



Antiepileptic drugs

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Epilepsy

→ داء عارٍ عن Motor manifestation

Def: A chronic disorder characterized by recurrent spontaneous seizures due to abnormal discharge of cerebral neurons.

Consists of 3 phases: 1- **Aura** — early part of a seizure, may include odd smells or tastes. 2- **Ictal** — time from first symptom to end of seizure activity. 3- **Postictal** — period of gradual recovery back to pre-seizure baseline level of function/awareness.

Types:

Generalized seizures

- Tonic-clonic seizures ("grand mal")
- Absence seizures ("petit mal")

Focal seizures

- Focal seizures with awareness ("simple partial")
- Focal seizure with impaired awareness ("complex partial")

EpilepsyDisease.com

ILAE 2017 CLASSIFICATION OF SEIZURE TYPES BASIC VERSION



**FOCAL
ONSET**

AWARE

**IMPAIRED
AWARENESS**

**MOTOR ONSET
NONMOTOR ONSET**

FOCAL TO BILATERAL TONIC-CLONIC



**GENERALIZED
ONSET**

MOTOR

**TONIC-
CLONIC**

**OTHER
MOTOR**

NONMOTOR (ABSENCE)



**UNKNOWN
ONSET**

MOTOR

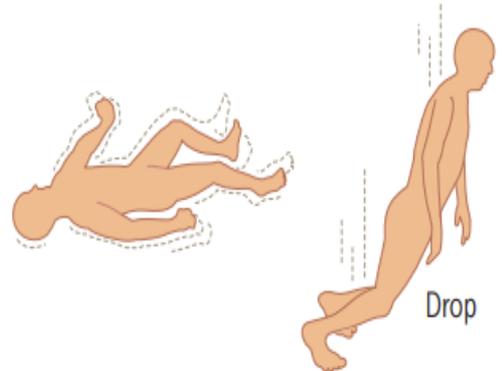
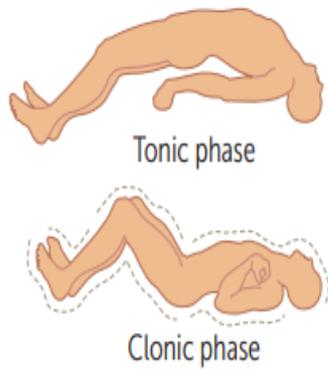
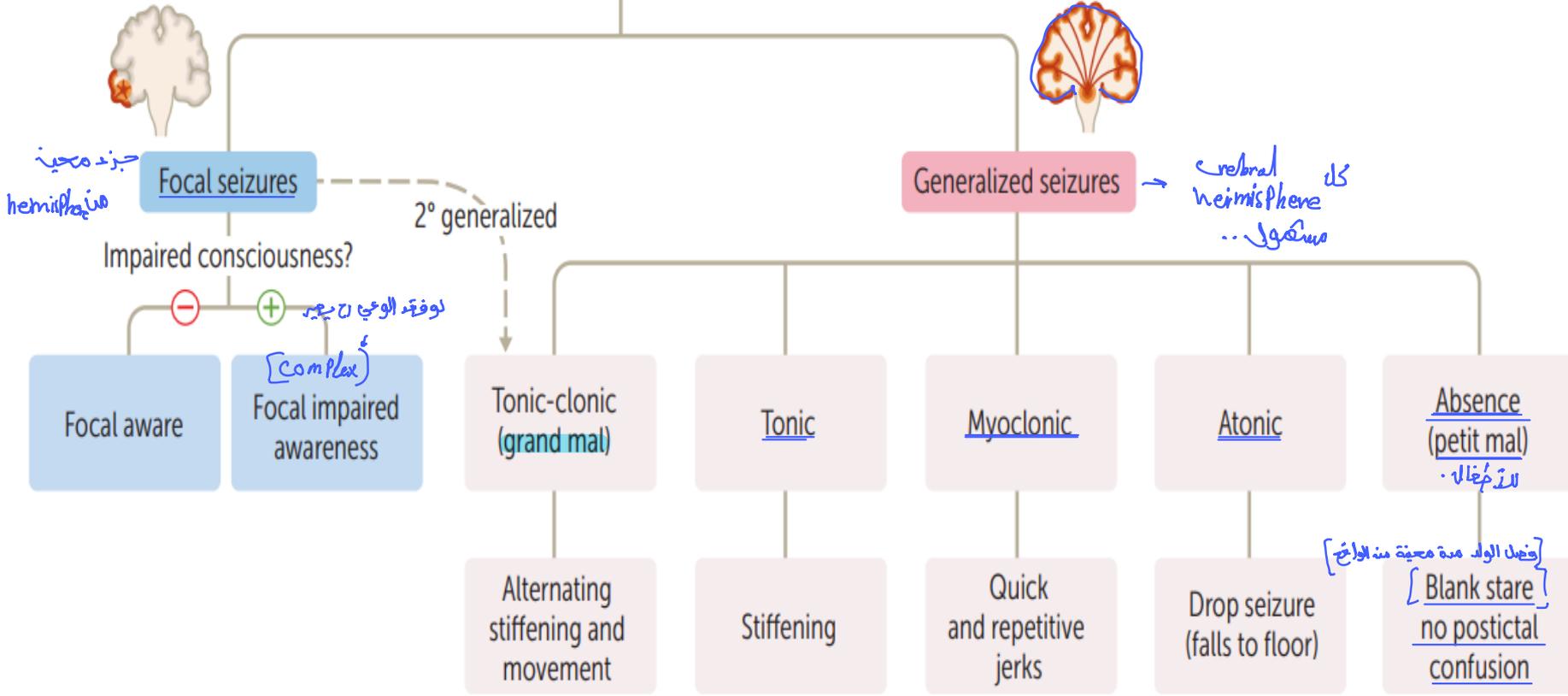
**TONIC-
CLONIC**

