#11-13

Drugs used in epilepsy

Objectives:

- Describe types of epilepsy
- List the antiepileptic drugs
- Describe briefly the mechanism of action of antiepileptic drugs.
- Enumerate the clinical uses of each drug
- Describe the adverse effects of each antiepileptic drug
- Describe treatment of status epilepticus

Color index:

- Drugs names
- Doctors notes
- Important
- Extra

Epilepsy

Epilepsy is a chronic medical condition characterized by 2 or more unprovoked seizures (within 6-12 months). It is a syndrome.

the difference between **seizure** & **epileptic syndrome**

Seizures are abnormal movements or behavior due to unusual electrical activity in the brain, are a symptom of epilepsy	**Epilepsy is** a group of related disorders characterized by a tendency for **recurrent** seizures

The difference between a syndrome and a disease is:
A syndrome is a set of medical signs and symptoms that occur together and suggest the presence of a certain disease or an increased chance of developing the disease. **A disease** is the actual diagnosed impairment of health or a condition of abnormal functioning

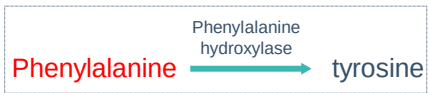
Etiology(causes):

1. •Congenital defects, head injuries, trauma, hypoxia
2. •Infection (bacteria or virus) e.g. meningitis, brain abscess, viral encephalitis.
3. •Concussion, depressed skull, fractures.
4. Brain tumors (including tuberculoma), vascular occlusion, stroke
5. •Drug withdrawal, e.g. CNS depressants, alcohol or drug abuse or drug overdose ,e.g. penicillin.
6. •A poison, like lead
7. •Fever in children (febrile convulsion).
8. •Hypoglycemia
9. •PKU Phenylketonuria is a rare inherited disorder that causes an amino acid called phenylalanine to build up in body caused by absent or virtually absent phenylalanine hydroxylase (PAH) enzyme activity
10. •Photo epilepsy is a type of epilepsy, in which all, or almost all, seizures are triggered by flashing or flickering light

Triggers

- **Fatigue**
- **Stress**
- **Sleep deprivation**
- **Poor nutrition**
- **Alcohol**

Triggers can cause an episode even under medication



Classification of Epilepsy

Partial (focal)

Arise in one cerebral hemisphere

[1] Simple:
consciousness is retained

[2] Complex (psychomotor): Altered consciousness

Secondarily generalized

Begins as partial (simple or complex) and progress into tonic- clonic (grand mal) seizure.

8:49 min | very helpful!

Primary Generalized

Both hemispheres + loss of consciousness.

They are interconnected sometimes

- **Tonic-clonic (Grand mal):** Stiffness (15-30 sec) followed by violent contractions & relaxation (1-2 minute)
- **Tonic:** Muscle stiffness
- **Clonic:** Spasms of contraction & relaxation
- **Atonic (loss of tone):** Patients legs give under him & drop down
- **Myoclonic:** Jerking movement of the body
- **Absence(Petit mal):** Brief loss of consciousness with minor muscle twitches eye blinking In children
- **Status epilepticus:** when a seizure lasts too long or when seizures occur close together and the person doesn't recover between seizures (Emergincy situation)

General rules for treatment of epilepsy:

- Epilepsy is usually controlled but **not cured** with medication.
- Up to 80% of pts can expect **partial or complete** control of seizures with appropriate treatment.
- Antiepileptic drugs are indicated when there is two or more seizures occurred in short interval (6 m -1y)
- An initial therapeutic aim is to use only one drug (**monotherapy**).

- Drugs are usually administered **orally** except in status epilepsy (IV).
- **Monitoring plasma** drug level is useful
- **Triggering factors** can affect seizure control by drugs.
- Sudden **withdrawal** of drugs should be avoided.

Withdrawal considered متى نقدر نقطع الدواء عن المريض؟

- Seizure–free period of 2-5 years or longer
- Normal IQ
- Normal EEG (Electroencephalography (**EEG**) is an electrophysiological monitoring method to record electrical activity of the brain) prior to withdrawal
- No juvenile myoclonic epilepsy
- Relapse rate when antiepileptic's are **withdrawn** is 20-40%.

