King Saud University

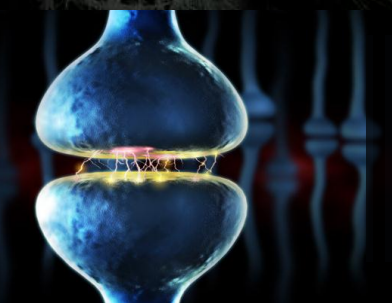
College of Medicine

2nd Year, 1st Block

PHARMACOLOGY 433

MED 433 Teams

L8&9 DRUGS USED IN EPILEPSY



CNS Block

Objectives :

1- Describe types of epilepsy

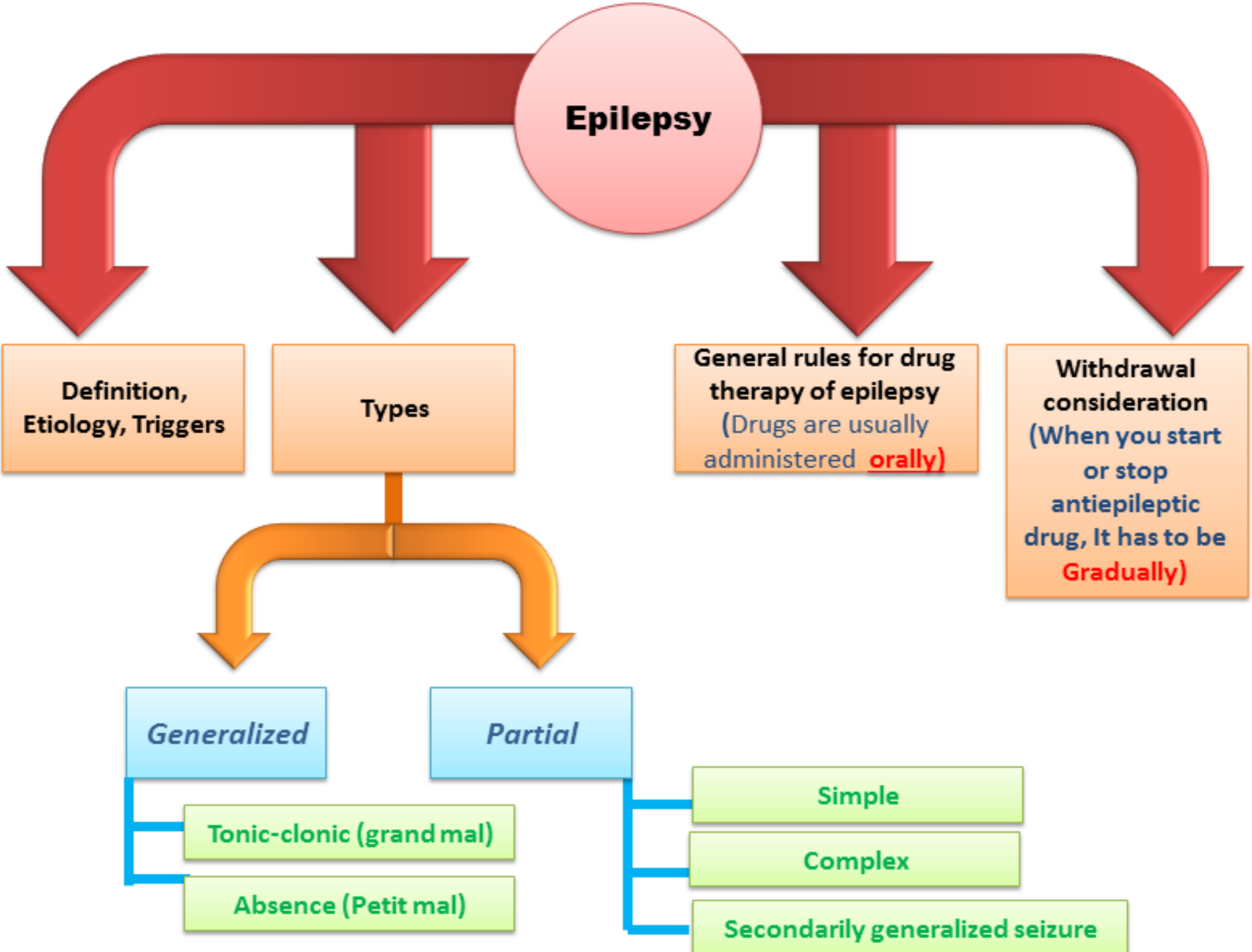
2- List the antiepileptic drugs

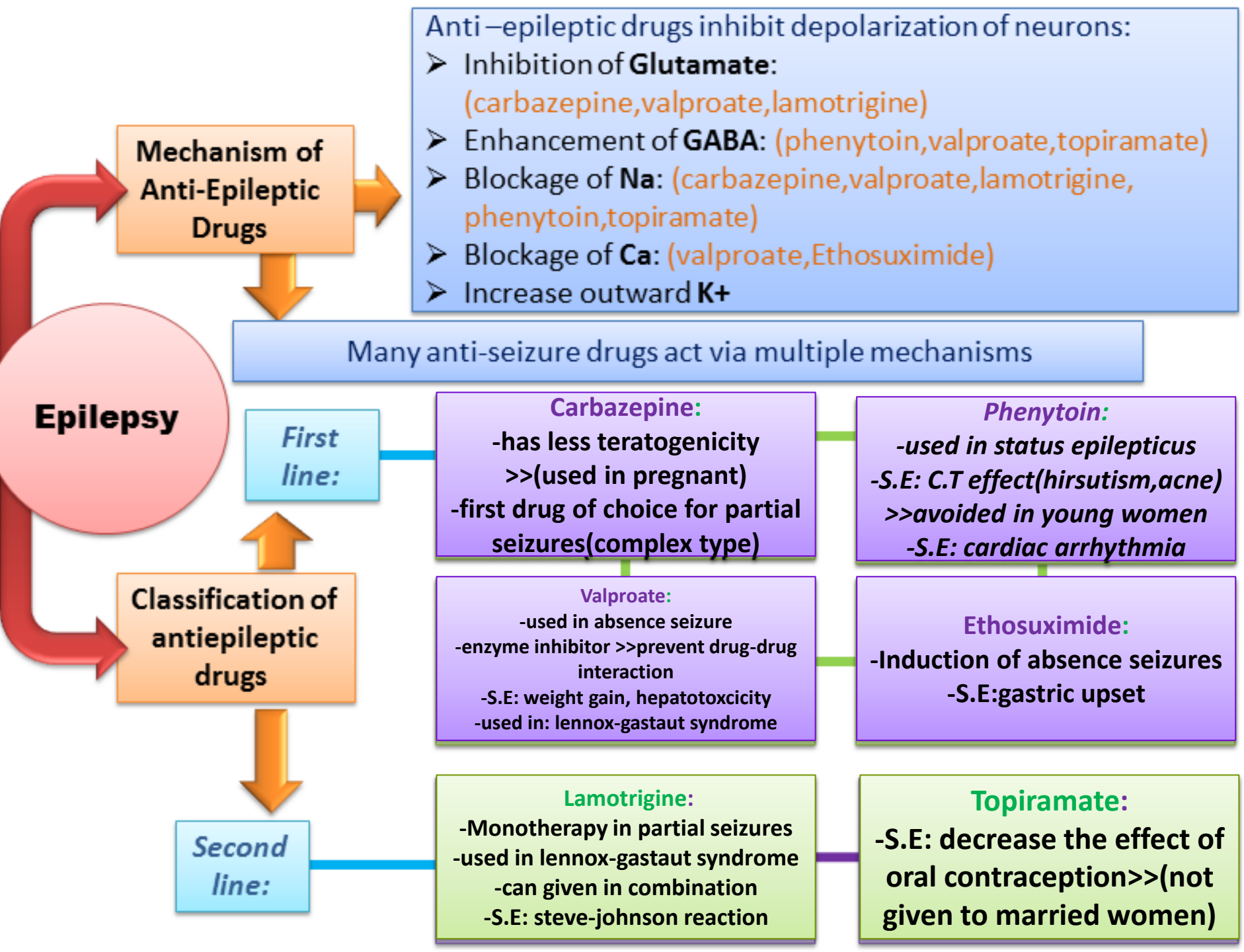
3- Describe briefly the mechanism of action of antiepileptic drugs.

