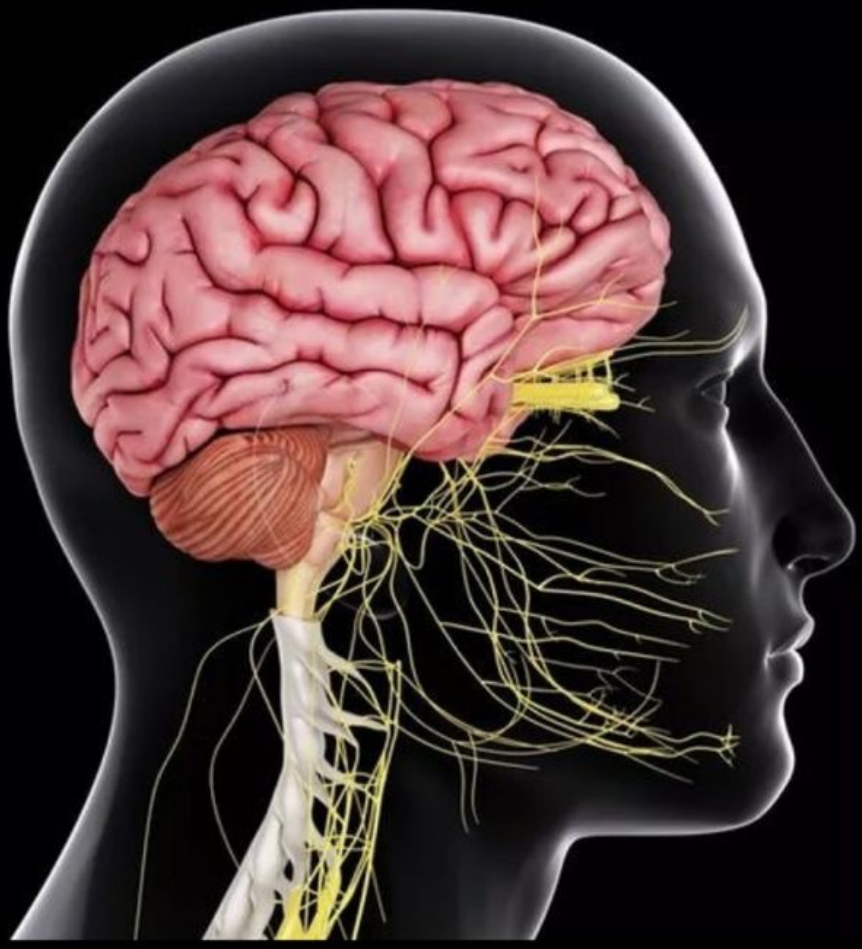
CENTRAL NERVOUS SYSTEM



SUBJECT : Pharmacology

LEC NO. : 7

DONE BY : Batool ALzubaidi

وَقُل رَّبِّ زِدْنِي عِلْمًا

Antiepileptics

Pharmacology and Toxicology

Central Nervous System Module

Third Year Medical Students

Tareq Saleh

Faculty of Medicine

The Hashemite University

Each convulsion is a seizure but not every seizure is a convulsion

Overview: Epilepsy

- **Seizures**
  - Abnormal excessive neuroactivity in the brain

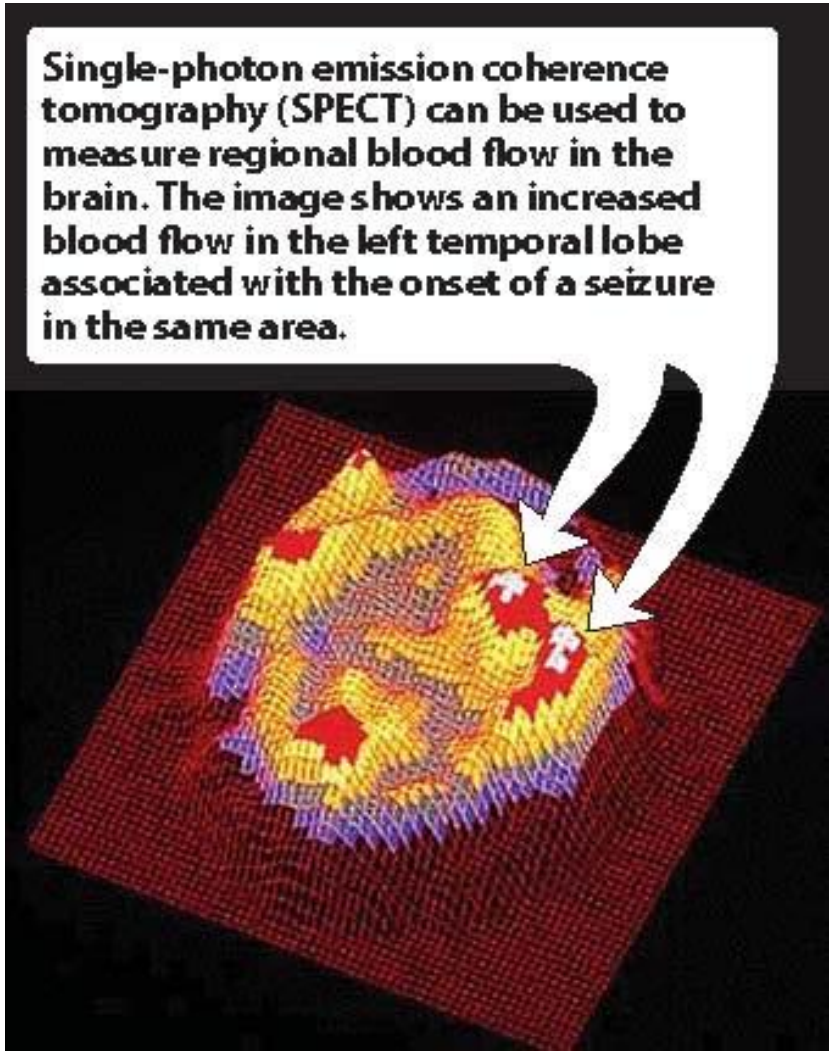
Abnormal brain activity, it's effect depends on which area of the brain it occurs, it could be without motor symptoms like absence seizures

- **Convulsions:**
  - Rapid, repeated muscle contraction and relaxation resulting from excessive neuroactivity in the brain.

Seizure associated with motor symptoms mostly uncontrolled muscle contractions

- **Epilepsy:**
  - A neurological disorder of multiple, different seizures resulting from excessive discharge of cerebral neurons.

