# Types of epilepsy

We have different types of epilepsy, so it is not one type of seizures that the patient can suffer from; we can find some patients with generalized or partial seizure.

So, there are two types of seizures:

1)**Generalized type:** seizure activity involve the whole brain, it is divided into:

A-**Absence seizure (petit mal)**: in this type, the patient loses contact with real life for a brief period.

B-**Myoclonic seizure**: the patient has **jerky** movement of a muscle or muscle group without loss of consciousness.

C-**Tonic seizures:** Some pts, after dropping unconscious experience only the tonic or clonic phase of seizure.
D-**Tonic-Clonic seizure (grand mal)**: the most severe type, the patient is suffering from symptoms like **tetanus** at the beginning, followed by jerky movement which is very strong, falling down, and then losing contact with life (awake but unaware).

E-**Atonic seizure**: common in **children** (2-4 years); the child is standing and then falling heavily on the ground (the child may or may not have jerky movement).

F- **Status epilepticus** ( re-occuring seizure ). Continuous seizure without intervening return of consciousness.

2) **Partial seizure**: is divided into:

A- **Simple**: seizure activity when the person is **alert**.

B- **Complex**: seizure activity with **change** in **awareness** of surroundings.

C- **Secondary generalized**: seizure activity begins in one area and then spreads (partial activity then it becomes generalized).

**Dealing** with antiepileptic drugs is the most difficult thing in our medical life because of two main things:

1) Their **narrow** therapeutic index.

**2) We depress the CNS, thus producing drowsiness, sedation, dizziness, weight gain or loss (we affect the appetite), also the vision is affected.**

---

## *Basic Pharmacological treatment of Epilepsy*

**Most of anti-epileptic agents act either by:**

**1) Blockade of depolarization channels:**

**A) Na+ channels, which is similar to the mechanism of action of local anesthesia.**

**B) Ca++ channels.**

**- The excitation in the CNS is linked to the Na+, Ca++, but more towards Na+ so we want to block Na+ channels.**

**- So we increase the threshold of AP, thus enhancing hyperpolarization.**

**- We can have also block the effect of K+ channels (increasing the effective refractory period).**

**- We should notice that the mechanism of action of anti-epileptic agents (by blocking Na+, Ca++) is similar to anti-arrhythmic drugs.**

**2) AND/OR enhancing the activity of GABA (neurotransmission inhibition).**

**3) New agents that cause inhibition to Glutamate release.**

***Usually we do not have pure anti-epileptic drugs, because when we are inhibiting Ca++ or Na+ channels, we are also inhibiting the release of the NTs (Polymechanisms of action).***

**More number of actions ------> more generalized activity ---------> more covering ---------->wider spectrum.**

**Less number of actions --------> directed towards one type of epilepsy (for example : in absence seizure, we use one or two drugs to treat it because it is linked with Ca++ mainly, and we do not want to affect Na+, because if we affect Na+, it will increase the incidence of absence seizure).**

---

# Pharmacotherapy

- Just under 60% of all people with epilepsy can become seizure-free with drug therapy (so it is effective and we should describe it).
- In another 20%, seizure can be dramatically reduced (like instead of becoming once or twice every week or 3 times every month, it becomes one or two times in a year).
- In another 20% of epileptic patients, seizure is refractory to currently available drugs.
- Because of overlapping mechanisms of actions, best drug can be chosen based on minimizing side effects in addition to efficacy.
- There is no comparison between the risk of seizure and the risk of side effects; the risk of seizure is really, really bad!

---

# Categories of Anti-epileptic Drugs

- Hydantoins (phenytoin, Carbmazepine).
- Succinimides.
- Benzodiazepines (4th line therapy in treatment of epilepsy. Also, we should remember that Diazepam is used to treat status epilepticus).
- Barbiturates (used in children sometimes, but we reduced the usage of this drug because of its narrow therapeutic index and sedative effects).
- Miscellaneous.

---

We will start now talking about ***phenytoin*** :

- First line for partial seizures. Some use it for tonic-clonic seizures by blocking Na+ channels to reduce the excitability and increasing the duration of inactivation.
- The efficacy of this drug is not so great; it is not the first line therapy for treatment of Grand Mal seizure (tonic-clonic seizure), but sometimes we can use it for tonic-clonic seizures though it is not the first line therapy.

