MED437
KING SAUD UNIVERSITY

Pharmacology
435 team

Pharmacology
Team 437

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 & treatment of status epilepticus.
- Classify antiepileptic drugs according to the type of epilepsy treated and generation introduced
- Expand on pharmacokinetic and dynamic patterns of first and second generation antiepileptic drugs.

Color index:

- Drugs names
- Doctors notes
- Important
- Extra

Editing File

وأن أثابر في طلب العلم؛ أسخره لنفع الإنسان

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**

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

: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(Usually not curable, **idiopathic & combination of symptoms**).

A disease is the actual diagnosed impairment of health or a condition of abnormal functioning (Usually curable , **non- idiopathic & it's a combination of symptoms)** .

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). (Februs in Latin means fever)
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:** Re-occuring tonic-clonic seizure (30 min or more)(Emergency situation may lead to death by Resp. failure)

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. 20% has resistance
- Antiepileptic drugs are indicated when there is two or more seizures occurred in short interval (6 m -1y) with no cause
- 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

- Seizure–free period of 2-5 years or longer
- Normal IQ
- Normal EEG prior to withdrawal
- No juvenile myoclonic epilepsy (in children)
- Relapse rate when antiepileptics are **withdrawn** is 20-40%.

Treatment of Epilepsy

- Drugs mainly
- Vagal nerve stimulation
- Surgery
- Ketogenic diet

Ketogenic diet may help because it will lead to accumulation of Ketones which are acidic compounds and acidosis cause neuronal suppression

Mechanism of anti-epileptic
:inhibit depolarization of neuron by

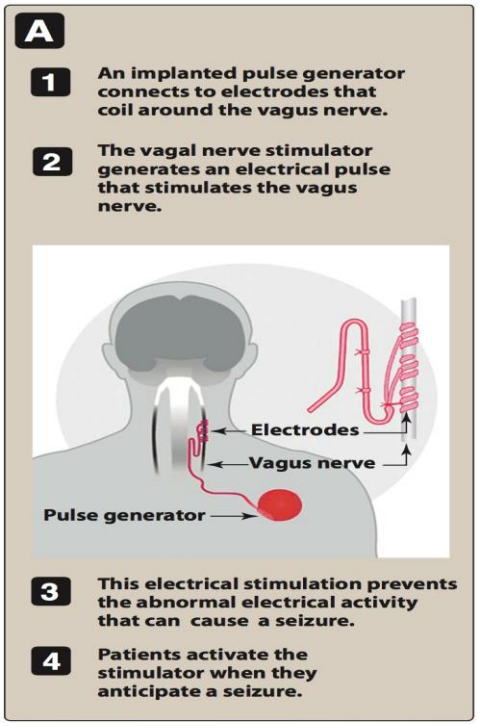
- Inhibition of excitatory NTs (glutamate)
- enhancement of inhibitory NTs (GABA)
- Blockage of voltage-gated positive current (Na,Ca)
- Increase outward positive current (K)

Vagal nerve stimulation

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

Who are sensitive to many adverse effects of antiepileptic drugs

It is an expensive procedure
Not very effective



Important notes

Prof. Yieldez said :

- **important to know Mechanism of action, characteristic ADRs & uses for each drug .**
- **Case: A boy was playing and suddenly he stopped,also he was staring , blinking and then he got back to normal , wath is this condition?**
  Absence(batite) seizure.
- **If we have to treat pregnant woman , We use the least harmful drug which is Topiramate**
- **Valproate, phenytoin & Carbamazepine are contraindicated during pregnancy.**

Classification of antiepileptic drugs

First generation

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

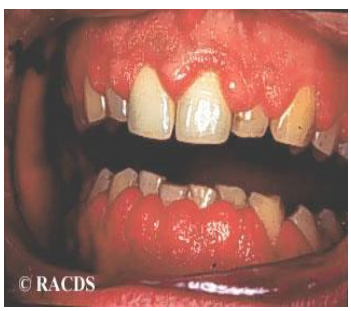
Seconds generation

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

Mnemonics:
-Phenytoin:
(ADRs:gingival) فيني؟ ب جينجيفال
-Carbamazepine:
لما تأكلين carb تعطشين
(ADRs: hyponatremia & water intoxication)
-Lamotrigine
(ADRs: skin rash) لمو(لمى) تستخدم كريم جونسون لبشرتها
-Topiramate
رميته لأنه صار وسيع (ثوبي)توبي
(ADRs: weight loss)

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	Fosphenytoin	Phenytoin
Mech. of action	M.O.A is very important - **Blockade** of **Na^+ & Ca^{2+}** influx into neuronal axon. - **Inhibit the release** of **excitatory** transmitters . - **Potentiate** the action of **GABA**.	
P.K	○ **Parenteral form of phenytoin (**IV & IM) o A Prodrug. o rapidly converted to **phenytoin** in the body. o **Advantage over phenytoin:** o more rapid IV administration than **phenytoin** o may be administered by IM injection o **Lower** local tissue and **cardiac toxicity** than **phenytoin** o Less pain and phlebitis at injection site than **phenytoin**	o Given orally, well absorbed from GIT.(most drugs here are taken orally) o Also available as capsule & **IV** ○ **Enzyme inducer.** (increase its metabolism → the action decreases) o Metabolized by the liver to inactive metabolites. o Half life approx. 20 hr. o Excreted in urine.
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 due to increased GABA • **Gum(gingival) hyperplasia.** (very important) • Hirsutism.(abnormal hair growth, not a good option in females) • Acne. (حب الشباب) • Folic acid deficiency. (megaloblastic anemia) • Vit D deficiency → (osteomalacia) • Teratogenic effects. (very common side effect in all antiepileptics)	

1st Generation (cont.)