Treatment of Epilepsy

- drug
- Vagal nerve stimulation
- Surgery
- Ketogenic diet

The **ketogenic diet** is a high-fat, adequate-protein, low carbohydrate diet that in medicine is used primarily to treat difficult-to-control (refractory) epilepsy in children.
- When **fat** is the **primary source of calories**, ketones are formed.

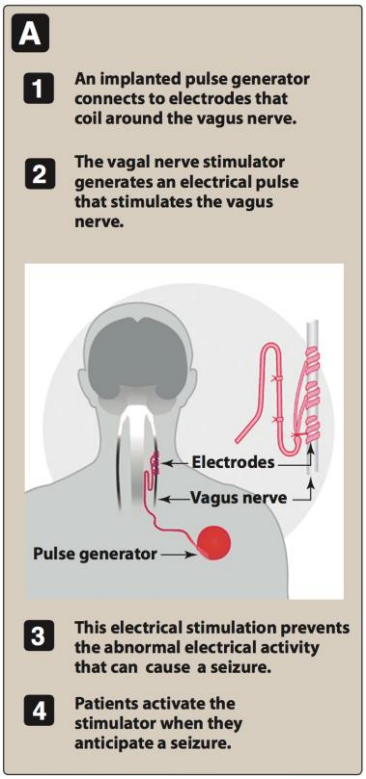
Remember that acidosis decreases neuronal activity.

Vagal nerve stimulation

It is an alternative for patients who have been **refractory to multiple drugs**.

Who are sensitive to many adverse effects of anti-epileptic drugs

It is an expensive procedure
Not very effective



Classification of antiepileptic drugs

First generation

- **Phenytoin**
- **Carbamazepine**
- **Valproate**
- **Ethosuximide**
- Phenobatbital & Primidone
- Benzodiazepines (e.g. Clonazepam, **lorazepam** and diazepam)

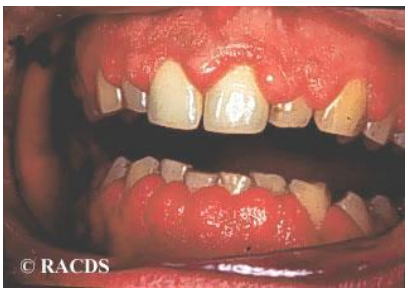
Drugs written in **bold** are important.

Seconds generation

- **Lamotrigine**
- **Topiramate**
- Levetiracetam
- Gabapentin
- Vigabatrin
- Felbamate
- Zonisamide

Differ from the 1st generation in the effect on microsomal enzymes, most of the 2nd gen drugs don't have this effect

1st Generation

Drug	Phenytoin	Fosphenytoin
Mech. of action	- **Blockade** of **Na^+ & Ca^{2+}** influx into neuronal axon. - **Inhibit the release** of **excitatory** transmitters . - **Potentiate** the action of **GABA**.	
P.K	○ Given orally, well absorbed from GIT.(most drugs here are taken orally) ○ Also available **IV** and IM → (**fosphenytoin**) ○ **Enzyme inducer.** (increase its metabolism → the action decreases) ○ Metabolized by the liver to inactive metabolites. ○ Half life approx. 20 hr. ○ Excreted in urine.	○ **Parenteral form of phenytoin** ○ A Prodrug. ○ Given **IV** or **IM** and rapidly converted to **phenytoin** in the body. ○ **Avoids local complications** associated with **phenytoin**. → avoid toxic epidermal necrosis. ○ Lower local tissue and cardiac toxicity than **phenytoin**.
Therapeutic Uses	• Partial and generalized tonic-clonic seizures. • **Not** in **absence seizure**. • In **status epilepticus**, given **IV**.	
ADRs	• Nausea or vomiting. • Neurological like headache, vertigo, ataxia, diplopia , nystagmus. • Sedation. • **Gum hyperplasia.** (very important side effect) • Hirsutism.(abnormal hair growth) • Acne. (حب الشباب) • Folic acid deficiency. (megaloblastic anemia) • Vit D deficiency → (osteomalcia) • Teratogenic effects. (very common side effect)	

1st Generation (cont.)