**OTHER
MOTOR**

NONMOTOR

UNCLASSIFIED

Seizure





Cellular Mechanisms of Seizure Generation

❖ Excitation (too much)

[GABA]
[inhibition]

- Ionic-inward Na⁺, Ca⁺⁺ currents
- Neurotransmitter: glutamate,
excitatory transmitter:—
[λ Rec] 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 topirimate

Antiepileptic



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

liver تأثيره < → enzyme inducer

I- Phenytoin and Fosphenytoin



↑ more water soluble.

Pharmacokinetics:

A: Oral absorption is complete.

D: pass blood brain barrier and placenta

About 90% bound to plasma protein. → drug interaction

• 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 parenteral use in status epilepticus (i.v or i.m).

lova ... ←
di ... ←

Metabolism of Phenytoin

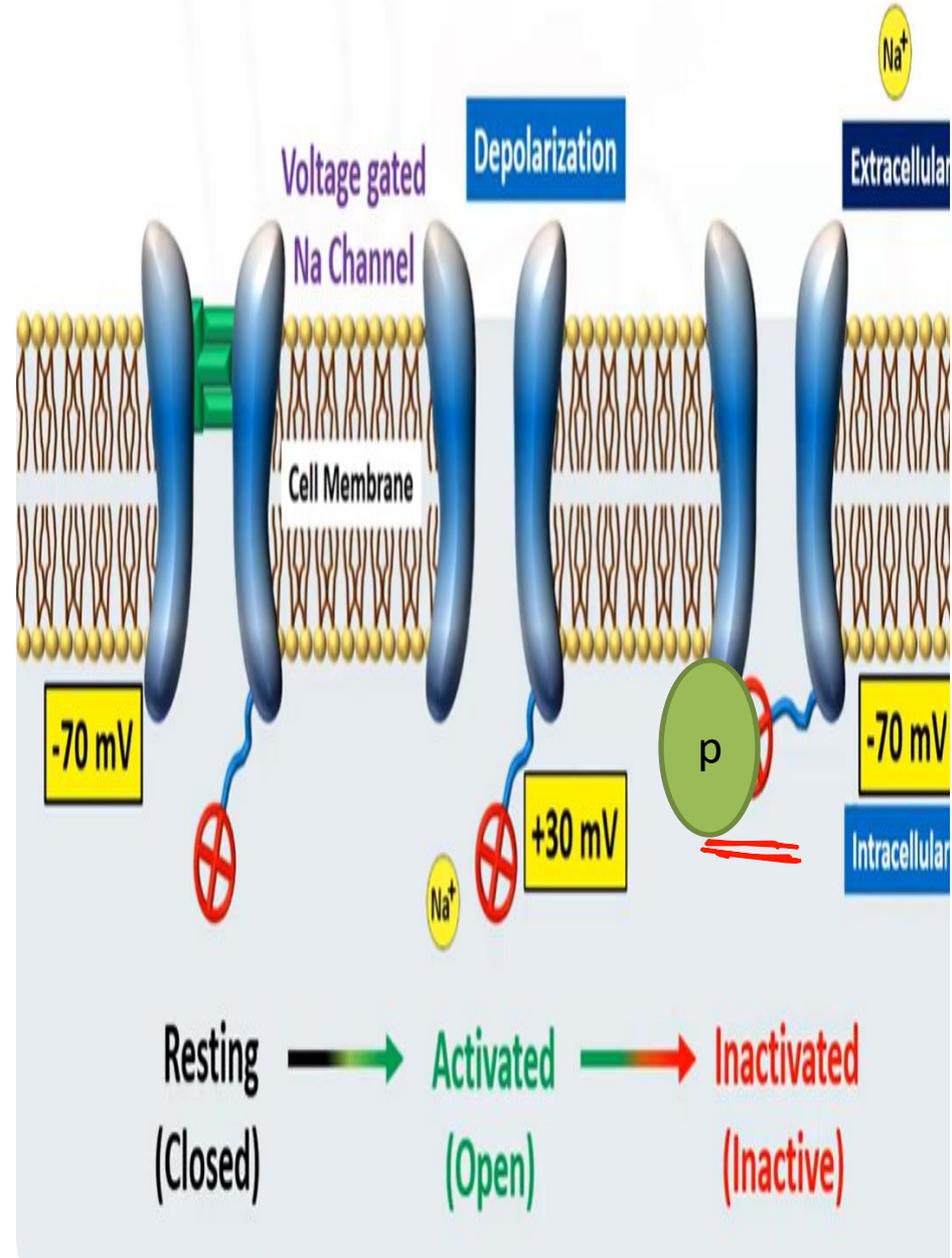


- **Mechanism of action**

- It blocks voltage-gated **Na⁺ channels**.

- At higher concentrations. It can block voltage-dependent **Ca⁺⁺ channels**

