Antiepileptic drugs

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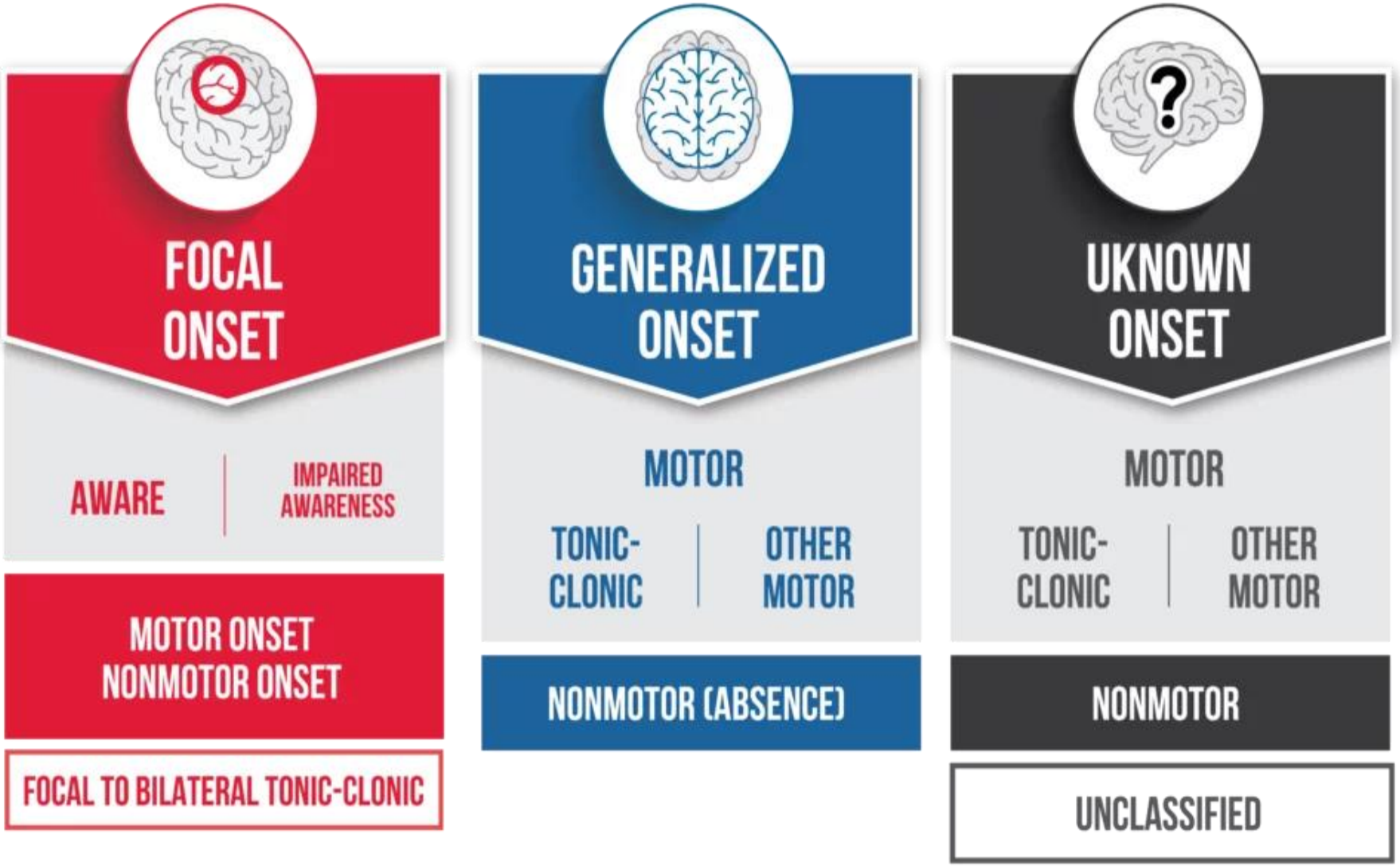
Epilepsy

Chronic disorder characterized by recurrent seizures due to abnormal discharge of cerebral neurons

Types:

ILAE 2017 CLASSIFICATION OF SEIZURE TYPES BASIC VERSION



Cellular Mechanisms of Seizure Generation

- **Excitation (too much)**
  - Ionic-inward Na^{+}, Ca^{++} currents
  - Neurotransmitter: glutamate, aspartate

- **Inhibition (too little)**
  - Ionic-inward Cl; outward K^{+} currents
  - Neurotransmitter: GABA

Mechanism of action of antiepileptic drugs

1.Reduction of cell membrane permeability to Na

e.g. phenytoin, carbamazepine, valproate & lamotrigine.