Carbamazepine

MOA

- Blockade of Na^+ & Ca^{2+} influx into neuronal axon.
- Inhibit the release of excitatory transmitters.
- Potentiate the action of GABA.
- (similar to **Phenytoin** in many things)

P.K

- Available **only** orally.
- Well absorbed.
- **Strong enzyme inducer.** (including its own metabolism)
- Metabolized by the liver to active & inactive metabolites.
- $T_{1\2}$=18-35 hr.
- Excreted in urine.

Indications

- **Drug of choice in partial seizures.**
- Tonic-clonic seizures. (1ry & 2ry generalized)
- **Not in absence seizures**. → because it may cause an increase in seizures

ADRs

- GIT upset.
- **Hypersensitivity reactions**.
- Drowziness , ataxia, headache & diplopia.
- **Hyponatremia.** (anti-diuretic effect, and thus it should not be given to children or old patients)
- **Water intoxication**.
- Teratogenicity.

Ethosuximide

MOA

- **Inhibits T- type Ca^{2+} channels** in thalamocortical neurons.

P.K

- Absorption is complete.
- Syrup & capsule forms. (to be easily taken for children)
- Not bound to plasma proteins or tissues.
- Metabolized in liver.
- $T_{1\2}$ = 52-56 hr.
- 10-20% of a dose is excreted unchanged the urine.

Indications

- **Absence seizures.** Mainly given to children

ADRs

- **Gastric distress** :
  - Nausea
  - vomiting
- Drowsiness, fatigue, hiccups, headaches.

لأنه يعطى للأطفال ما نقدر نقول إنه teratogenic

1st Generation (cont.)

Drug

Sodium Valproate

MOA

- Blocks activated Na^+ channels.
- Enhances **GABA synthesis** & **reduces degradation**.
- Suppress glutamate action.
- **Blocks T-type Ca^{2+} channels.** (that's why it can be used for **absence seizures**)

P.K

- **Broad spectrum antiepileptic**
- Available as capsules, Syrup, **I.V**.
- Metabolized by the liver. (to inactive form)
- **Enzyme inhibitor.** Inducers اللي قبل كانوا
- $T_{1\backslash2}$=12-16 hr.
- Excreted in urine.

Therapeutic Uses

- **It is effective for all forms of epilepsy** → **very broad spectrum**
  - Generalized tonic-clonic seizures. (1^{ry} & 2^{ry})
  - **Absence seizures.**
  - Complex partial seizures.
  - Myoclonic.
  - Atonic.
  - photosensitive epilepsy.

ADRs

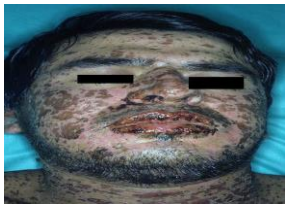
- Weight gain (↑ appetite).
- Transient hair loss, with re-growth of curly hair.
- **Thrombocytopenia**.
- **Hepatotoxicity**. (we do periodic assessment)
- Teratogenicity.

