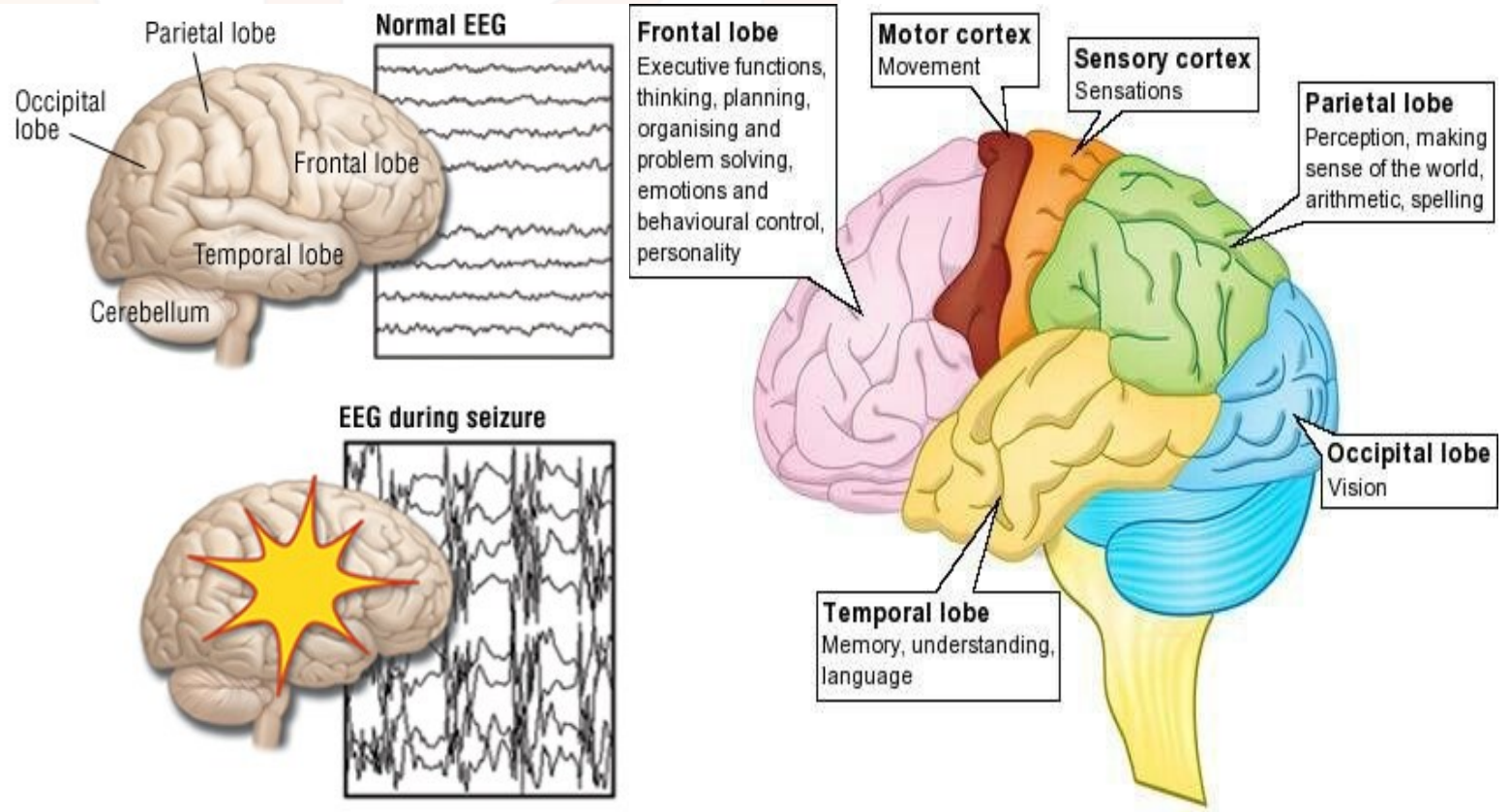
- 🧠 Introduction
- 🧠 Epilepsy/Seizure
- 🧠 Types of Epilepsy
- 🧠 Etiology
- 🧠 Pathogenesis
- 🧠 Diagnosis
- 🧠 Pharmacotherapy (Drug Classification)
- 🧠 Drug of Choice
- 🧠 Drugs, mode of Action, Use