Recurrent repeated uncontrolled, unknown etiology



Seizures: Etiology

- Trauma
- Encephalitis
- Drugs
- Withdrawal from depressants
- Tumor

Infection of central nervous system

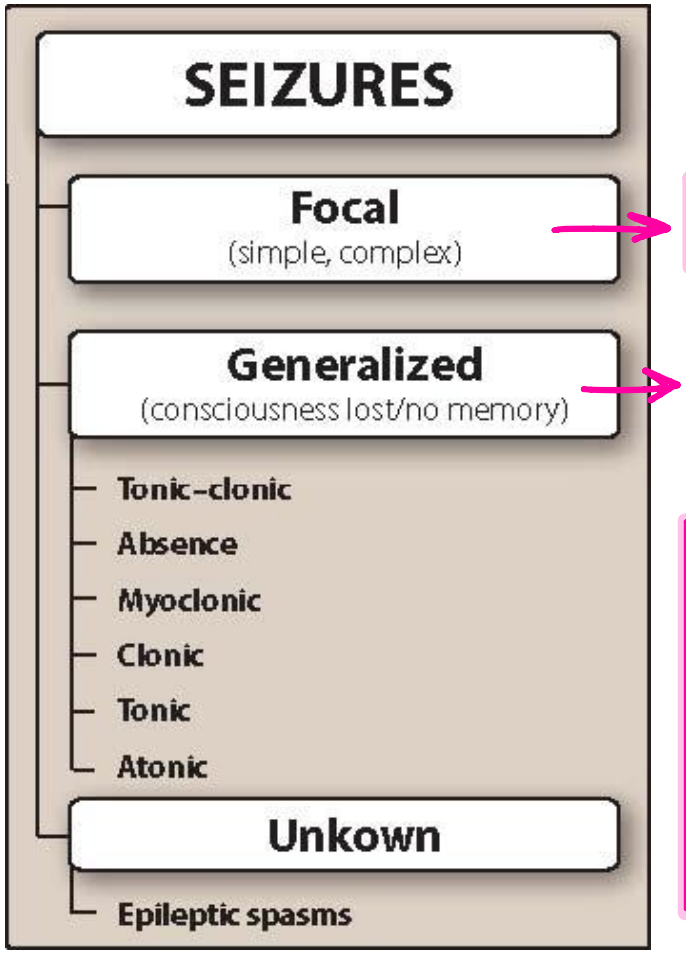
Cause could be metabolic » electrolyte imbalance

- High fever
- Hypoglycemia
- Extreme acidosis
- Extreme alkalosis
- Hyponatremia
- Hypocalcemia
- Idiopathic

Rapid elevation of temperature

Most cases of epilepsy are idiopathic

Classification of Seizures



Partial seizures

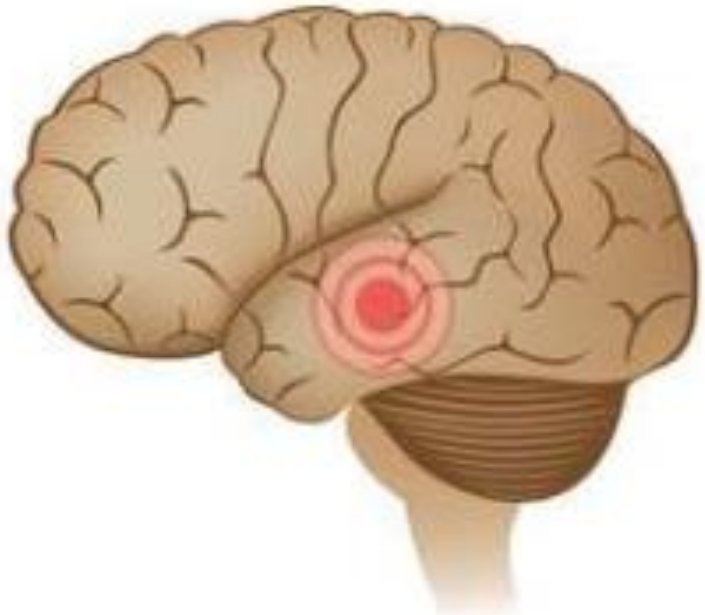
Most common type, classic type

Seizure starts as single focal on the brain if it spreads through out it will become generalized, focal comes with presentation related to that area of the brain depending on function, if it spreads will become generalised

Overview: Epilepsy

- **Focal (partial) seizures:**

- Involves one portion of the brain i.e. one lobe.
- Symptoms depend on the site of discharge "primary focus".
- Possibility of progressing into a generalized tonic-clonic seizure.



Partial seizure

Focal (partial) seizures:

Simple partial

- Confined to a single locus in the brain
- NO loss of consciousness
- Single muscle group or a limb

Complex partial

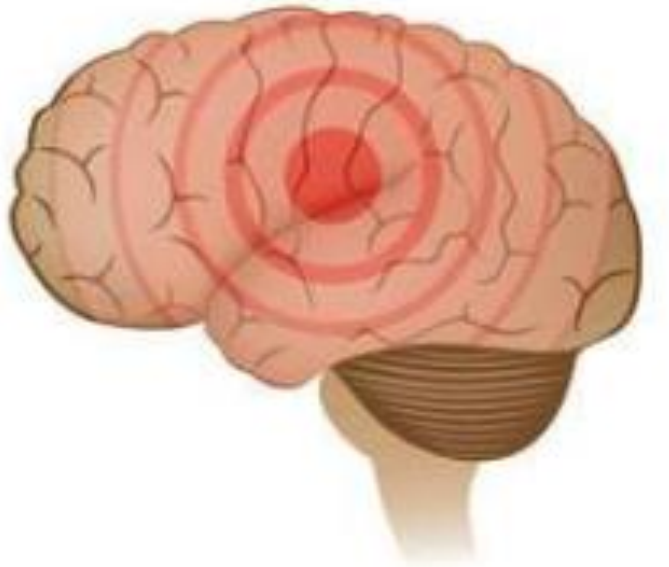
- Consciousness is altered
- Motor dysfunction/hallucination /distortion

Overview: Epilepsy

الي بميز ال generalised عن ال partial مش ال motor activity
لانه ال partialممكن يصير فيها شوية motor activity ببعض
الاحيان حسب المنطقة بالدماغ الي بميزهم عن بعض انه ال
generalised بصير فيها loss of consciousness

- **Generalized seizures:**

- Starts at a focal point and spreads to involve both hemispheres.
- Could be convulsive or nonconvulsive.
- Associated with immediate loss of consciousness.