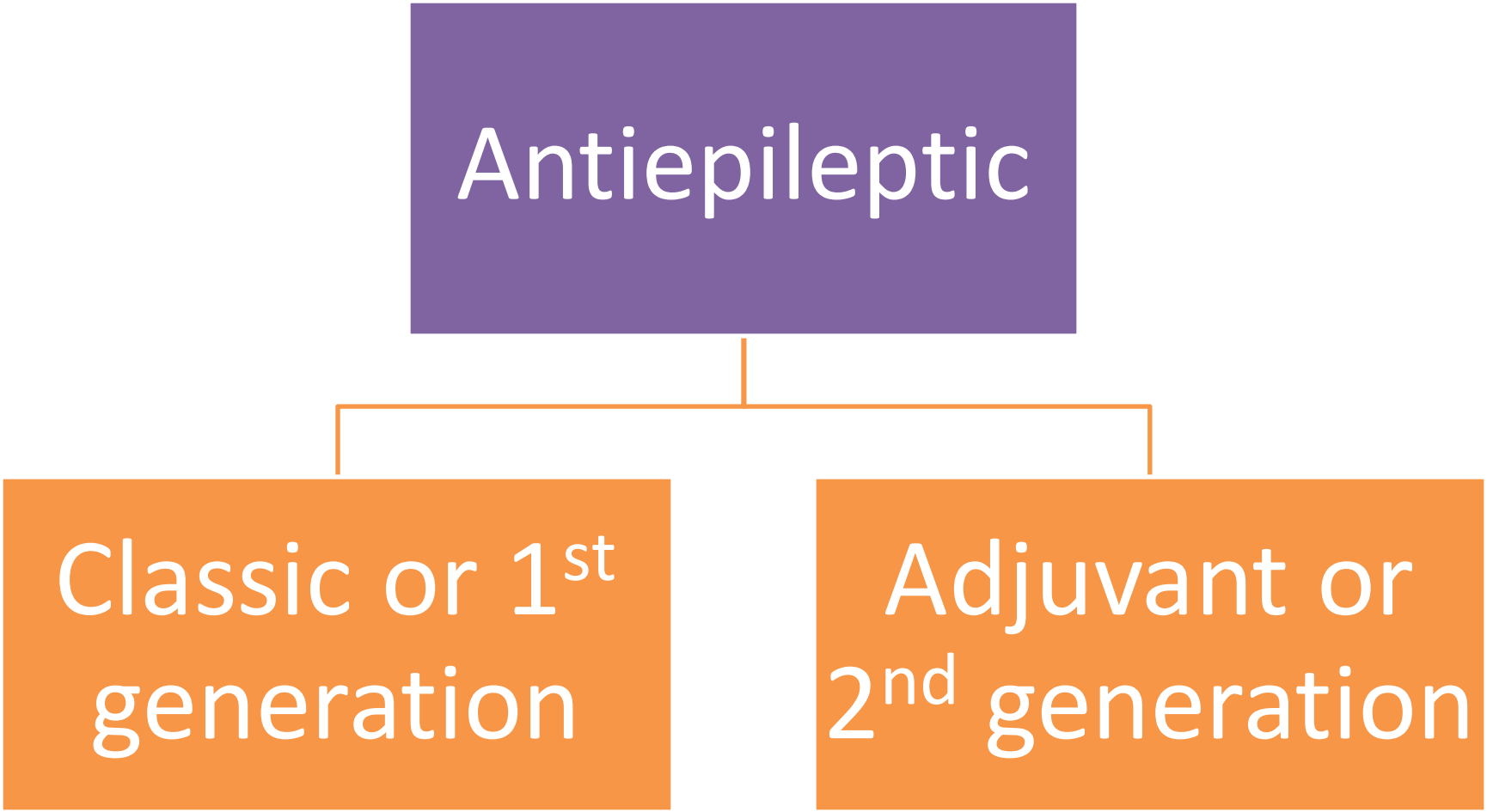
2. Block of voltage-dependent T-Calcium channels

e.g. ethosuximide, valproate.

3.Modifying neurotransmitters:

A. Enhancement of GABA mediated synaptic inhibition *e.g. barbiturates, benzodiazepines, vigabatrin & valproate*.

B. Decreased excitatory amino acid function *e.g. felbamate and toprimate*



Due to high toxicities of most antiepileptic drugs, monotherapy is preferred and only used Only add on therapy in unresponsive cases or refractory epilepsy

I- Phenytoin and Fosphentoin

Pharmacokinetics:

A: Oral absorption is **complete**.

