

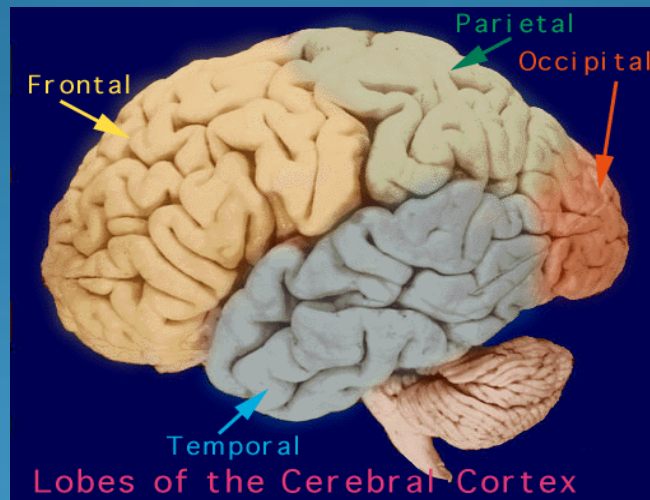
PHARMACOLOGY TEAM



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Antiepileptic drugs



Team notes in **dark red color**



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Objectives

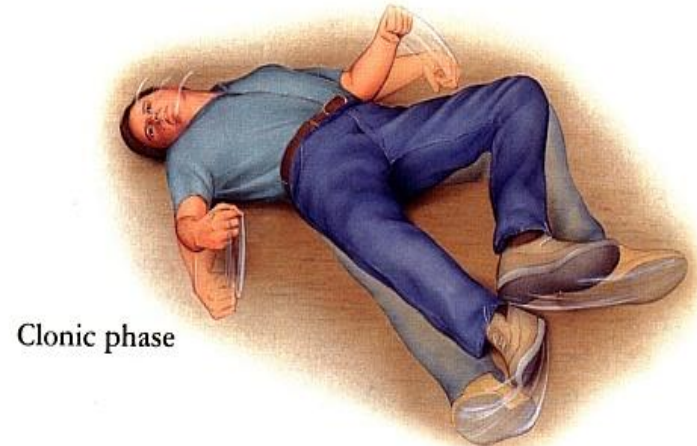
At the end of the lectures, students should

- 1- Describe types of epilepsy
- 2- List the antiepileptic drugs
- 3- Describe briefly the mechanism of action of antiepileptic drugs.
- 4- Enumerate the clinical uses of each drug
- 5- Describe the adverse effects of each antiepileptic drug
- 6- Describe treatment of status epilepticus



Definition

- Epilepsy is a *chronic* medical condition characterized by 2 or *more unprovoked seizures*.
- *It is not a disease, it is a syndrome (what is the difference).*



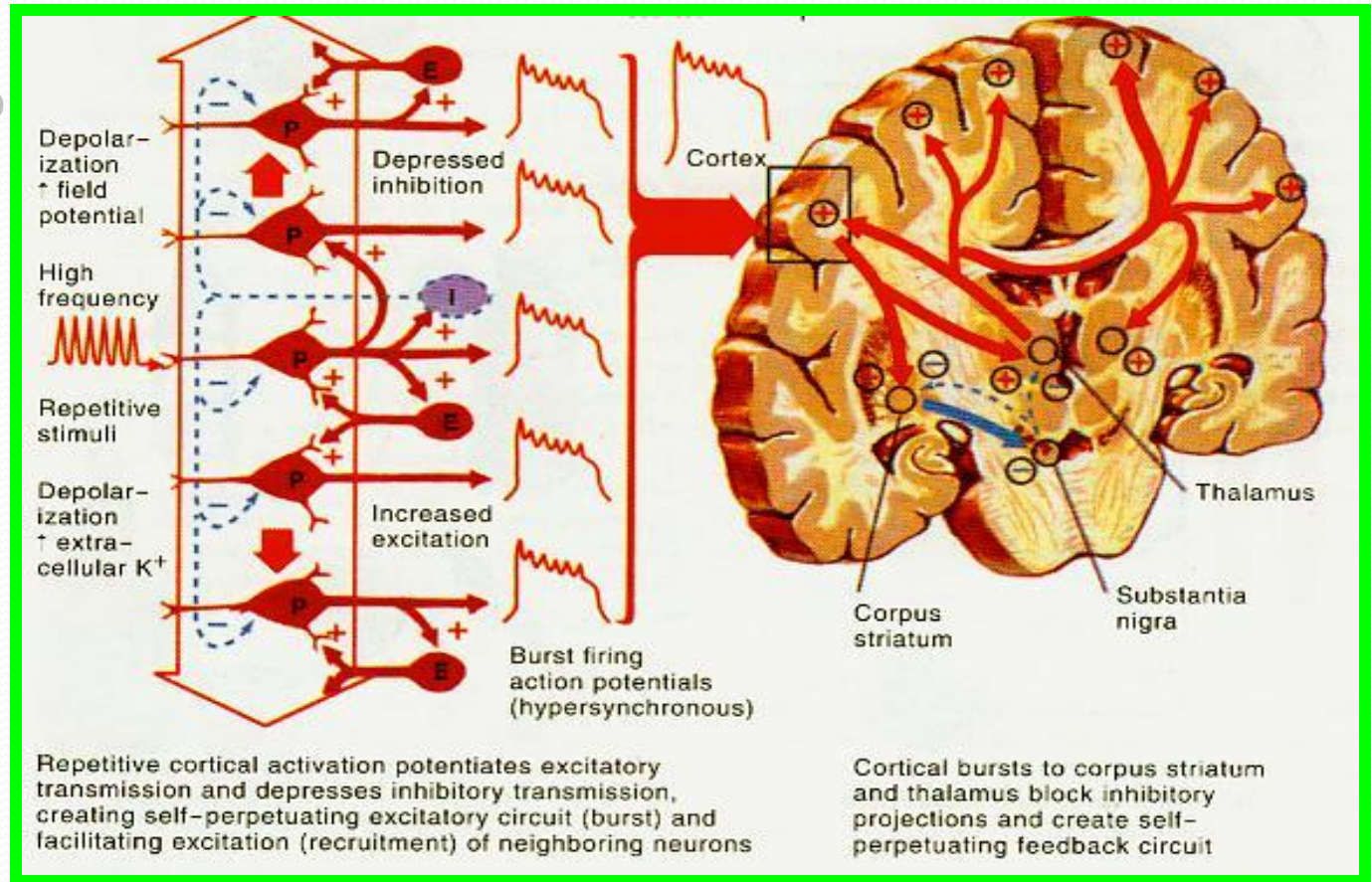
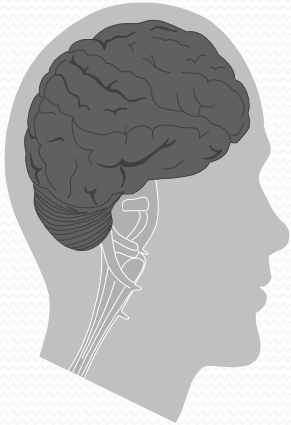
Clonic phase