Generalized seizure

Generalized seizures

Tonic-clonic

- Loss of consciousness
- **Tonic** (continuous contractions) and **clonic** (rapid contraction and relaxation)
- Followed by confusion/exhaustion

Most common type

Seizure is followed by something called postictal (self urination, confusion, loss of memory)

Absence

- Brief, abrupt, self-limiting
- Pediatric: 3-5 until puberty
- Starring/rapid-eye blinking
- Characteristic EEG profile

Seizure doesn't have to have motor component

Will loose consciousness

Myoclonic

- Short episodes of muscle contractions i.e., jerks of the limbs

Clonic

- Also brief episodes of muscle contraction similar to myoclonic
- Consciousness is more impaired with clonic

Tonic

- Increased muscle tone
- < 60 seconds

Atonic

- Sudden loss of muscle tone "drop attacks"

Epilepsy: Therapeutic Strategy

- "No cure"
- Complete suppression of seizures, or
- Decrease the number of episodes with minimal side effects.

مثلا لو كان السبب brain tumor اكيد لو شلناه لازم تنحل المشكلة بس most cases of epilepsy are idiopathic عشانه هيك احنا ال treatment to manage symptoms to prevent seizures recurrence الهدف انه يكون ال patient seizure free

How?

- Pharmacological
- Ketogenic diet
- Surgery/Vagal Nerve Stimulation
- Correct the underlying cause

For refractory resistant epilepsy that doesn't respond to treatment

Epilepsy: How to select which drug?

Choice of drug treatment is based on:

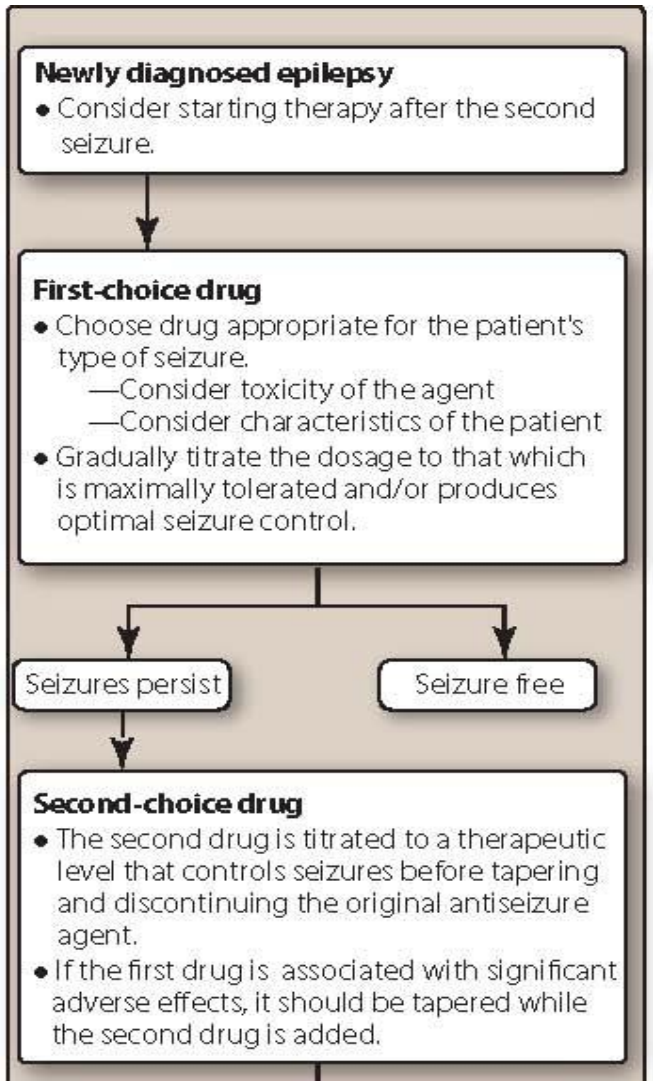
1- type of seizure

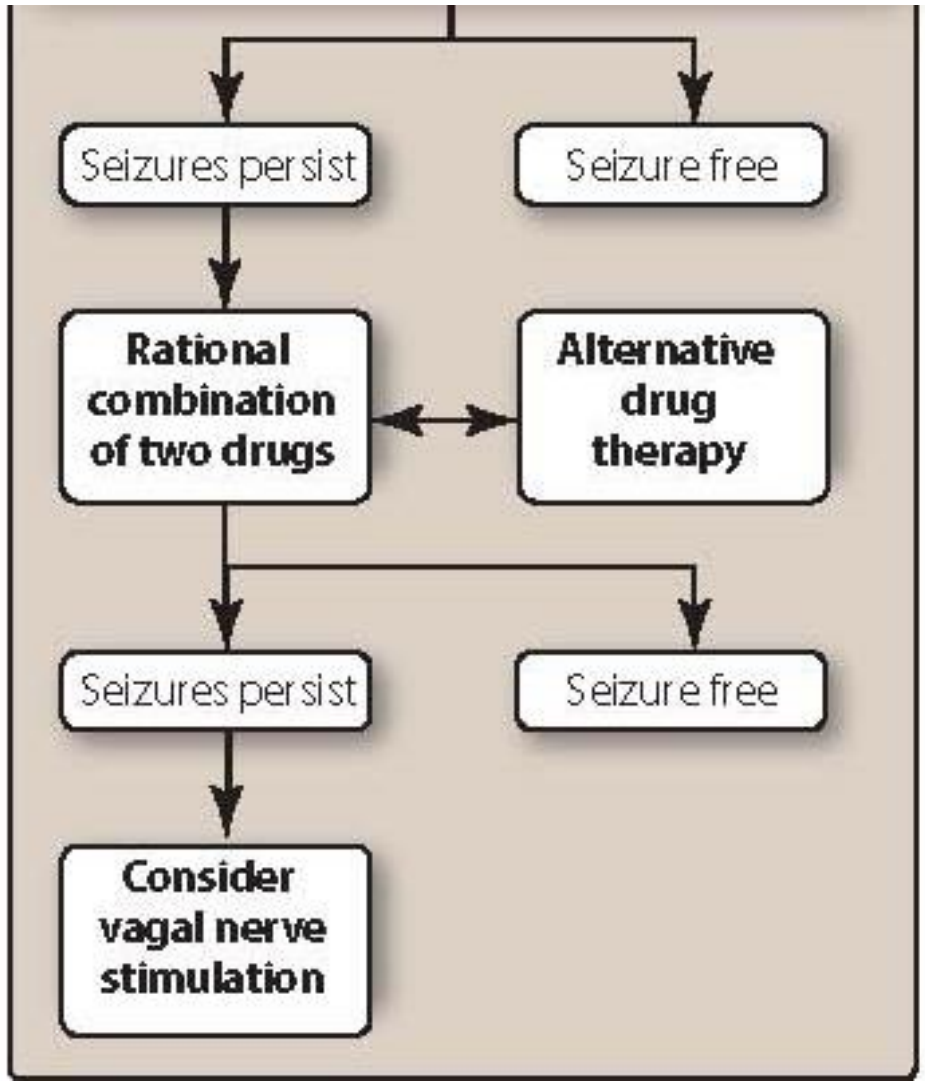
2- patient-specific variables (age, comorbidities, lifestyle….)