D: pass blood brain barrier and placenta

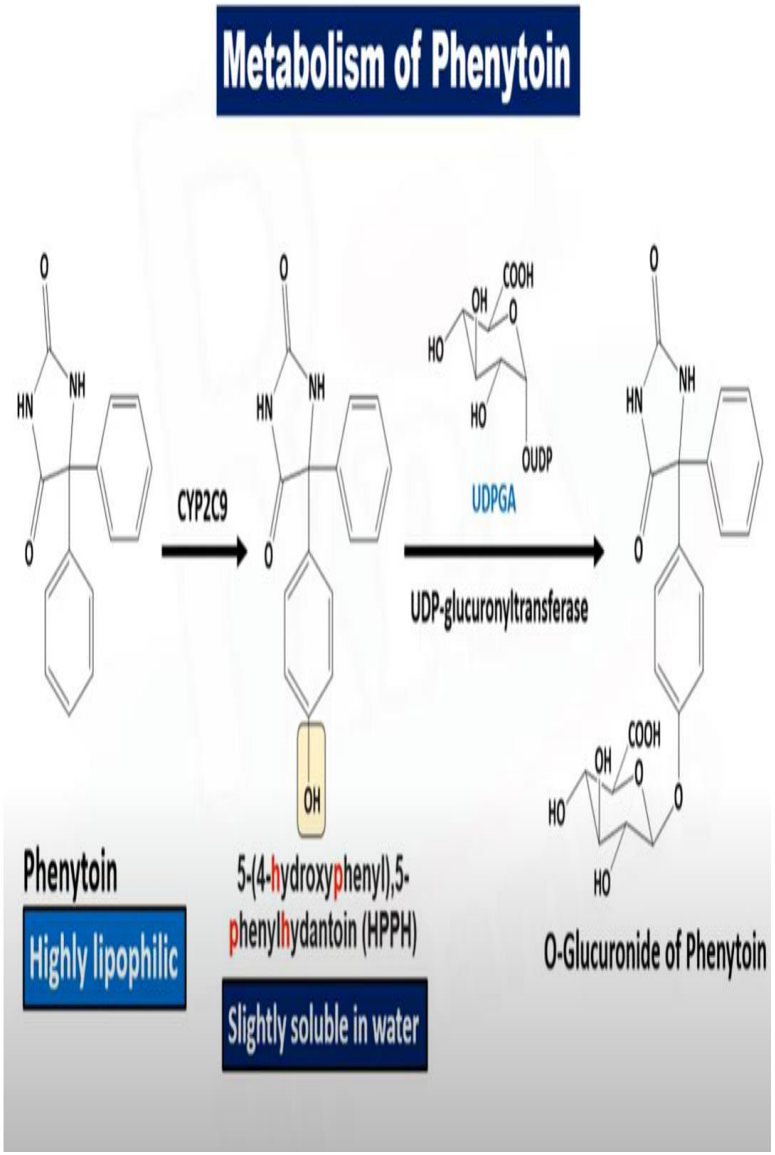
About 90% bound to **plasma protein.**

- T1/2 = 12-36 hours.