Drug	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 as capsule & syrup **only** orally. ○ Well absorbed. ○ **Strong enzyme inducer.** (including its own metabolism) ○ Metabolized by the liver to active & inactive metabolites. ○ $T_{1\backslash 2}$=18-35 hr. ○ Excreted in urine.
uses	○ **Drug of choice in partial seizures.** (Both simple & complex) ○ Tonic-clonic seizures. (1ry & 2ry generalized) ○ **Not in absence seizures.** → because it may cause an increase in seizures ○ **Other uses:** Bipolar depression , Trigeminal neuralgia
ADRs	*carbamazepine will cause thirst >> excessive water intake >> disturbances in water-electrolytes balance >> water intoxication ○ GIT upset. ○ **Hypersensitivity reactions.** ○ Drowsiness , ataxia, headache & diplopia. ○ **Hyponatremia & *Water intoxication.** (anti-diuretic effect, and thus it should not be given to children or old patients) ○ Teratogenicity.

Drug	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. ○ $T_{1\backslash 2}$ = 52-56 hr. ○ 10-20% of a dose is excreted unchanged the urine.
uses	○ **Absence seizures.** Mainly given to children

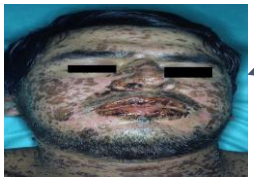
ADRs	○ **Gastric distress** :
	  ○ Nausea
	  ○ vomiting
	○ Drowsiness, fatigue, hiccups, headaches.

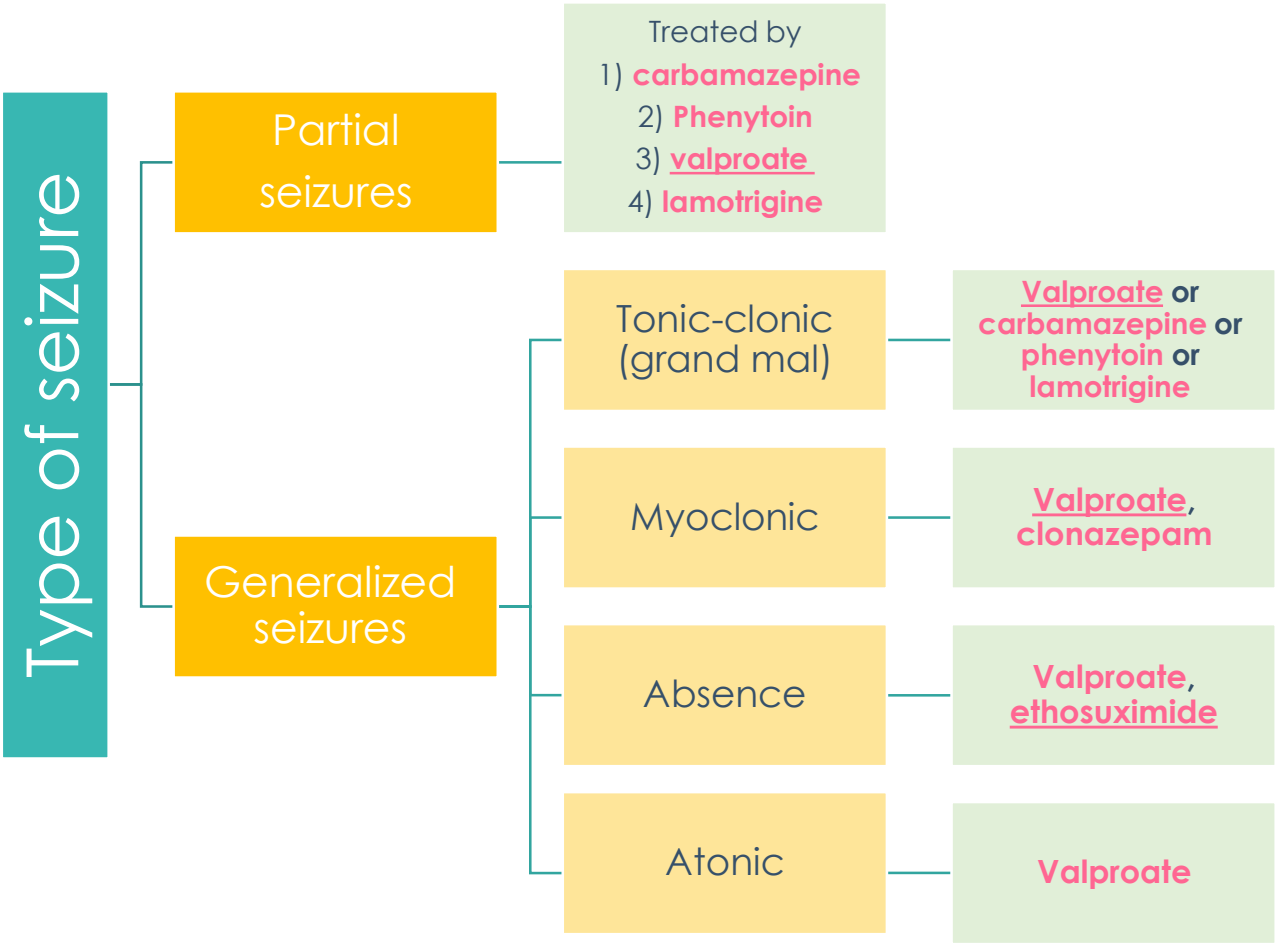
1st Generation (cont.)