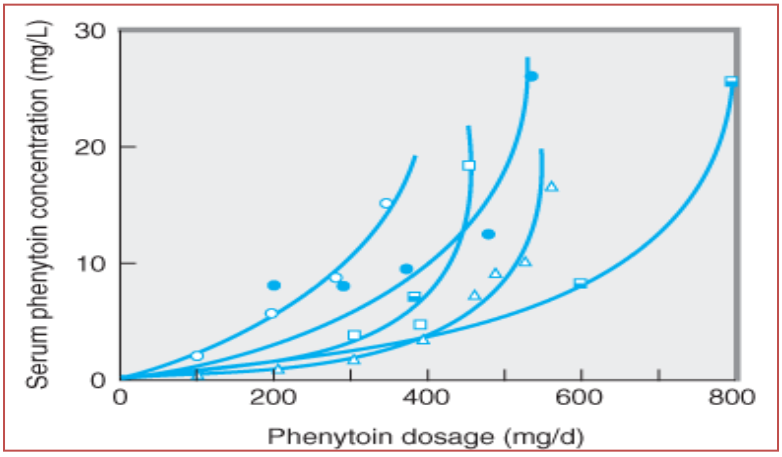
- **The first line therapy in treatment of Grand mal seizure is Valproic acid, which covers Na+/Ca++/K+ & increases GABA, so we are hitting 3-4 mechanisms of action (more efficacious & has multiple actions).**
- **Phenytoin has narrow therapeutic index, so we should monitor the patient.**

- **Side effects of *phenytoin*:**
  - ✓ **The first side effect you will see is nystagmus; even with normal doses.**
  - ✓ **Nausea and vomiting.**
  - ✓ **Impaired brain stem & cerebellar function (dizziness, tremor, nervousness, blurred vision)**
  - ✓ **Skin rash.**
  - ✓ **Because it has anti-arrhythmic activity, it may cause tachycardia (anti-arrhythmic drugs are pro-arrhythmic).**
  - ✓ **Vit.D and Folic acid deficiency (for long-term use, it will cause folic acid deficiency and Gingival hyperplasia, which also occurs when we use Ca++ channels blockers for hypertension).**

- **There is another problem regarding Phenytoin which is (Excretion saturation):**

  - ➢ **You give a certain amount of drug ----->**
    **and this amount saturates excretion site and if you give more than this -----> excretion won't increase further (the dose or the level of the drug in the blood will increase very fast producing ----> zero order Kinetic)**
    **(unlike 1st order kinetics where the excretion rate is equal to that of administration)**

- **Look at the following diagram:**




**1) Saturation in different patients happens at different doses, so we should start with 300 mg/dl (it is still linear (1st order) but if we increase the dose more than 300 mg/dl ----> we have a large increase in the level of this drug.**

**2) Bottom-line of the story is that we should not jump from (300 to 400 mg/dl) but from (300 to 320 mg/dl), increasing the dose a little every time & monitoring its (phenytoin) concentration in the blood.**

**3) Some patients need 300mg/dl for the drug to be effective; others may need 400 …, so we have to give the best value of the dose that we are going to give to our patient.**

- **Phenytoin is one of the main inducers of P-450, so we should monitor it.**
- **Every person has a different P-450 activity than the other (fast metabolizer, intermediate, slow).**
- **50% of drugs are metabolized by p-450.**
- **Phenytoin is not a good drug in poly-pharmacy patients, because of drug-drug interaction & enhancing activity of p-450. So we do not use it along withCa++ channels blocker, corticosteroids …**
- **The benefit of phenytoin still outweighs the risks, by good management and monitoring.**

---

## Carbamazepine

**Used for partial seizure; some use in tonic-clonic seizure. It has a narrow therapeutic index too.**

**Acts by:**

- **Blocking Na+ channels to inhibit repetitive firing.**
- **Decreasing the production (or release) of Glutamate (excitatory chemical).**