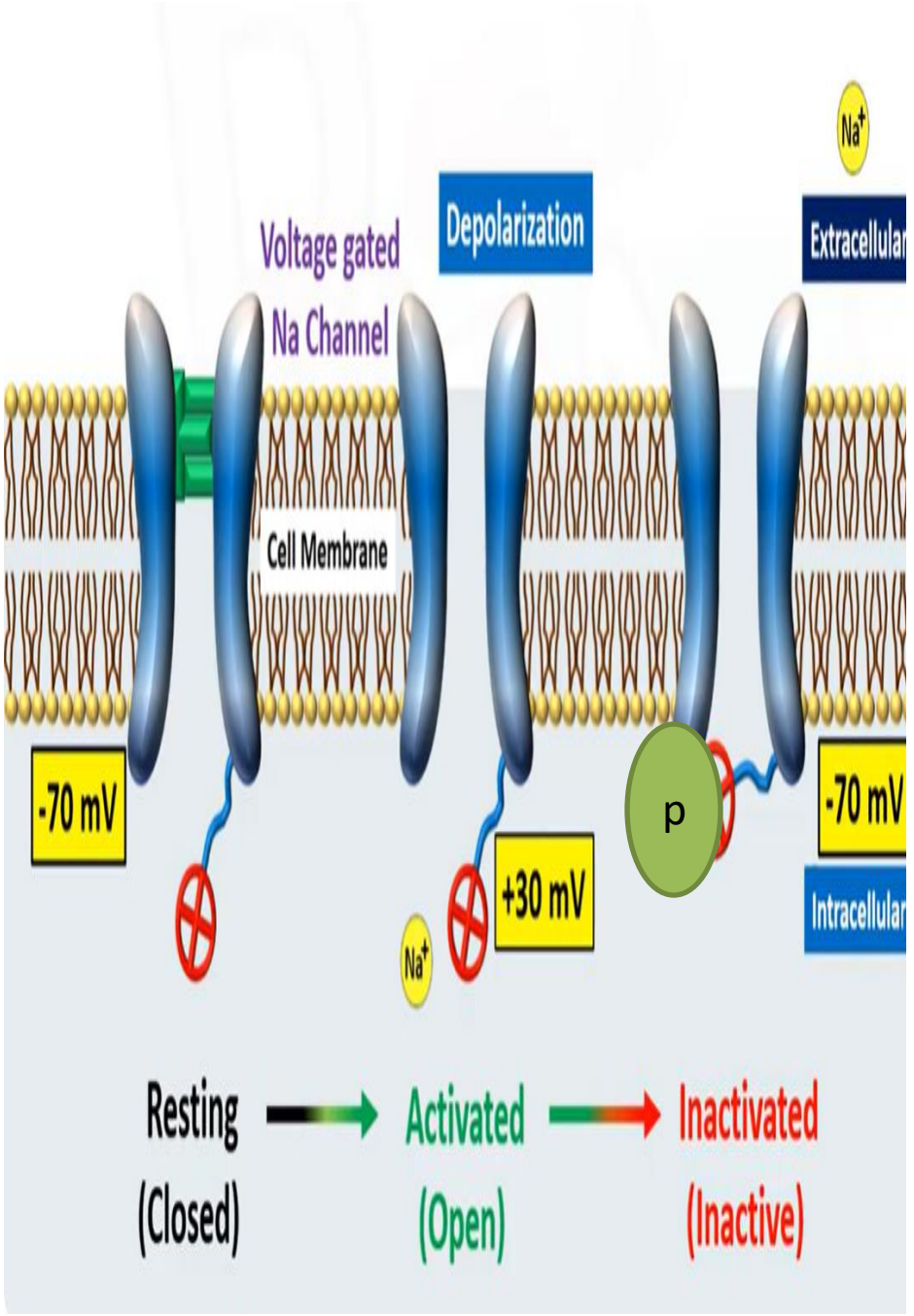
M: It is **hydroxylated** in the liver and this needs **folic acid** as cofactor THEN glucuronation to final metabolites

E: Elimination follows **saturable** kinetics.

NOTE: Fosphenytoin: **prodrug (water soluble)** of phenytoin, available for **parentral** use in **status epilepticus (i.v or i.m).**



- **Mechanism of action**
- It blocks voltage-gated **Na+ channels**.
- At higher concentrations. It can block voltage-dependent **Ca++ channels** & interferes with **release of neurotransmitters**.



Pharmacological actions:

1.Antiepiletic: it has selective antiepileptic action without causing CNS depression.

2.Antiarrythmic: it depresses automaticity, excitability & increased conduction velocity, so abolish reentry arrhythmias.

Therapeutic uses:

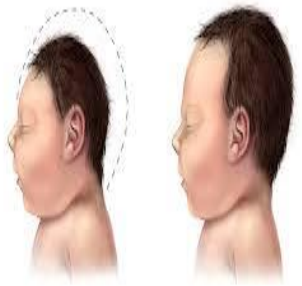
1.Antiepileptic:

A. focal seizures

B.Status epilepticus (Fosphenytoin).

2.Ventricular arrhythmia.

Side effects



1. C.N.S: Nystagmus, diplopia, ataxia & vertigo.
2. Liver: enzyme inducer
3. Blood : Megaloplastic anemia

it interferes with folate absorption and/or metabolism

4- Teratogenicity:

- cleft palate and hare lip (fetal hydantoin syndrome) if taken in the first trimester.
- Cardiac septal defect
- Hypoprothrombinemia of the baby, if taken before labor.
- Neural tube defect (spina bifida)