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Introduction

🧠 **Epilepsy** is a brain disorder, characterized by seizure (excessive neuronal discharge or impulse firing), thus it is also called **seizure disorders**



Epilepsy

- 💡 The word Epilepsy is come form a Greek word “Epilepsia”. Epi means upon and Lapsis means seizure
- 💡 WHO: Two or more unprovoked seizures is the cause of epilepsy. A chronic noncommunicable disorder of the brain that affects people of all ages.
- 💡 30 million people worldwide are epilepsy sufferers (WHO)
- 💡 Prevalence: 4-6 people per 1000; 0.5%
- 💡 **Seizure:** there are abnormal electrical activity in the brain, associated with episodic high frequency discharge of impulse by a group of neurons in the brain and may alter the person’s consciousness movements or actions depends upon the affected area.

Epilepsy

💡 The form of seizure is depend upon on the parts of brain affected. Involvement of

- **motor cortex** produce **convulsion**.
- **hypothalamus** causes **peripheral autonomic discharge**;
- **reticular area** causes **loss of consciousness**.

💡 **Convulsion:** A **convulsion** is a medical condition where body muscles contract and relax rapidly and repeatedly. So sometime also called **Convulsive disorders**



Types of Epilepsy

I. PARTIAL SEIZURES: Impulse discharge begins locally and often remains locally. Symptoms depending on brain area.

a) Simple partial seizure- cortical focal epilepsy, without loss of consciousness.

b) Complex partial seizure- temporal lobe epilepsy; psychomotor epilepsy with loss of consciousness.

c) Simple partial or complex partial seizure or secondarily generalized-
The partial seizure occurs first and evolves into generalized tonic-clonic seizure with loss of consciousness.

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Types of Epilepsy

II. GENERALISED SEIZURES: Involved in whole brain.

a) **Generalized tonic-clonic/grand mal seizure: commonest.**

b) **Absence/petit mal seizure**

c) **Atonic/akinetic seizure**

d) **Myoclonic seizure**

e) **Infantile spasm**

III. Unclassified Seizure: Neonatal Seizure

IV. Status Seizure: Seizure occur repeatedly with no recovery of consciousness between attacks

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Partial Seizure

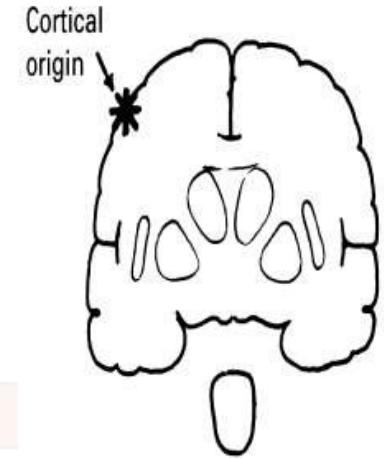
- 💡 Most common type (80%)
- 💡 Impulse discharge begins locally and often remains locally. Symptoms depending on brain area.

A. Simple partial seizure- cortical focal epilepsy,

- 💡 without loss of consciousness

Sign & Symptoms:

- 💡 motor – convulsive jerking, chewing motions, lip smacking
- 💡 Sensory & somatosensory – paresthesias, auras
- 💡 Automatic – sweating, flushing, pupil dilation
- 💡 Behavioural – hallucinations, dysphasia, impaired consciousness (rare).



Partial Seizure

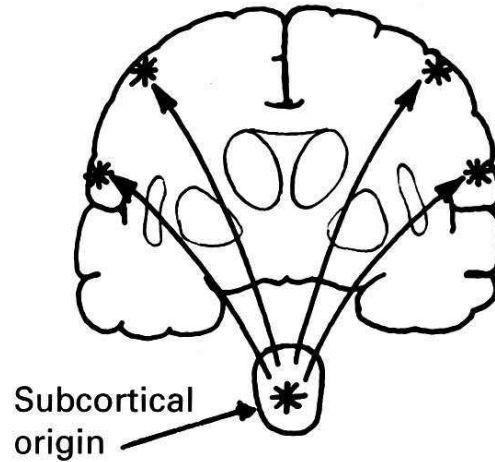
B. Complex partial seizure

- 🧠 **temporal lobe epilepsy; psychomotor epilepsy** characterized by
- 🧠 involuntary muscle contractions,
- 🧠 abnormal sensory/autonomic discharge,
- 🧠 alter mood and behaviours and
- 🧠 visual, auditory, or olfactory hallucinations
- 🧠 **loss of loss of consciousness.**

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Generalised Seizure

🧠 Involved in whole brain (affects both hemisphere)



a) Generalized tonic-clonic/grand mal seizure: commonest, the usual sequence occurs is aura—cry—unconsciousness—tonic spasm—clonic jerking followed by prolongation sleep and CNS depression.