- interferes with the **release of neurotransmitters**.



Pharmacological actions:

1. Antiepileptic: It has a selective antiepileptic action without causing CNS depression.

2-Antiarrhythmic: (Class IB antiarrhythmic)

It depresses automaticity, excitability & increased conduction velocity, so abolish reentry arrhythmias.

Therapeutic uses:

1. Antiepileptic:

A. focal seizures

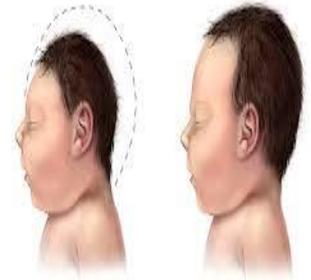
B. Status epilepticus

(Fosphenytoin). 

2. Ventricular arrhythmia.

لأنه يعيدى كلاً حاجة .

Side effects



1. **C.N.S:** Nystagmus, diplopia, ataxia & vertigo.

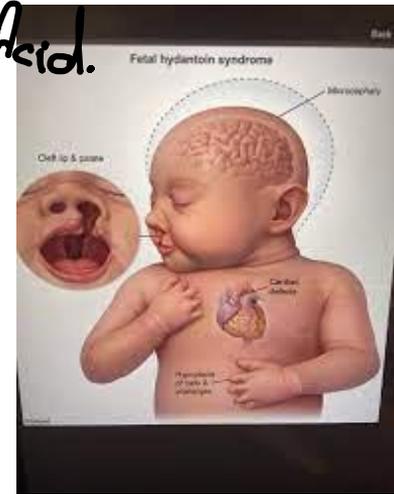
2. **Liver:** enzyme **inducer**

3. **Blood:** Megaloblastic anemia *due to consume Folic Acid.*

it interferes with folate absorption and/or metabolism.

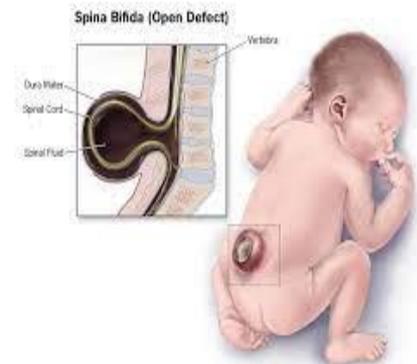
4- Teratogenicity:

- If taken in the **first trimester**, cleft palate and hare lip (**fetal hydantoin syndrome**).