5. Gingival hyperplasia.

6. Hypersensetivity reactions as rash, fever, **lymphadenopathy**.

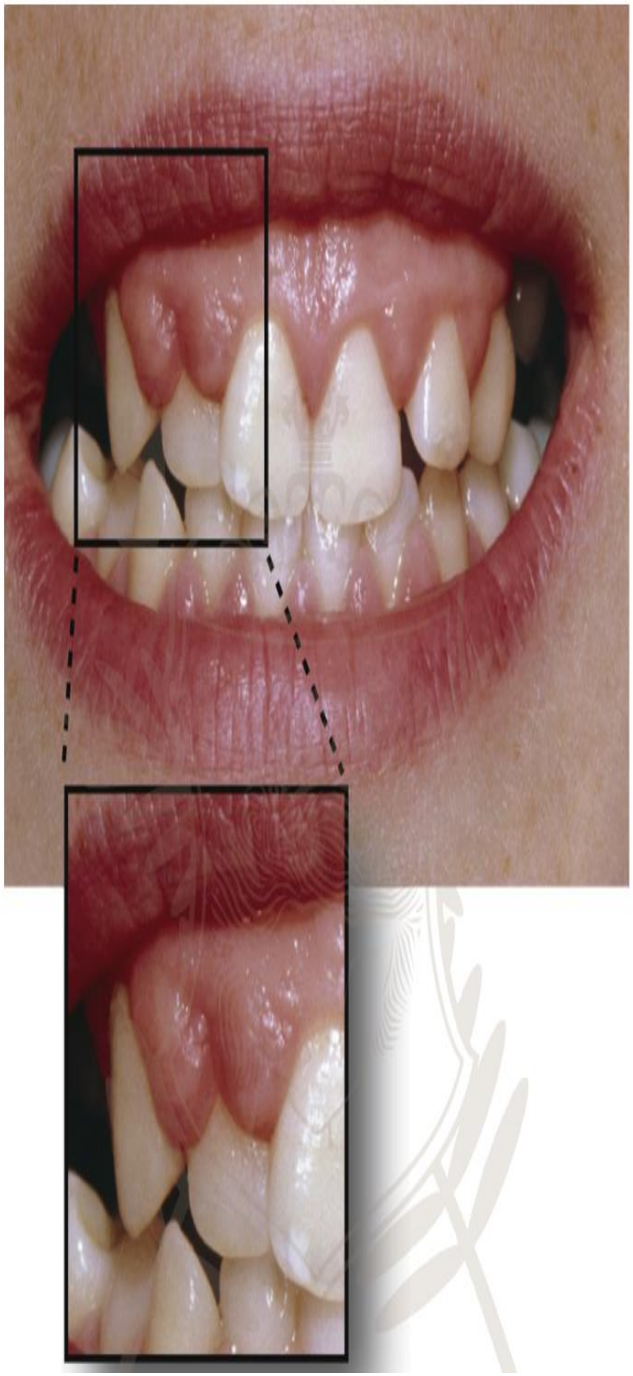
7. Hirsutism and acne due to increased androgen secretion

8.Osteomalacia with hypocalcemia

- occurs with chronic use (it interferes with vit D hydroxylation and reduces G.I. absorption of calcium).

9. Inhibit insulin release (hyperglycemia)

10. Neuropathies due to folate deficiency



HOW TO REMEMBER *SIDE EFFECTS OF PHENYTOIN*

IN 2 MINS

H	HIRSUTISM
O	OSTEOMALACIA
T	TERATOGENICITY
M	MEGALOBLASTIC ANEMIA
A	ARRHYTHMIA (at toxic doses)
I	INHIBITS INSULIN RELEASE
L	LYMPHADENOPATHY
G	GUM HYPERTROPHY
A	ATAXIA (at toxic doses)
N	NYSTAGMUS (at toxic doses)
D	DIPLOPIA (at toxic doses)
K	VITAMIN K DEFICIENCY

FETAL HYDANTOIN SYNDROME

- Cleft Lip
- Cleft Palate
- Microcephaly
- Hypoplastic phalanges

Drug interactions of phenytoin:

1. Displacement of phenytoin from plasma proteins: phenylbutazone, oral anticoagulants & sulfonamides.

2. Inhibition of phenytoin metabolism by chloramphenicol & valproic acid.

3. Phenytoin metabolism is enhanced by enzyme inducers: carbamazepine and phenobarbitone.

4. Phenytoin (enzyme inducer) can increase the metabolism of ***warfarin, steroids.***

Precautions:

1.**Serum level** monitoring is essential.

2.**Oral hygiene** (frequent brushing, gum massage).

3.**Vit D and folate** supplements should be given when necessary.