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 ○ $T_{1\backslash 2}$=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** **But** Ethosuximide it's drug of choice in this coundiction, cause it's selective . ○ Complex partial seizures. ○ Myoclonic. ○ Atonic. ○ photosensitive epilepsy.
ADRs	○ GI (nausea, vomiting, heart burn). ○ Weight gain (↑ appetite). ○ Transient hair loss, with re-growth of curly hair. ○ **Thrombocytopenia** decreased platelet.(not used with aspirin or coumadin " antiplatelet drugs") ○ **Hepatotoxicity**(Transient increase in liver enzymes). (we do periodic assessment) ○ Teratogenicity (neural tube defect) C.I in pregnancy
Other uses	○ Bipolar disorder and mania. (as a mood stabilizer) **(Sodium Valproate is more favorable to treat bipolar disorder than carbamazepine)** ○ 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

2nd generation

Drug	Topiramate	Lamotrigine
MOA	○ Blocks **Na^+** channels (membrane stabilization) ○ Potentiates the inhibitory effect of GABA.	○ Blockade of **Na^+** channels ○ Inhibits excitatory amino acid release (glutamate & aspartate)
P.K	○ 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	○ 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**) ○ $T_{1\backslash 2}$= approx. 24 hr
Therapeutic Uses	○ Can be used alone for **partial**, **generalized tonic-clonic**, and **absence seizures**. ○ Lennox- Gastaut syndrome (or **lamotrigine**, or **valproate**).	○ As add-on therapy or as **monotherapy** in partial seizures & generalized tonic-clonic seizures → to be more effective. ○ **Lennox-Gastaut syndrome** ○ **Bipolar depression**
ADRs	○ Psychological or cognitive dysfunction ○ **Weight loss** (can be desirable side effect) ○ Sedation ○ Dizziness ○ Fatigue ○ Urolithiasis (kidney stone) ○ Paresthesias (abnormal sensation) ○ Teratogenicity (in animal but not in human)	○ Influenza-like symptoms. ○ **Skin rashes** (may progress to **Steven – Johnson syndrome**) ○ Somnolence (sedation) ○ Blurred vision ○ Diplopia ○ Ataxia (can be teratogenic)





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**.

Antiepileptics used in **status epilepticus**
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** & **Carbamazepine** are **contraindicated** during pregnancy.
- Patient has to **continue** therapy.

(Summary (important

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**.

Summary of 1st Generation Drugs

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

Summery of 2nd generation drugs

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

Questions

MCQs

1) Which of the following drugs is an enzyme inhibitor?
A-Sodium Valproate
B-Carbamazepine
C-Phenytoin
D-Ethosuximide

2) Which of the following drugs is a broad spectrum antiepileptic?
A-Lamotrigine
B-Phenytoin
C-Sodium Valproate
D-Topiramate

3) Which drug has a minimum adverse effects?
A-Carbamazepine
B-Topiramate
C-Lamotrigine
D-Ethosuximide

4) Steven-Johnson syndrome is a possible adverse effect of?
A-Phenytoin
B-Lamotrigine
C-Sodium Valproate
D-Topiramate

5) What is the drug of choice in case of partial seizures?
A-Carbamazepine
B-Ethosuximide
C-Lamotrigine
D-Phenytoin

Questions

MCQs

6) Which of the following drugs may cause psychological effect ?
A-Topiramate
B-Sodium Valproate
C-Ethosuximide
D-Fosphenytoin

7) Which drug is contraindicated in females ?
A-Lamotrigine
B-Carbamazepine
C-Fosphenytoin
D-Topiramate

8) Which drug is the drug of choice in case of Status Epilepticus ?
A-Phenobarbital
B-Benzodiazepines
C-Fosphenytoin
D-Valproate

MCQs answers:
1-A
2-C
3-D
4-B
5-A
6-A
7-C
8-B

SAQ

Q1) a 5 years old epileptic boy came to the dentist suffering from enlargement of his gum due to antiepileptic drug.

Which drug did he use ?

Fosphenytoin

What is the mechanism of action of this drug ?

Block of Na and Ca influx
potentiate the action of GABA

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References:

- Doctors' slides and notes.
- pharmacology Team 435.

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