- **Cardiac septal defect**

- **Hypoprothrombinemia** of the baby, if taken before labor. *↓ microencephalo Pathly*



- **Neural tube defect (spina bifida)**

↓
low Folic Acid

كثير مصيبة الله



5. Gingival hyperplasia.

6. Hypersensitivity reactions such as rash, fever, and lymphadenopathy.

بعض مرات

بكون misdiagnosed

7. Hirsutism and acne due to increased androgen secretion

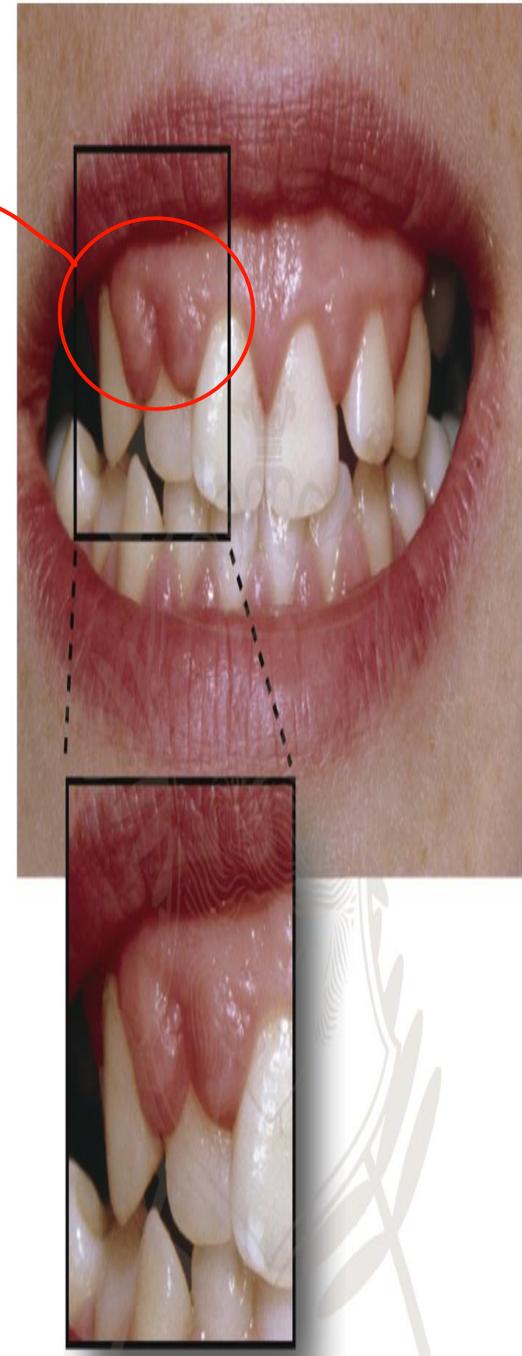
Phenyton => سحر كشيخا

8. Osteomalacia with hypocalcemia

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

9. Inhibit insulin release (hyperglycemia)

10. Neuropathies due to folate deficiency



Hot mail G And K

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

HOW TO REMEMBER SIDE EFFECTS OF PHENYTOIN

IN 2 MINS

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 and 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)

Phenyl
Toluene
Amide

oxcarbamazepine



• Pharmacokinetic:

A: Following oral absorption

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

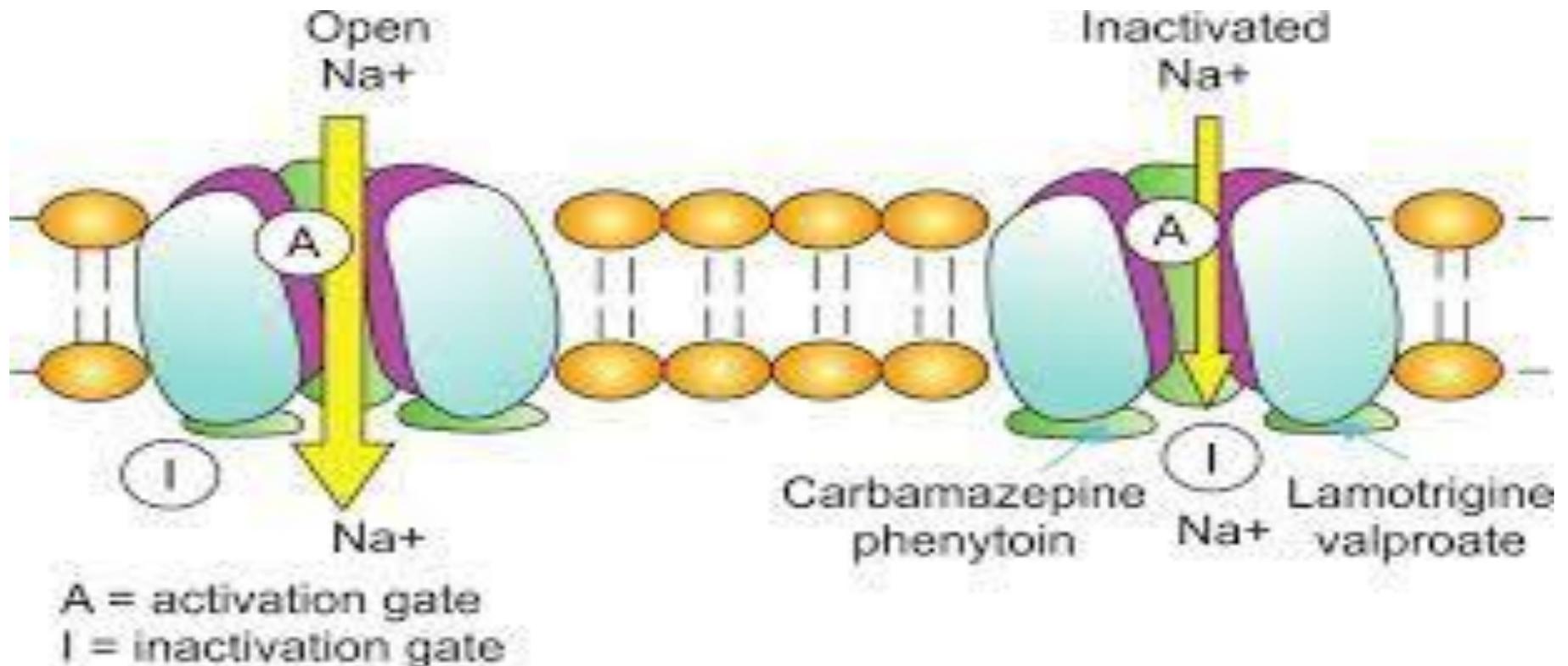
M: It induces hepatic microsomal enzymes.

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 the Na⁺ channel, thereby reducing the propagation of abnormal impulses in the brain.



• Therapeutic uses:

1. **Focal seizures.**
2. **Trigeminal neuralgia.** [migraine, neuropathic pain] → Pain on nerve.
3. **Cerebral or nephrogenic diabetes insipidus** → ↓ ADH

• First drug of choice: carbamazepine.

و جدوا منه
ال Carbamazepine
↑ Secret ADH

• Side effects:

C → Carbamazepine

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

2. Liver dysfunction

3. Blood: Aplastic anemia, agranulocytosis

(causes 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.

5. Not used in the treatment of absence seizures

altering cortical
excitability can
enhance
thalamocortical
rhythmicity, thereby
increasing spike-and-
wave discharges

- **Oxcarbazepine:**

No side effect on liver or Bone marrow

- It is A prodrug that converts to an active metabolite, MHD (10-monohydroxy derivative).
- It is an anticonvulsant.
- C.N.S. toxicities are similar to those of carbamazepine, but lesser.
- Lesser hepatic enzyme inducer with no autoinduction.
- There are no reports of hepatic failure or bone marrow abnormality.
- More pronounced hyponatremia.

III- Valproic acid, valproate, divalproex



mainly on GABA

Broad. (الوجوه)

- 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** ^(transport) 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) ↖ ما يفتقر الشعر فرق بينه وبين

Phenytoin → hantuisim.

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

Not toxic
No seizures → with Absence of SEIZURES

(LEAST TOXIC ANTIPILEPTIC)



- Pharmacokinetics:

- Well absorbed orally.
- Not bound to plasma protein. → Sex Not Bound to Plasma.
- 75% are metabolized.
- 25% are excreted unchanged.