Postictal state

Generalized Tonic-Clonic Seizure

Seizure



Normal CNS Function



Abnormal Excitation



Membrane depolarization leads to enhanced excitatory receptor function and reduced GABA receptor function. This pattern of 'voltage-dependence' leads to an even greater level of excitation.

Etiology

Idiopathic (**primary**)

- Inherited abnormality in the C.N.S.
- Patients are treated chronically with antiseizure drugs or vagal nerve stimulation (**it is explained in last slides**)

Symptomatic (**secondary**)

- Tumors
- Head injury
- Hypoglycemia
- Meningeal infections
- Drug withdrawal (**sudden stop of the intake of drug or alcohol**)
- Photo epilepsy (by watching TV)

Triggers

- Fatigue
- Stress
- Sleep deprivation
- Poor nutrition

مهم معرفتها لأنه مو كل مريض يجي بـ

Seizure

يعتبر عنده **epilepsy**

So you have to ask the patient if he sleep and eat well and if he gets stress. Also follow him for detect the recurrence with a period (as we will see in rules of treatment)

Types of epilepsy :

Memorize the type of epilepsy (partial , generalized and so on for treatment (e.g. They may ask about drug of choice for certain type of seizure

First type :

Generalized:

Both hemispheres + loss of consciousness.

**1- Tonic-clonic
(Grand mal)**

Stiffness (15-30 sec) (**tonic phase**) followed by violent contractions & relaxation (1-2 minute) (**clonic phase**)

**2- Absence
(Petit mal)**

*****Brief** loss of consciousness
with minor muscle twitches
eye blinking***

3- Myoclonic

Rhythmic, jerking spasms (**continuous contraction**)

4- Clonic

Spasms of contraction & relaxation

5- Tonic

Muscle stiffness

6- Atonic

Sudden loss of all muscle tone.

Second type : Partial :
Arise in one cerebral hemisphere

[1] Simple (consciousness is retained)

Features depend on part of brain affected

**Motor
(Jacksonian epilepsy)**

Jerking, muscle rigidity, spasms, head-turning

Sensory

Unusual sensations

Autonomic

Psychologic

Memory or emotional disturbances

[2] Complex (Altered consciousness)

Automatisms & behavioral changes

[3] Secondarily generalized seizure

Begins *as partial* (simple or complex) and progress into grand mal seizure (*generalized*)

