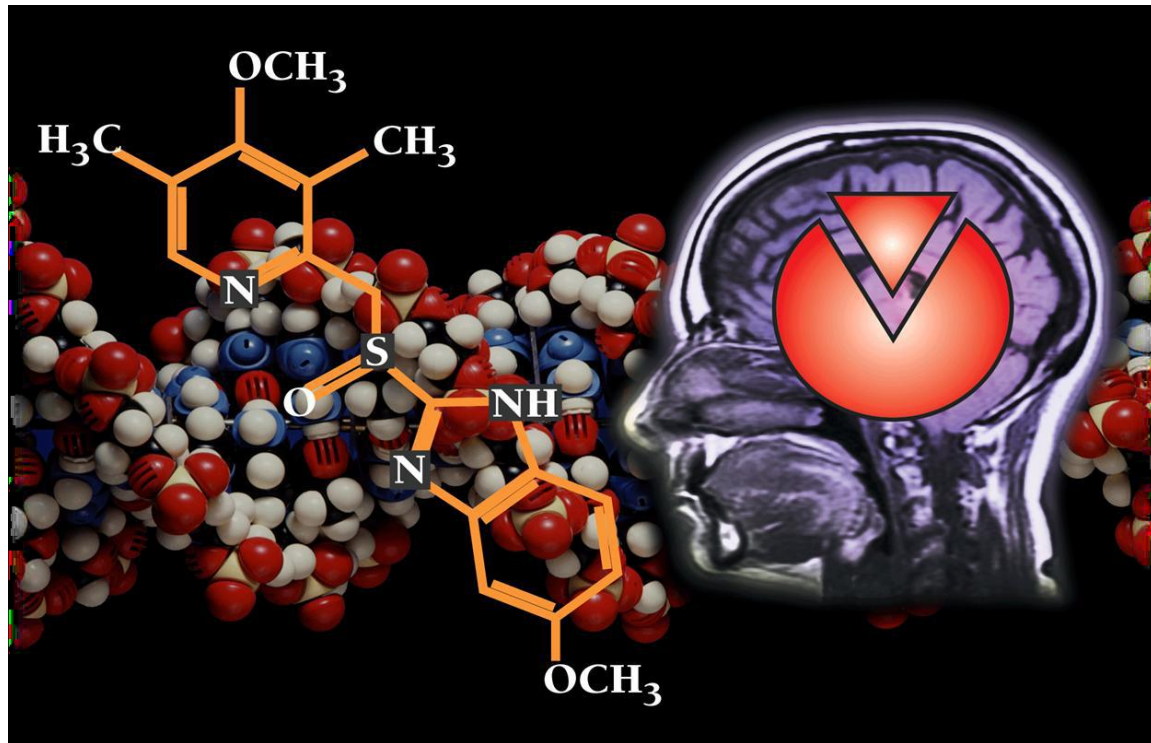


Anti-epileptic Drugs



Done By:

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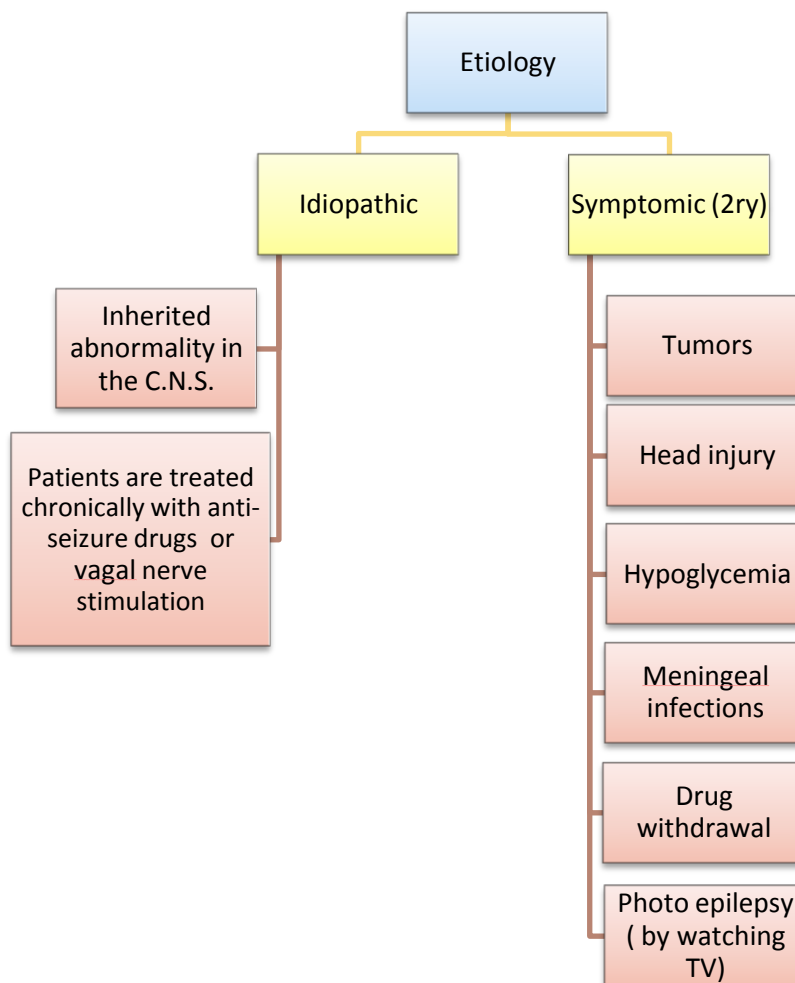
Anfal alshaya

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Introduction

What is epilepsy?

- *Is a disorder of the brain's electrical system. Abnormal electrical impulses cause brief changes in movement, behavior, sensation or awareness. These interruptions, known as seizures. The attack may last from a few seconds to a few minutes. People who have two or more seizures (within 6 -12 months) are considered to have epilepsy.*
- Epilepsy is the second most common neurological disorder, after stroke.
- The patient needs at least 2 seizure episodes in one year to be **considered Epileptic**.



»Triggers of seizures:

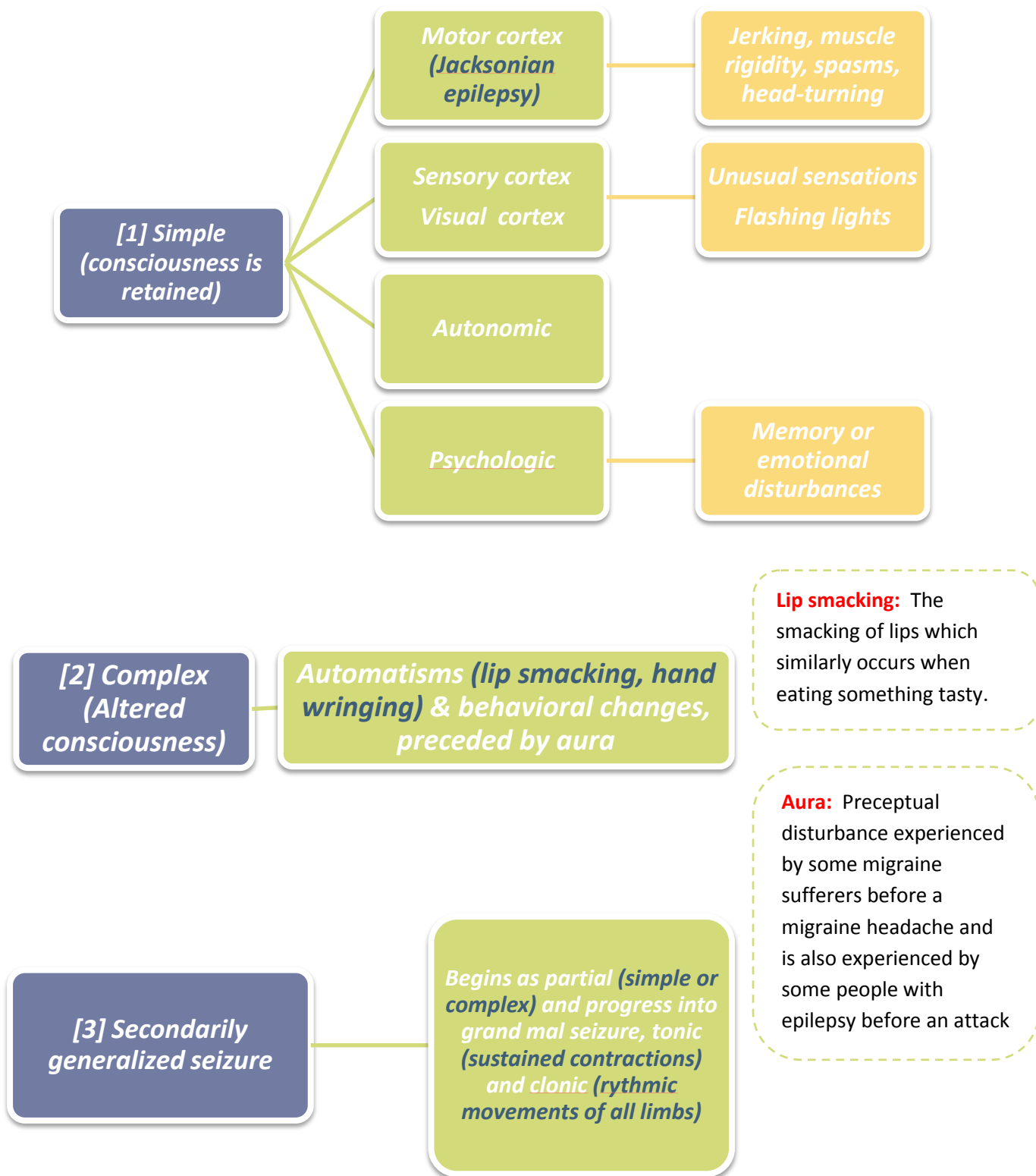
- Fatigue
- Stress
- Sleep deprivation
- Poor nutrition

» Types of seizures:

A. **Partial seizures** (Arise in one cerebral hemisphere):

[1] **Simple**: consciousness is often preserved. (e.g. deviation of the head & eyes to one side).

[2] **Complex**: loss of awareness or contact with the environment, often associated with behavioral or complex motor movements for which the patient is **amnesic** after the attacks.



B. **Generalized seizures** (Arises in both hemispheres and loss of consciousness occurs):

- **Absence seizures (Petit mal)**: brief loss of consciousness accompanied by minimal motor manifestations, cessation of an ongoing behavior also occurs. Full recovery is evident after (5-15) seconds.