II- Carbamazepine and oxcarbamazepine (TCA related)

- **Pharmacokinetic:**

A: Following oral absorption

D: it enters the brain rapidly, cross placenta, bound to plasma protein

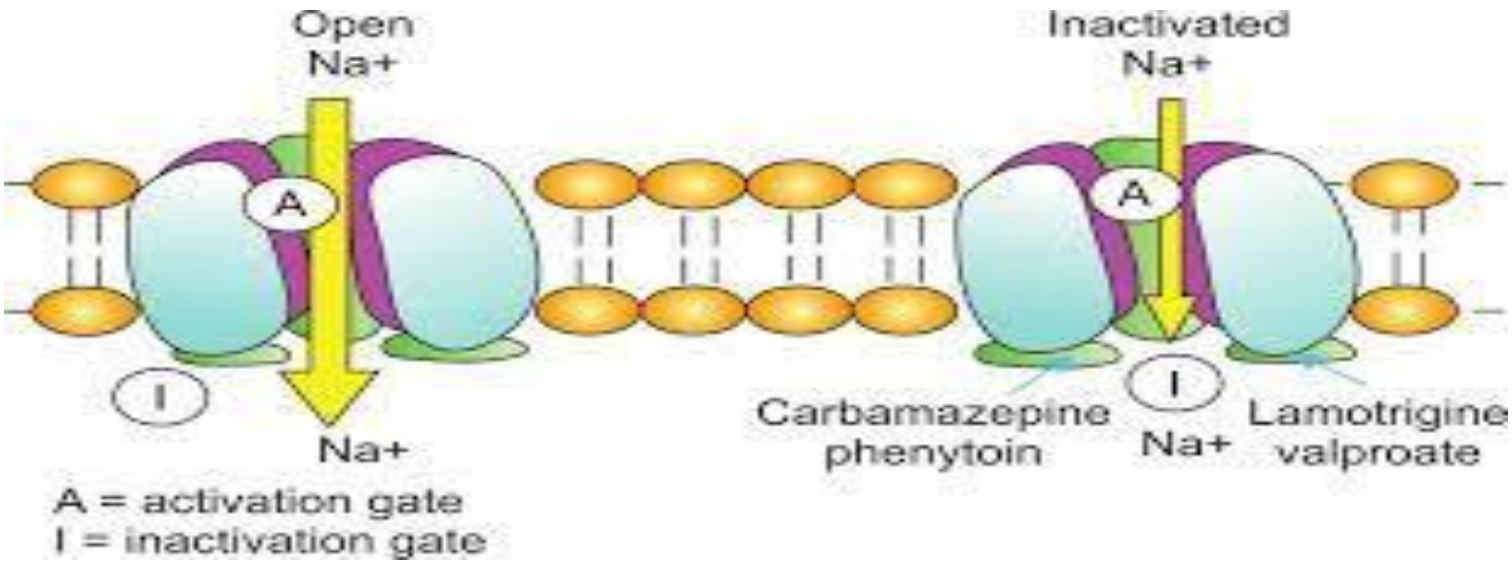
M: It induces hepatic microsomal enzymes.

Its half life decreases with chronic administration due to auto- induction

- The enhanced activity of liver microsomal enzymes also increases metabolism of many other drugs including anti-epileptics

Mechanism of action:

- It **blocks Na+ channels** and so reduces the propagation of abnormal impulses in the brain.



• Therapeutic uses:

1. Focal seizures.
2. Trigeminal neuralgia.
3. Cerebral or nephrogenic diabetes insipidus

• Side effects:

1- C.N.S: Nustagmus, Diplopia, Ataxia & **drowsiness**.

2 .Liver dysfunction

3.Blood: Aplastic anemia, agranulocytosis (cause bone marrow depression).

Teratogenicity: craniofacial anomalies and spina bifida

2. G.I.T: nausea & vomiting.

3. Allergy: rash & photosensitivity.

4. Hyponatremia, water toxicity due to ↑ ADH effects.

Not used in treatment of absence seizures

- **Oxacarbazepine:**
- **prodrug convert to active metabolite**
- It is anticonvulsant.
- C.N.S. toxicities are similar to that of carbamazepine
- Lesser hepatic enzyme inducer
- There are no reports of hepatic failure or bone marrow abnormality.

III- Valproic acid, valproate and divalproex

- **Pharmacokinetics:**
  - Well absorbed orally.
  - 90% bound to plasma proteins.
  - Metabolized in the liver to toxic metabolites.
- **Mechanism of action:**
- It acts by increasing GABA concentrations in synaptic regions through:

-Inhibition of ***GABA transaminase*** (enzyme that breaks GABA) or

-Inhibition of ***GABA reuptake*** by nerve endings.

- It blocks Na+ channels & T-Ca+ channels.

Therapeutic uses:

1. **Broad** spectrum antiepileptic:

effective in generalized epilepsy & focal seizures but it is not the drug of choice (**sedation** & **hepatotoxicity**).