(a) Partial (focal) seizure



(b) Primary generalized seizure



(c) Partial seizure with secondary generalization

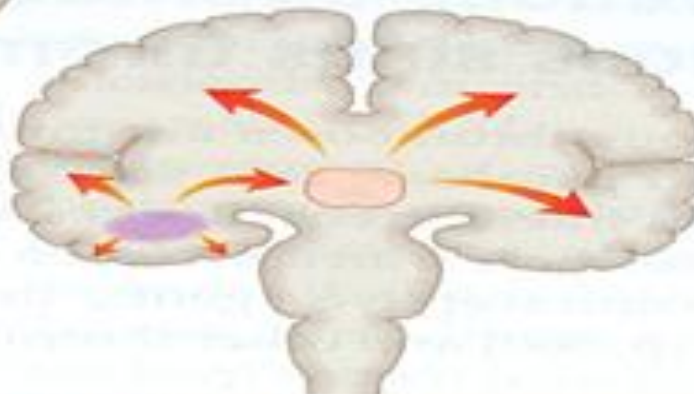
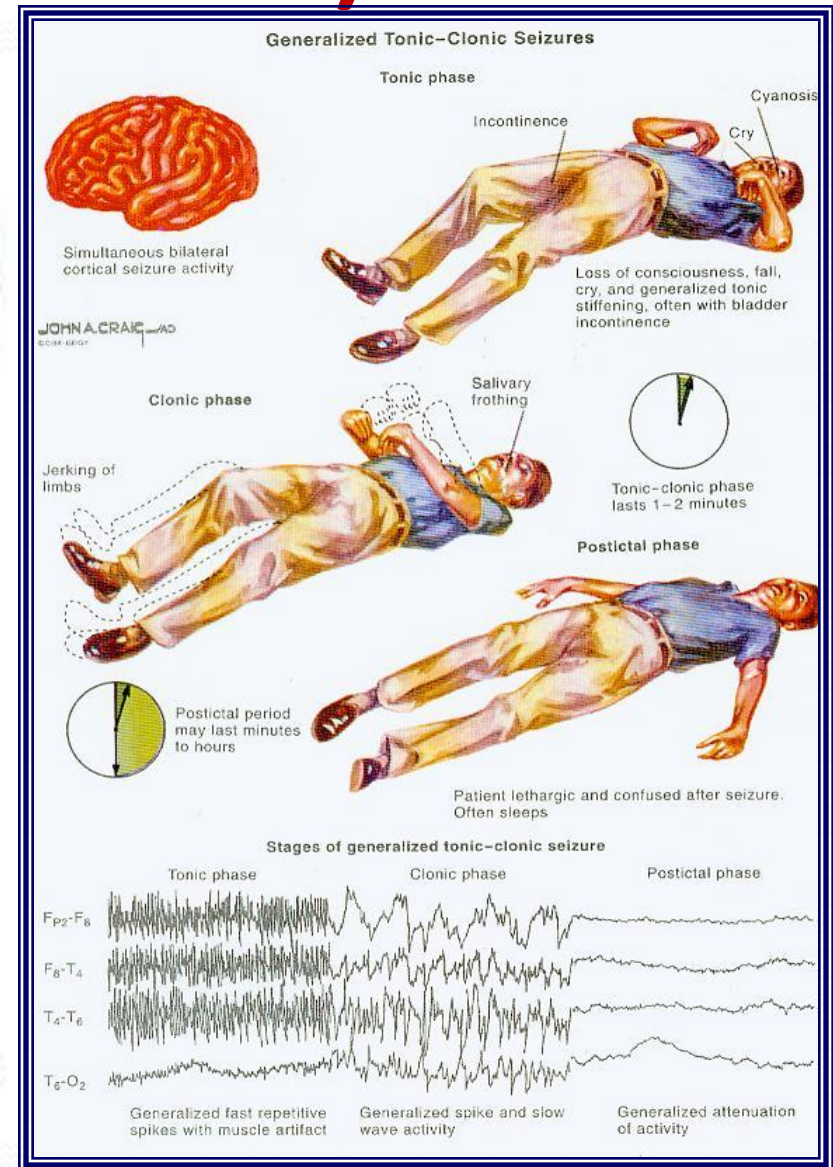
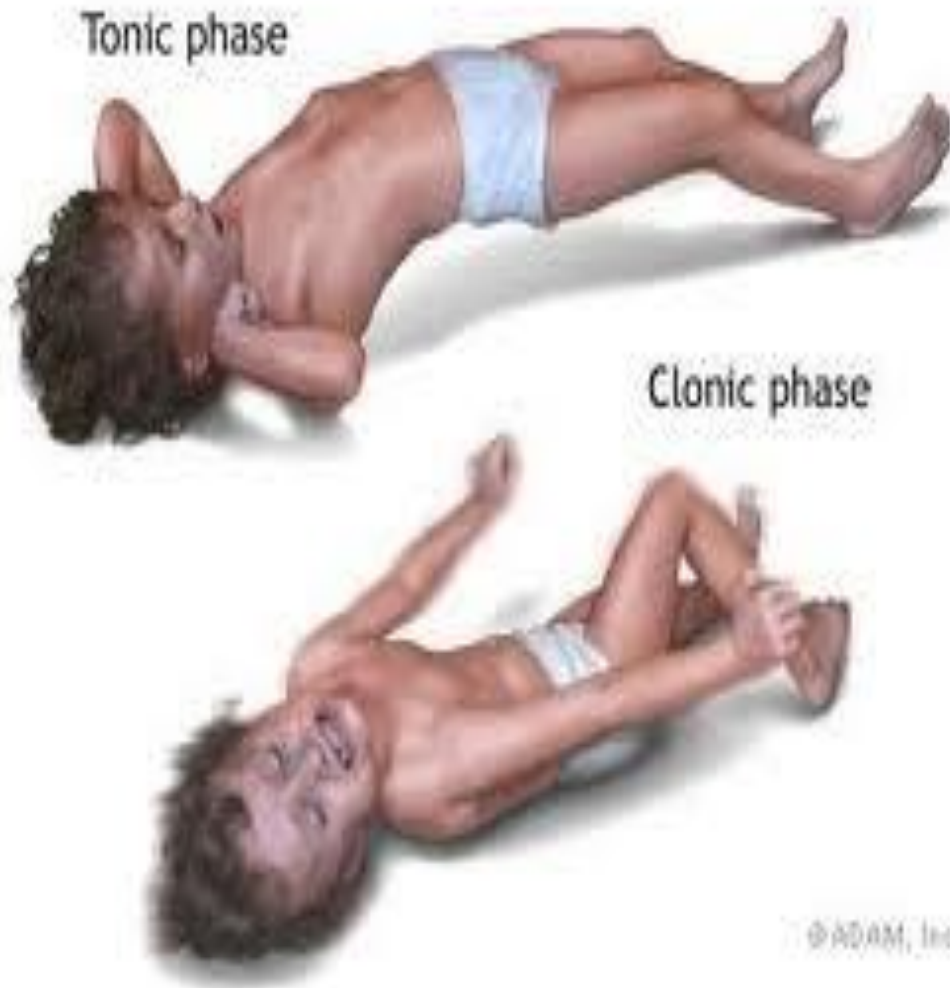