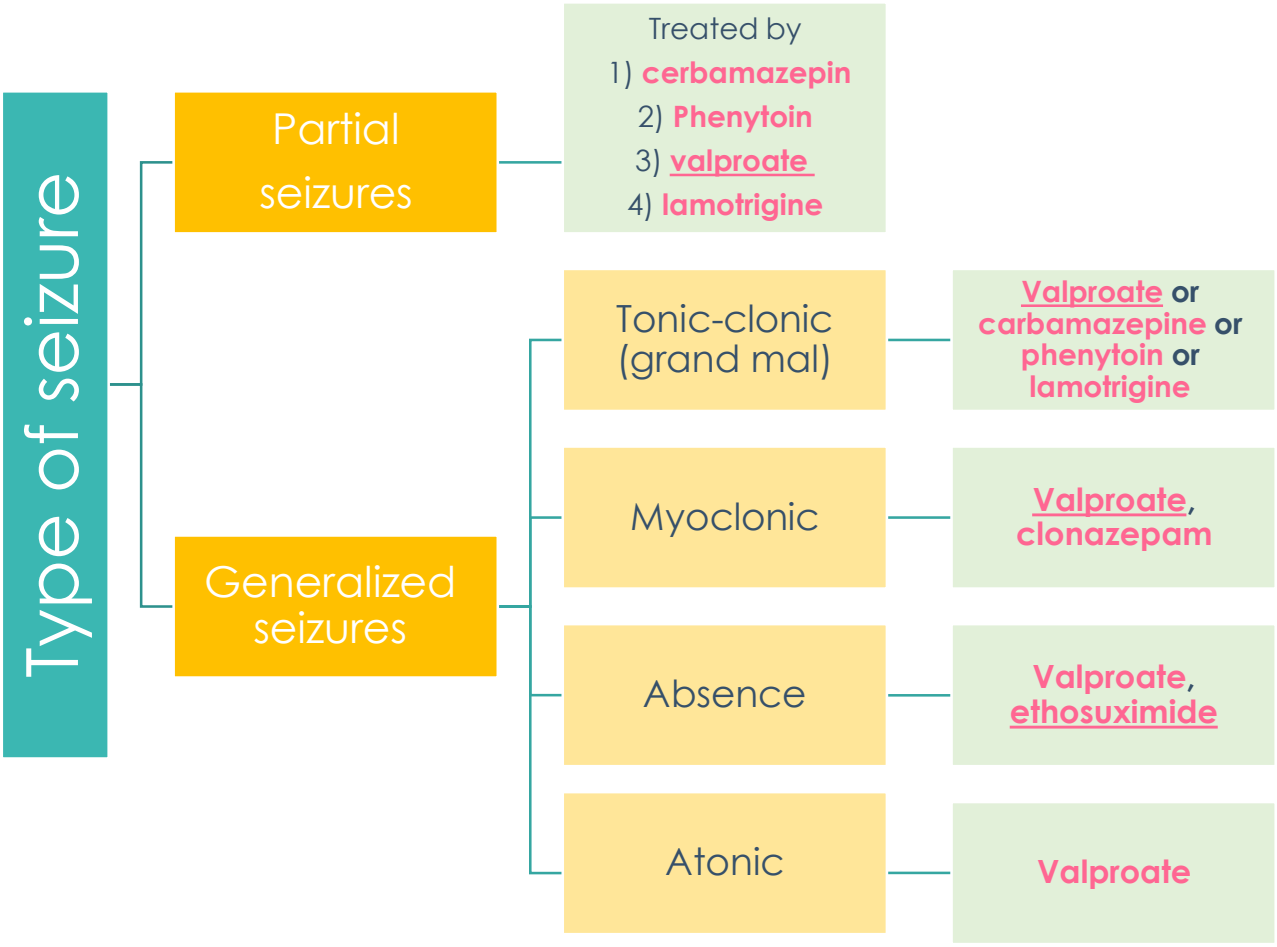
Other uses

- Bipolar disorder and mania. (as a mood stabilizer)
- Prophylaxis of migraine.
- **Lennox-Gastaut syndrome**.

→ The Lennox-Gastaut syndrome (LGS) is a type of **epilepsy** with multiple different types of **seizures**, particularly tonic (stiffening) and atonic (drop) **seizures**. Intellectual development is usually, but not always, impaired. **(not very important but you should read it)**

2nd generation

Drug	Lamotrigine	Topiramate
MOA	○ Blockade of **Na^+** channels ○ Inhibits excitatory amino acid release (glutamate & aspartate)	○ Blocks **Na^+** channels (membrane stabilization) ○ Potentiates the inhibitory effect of GABA.
P.K	○ Available as oral tablets ○ Well absorbed from GIT ○ Metabolized primarily by **glucuronidation**. ○ **Does not induce or inhibit C. P-450 isozymes** (most important difference from the **first gen**) ○ $T_{1\backslash2}$= approx. 24 hr	○ Well absorbed orally (80 %) ○ Food has no effect on absorption ○ **Has no effect on microsomal enzymes** (most important difference from the **first gen**) ○ 9-17 % protein bound (minimal) ○ Mostly excreted unchanged in urine. ○ Plasma t½ 18-24 hrs
Uses	○ As add-on therapy or as **monotherapy** in partial seizures → to be more effective. ○ **Lennox-Gastaut syndrome**	○ Can be used alone for **partial**, **generalized tonic-clonic**, and **absence seizures**. ○ Lennox- Gastaut syndrome (or **lamotrigine**, or **valproate**).
ADRs	○ **Influenza-like symptoms**. ○ **Skin rashes** (may progress to **Steven –Johnson syndrome**)  ○ Somnolence (sedation) ○ Blurred vision ○ Diplopia ○ Ataxia (can be teratogenic)	○ Psychological or cognitive dysfunction ○ **Weight loss** (can be desirable side effect) → الأدوية الثانية كانت تزيد الوزن ○ Sedation ○ Dizziness ○ Fatigue ○ Urolithiasis ○ Paresthesias (abnormal sensation) ○ Teratogenecity (in animal but not in human)



Drugs used for treatment of Status Epilepticus

Most seizures last from few seconds to few minutes. When seizures follow one another without recovery of consciousness, it is called "**status epilepticus**". It has a **high mortality rate**.
Death is from **cardiorespiratory failure**.