2. focal seizures **divalproex**

3. Absence epilepsy. **divalproex**

4. Febrile convulsion.

5. Myoclonus and tonic -clonic **divalproex**

6. Prophylaxis of migraine

Side effects:

1. CNS: N,A,D
2. liver: Hepatotoxicity.
3. Teratogenic: more increased incidence of spina bifida of any antiepileptic. Decrease I.Q for child.

4- G.I.T: anorexia, nausea & vomiting.

5- Hair loss (alopecia)

Drug interactions:

- Valproic acid inhibits the metabolism of phenobarbitone, phenytoin and carbamazepine.
- It displaces phenytoin from plasma protein binding sites.

V- Barbiturates (Bb and benzodiazepine Bz)

- **Phenobarbitone**: it has selective anticonvulsant activity & it may act through **potentiating the inhibitory pathway (GABA).**

.**Diazepam, Clonazepam & Lorazepam** : drug of choice for treatment of status epilepticus (rapid onset).

IV- Ethosuximide
(LEAST TOXIC ANTIEPILEPTIC)

- **Pharmacokinetics**:
  - Well absorbed orally.
  - Not bound to plasma protein.
  - 75% are metabolized.
  - 25% are excreted unchanged.
- **Mechanism of action:**

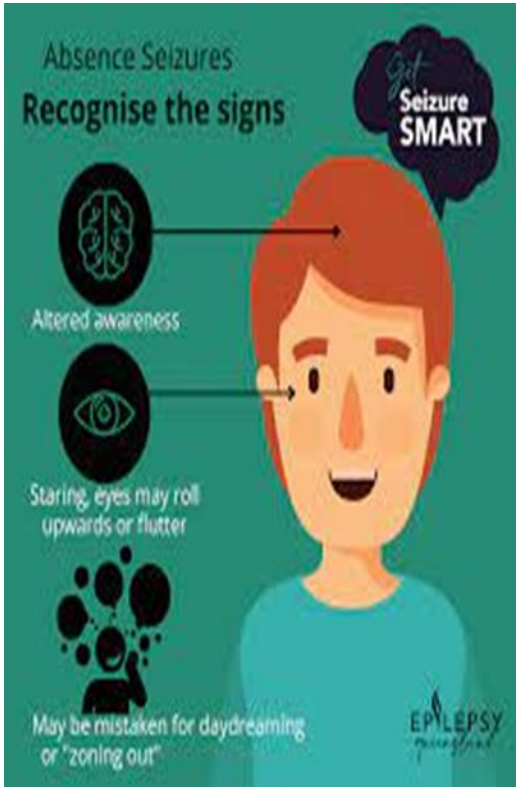
  It blocks voltage-gated **T-Ca++ channels.**
- **Therapeutic uses:**

  It is the drug of first choice in **absence** seizures

- **Side effects:**

1.G.I.T: nausea, vomiting & diarrhea

2.Allergy: skin rash & urticaria.



Absence Seizure

involves sudden lapse in consciousness and staring blankly into space, the episodes last less than 15 seconds

- Newer antiepileptic drugs (2^{ND} generation)