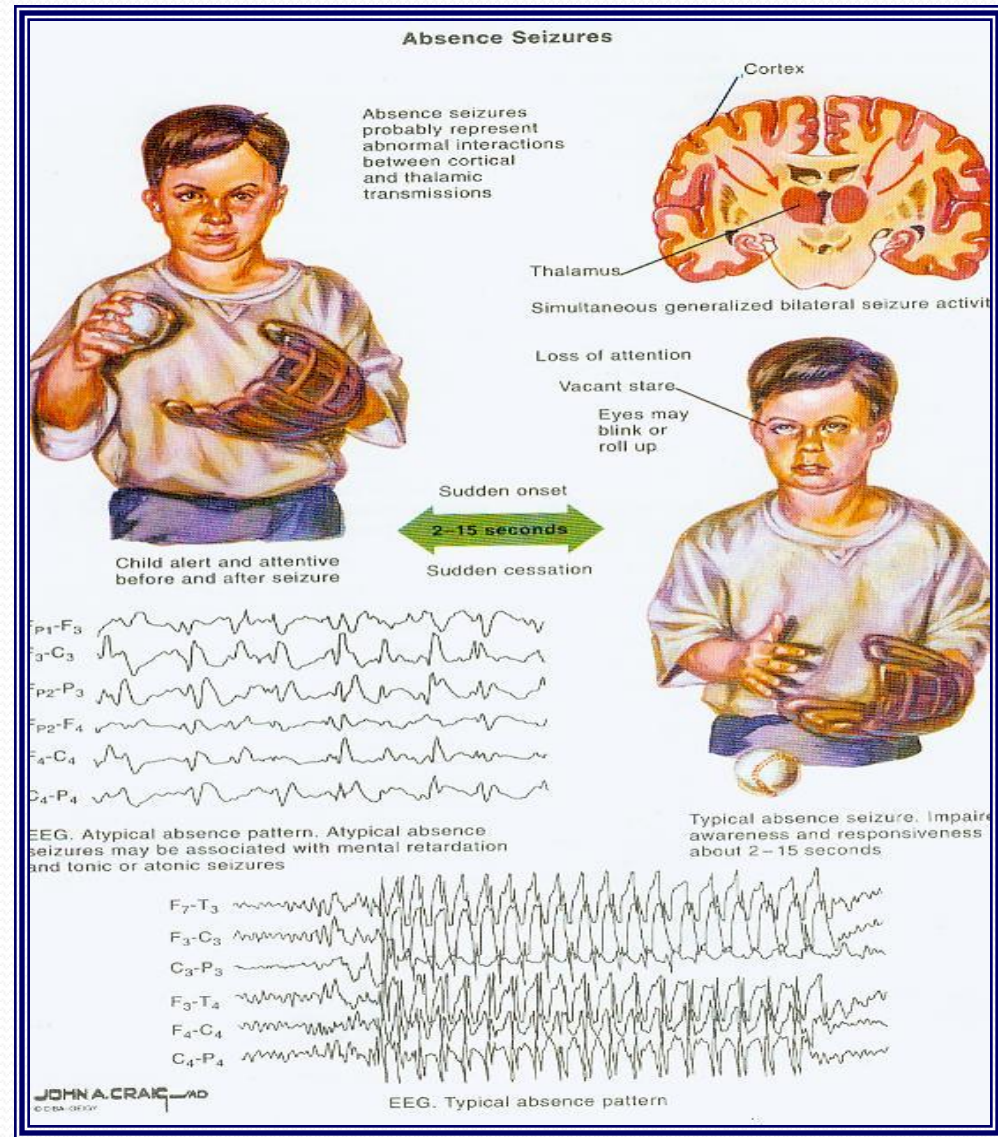
Fig. 20.23 Seizure types. (a) Partial (focal) seizure. (b) Primary generalized seizure. (c) Partial seizure with secondary generalization.

Tonic-clonic (grand mal) seizures



Absence seizures

- brief; loss of consciousness accompanied by minimal motor manifestations
- cessation of an ongoing behavior
- full recovery is evident after 5-15 sec.