Generalised Seizure

Tonic phase:

- Pt become rigid & falls to the ground
- Respiration are interrupted
- Back arches
- Lasts about 1min

Clonic phase:

- Rapid muscle jerking
- Muscle flaccidity
- Incontinence, tongue biting,
- tachycardia, heavy salivation

Generalised Seizure

b) Absence/petit mal seizure: mainly in children,

- 💡 Alterations of consciousness (absence) lasting 10-30sec
- 💡 Staring (with occ. eye blinking) & loss in postural tone
- 💡 'freez' conditions.

c) Atonic/akinetic seizure:

- 💡 loss of consciousness with relax all muscles.
- 💡 Sudden loss of postural tone, pt falls to the ground
- 💡 Occur primarily in children

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Generalised Seizure

d) Myoclonic seizure:

- 💡 shock like momentary contraction of all muscles
- 💡 sudden, Involuntary jerking of facial, limb or trunk

e) Infantile spasm: mainly showed in infants, intermittent muscle spasm and progressive mental deterioration.

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Etiology

- 🧠 Stroke
- 🧠 Brain tumor
- 🧠 Brain infection
- 🧠 Past head injury
- 🧠 Drug use, alcohol withdrawal
- 🧠 Metabolic problems
- 🧠 Other neurological conditions
- 🧠 High fever, especially in infants
- 🧠 Genetic factors

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Pathogenesis

Paroxysmal discharges of impulse in cortical neurons
(A seizure originates from grey matter of any cortical or subcortical area)



Abnormal firing of neurons



Breakdown of normal membrane conductance & inhibitory synaptic currents



Locally



Focal seizure



widely



Generalized seizure

Pathogenesis

- ✓ Abnormality of Potassium conductance
- ✓ Defect in voltage sensitive ion channels
- ✓ Deficiency in membrane ATPase Abnormal firing of neurons



Neuron membrane instability



Seizure

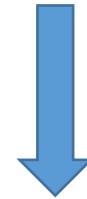
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Pathogenesis

- ✓ Deficiency of inhibitory neurotransmitters
- ✓ Increase in excitatory neurotransmitters



Abnormal Neuronal activity



Seizure

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Diagnosis

- 💡 Electroencephalogram (EEG)
- 💡 Neurological imaging studies
 - Magnetic Resonance Imaging (MRI)
 - Functional MRI (fMRI)
 - Computed Tomography (CT)
 - Positron emission tomography (PET)
 - Single-photon emission computerized tomography (SPECT)

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Pharmacotherapy

1. Barbiturate: Phenobarbitone
2. Deoxybarbiturate: Primidone
3. Benzodiazepines: Clonazepam, Clobazam, Diazepam
4. Hydantoin: Phenytoin
5. Succinamide: Ethosuximide-
6. Carboxylic acid: Sodium valproate
7. Iminostilbene: Carbamazepene, Oxcarbamazepene
8. Phenyltriazine: Lamotrigine
9. Cyclic GABA analouge: Gabapentin
10. Newer drugs: Topiramate, Vigabatrin (γ -vinyl GABA), Tiagabin, Levatiracetam, Felbamate, Zonisamide (Sulphonamide analouge)

Drug of Choice

Epilepsy	First Line Drugs
Partial / Secondary Generalized Tonic-Clonic Seizures	Carbamezapine
Tonic-Clonic Seizures (Grand mal Epilepsy)	Valproate
Absence Seizure (Patit mal Epilepsy)	Ethosuximide
Myoclonic Seizure	Valproate
Infantile Spasms	ACTH/Prednisolone
Status Epilepsy	Diazepam (10 mg iv)