- Mechanism of action:

It blocks voltage-gated **T-Ca++ channels**.

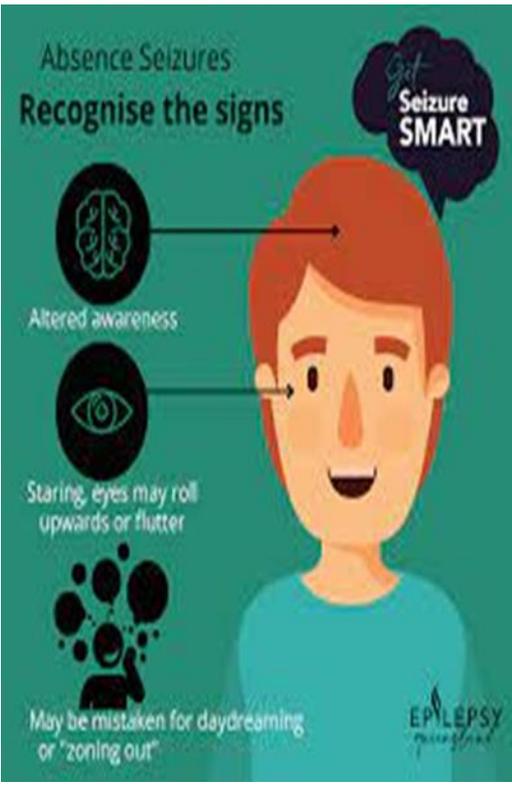
- Therapeutic uses:

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

• Side effects: خفيفا جدا

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

بroad

← (2ND generation)

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

Feature	Old AEDs	New AEDs
Seizure coverage	Narrow to broad	<u>Mostly broad</u>
Side effects	More severe, frequent	<u>Less severe, better tolerated</u>
Drug interactions	Many	Few
Monitoring	Often required	Usually not required
Cost	Low	High

status epilepticus

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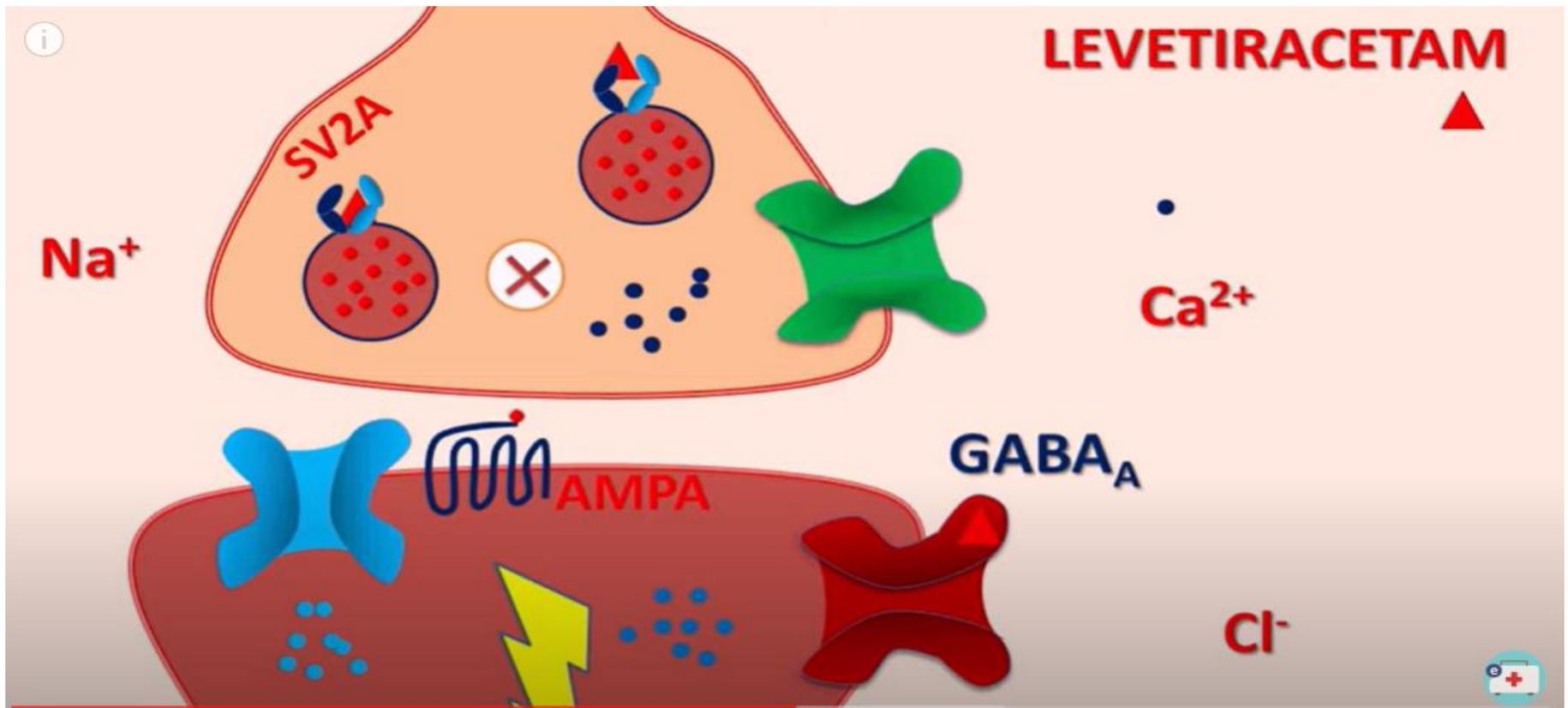
كل مريض ما علاجها ال