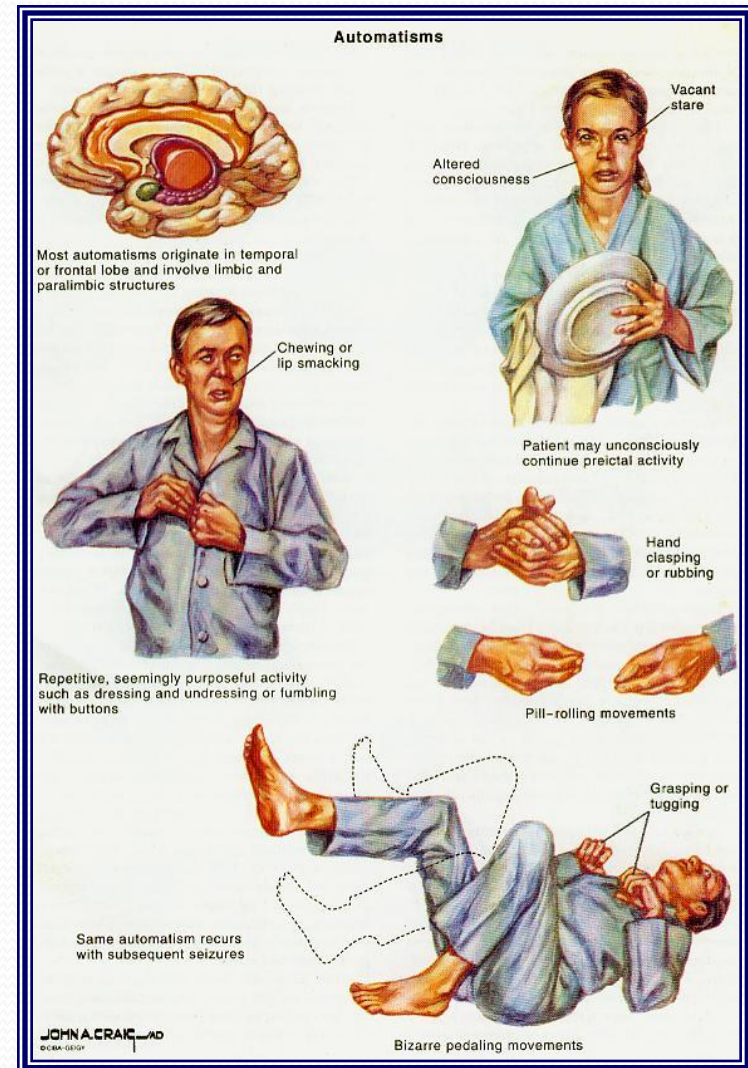
Partial seizures

Simple

consciousness is often preserved.
(e.g. deviation of the head
& eyes to one side)

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



General rules for treatment of epilepsy

- Antiepileptic drugs suppress but not cure seizures
(because *It is not a disease, it is a syndrome*)
- Antiepileptic drugs are indicated when there is two or more seizures occurred in short interval (6 m-1y)
(when patient has a seizure we must follow him in 6 months to year . if it is reoccurred start treatment if it not never use Antiepileptic drugs)
- An initial therapeutic aim is to use only one drug (monotherapy).
(start with one drug only if it is not effective start polytherapy)

- Drugs are usually administered orally
(**cause epilepsy is chronic**)
- Monitoring plasma drug level is useful
- Triggering factors can affect seizure control by drugs.
(as we explained in slide of Triggers)
- Sudden withdrawal of drugs should be avoided
(**NEVER stop the drug suddenly**)

Withdrawal started

(rules of stopping the drug)

1- After seizure –free period of 2-3 or more years from the last fit.

(no seizure attack in period of 2-3 years)

2- Normal neurological examination , Normal EEG

3- Relapse rate (recurrence of seizure) is 20-40%

How Drugs Act?

(it is the main mechanism for most of all antiepileptic drugs)

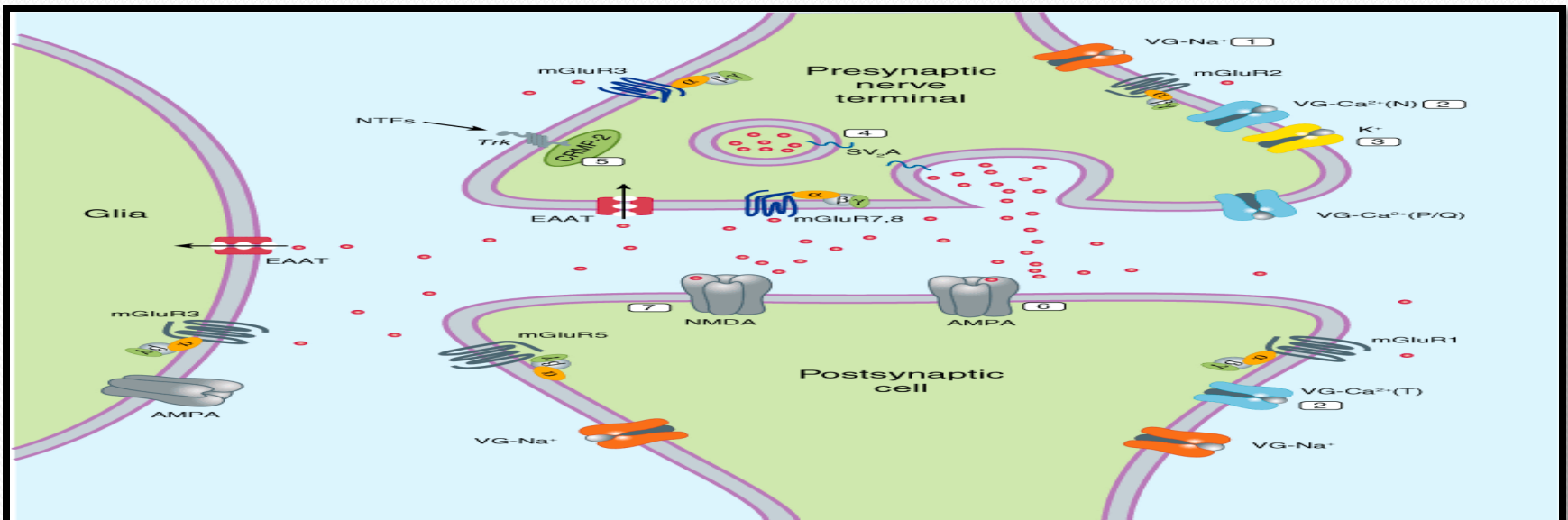
- Blockade of voltage –gated channels (Na^+ or Ca^{++})