4- Enumerate the clinical uses of each drug

5- Describe the adverse effects of each antiepileptic drug

6- Describe treatment of status epilepticus


Epilepsy
Definition, Etiology, Triggers
Types
General rules for drug therapy of epilepsy (Drugs are usually administered orally)
Withdrawal consideration (When you start or stop antiepileptic drug, It has to be Gradually)
Generalized
Partial
Tonic-clonic (grand mal)
Absence (Petit mal)
Simple
Complex
Secondarily generalized seizure


Anti –epileptic drugs inhibit depolarization of neurons:
Inhibition of Glutamate: (carbazepine,valproate,lamotrigine)
Enhancement of GABA: (phenytoin,valproate,topiramate)
Blockage of Na: (carbazepine,valproate,lamotrigine, phenytoin,topiramate)
Blockage of Ca: (valproate,Ethosuximide)
Increase outward K+
Mechanism of Anti-Epileptic Drugs
Many anti-seizure drugs act via multiple mechanisms
Epilepsy
First line:
Carbazepine:
-has less teratogenicity >>(used in pregnant)
-first drug of choice for partial seizures(complex type)
Phenytoin:
-used in status epilepticus
-S.E: C.T effect(hirsutism,acne) >>avoided in young women
-S.E: cardiac arrhythmia
Valproate:
-used in absence seizure
-enzyme inhibitor >>prevent drug-drug interaction
-S.E: weight gain, hepatotoxcicity
-used in: lennox-gastaut syndrome
Ethosuximide:
-Induction of absence seizures
-S.E:gastric upset
Classification of antiepileptic drugs
Second line:
Lamotrigine:
-Monotherapy in partial seizures
-used in lennox-gastaut syndrome
-can given in combination
-S.E: steve-johnson reaction
Topiramate:
-S.E: decrease the effect of oral contraception>>(not given to married women)

Introduction

(to understand)

- **Epilepsy:**

Is a chronic medical condition viewed as a symptom of disturbed electrical activity in the brain caused by a wide variety of disorders .

***seizure:**
symptoms that reflect functions of brain including changes in movement, behavior, sensation or awareness.

***People who have two or more seizures (with in 6 -12 months) are considered to have epilepsy.**

- **There are two types of epilepsy:**

all types of epilepsy show seizures , but not all seizures are symptoms of epilepsy.

1. Generalized → Both hemispheres + loss of consciousness.

Type	Description
Tonic-clonic (Grand mal)	Stiffness (tonic) 15-30 sec , followed by violent contractions & relaxation (clonic) (1-2 minute)
Absence (Petit mal)	Brief loss of consciousness with minor muscle twitches eye blinking , cessation of an ongoing behavior , full recovery is evident after 5-15 sec.
Myoclonic	Rhythmic, jerking spasms
Clonic	Spasms of contraction & relaxation
Tonic	Muscle stiffness
Atonic	Sudden loss of all muscle tone
Status epilepticus	Re-occuring seizure

2. Partial → Arise in one cerebral hemisphere

Type	Description
Simple (consciousness is retained)	Features depend on part of brain affected
A- Motor cortex (Jacksonian epilepsy)	Jerking, muscle rigidity, spasms, head-turning
B- Sensory cortex	Unusual sensations
C- Visual cortex	Flashing lights
D- Autonomic	Autonomic disturbance (salivation , micturition , defecation …)
E- Psychologic	Memory or emotional disturbances
Complex (Altered consciousness)	Automatisms = تكرار الحركة (lip smacking, hand wringing) & behavioral changes, preceded by aura , the patient is amnesic after the attacks.
Secondarily generalized seizure	Begins as partial and progress into grand mal seizure, tonic and clonic of all limbs.

General rules for drug therapy of epilepsy

Antiepileptic drugs suppress but not cure seizures

تقلل من الاعراض لكن لاتشفي

Antiepileptic drugs are indicated when there is two or more seizures occurred in short interval (6 m-1y)

Monotherapy is an initial therapeutic aim .