» **General rules for treatment of epilepsy :**

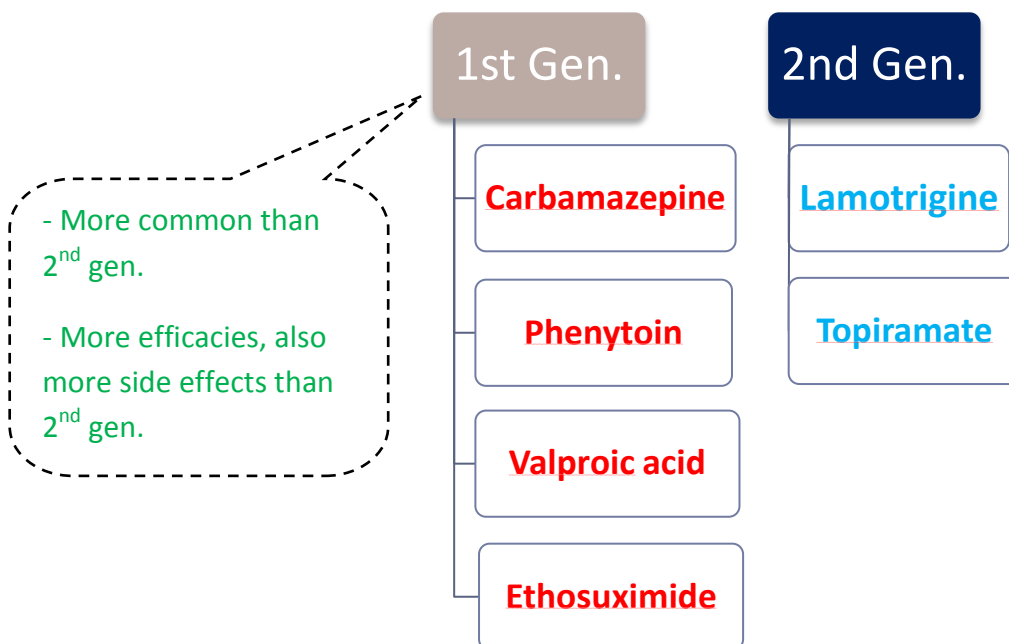
- ❖ Antiepileptic drugs suppress **but not cure** seizures.
- ❖ Antiepileptic drugs are indicated when there is two or more seizures occurred **in short interval** (6m-1y).
- ❖ An initial therapeutic aim is to use only one drug **(monotherapy)**.
- ❖ Drugs are usually administered **orally** **(in severe case or during attack I.V/IM)**.
- ❖ Monitoring plasma drug level is useful.
- ❖ Triggering factors (listed above) can affect seizure control by drugs.
- ❖ Sudden withdrawal of drugs should be avoided - **Withdrawal should be slow**.
- ❖ Withdrawal of drugs should be **after 2-3 years up to 5 years of seizure-free period**.
- ❖ To check if the patient is seizure-free **you must perform EEG on the patient**.

» Targets for Anti-Epileptic Drugs:

These drugs inhibit depolarization of neurons by the following mechanisms:

- **Inhibition** of excitatory neurotransmission
 - Glutamate
 - **Enhancement** of inhibitory neurotransmission
 - GABA
 - **Blockage** of voltage-gated positive current
 - Na^+
 - Ca^{2+}
 - **Increase** outward positive current
 - K^+
- Many anti-seizure drugs act via multiple mechanisms.

» Classification of antiepileptic drugs:



1-Carbamazepine:

I. Pharmacokinetics:

- Oral only
- **Potent liver enzyme inducer (Induces its own metabolism).** [When used with an Enzyme inhibitor e.g. **Cimetidine**, it causes Carbamazepine toxicity due to high plasma levels of the drug] and because it induces its own metabolism , the dose should be increase gradually with the course of treatment
- **Depress bone marrow activity.**

II. MOA:

- Blockade of **Na** channels, which reduces cell excitability.
- Reduces propagation of abnormal impulses in brain
- **Suppresses repetitive neuronal firing.**
- Attenuates action & release of Glutamate. (Attenuate = Weaken or Reduce)

III. Therapeutic uses:

- Drug of choice in **Partial & 2ry generalized tonic-clonic seizures.**
- Trigeminal neuralgia
- Bipolar depression “Mania” (as a mood stabilizer)

NOT USED IN:

Myoclonic or Absence seizures. (Because in absence seizures the ion channel for excitation is **Ca** and Carbamazepine works on **Na** channels)

IV. Adverse effects:

- GIT upset.
- Skin rashes.
- CNS toxicity (confusion, ataxia, double vision “Diplopia”)
- **Leukopenia** (decrease in WBCs) due to bone marrow suppression.
- Aplastic anemia & Agranulocytosis (**Marked decrease in the number of Granulocytes**) (common in elderly)
- Hyponatremia ↓Na + water intoxication
- **Teratogenicity** (Malformation of fetus)
- **Induction of hepatic P₄₅₀** (drug interactions)