- ❖ **Can also be used in the treatment of neuropathic pain; such as: Trigeminal neuralgia (is the drug of choice here), phenytoin can be used too but it is not as good.**

**Side effects of Carbamazepine:**

- ✓ **Nausea and Vomiting (especially early in treatment).**
- ✓ **Constipation, diarrhea and anorexia.**
- ✓ **Skin irritation.**
- ✓ **CNS toxicity: sedation, dizziness, drowsiness, confusion.**
- ✓ **Bone marrow suppression (leukopenia) which is rare to occur.**

**Carbamazepine has even more complex drug-drug interaction and interferes with (CYP-3A4, CYP-1A2). So it increases the metabolism of many drugs, and decreases their activity.**

- **The drugs of choice in treating partial seizure are Carbamazepine and phenytoin, but we prefer Carbamazepine.**
- **But sometimes, the patient cannot tolerate carbamazepine because of its large side effects (e.g. constipation is very severe) so we use phenytoin.**
- **Like phenytoin, we have to monitor this drug because it has excretion saturation problem (but less than phenytoin).**

**The drug of choice in treating partial seizure:**

**1) Phenytoin.**

**2) Carbamazepine.**

**3) Oxacarbazepine: similar to carbamazepine but not used in Jordan.**

---

## *Succinimides - Ethosuximide*

- **First choice for patients with Absence seizures.**
- **Carbamazepine, Phenytoin and phenobarbital are contraindicated because they increase the frequency of absence seizure.**
- **Ethosuximide acts specifically on T-type channels in thalamus, and is very effective against absence seizures.**

- **Absence seizures are caused by oscillations between thalamus and cortex that are generated in thalamus by T-type (transient) $Ca^{2+}$ currents.**
- **Adverse effects: slightly wider therapeutic index:**
    - **Nausea, vomiting and anorexia.**
    - **Cerebellar disturbance (drowsiness, dizziness, photophobia, headache, depression).**
    - **Skin irritation.**
    - **Not to be used when pregnant (teratogenic)**

---

## Valproic acid

- **First-line therapy for generalized seizures(Grand Mal epilepsy), also used for partial seizures (but carbamazepine is more effective). It suppresses the initial seizure discharge and its spread.**

- **K+ channels have important inhibitory control over neuronal firing in CNS (repolarize membrane to end the action potentials). K+ channel agonists would decrease hyperexcitability in the brain.**
- **So far, the only antiepileptic drug with known actions on K+ channels is valproate.**
- **Also blocks Na+ channels and enhances GABAergic transmission (highly pleiotropic = Multiple actions ----> hitting 3 -4 mechanisms of action).**

**This drug doesn't have excretion saturation as in phenytoin and carbamazepine (doesn't build up).**

**There is a strong relation between antiarrhythmic and antiepileptic drugs.**

**In antiarrhythmic therapy, we use K+ channel blocker (Amiodarone) which increases effective refractory period and decreases slope in phase 3 of action potential.**

- **Adverse effects: (narrow therapeutic index)**
  - **GI upset (Nausea, vomiting, anorexia, abdominal pain and diarrhoea).**
  - **Weight gain (appetite stimulation) ⟶ important side effect to remember.**
  - **Transient hair loss.**
  - **Tremor.**
  - **Coma (rare).**
  - **Thrombocytopenia (platelets).**
  - **Oedema.**
  - **Severe hepatotoxicity (liver damage).**
  - **Contraindications: People with liver damage or history of hepatic dysfunction.**

---

## New Agents (Wider therapeutic Index)

**1) LAMOTRIGINE:**

- **Acts primarily on Na+ channels, and it also inhibits excitatory neurotransmitter glutamate (like Carbamazepine).**
- **Lamotrigine is effective in the treatment of partial(major effect) and secondarily generalized tonic-clonic seizures.**
- **It is generally well-tolerated but may cause serious ARs (allergic reactions) of the skin.**
  - **Including Stevens–Johnson syndrome (severe rash) in 1-2% of children who take the drug.**
- **Relatively safe, but not very wide therapeutic index.**

**Done by : Ameen Al-boreny**

**Special Thanks To : Moyad Almohtaseb , Bahaa Ashour .**