<p>Lamotrigine</p> <p><i>safe in pregnancy</i></p>	<p>Topiramate</p> <p><i>دواء top لانه بنخف</i></p>	<p>Zonisamide (Sulfa)</p>
<p>MOA:</p> <p>blocks Na & Ca⁺⁺ channels.</p> <p>used in</p> <p>all types of epilepsy except <u>status epileptics</u></p> <p>Side effects</p> <p>dizziness, headache & ataxia, Stevens Johnson syndrome</p> <p><i>↓ severe dermatitis</i></p>	<p>MOA:</p> <p>blocks Na & Ca⁺⁺ channels.</p> <p>Bind glutamate receptor</p> <p>Used in:</p> <p>focal, generalized epilepsy and absence seizures</p> <p>Side effects:</p> <p>impaired concentration, diplopia, <u>weight loss</u> & kidney stones</p>	<p>MOA:</p> <p>Blocks Na⁺ & Ca⁺⁺ channels.</p> <p>Used in:</p> <p>focal, generalized epilepsy and absence seizures</p> <p>Side effect:</p> <p><u>kidney stones</u> and <u>oligohidrosis</u>.</p> <p><i>↓ -& Adjuvant PMS</i></p>

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

Levetiracetam and brivaracetam

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



Ca²⁺
No
Flip
↓
refractory

Felbamate

- **MOA:**

It blocks Na⁺ & Ca²⁺ channels & competes with glycine cofactor at NMDA receptors.

- **Side effects:**

liver and bone marrow toxicities, so it is reserved for use in refractory epilepsy.

AED	Pregnancy Safety	Main Risk
Valproic acid	 Avoid	Neural tube defects, cognitive impairment
Carbamazepine	 Moderate	NTDs → neural tube defect.
Phenytoin	 Moderate	Fetal hydantoin syndrome
Phenobarbital	 Moderate	Vitamin K deficiency bleeding
Lamotrigine	 Safe	Low risk cleft palate
Levetiracetam	 Very safe	Minimal

Status epilepticus

Def: A medical emergency consisting of prolonged (> 10-minute) or repetitive seizures that occur without a return to baseline consciousness.

Common causes

Include anticonvulsant withdrawal/noncompliance, anoxic brain injury, sedative withdrawal or other drug intoxication, metabolic disturbances (eg, hyponatremia), head trauma, and infection.

Treatment: → hospitalized (i)

Maintain ABCs; consider rapid intubation for airway protection.

Administer ^{Ber Beri} thiamine, followed by glucose and naloxone to presumptively treat potential etiologies.
 Antidote for morphine

Give an IV benzodiazepine (lorazepam or diazepam) plus a loading dose of fosphenytoin.

If seizures continue, intubate and load with phenobarbital.

Initiate a meticulous search for the underlying cause

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*



Coming
Pills
Lead
Victory



Eyes
Vanish



Benzos
Protect
Fast



Thank You