2- Phenytoin:

Pharmacokinetics:

- Given orally
- **fosphenytoin** IVI & IMI
- Enzyme inducer
- Phenytoin metabolism shows saturation kinetics, a small increase in dose can cause large increase in plasma concentration of drug. (**if the dose is increased no more metabolism but it is for keeping the drug available in plasma for a long time**)

Mechanism of action:

- Blockade of **Na⁺ channels.**
- Interferes with the release of excitatory transmitters
- Potentiates the action of **GABA**
- (**At very high concentration, phenytoin can block voltage-dependent calcium channels**)

Therapeutic uses:

- Partial and generalized tonic-clonic seizures Not in absence seizure (Because the rate of sodium channel opening and closing too slow in absence seizure, phenytoin works mainly on highly active sodium channels).
Drug of choice for generalized tonic-clonic seizures, while carbamazepine for drug of choice in partial seizures
- In status epilepticus, IV.
- Cardiac arrhythmias (especially that induced by digoxin)
- **N.B. not used for long time**

Fosphenytoin:

- **A Prodrug.** Given i.v. or i.m. and rapidly converted to **phenytoin** in the body. (phenytoin itself NEVER given I.M)
- Avoids local complications associated with **phenytoin**: vein irritation, tissue damage, pain and burning at site, muscle necrosis with i.m. injection, need for large fluid volumes.
- Otherwise similar toxicities to phenytoin.

Adverse effects

A- Acute:

- C.N.S. toxicity (diplopia , vertigo,)(Depression of CNS occurs particularly in the cerebellum and vestibular system causing nystagmus and ataxia)
- Cardiac arrhythmias (in patient with no cardiac issues"bradycardia")
- Nausea, vomiting

B-Chronic:

- -Connective tissue effects (**gum hyperplasia, coarsening of facial features, hirsutism , acne**) . Better to be avoided in young women or adolescents.
- Folic acid deficiency (**megaloblastic anemia**)
- Vitamin D deficiency (**osteomalacia**)
- **Teratogenic effects** : this SE is common in all antiepileptic drugs e.g. cleft palate in phenytoin
- Induction of P450 enzymes



3- Sodium Valproate: Broad spectrum antiepileptic

Pharmacokinetics :

- Available as capsules, Syrup , I.V
- **Enzyme inhibitor**

Mechanism of action

- Blocks activated Na^+ channels.
- Enhances GABA synthesis & reduces degradation
- Suppress **glutamate action**.
- Blocks T-type Ca^{2+} channels
- (Valporic acid shares all mechanism of action that antiepileptic drugs has)

Therapeutic Uses:

[I] Epilepsy:

It is effective for all forms of epilepsy e.g.

- Generalized tonic-clonic seizures (**1^{ry}** or **2^{ry}**).
- Absence **seizures (not responding to ethosuximide)**
- Complex partial seizures
- Myoclonic
- Atonic
- photosensitive epilepsy
- drug of choice in combination seizures

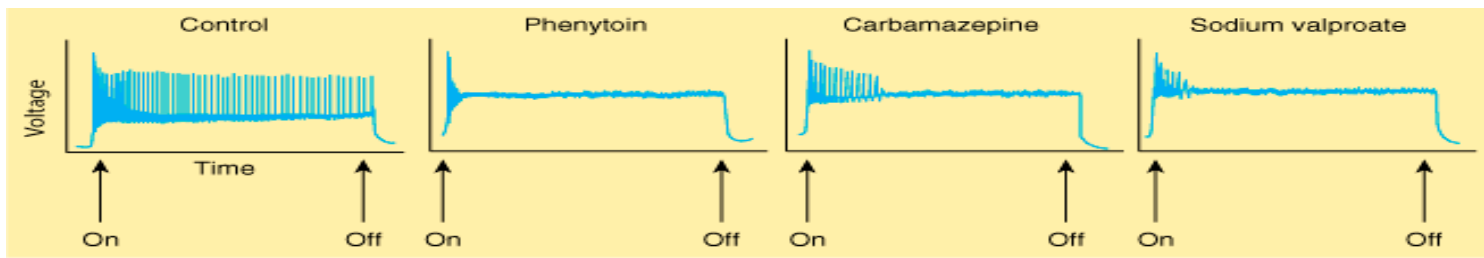
[II] Other uses:

- Bipolar disorder and mania
- Prophylaxis of migraine
- Lennox-Gastaut syndrome

Adverse Effects:

- **Weight gain (\uparrow appetite).**
- **Transient hair loss, with re-growth of curly hair**

- **Thrombocytopenia**
- **Severe hepatotoxicity** (because its metabolized in liver)
- **Teratogenicity** (spina bifida)
- **Enzyme inhibitor of P -450**



Source: Katzung BG, Masters SB, Trevor AJ: *Basic & Clinical Pharmacology*, 11th Edition; <http://www.accessmedicine.com>

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- ✓ Effects of three antiseizure drugs on sustained high-frequency firing of action potentials by cultured neurons.
- ✓ Intracellular recordings were made from neurons while depolarizing current pulses, approximately 0.75 s in duration, were applied (on-off step changes indicated by arrows).
- ✓ In the absence of drug (control), a series of high-frequency repetitive action potentials filled the entire duration of the current pulse.
- ✓ Phenytoin, carbamazepine, and sodium valproate all markedly reduced the number of action potentials elicited by the current pulses.

4-Ethosuximide:

Mechanism of action :

Inhibits T- type Ca^{2+} channels in thalamo- cortical neurons. (Ethosuximide is limited because of this very narrow spectrum).

Therapeutic uses:

The best drug (drug of choice) for Absence seizures (Absence seizure not controlled with ethosuximide, valproic acid and lamotrigine, alternative is clonazepam).

Adverse effects:

Gastric distress :

- **Pain**
- **Nausea**
- **Vomiting**

Note: Some researches show that it seems to be safe for pregnancy but is not 100% proved

So we give it with food

Second Generation:

1-Lamotrigine

Mechanism of action

- Blockade of **Na^+ channels**
- Interferes with synthesis of **glutamate & aspartate**
- Reduces **glutamate** release

Therapeutic Use

- **Add-on** therapy for partial & generalized seizures
- **Monotherapy** in partial seizures
- **Lennox-Gastaut syndrome**

Adverse effects:

- **Influenza-like symptoms.**
- **Skin rashes (may progress to Steven –Johnson syndrome)**
- **Somnolence (Strong desire for sleep)**
- **Blurred vision**
- **Diplopia**
- **Ataxia**

Lennox-Gastaut syndrome (pediatric epilepsy):

- ✚ Lennox-Gastaut syndrome is a severe form of epilepsy. Seizures usually begin before 4 years of age.
- ✚ Seizure types vary among patients, include
 - ✚ e.g. tonic (stiffening of the body, upward deviation of the eyes, dilation of the pupils),
 - ✚ Atonic (brief loss of muscle tone and consciousness, causing abrupt falls) and myoclonic (sudden muscle jerks).
- ✚ Most children with Lennox-Gastaut syndrome experience some degree of impaired intellectual functioning along with behavioral disturbances.

2- Topiramate:

MOA:

- Blockade of Na^+ channels
- Enhancing the action of GABA

Therapeutic Use:

- **Add-on** therapy for refractory partial seizures.
- Secondary generalized seizures.
- It is also approved for treatment of migraine.