3- characteristics of the drug (cost, adverse effects, interactions…)

في شوية قواعد رئيسية : اولا لو حدا صار عنده seizure you don't initiate pharmacological treatment، you start to consider using pharmacology اذا صار more than 2 uncontrolled seizures، ليش وحدة ما بنعطي لانها ممكن تكون incidental او السبب metabolic و ما راح ترجع بتقرر تبلش علاج ال epilepsy لما يصير repeated recurrent seizures .. ثانيا الهدفانه to use a monotherapy single drugwith the least dose that can control or prevent seizures later ليش لانه معظمهم الهم adverse effects فالهدف تبعي اني استخدم on single safest best anti-epileptic drug that can control the condition

Epilepsy: Therapeutic Strategy





نفرض انك اعطيت single drug في خيارين يا اما ال patient راح يصير seizure free او ال seizures will persist هون شو بتعمل و you will switch drug اذا alternative تعطي زبط بكون ممتاز و اذا ما زبط و كان resistant بدك تجرب تعمل combination و اذا ما زبطت بدك تفكر باشياء اخرى غير pharmacology

How do antiepilepsy medications work?

They should be neurosupressive

1. Blocking voltage-gated channels (Na^+ or Ca^{++})

If the seizures are characterized by just normal firing of neurons you can interfere with action potential propagation » interfering with voltage gated sodium or calcium channels

2. Enhancing inhibitory GABAergic impulses

3. Interfering with excitatory glutamate transmission

Antiepileptic drugs

Many anti-epiloptics have multiple mechanisms of actions

هاي السلايدة متكررة ١٠ مرات بعد كل دوا ف حذفتهم عشان يقل عدد السلايدات و نفسيا تحسوها صغيرة المحاضرة😂

Na^+-channels inhibitors

- Phenytoin
- Carbamazepine
- Oxcarbazepine
- Valproic acid
- Lamotrigine
- Topiramate

They slowdown propagation of action potional, slowdown firing of neurons

Ca^{++}-channels inhibitors

- Ethosuximide
- Lamotrigine
- Valproic acid

↑ GABAergic transmission

- Benzodiazepines
- Phenobarbital
- Valproic acid
- Gabapentin?, Pregabalin?
- Felbamate

Others:

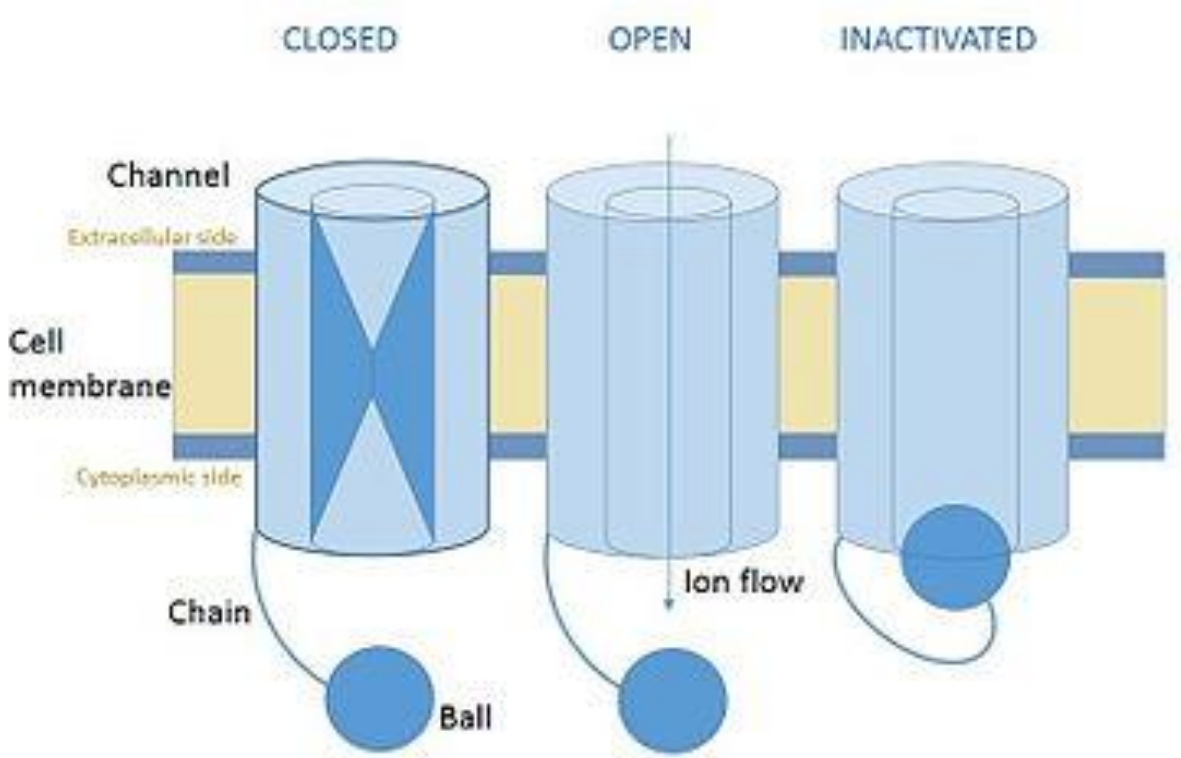
- **NMDA receptor blockers**: Felbamate , topiramate
- **AMPA receptor blockers**: Perampanel
- **H-current modulators**: Gabapentin, lamotrigine
- **Carbonic anhydrase inhibitors**: Topiramate, zonisamide
- **Neuronal potassium channel (KCNQ [Kv7]) opener**: Ezogabine