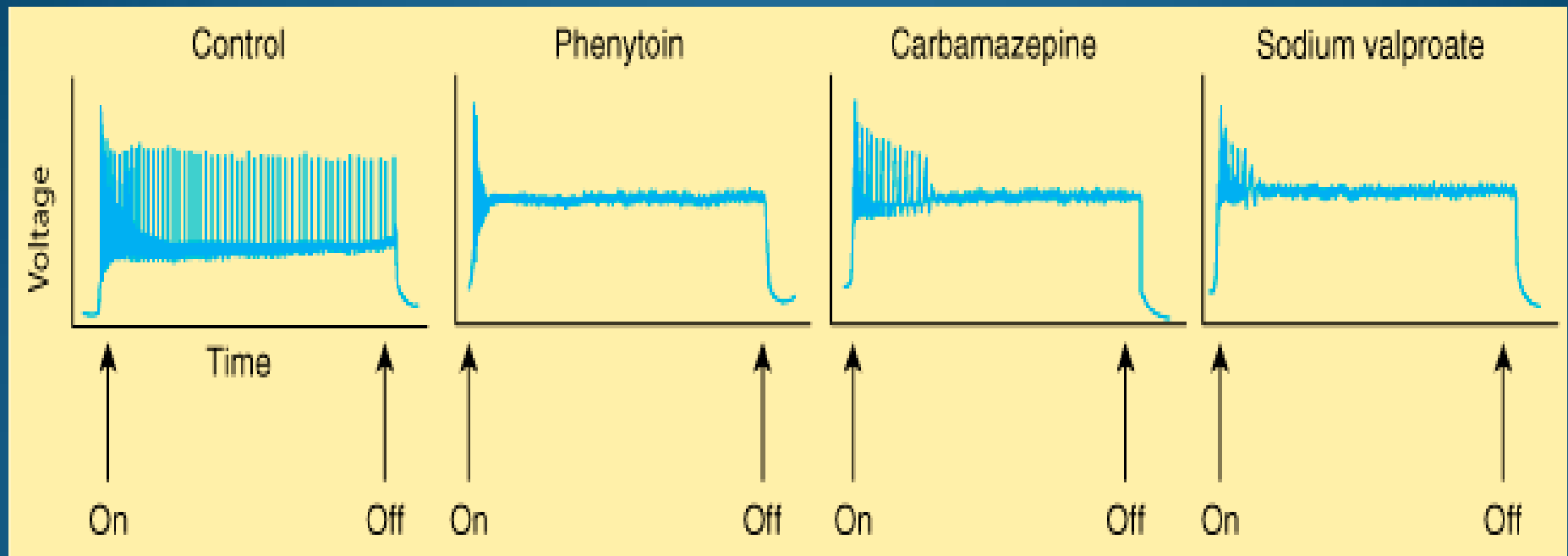
(Na channels in all types of seizure except absence seizure is Ca^{++} channel)

- Enhancement of GABA Or interference with

- Glutamate transmission

(as we know the cause of epilepsy is increase in glutamate(excitatory) and decrease in GABA (inhibitory))





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

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Classification of antiepileptic drugs

First-generation

- ❖ Phenytoin

- ❖ Carbamazepine

- ❖ Valproate

- They affect liver enzymes
So You must know it is
enzyme inducer or
inhibitor

Second-generation

- ❖ Lamotrigine

- ❖ Levitiracetam

- Do not affect liver
enzymes

Carbamazepine

- Pharmacokinetics :

- Available only orally

MCQ: is it used in status eplipsy ??

NO because it's available only in oral preparation

- Well absorbed

- **Strong enzyme inducer** including its own metabolism

Metabolized by the liver to active & inactive metabolites

- Excreted in urine

Carbamazepine

Mechanism of action

- Blockade of Na^+ channels
- reduce the propagation of abnormal impulses in the brain
- inhibit the generation of repetitive action potential
- Inhibit the release of glutamate and enhance GABA

Therapeutic uses:

- Drug of choice in **partial seizures**.
- Tonic-clonic seizures (1ry & 2ry generalized) but **Not** in absence seizures.