Drugs are usually administered **orally**

Triggering factors* can affect seizure control by drugs.

Sudden withdrawal of drugs should be avoided causing status epilepticus*.

* **Triggering factors:** Fatigue, Stress, Sleep deprivation, Poor nutrition. *تحفز حدوث النوبه*

* **status epilepticus:** more than one seizures within a five min period without returning consciousness between them, if treatment delayed cause death.

Withdrawal consideration

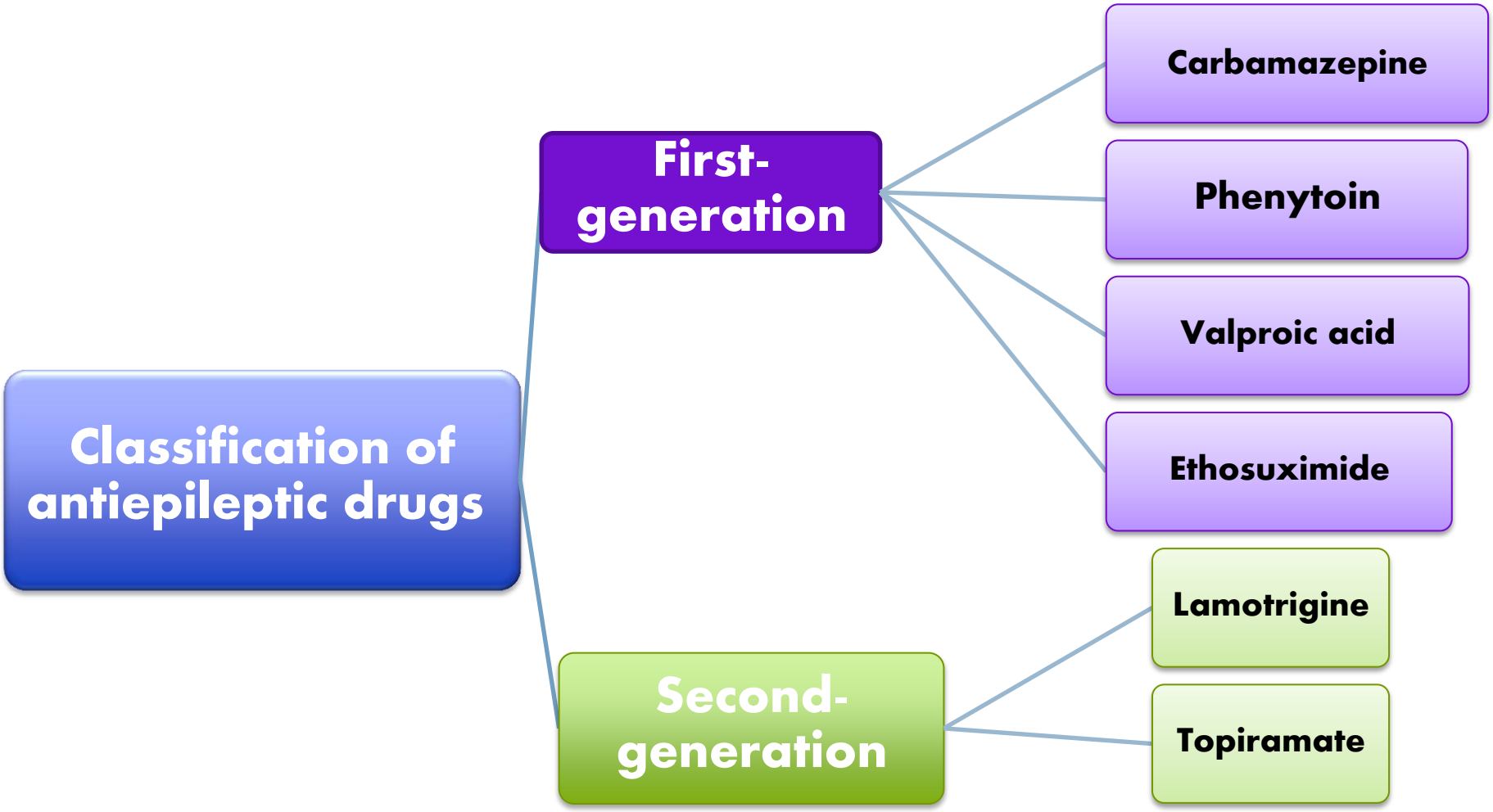
الوقت المناسب لسحب الدواء

- After seizure –free period of 2-3 up to 5 years from the last fit.
- Normal neurological examination.
- Normal EEG.
- Norma Brain Scan (CT, MRI).