Anti epileptics used in **status epileptics**
Through **IV** injection of:

- **Lorazepam**
  Diazepam
  (drug of choice)
- **Phenytoin**
- **Phenobarbital**
- **Fosphenytoin**
- **Sodium Valproate**

Lorazepam has a shorter pharmacokinetic half-life but stays in the brain longer than *diazepam*.

Pregnancy & anti-epileptics

- Seizure is very **harmful** for pregnant woman.
- **No** antiepileptic drug is **safe** in pregnancy.
- Monotherapy usually **better** than drug combination.
- **Valproate** & **phenytoin** are **contraindicated** during pregnancy.
- Patient has to **continue** therapy.

Summary (imp.)

1. Epilepsy is classified into **partial** or **generalized** according to the site of lesion.
2. The exact mechanism of action of AED is not known.
3. **Phenytoin** is mainly used for treatment of **generalized tonic-clonic seizures**.
4. **Carbamazepine** is mainly used for treatment **of partial seizures**.
5. **Sodium valproate** is a **broad spectrum** antiepileptic drug.
6. **Lamotrigine** & levetiracetam are used as monotherapy or adjunctive therapy in **refractory cases.**
7. Lorazepam, **diazepam**, **phenytoin** are used **intravenously** for treatment of **status epilepticus**.

Summery of 1st Generation Drugs

Drug	Phenytoin	Carpamazepine	Ethosuximide	Sodium valproate
Mech. of action	- Block influx of Ca^{2+} and Na^{+} into neuronal axon → potentiate the action of GABA. - Inhibit the release of excitatory transmitters. **Fosphenytoin** Parenteral form of **phenytoin**.	- Block influx of Ca^{2+} and Na^{+} into neuronal axon → potentiate the action of GABA - Inhibit the release of excitatory transmitters.	Block T type Ca^{2+} channels	- Block Na^{+} and T type Ca^{2+} channels - Enhances GABA synthesis - Supress glutamate action
Indications	1- status epilepticus 2- partial and generalized tonic-clonic seizures	Partial and generalized tonic-clonic seizures	Absence seizure	All types of epilepsy
ADRs	1- Folic acid & vit.D deficiency (osteomalcia) 3- teratogenic effect 4- hirsutism 5- gum hyperplaia	Hyonatremia and water intoxication Teratogenicity Hypersensitivity Git upset	Hiccups Gastric distress drowsiness	Hair loss Thrombocytoenia **Hepatotoxicity** Weight gain teratogenicity
Comments	Enzyme inducer Fosphenytoin is given I.V to treat status epilepticus its transforemed rapidly into phenytoin	Strong enzyme inducer Drug of choice in partial seizures Strong drug inducer	Has very long half life = 52-56 h	Enzyme inhibitor Could be used in 1-bipolar disorder and mania 2-in migraine as prophylactic drug 3- lennux-gastaut

Summery of 2nd generation drugs

Drug	Lamotrigine	Tobiramate
Mech. of action	- Block Na^+ channels - Inhibit glutamate and aspartate release.	- Block Na^+ channels - Potentiate the inhibitory effect of GABA
PK	○ Does not induce or inhibit C. P-450 isozymes	Has no effect on microsomal enzymes
Indications	Lennux-gastaut syndrome	
ADRs	-Infleunza like syndrome - Skin rashes → may progress to Steven –Johnson syndrome - Somnolenc (desire to sleep) - Ataxia	- Urolithiasis - Paresthesia - Weight loss - Teratogenicity
Ext info	- Metabolized by glucurondation - Does not induce or inhibit CP450 isoenzyme	

Flash Cards | MCQs | Editing File

Thank you for checking our team!

Pharmacology 435

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محمد السحيباني
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