Because it doesn't work on Ca channels

Other uses :

- Neuropathic pain
- Mood stabilizer

! More characteristic side effect in the red for all coming drugs

Side effects

- **Blood dyscrasis** (bone marrow depression)
- **Hyponatremia** (↓Na) **& water intoxication**
- **GI upset.**
- **Hypersensitivity reactions**
- **Drowsiness , ataxia, headache & diplopia**
- **Teratogenicity** (neural tube defects). (تشوه الجنين)
- **Induction of hepatic P₄₅₀**

Phenytoin

Pharmacokinetics :

- ❖ Well absorbed orally, it is also available as iv. (for emergency)
- ❖ **Enzyme inducer**
- ❖ Metabolized by the liver to inactive metabolites
- ❖ Excreted in urine

Phenytoin

Mechanism of action

- Blockade of Na^+ channels.
- Interfere with the release of excitatory transmitters (“Glutamate”)
- Potentiate the action of GABA

Therapeutic uses:

- Partial and generalized tonic-clonic seizures **Not** in **absence seizure**.

Because it doesn't work on Ca channels

- In **status** epilepticus, IV .
- Cardiac arrhythmias

Side effects

Not important to memorize if it dose related or not

A) dose-related :

- Nausea or vomiting
- **Neurological like** : headache, vertigo, ataxia, diplopia , nystagmus
- Sedation

B) Non –dose related

- **Gum hyperplasia** انتفاخ في اللثة
- **Coarsening of facial features** Enlargement in the nose or lips
- **Hirsutism** excessive hair in abnormal sites as face in females
- **Acne**
- **Megaloblastic anemia** deficiency in folic acid
- **Osteomalcia** deficiency in Vit D
- Teratogenic effect
- Enzyme inducer

Sodium Valproate

Broad spectrum antiepileptic

- **Pharmacokinetics :**
 - Available as capsules, Syrup , I.V
 - Metabolized by the liver (inactive)
 - **Enzyme inhibitor**
 - Excreted in urine

Sodium valproate

Mechanism of action :

- Blockade of Na⁺ channels.
- **Blocks T-type Ca²⁺ channels**

There are 2 types of Ca channels

T-type → in the brain

L-Type → in the Heart & Bld Vessels

- **Inhibits GABA –transaminase**

It's the enzyme which responsible for the breakdown of GABA

If it is inhibited lead to the accumulation of GABA

- Suppress glutamate action.

[II] Other uses:

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

it's a mixed seizures in children mainly ,
hard to be treated

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**

Ca channels لانه يشتغل ايضا على

- Complex partial seizures
- Myoclonic
- Atonic
- photosensitive epilepsy

Side effects:

- **Weight gain** (↑appetite).
- **Transient hair loss, with re-growth of curly hair**
- **Thrombocytopenia** (↓ in platelet)
- **Hepatotoxicity** that's why we do a liver function test
- **Teratogenicity** (spina bifida)
- **Enzyme inhibitor of P -450**

? Patient with epilepsy and his liver function tests showed abnormal results what is the drug which is most likely used in this case?

Sodium Valproate



New generation drugs

!! Team notes

- The new generation drugs different from the old by :
 - Don't effect on hepatic enzymes = minimal drug-drug interactions
 - Less **Teratogenic effect on human**
 - Most of them used as add-on therapy

Lamotrigine

Mechanism of action

- Blockade of Na^+ channels
- Inhibits excitatory amino acid release (glutamate & aspartate)

Therapeutic Use

- As add-on (adjustment) therapy or
- as monotherapy in partial seizures
- Lennox-Gastaut syndrome

!! Team notes

- Most of the new drugs use as :
- add on (adjustment drug) أدوية مساعدة with old drugs cause there is no much information about their side effects and contraindicated.
- Lamotrigine is used as adjustment in refractory case (resistant case which needs more than one drug)

! More characteristic side effect in the red for all coming drugs

Side effects

- **Influenza-like symptoms.**
- **Skin rashes (may progress to Steven –Johnson syndrome)**

About 5% of patients can develop steven-johnson syndrome, very severe and can be fatal

- Somnolence **النعاس**
- Blurred vision
- Diplopia
- Ataxia

Levetiracetam

- Pharmacokinetics :

- Taken orally (tablets or solutions)
- Not metabolized & excreted unchanged in urine
- Does not **affect** liver enzymes

Remember the new drugs,
levetiracetam + Lamotrigine
Don't affect liver enzymes

Levetiracetam



Mechanism of action

- Unknown

Therapeutic Uses

**Adjunctive(add on)
therapy in :**

- Partial seizures
- Generalized tonic-clonic seizures

Monotherapy

- Myoclonic seizures

Side effects

- **Somnolence** النعاس
- **Pin & needles sensation in extremities**
- Blurred vision
- Ataxia
- Dizziness

Other antiepileptics

Old:

- *Phenobarbital and Primidone*
- *Benzodiazepines (e.g. **Diazepam** and **Lorazepam**)*

Lorazepam or Diazepam : Status epilepsy (imp)

- **New antiepileptics for adjunctive treatment:**
 - *Gabapentin, vigabatrin, Felbamate, topiramate and others*

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”. It has a high mortality rate . Death is from cardiorespiratory failure.

Intravenous Injection of :

- Lorazepam **is the drug of choice ,very imp😊**
- Diazepam
- Phenytoin
- fosphenytoin
- phenobarbital .