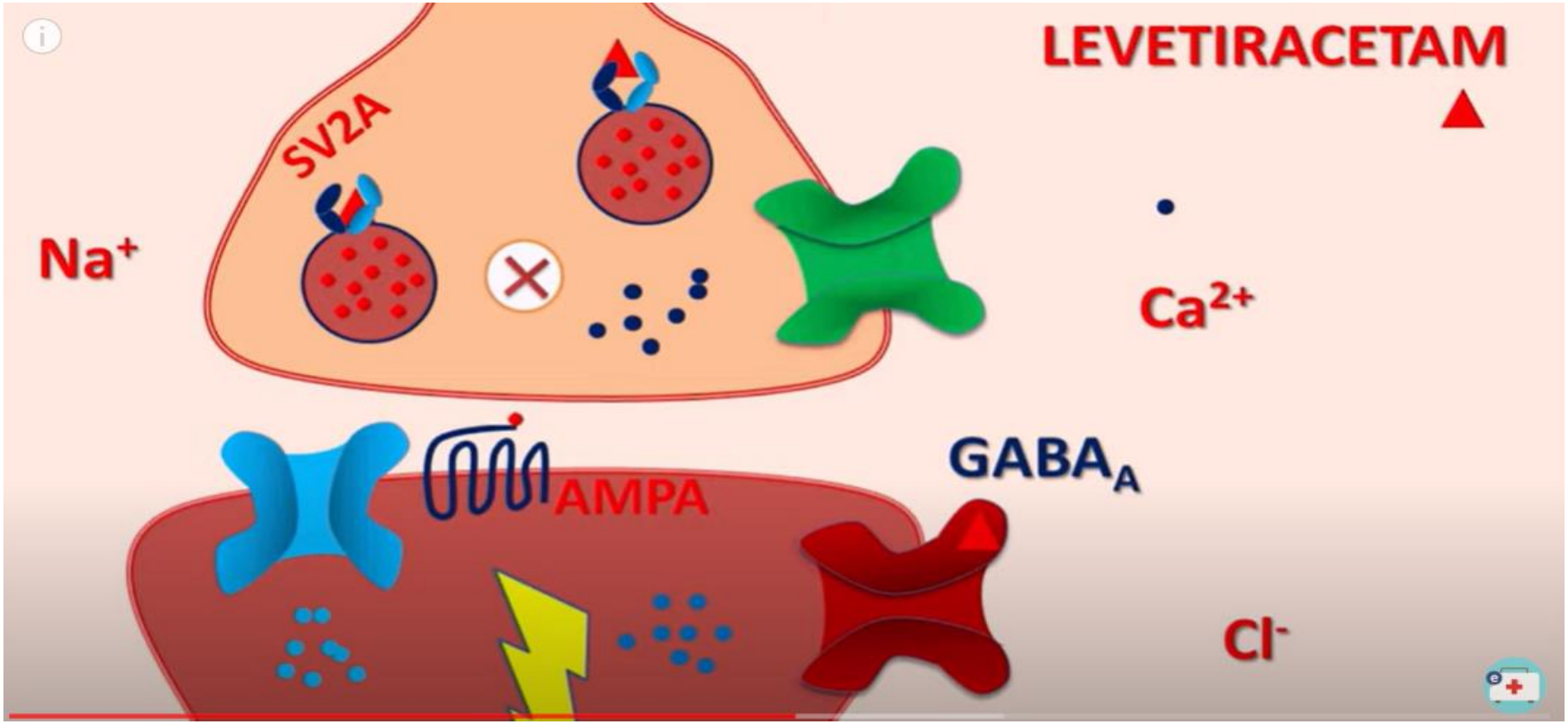
- All are used as add-on therapy in **refractory** epilepsy.
- Some of them have proved efficacy as **monotherapy**

Lamotrigine	Topiramate	Zonisamide (Sulfa)
• blocks Na & Ca++ channels. • used in **all type of epilepsy except status epileptics** • Side effects: dizziness, headache & ataxia, Stevens Johnson syndrome	• blocks Na & Ca++ channels. • Bind glutamate receptor • Used in: focal, generalized epilepsy and absence seizures • Side effects: impaired concentration, diplopia, weight loss & kidney stones	• Blocks Na+ & Ca++ channels. • Used in: focal, generalized epilepsy and absence seizures Side effect: kidney stones and oligohidrosis.

Gabapentin	Vigabatrine	Tiagabine	Pregabalin
• Enhance release of GABA. • They interfere with voltage-dependent Ca++ channels Uses: • Migraine and **neuropathic pain (post-herpetic neuralgia and diabetic neuropathy)**. • Approved as adjunct therapy for focal convulsions **Side effects:** dizziness, headache & ataxia	• It is irreversible inhibitor of GABA transaminase, increasing concentration of GABA. • Used in grand mal and focal seizures(refractory) • **Side effects**: sedation, dizziness & behavioral changes, **irreversible vision affection**	• It blocks GABA uptake (Transporter) into presynaptic neurons. • **Used in:** focal seizures • **Side effect:** dizziness & GI upset.	• They interfere with voltage-dependent Ca++ channels • INHIBIT excitatory transmitter release • **Used in:** focal seizures **Side effects:** dizziness, headache & ataxia

Levetiracetam and brivaracetam

- Modifies the release of glutamate and GABA by binding to synaptic vesicle protein(SV2A)
- **Used in: broad spectrum antiepileptic used in all types of epilepsy except stsatus**
- **Side effects:** dizziness & sleep disturbances, behavioral changes.



Felbamate

- **Mechanism of action :** It blocks Na+ & Ca++ channels & competes with glycine cofactor at NMDA receptors.
- **Side effects:** liver and bone marrow toxicities, so it is reserved for use in refractory epilepsy.

Seizure Type	Effective Drugs
Partial—simple or complex	Valproic acid, phenytoin, carbamazepine, lamotrigine
General—tonic-clonic	Valproic acid, phenytoin, carbamazepine, lamotrigine
General—absence	Ethosuximide, valproic acid
Status epilepticus	Lorazepam, diazepam, phenytoin, or fosphenytoin*


Thank You