Adverse effects:

- **Ataxia**
- **Dizziness**
- **Somnolence**
- **Weight loss**
- **Renal stones rarely**
- **Decreases the ethinyl estradiol concentration of oral contraceptive preparations (it may cause oral contraceptive failure)**

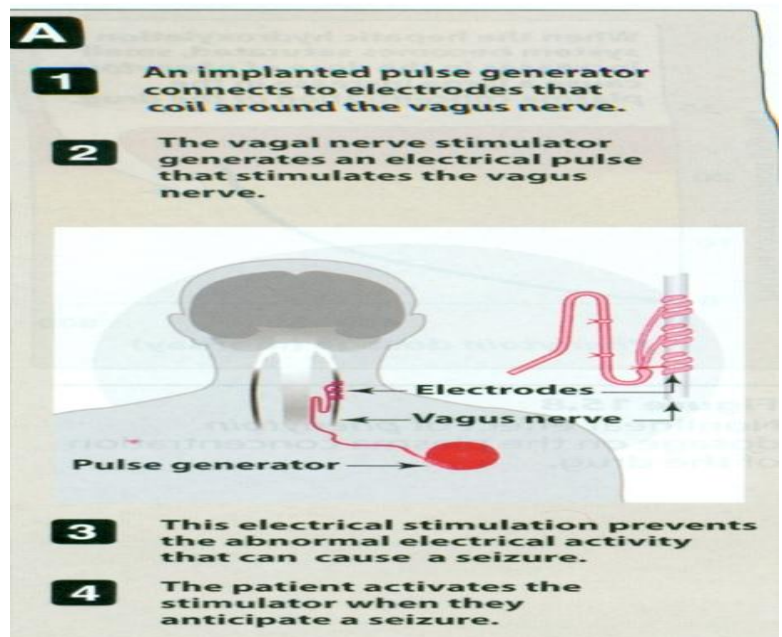
Drugs used for treatment of Status Epilepticus:

- Most seizures stop within 5 minutes. When seizures follow one another without recovery of consciousness, it is called “status epilepticus” or 2 episodes within 20 to 30 minutes . It has a high mortality rate . Death is from cardiorespiratory failure.

- Lorazepam Or diazepam **I.V** (old drug)
- Phenytoin Or fosphenytoin (**I.V**)
- Phenobarbital (old drg)

Vagal nerve stimulation (brain base maker)

- It is an alternative for patients who have been refractory to multiple drugs.
- It is an expensive procedure
- The mechanism of action of vagal stimulation is not fully known??
- Who are sensitive to the many adverse effects of antiseizure drugs vagal nerve stimulation is used
- May cause bradycardia



Pregnancy & antiepileptic medications:

- NO antiepileptic drug is safe in pregnancy.
- Patient has to continue therapy.
- Using the less risky drug follow up pregnancy.

Summary:

- ✓ Epilepsy is classified **into partial or generalized** according to the site of lesion.
- ✓ The main mechanism of antiepileptic action is through **blocking the activated sodium channels**
- ✓ **Phenytoin** is mainly used for treatment **of generalized tonic-clonic seizures**.
- ✓ The adverse effects of **phenytoin include gum hyperplasia, teratogenicity**.
- ✓ **Carbamazepine** is mainly used for treatment of **partial seizures**
- ✓ The main adverse effects of **carbamazepine** includes :
- ✓ **Blood dyscrasis** (A diseased state of the blood) **& hepatic toxicity**
- ✓ **Sodium valproate** is a **broad spectrum antiepileptic drug**
- ✓ The adverse effects of **sodium valproate** includes **hepatic toxicity , increase body weight**
- ✓ **Lamotrigine & levetiracetam** are used as **monotherapy or adjunctive therapy in refractory cases**
- ✓ **Lorazepam , diazepam , phenytoin** are used intravenously for treatment of status epilepticus

Summary therapeutic uses

- **Seizures type and drug of choice:**
- **Partial-simple or complex:** valproic acid , phenytoin , carbamazipine
- **General Tonic –clonic:** valproic acid , phenytoin , carbamazipine
- **General-Absence:** Ethosuximide, valproic acid, clonazepam
- **General-myclonic:** valproic acid, clonazepam
- **Status epilepticus:** lorezapam/diazepam. Fosphenytoin, Midozalam/phenobarbitone