Phenytoin

MOA:

Blocks voltage-gated Na^+ channels by binding to inactive state → slow recovery

لما هدول ال gates يتسكروا يعني ما في depolarisation يعني ال neuron بضل على ال resting membrane potential



في البداية بكونوا closed بس يجي action potential راح يفتحوا و يصير في sodium influx، خلال ال refractory period راح يكونوا inactive لاته عندهم internal gate راح تسكر و ال phenytoin برتبط بال inactive state not the closed

Phenytoin

MOA:

Blocks voltage-gated Na^+ channels by binding to inactive state→ slow recovery

Second line for epilepsy

Indications:

- Focal seizures
- Tonic-clonic
- NOT good for absence seizures
- Status epilepticus (after BZD)
- Antiarrhythmic/digoxin toxicity

Second line

مهمة لما تعمل combination

Pharmacokinetics:

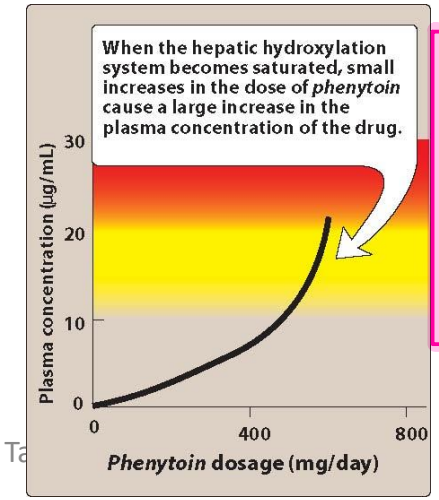
- Induces CYP2C, CYP3A, UGT
- "saturable enzyme metabolism"
- Non-linear kinetics
- Toxicity ↓

consistent مش concentration ال مع effect ال

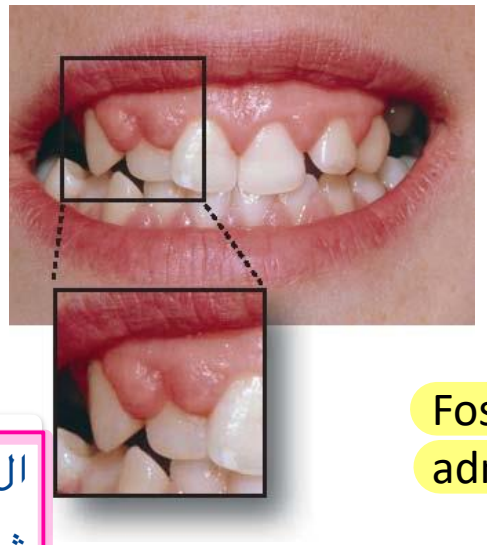
large effect بتعمل increase in dose شوية

Adverse effects

- Nystagmus, ataxia
- Diplopia, sedation
- Gingival hyperplasia
- Peripheral neuropathy/osteoporosis
- Teratogenic
- Blood: ↓ folate → Megaloblastic anemia
- Drug-drug interactions: e.g., warfarin



ما بستخدمهم في ال absence ولا بالاطفال لانه بخلي الوضع اسوء



Fosphenytoin for IM administration

Carbamazepine

MOA:

Blocks Na^+ channels

Indications:

- Focal seizures
- Tonic-clonic
- NOT good for absence seizures
- Trigeminal neuralgia
- Bipolar disorder — Mood enhancement

Has some analgesic effects for neuropathic pain

Pharmacokinetics:

- Absorbed slowly
- Long half-life (~ 30 hours)
- Induces CYP2C, CYP3A, UGT

Adverse effects

- Hyponatremia
- Aplastic anemia
- Teratogenic: Spina Bifida
- Drowsiness; headache; dizziness; nausea

Oxcarbazepine

- Prodrug
- Less side effects

V.I

Valproic acid

Very important anti-epileptic, broad spectrum used for multiple types of epilepsy

MOA:

- Blocks Na^+ channels
- Blocks GABA transaminase (GABA-T)
- Blocks T-type Calcium channels

Indications:

- Focal seizures
- Generalized seizures
- Absence seizures
- Bipolar disorder

Preferred option

Adverse effects

- Hepatotoxicity
- Teratogenicity
- CNS-related

مهم تعرف مين الادوية ال teratogenic

Pharmacokinetics:

- Inhibits CYP2C9, UGT, epoxide hydroxylase

Valproic acid

vs

Sodium valproate

vs

Divalproex sodium

Lamotrigine

MOA:

- Blocks Na^+ channels
- Blocks voltage-gated Ca^{++} channels

Indications:

- Focal seizures
- Generalized seizures
- Absence
- Lennox-Gastaut syndrome
- Bipolar disorder

Repetitive therapy resident seizures

Adverse effects

- CNS-related side effects
- Severe skin reaction (life-threatening)

Pharmacokinetics:

- Metabolized by UGT
- What will happen when combined with *phenytoin*? *Valproic acid*? فكروا فيه

Tareq Saleh ©

Wolters Kluwer

Not first line

Topiramate

MOA:

- Blocks Na^+ channels
- Blocks L-type Calcium channels
- Carbonic anhydrase inhibitor
- NMDA blocker

Adverse effects

- Somnolence
- Weight loss
- Paresthesia
- Renal stones
- Oligohidrosis
- hyperthermia

Sedation

Indications:

- Focal seizures
- Generalized seizures
- Migraine prevention

Pharmacokinetics:

- Inhibits CYP2C9

Zonisamide

MOA:

- Blocks Na^+ channels
- Blocks T-type Calcium channels
- Limited carbonic anhydrase inhibitor

Indications:

- Focal seizures

Adverse effects

- CNS adverse effects
- Nephrolithiasis
- Oligohidrosis
- Contraindicated in patients with sulfonamide hypersenesitivity

Kidney stones when long term usage

Ethosuximide

MOA:

- Blocks T-type Calcium channels

Indications:

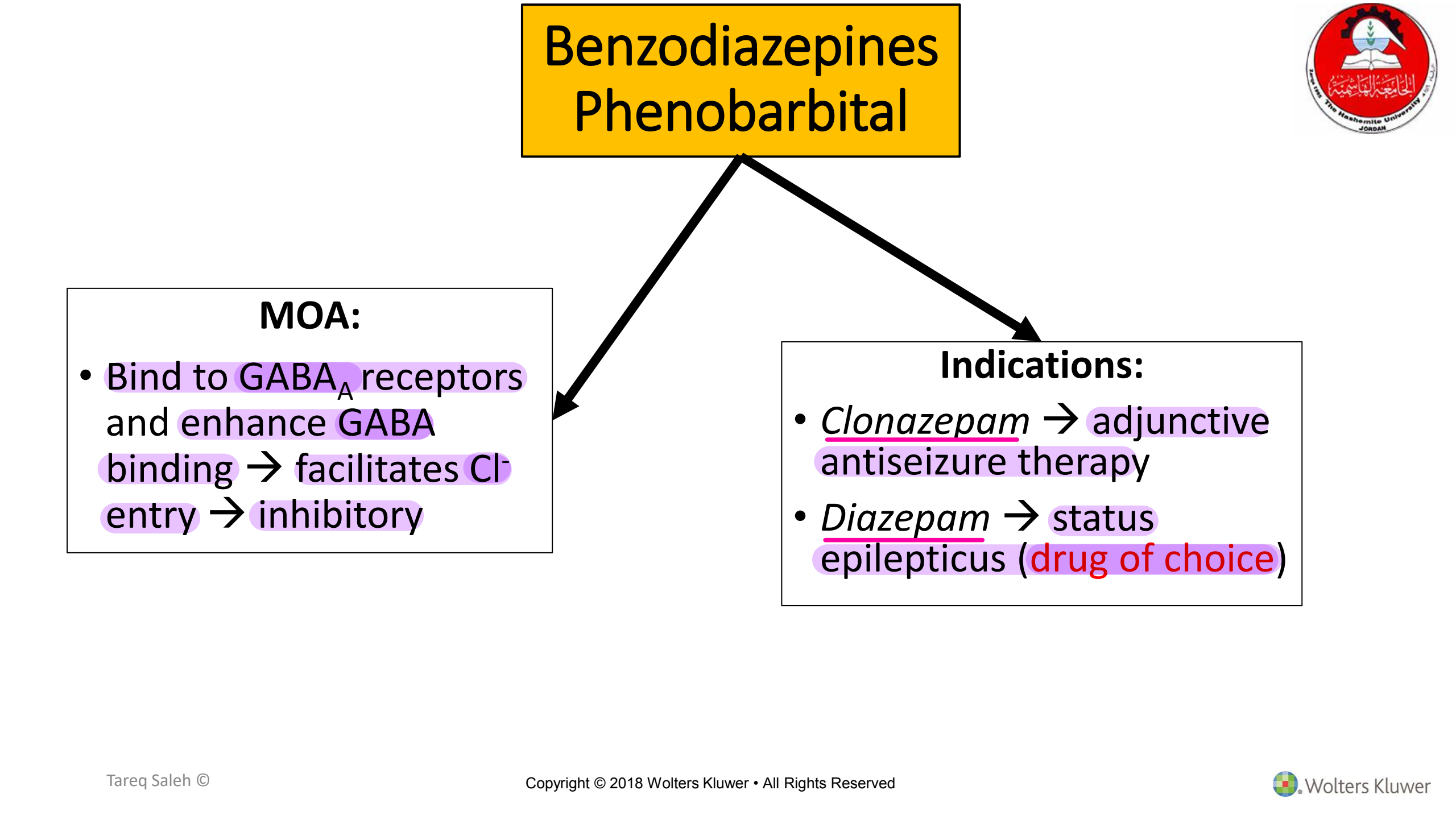
- Absence seizure only

(Drug of choice)

Pharmacokinetics:

- Half-life: 30-60 hrs

Benzodiazepines Phenobarbital



MOA:

- Bind to $GABA_A$ receptors and enhance GABA binding → facilitates Cl^- entry → inhibitory

Indications:

- *Clonazepam* → adjunctive antiseizure therapy
- *Diazepam* → status epilepticus (drug of choice)

I

Gabapentin
Pregabalin

MOA:

- Analog of GABA
- It does NOT act at GABA receptor
- MOA is unknown

Adverse effects

- Sedation
- Euphoria

Risk of abuse

Indications:

- Adjunct therapy for focal seizures

Preferred with elderly

- Neuropathic pain, e.g., postherpetic neuralgia, diabetic neuropathy

Pharmacokinetics:

- Secreted unchanged
- Few drug interactions
- Suitable for elderly

Felbamate

MOA:

- Blocks voltage-gated Na^+ channels
- Blocks NMDA receptors
- Blocks Ca^{++} channels
- Potentiates GABA

Adverse effects

- Aplastic anemia
- Hepatic failure
- Dangerous drug

Indications:

- Reserved for refractory epilepsy
- Lennox-Gastaut syndrome

Pharmacokinetics:

- Inhibits CYP2C19
- Induces CYP3A4

Ezogabine

MOA:

- Open voltage-gated M-type potassium channels → stabilizing resting membrane potential

Adverse effects

- Urinary retention
- QT interval prolongation
- Blue skin discoloration
- Retinal abnormalities

Pharmacokinetics:

- No drug interactions at low doses

V.I

Levetiracetam

MOA:

- unknown

Indications:

- Focal (simple and complex) seizures
- Adjunct therapy for generalized seizures

Adverse effects

- Dizziness
- somnolence

Status Epilepticus

- *Continuous or repetitive seizures (> 20 min) with impaired consciousness during the interictal period.*
- **Management**