1- I.V drugs = acute attack
2- They're arranged according to importance

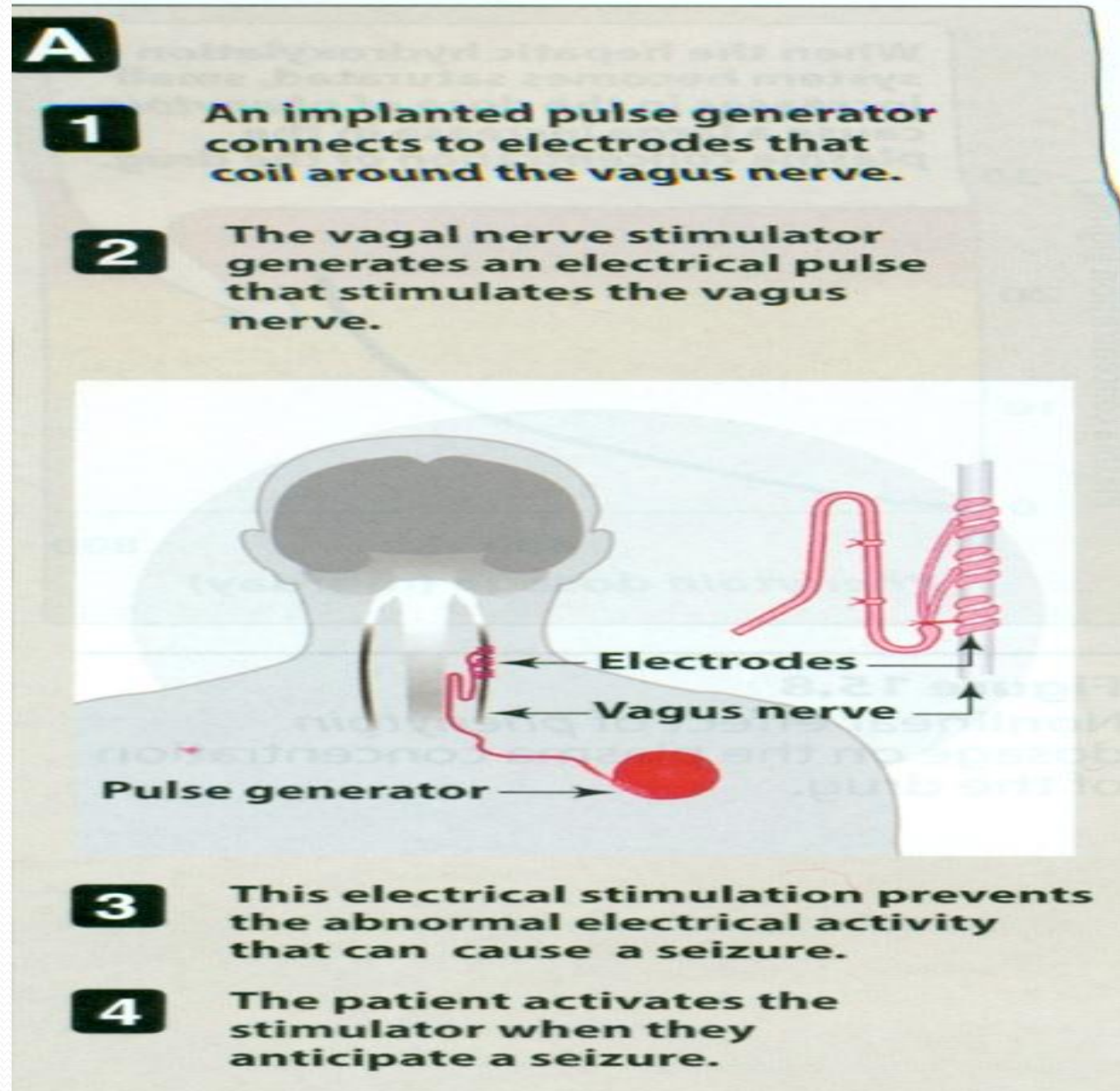
Type of seizure	Choice among drugs
Partial seizures: Carbamazepine or phenytoin or valproate or lamotrigine.	
Generalised seizures:	
Tonic-clonic (grand mal)	Valproate or carbamazepine or phenytoin or lamotrigine
Myoclonic	Valproate, clonazepam
Absence	Ethosuximide or valproate
Atonic	Valproate

Vagal nerve stimulation

- It is an alternative for patients who have been refractory to multiple drugs .
- Who are sensitive to the many adverse effects of antiseizure drugs
- It is an expensive procedure

If the drugs not effective ,
we can use this method
(vagus nerve stimulation)
Put pulse generator
around vagus nerve .

so when the patient feels
that he'll have seizure,
turn it on = stimulation of
vagus nerve= inhibition
of abnormal electrical
activity = no seizure =)



Pregnancy & antiepileptic medications

- **NO antiepileptic drug is safe in pregnancy.**
- **Patient has to continue therapy.**
- **If follow up of pregnancy reveals teratogenic effect, terminate this 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 , teratogenecity.
- Carbamazepine is mainly used for treatment of partial seizures

Summary (con.)

- The main adverse effects of carbamazepine includes :
- Blood dyscrasis & 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