Drugs, MOA & Use

DRUGS	MECHANISM	USE
Phenobarbitone	Activate GABA _A mediated Cl ⁻ ion channel, Antiglutamate and reduce Ca ²⁺ entry	All type of seizures except Absence seizure
Primidone	Activate GABA _A mediated Cl ⁻ ion channel	Used as an adjuvant to phenytoin or carbamazepine
Diazepam	Facilitate the GABA _A mediated Cl ⁻ ion channel	First choice of Febrile and Status epilepsy
Phenytoin	Neuronal membrane stabilizer, Prolongation of Na ⁺ channel inactivation	All type of seizures except Absence seizure
Ethosuximide	Inhibit T-Type Ca ²⁺ channel	Effective only in Absence Seizure
Valproate	Prolongation of Na ⁺ channel inactivation, Inhibit T-Type Ca ²⁺ channel, Induce GABA mediated action through inhibit its degradation by GABA-transaminase.	Preferred in Absence, Myoclonic and Atonic seizures

Drugs, MOA & Use

DRUGS	MECHANISM	USE
Carbamazepine	Prolongation of Na ⁺ channel inactivation	All type of seizures except Absence seizure, preferred in Generalized tonic clonic, and Coplex partial seizure
Lamotriagine	Prolongation of Na ⁺ channel inactivation, Direct block of presynaptic voltage sensitive Na ⁺ channel and prevent release of excitatory amino acids	All Type
Gabapentin	Lipophilic GABA derivative, cross BBB and enhance the GABA release in brain	Partial Seizure
Vigabatrin	GABA-transaminase inhibitor, Antagonism of Glutamate receptor, Prolongation of Na ⁺ channel inactivation, Potentiation of GABA action	All Type
Topiramate	Weak carbonic anhydrase inhibitor, Antagonism of Glutamate receptor, Prolongation of Na ⁺ channel inactivation, Potentiation of GABA action	All type of seizures except Absence seizure

Drugs, MOA & Use

DRUGS	MECHANISM	USE
Tiagabine	Inhibit GABA uptake through block GABA transporter (GAT-1)	Partial seizure
Levetiracetam	???mechanism is unknown	Partial seizure
Zosinamide	It may inhibit T-Type Ca^{2+} channel , Prolongation of Na^{+} channel inactivation	
Felbamate	Inhibit NMDA receptor mediated Na^{+} channel, Potentiation of GABA action	

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CARBAMAZEPINE

↳ Chemically imipramine deriv., introduced in 1960s for trigeminal neuralgia

↳ Now 1st line drug for Partial Seizure & GTCS

MOA - Prolongation of Inactivated state of voltage gated Na⁺ channel

Action - Similar as phenytoin but exp. studies shows that Carbamazepine modifies maximal electroshock Seizure as well as raises threshold to PTZ & Electroshock convulsion

It has also Lithium like action in mania & bipolar mood disorder.

↑ ADH action → Antidiuretic effects

P'kinetics: - slow oral absorption, PB 75%, metabolized by oxidation (Liver) & form epoxide and also by hydroxylation & conjugation.

* It is a substrate as well as inducer of Cyp3A4 & Cyp2C9, $t_{1/2} = 20-40h \rightarrow 10-20h$ (Autoinduction)

ADR: → # Dose related Neurotoxicity → Sedation, dizziness, Vertigo, diplopia and ataxia.

Acute intoxication → coma, convulsion, cvs collapse

Allergy # Water Retention

USES → Seizure and Trigeminal Neuralgia

SOD. VELPROATE

Branched chain aliphatic carboxylic acid with broad spectrum anticonvulsant action.

It is more potent in blocking PTZ Seizure than in modifying maximal electroshock.

Exp. Seizure foci & kindling are also prevented

It also produce Sedation and other CNS effect

MOA: - # ↑ Na⁺ channel inactivation

↓ Ca²⁺ mediated T-Current

↑ release of GABA

↓ NMDA mediated action

P'kinetics → Good Oral Abs, 90% PB, metabolised by liver (2C9, 2C19), excreted through urine, $t_{1/2} = 10-15h$

ADR - # Anorexia, vomiting, loose motion - Common

Drowsiness, Ataxia, tremor - at high dose

Alopecia, weight gain, ↑ bleeding, Allergy

↑ Serum transaminase - liver damage

Teratogenic effect

Uses - Drug of choice for - Absence Seizure
1st Line drug → Partial & GTCS

Interaction - ↳ ↓ metabolism of phenobarbitone

↳ ↓ the metabolism of carbamazepine epoxide

↳ + Clonazepam → ppt Absence seizure



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