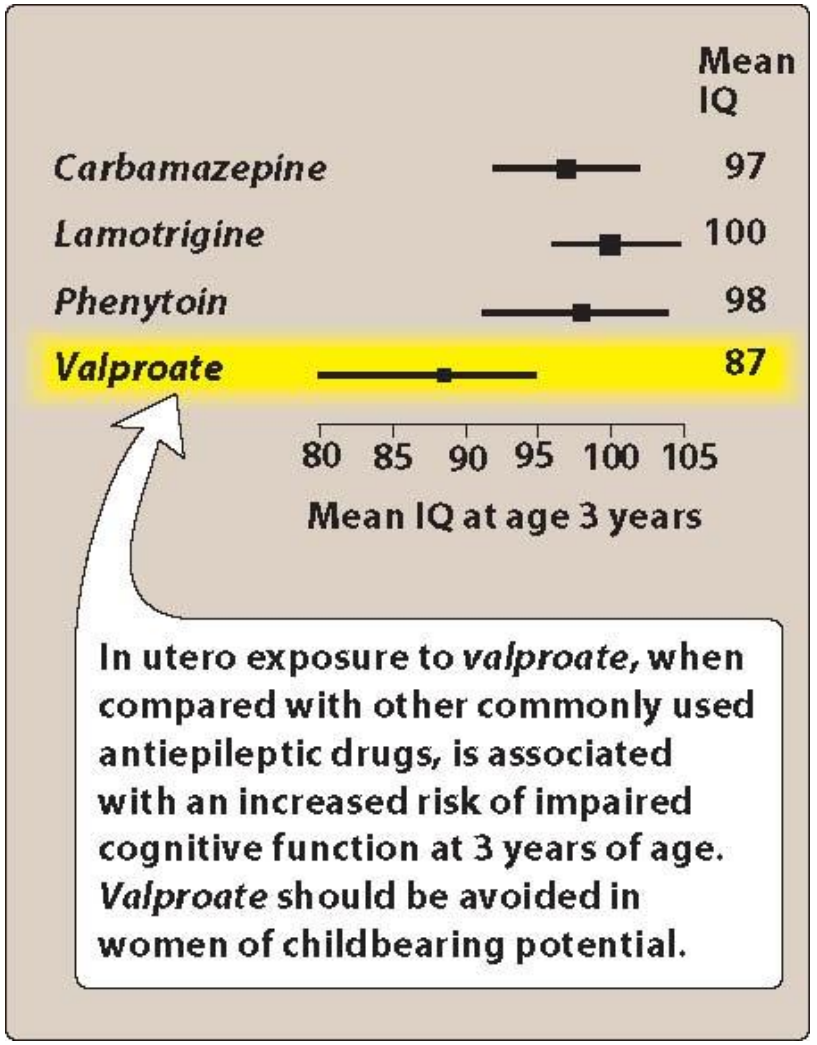
1. **Diazepam** (IV or rectal) → for rapid control.
2. **Fosphenytoin** (prodrug) or **phenytoin** → long-acting, to maintain control.
3. **Phenobarbital** → 2nd choice to phenytoin.
4. **Propofol** (IV anesthesia) → in resistant cases.

Antiepileptics during pregnancy

Using folic acid with epilepsy is a must

- Monotherapy
- The lowest possible dose
- Lamotrigine; gabapentin = safe
- Valproic acid; phenobarbital; phenytoin, others = contraindicated
- *Cleft lip, neural tube defect* (patients considering pregnancy while on antiepileptics should receive folic acid supplements)

Gradual withdraws always



V.V.I

AAN Guidelines for Epilepsy Treatment

Level	Recommendation
Level B	LTG use should be considered to decrease seizure frequency.
Levels B and Level C	LTG use should be considered (**Level B**) and GBP use may be considered (**Level C**) to decrease seizure frequency in patients aged ≥60 years.
Level C	LEV use may be considered to decrease seizure frequency.
Level C	ZNS use may be considered to decrease seizure frequency.
Level C	VGB use appears to be less efficacious than immediate-release carbamazepine (CBZ) use and may not be offered; furthermore, toxicity profile precludes VGB use as first-line therapy.
Level C	PGB use at 150 mg/d is possibly less efficacious than LTG use at 100 mg/d.
Level U	Evidence is insufficient to consider GBP, OXC, or TPM instead of CBZ.
Level U	Evidence is insufficient to consider TPM instead of phenytoin in urgent treatment of new-onset or recurrent focal epilepsy, unclassified generalized tonic-clonic (GTC) seizures, or generalized epilepsy (GE) presenting with GTC seizures.
Level U	Data are lacking to support or refute use of third-generation AEDs, CLB, FBM, or VGB in treating new-onset epilepsy.
Level U	Data are lacking to support or refute use of newer AEDs in treating unclassified GTC seizures.

Recommendation for childhood absence epilepsy

Level	Recommendation
Level B	Unless there are compelling reasons based on adverse events (AEs) profile, ethosuximide (ETS) or VPA use should be considered before LTG use to decrease seizure frequency in treating absence seizures in childhood absence epilepsy.

Figure 12.4 in chapter 12 is very important

Summary of Therapeutic Strategy

Proper diagnosis

Monotherapy

Start with ***a small dose*** and **a single drug** then gradually increase the dose

Termination of therapy:

- After 2 years (no fits)
- Gradually

Pregnancy:

- Least effective dose of least teratogenic drug
- Folic acid supplements

Consider monitoring of serum drug levels

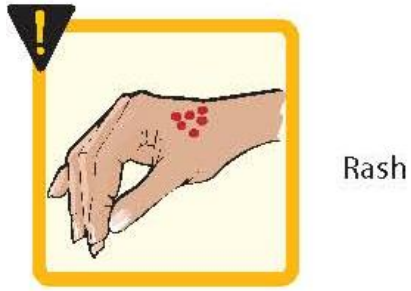
DRUG	MECHANISM OF ACTION	ADVERSE EFFECTS AND COMMENTS
Carbamazepine	Blocks Na^+ channels	Hyponatremia, drowsiness, fatigue, dizziness, and blurred vision. Drug use has also been associated with Stevens-Johnson syndrome. Blood dyscrasias: neutropenia, leukopenia, thrombocytopenia, pancytopenia, and anemias.
Divalproex	Multiple mechanisms of action	Weight gain, easy bruising, nausea, tremor, hair loss, GI upset, liver damage, alopecia, and sedation. Hepatic failure, pancreatitis, and teratogenic effects have been observed. Broad spectrum of antiseizure activity.
Eslicarbazepine acetate	Blocks Na^+ channels	Nausea, rash, hyponatremia, headache, sedation, dizziness, vertigo, ataxia, and diplopia.
Ethosuximide	Blocks Ca^{2+} channels	Drowsiness, hyperactivity, nausea, sedation, GI upset, weight gain, lethargy, SLE, and rash. Blood dyscrasias can occur; periodic CBCs should be done. Abrupt discontinuance of drug may cause seizures.
Ezogabine	Enhances K^+ channels	Urinary retention, neuropsychiatric symptoms, dizziness, somnolence, QT prolongation, reports of blue skin discoloration, and retina changes.
Felbamate	Multiple mechanisms of action	Insomnia, dizziness, headache, ataxia, weight gain, and irritability. Aplastic anemia and hepatic failure. Broad spectrum of antiseizure activity. Requires patient to sign informed consent at dispensing.
Gabapentin	Unknown	Mild drowsiness, dizziness, ataxia, weight gain, and diarrhea. Few drug interactions. One hundred percent renal elimination.
Lacosamide	Multiple mechanisms of action	Dizziness, fatigue, and headache. Few drug interactions; Schedule V.
Lamotrigine	Multiple mechanisms of action	Nausea, drowsiness, dizziness, headache, and diplopia. Rash (Stevens-Johnson syndrome—potentially life threatening). Broad spectrum of antiseizure activity.
Levetiracetam	Multiple mechanisms of action	Sedation, dizziness, headache, anorexia, fatigue, infections, and behavioral symptoms. Few drug interactions. Broad spectrum of antiseizure activity.
Oxcarbazepine	Blocks Na^+ channels	Nausea, rash, hyponatremia, headache, sedation, dizziness, vertigo, ataxia, and diplopia.
Perampanel	Blocks AMPA glutamate receptors	Serious psychiatric and behavioral reactions, dizziness, somnolence, fatigue, gait disturbance, and falls, long half-life.
Phenytoin	Blocks Na^+ channels	Gingival hyperplasia, confusion, slurred speech, double vision, ataxia, sedation, dizziness, and hirsutism. Stevens-Johnson syndrome—potentially life threatening. Not recommended for chronic use. Primary treatment for status epilepticus (*fosphenytoin*).
Pregabalin	Multiple mechanisms of action	Weight gain, somnolence, dizziness, headache, diplopia, and ataxia. One hundred percent renal elimination.
Rufinamide	Unknown	Shortened QT interval. Multiple drug interactions.
Tiagabine	Blocks GABA uptake	Sedation, weight gain, fatigue, headache, tremor, dizziness, and anorexia. Multiple drug interactions.
Topiramate	Multiple mechanisms of action	Paresthesia, weight loss, nervousness, depression, anorexia, anxiety, tremor, cognitive complaints, headache, and oligohidrosis. Few drug interactions. Broad spectrum of antiseizure activity.
Vigabatrin	Irreversible binding of GABA-T	Vision loss, anemia, somnolence, fatigue, peripheral neuropathy, weight gain. Available only through SHARE pharmacies.
Zonisamide	Multiple mechanisms of action	Nausea, anorexia, ataxia, confusion, difficulty concentrating, sedation, paresthesia, and oligohidrosis. Broad spectrum of antiseizure activity.

ANTIEPILEPSY MEDICATION	PROTEIN BINDING*	HALF-LIFE	ACTIVE METABOLITE	MAJOR ORGAN OF ELIMINATION	DRUG INTERACTIONS
Carbamazepine	Moderate	6–15	CBZ-10,11-epoxide	Liver	✔
Eslicarbazepine acetate **^	Low	8–24	Eslicarbazepine (S-licarbazepine)	Kidney	✔
Ethosuximide	Low	25–26		Liver	✔
Ezogabine	Moderate	7–11	monoacetylated metabolite	Liver	✔
Felbamate	Low	20–23		Kidney/Liver	✔
*Fosphenytoin***	High	12–60	phenytoin	Liver	✔
Gabapentin	Low	5–9		Kidney	
Lacosamide	Low	13		Various	
Lamotrigine	Low	25–32		Liver	✔
Levetiracetam	Low	6–8		Hydrolysis	
*Oxcarbazepine***	Low	5–13	Monohydroxy metabolite (MHD)	Liver	✔
Phenobarbital	Low	72–124		Liver	✔
Phenytoin	High	12–60		Liver	✔
Primidone	High	72–124	Phenobarbital, PEMA	Liver	✔
Perampanel^	High	105		Liver	✔
Pregabalin	Low	5–6.5		Kidney	
Rufinamide	Low	6–10		Liver	✔
Tiagabine	High	7–9		Liver	✔
Topiramate	Low	21		Various	✔
Vigabatrin	Low	7.5		Kidney	✔
Valproic Acid (Divalproex)	Moderate/ High	6–18	Various	Liver	✔
Zonisamide	Low	63		Liver	✔

*Low = 60% or less, Moderate = 61%-85%, High = >85%; ^Newly approved. Limited data in patients available. **Prodrug.

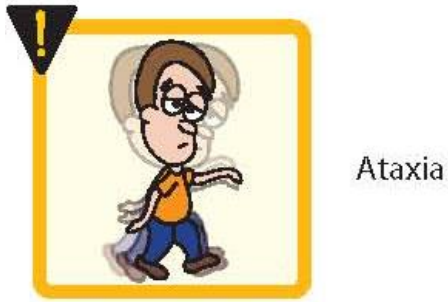
Name an AED that is associated with each of the following adverse effects

Phenobarbital

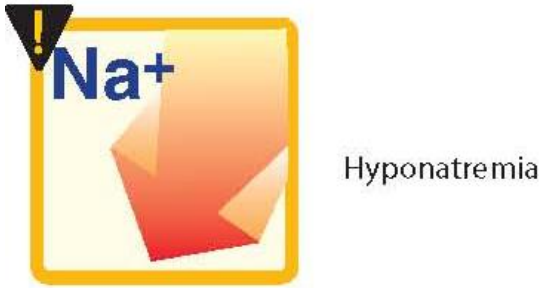


Lamotrigine

Topiramate



Phenytoin



Carbamazepine

Valproic acid

Several classes of antiepileptic drugs (AEDs) interfere with the propagation of action potentials in hyperactive epileptic foci by inhibiting the activation of voltage-gated Na+ channels. All of the following medications share this mechanism of action, EXCEPT:

A) Zonisamide
B) Carbamazepine
C) Conazepam
D) Valproic acid
E) Phenytoin

All of the following mechanisms of action account for the antiepileptic effects of the drug topiramate, EXCEPT:

a) Voltage-gated Na+ channel blockade
b) L-type Ca++ channel blockade
c) Carbonic anhydrase inhibition
d) Glutamate NMDA receptor antagonist
e) Facilitation of Cl- influx at GABA receptor

A 25-year-old woman with generalized epilepsy is well controlled on valproate. She indicates that she is interested in becoming pregnant in the next year. With respect to her antiseizure medication, which of the followings should be considered?

a) Leave her on her current therapy and start folic acid supplaments.
b) Consider switching to lamotrigine.
c) Consider adding another antiseizure drug.
d) Decrease her valproate dose

A 52-year-old man has had several focal seizures with impaired consciousness over the last year. Which is the most appropriate initial therapy for this patient?

a) Ethosuximide
b) Levetiracetam
c) Diazepam
d) Phenytoin/Carbamazepine combination