Mechanism of Anti-Epileptic Drugs

Anti –epileptic drugs **inhibit depolarization of neurons** by 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^{+})



Note:

- Most antiepileptic drugs block Na channels as a mechanism of action .
- All antiepileptic drugs have CNS effects and GIT upset as side effects.

1.Carbamazepine

Pharmacokinetics	• Available only orally • Potent enzyme inducer & has the ability to induce its own metabolism .
Mechanism of action	• Blockade of Na^+ channels → reduces cell excitability → Reduces propagation of abnormal impulses in brain → Suppresses repetitive neuronal firing. • ↓action of glutamate.
Therapeutic uses	• First drug of choice for partial seizures especially complex type. • generalized tonic-clonic seizures.
Side effects	• Leucopenia , aplastic anemia & agranulocytosis *. • Hyponatremia & water intoxication • Teratogenicity . • Induction of hepatic P_{450} • GIT upset. • Skin rashes • Neurosensory (confusion , ataxia, diplopia, blurred vision, nystagmus).
Not used in	○ Absence seizures , status epilepticus, Myoclonic .

* The doctor should ask for blood count during the course of treatment.

2. Phenytoin

Fosphenytoin

- **A Prodrug.**
- **Given i.v. or i.m. and rapidly converted to phenytoin in the body.**
- **Avoids local complications associated with phenytoin injection.**

Pharmacokinetics	• **Given orally (fosphenytoin IV & IM)** • **Enzyme inducer P450(but only to the other drugs not to it self.)** • **Half life approx. 20 hr**	
Mechanism of action	• **Blockade of Na^+ channels.** • **Interferes with the release of excitatory transmitters** • **Potentiates the action of GABA .**	
Therapeutic uses	• **Partial and generalized seizures** • **In status epilepticus (because it can be given Iv) +++**	
Not used in	**Absence seizure**	
Side effects	**Acute** • **C.N.S. toxicity (diplopia, vertigo, nystagmus)** • **Cardiac arrhythmias** • **Nausea, vomiting**	**Chronic** • **connective tissue effects (gum hyperplasia تضخم اللثة, 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** • **Induction of P450 enzymes.**

	3.Sodium valproate (broad spectrum antiepileptic)	4.Ethosuximide
Pharmaco-kinetics	Available as capsules, syrup and enteric-coated tablest. Enzyme inhibitor : Inhibits the metabolism of other drugs.	• Absorption is complete • Syrup & capsule forms • Not bound to plasma proteins or tissues • Metabolized in liver • 10-20% of a dose is excreted unchanged the urine
Mechanism of action	• Blocks activated Na^+ channels. • Enhances GABA synthesis & reduces degradation • Suppress glutamate action. • Blocks T-type Ca^{2+} channels *That's why we use it in absence seizure*	• Inhibits NADPH-linked aldehyde reductase necessary for the formation of ý-hydroxybutyrate which has been associated with the induction of absence seizures. • Inhibits T- type Ca^{2+} channels in thalamo- cortical neurons
Uses	• It is effective for all forms of epilepsy. • use in Absence seizure • But Not in status epilepticus. • Bipolar disorder and mania • Prophylaxis of migraine • Lennox-Gastaut syndrome	• Drug of choice in Absence seizures • Not effective in status epilepticus.
Adverse effects	• Weight gain*, Alopecia (temporary) (hair loss) • Thrombocytopenia , Hepatotoxicity • Teratogenicity (spina bifida) • Enzyme inhibitor of P -450 *because of the stimulation of the feeding center.	• Gastric upset (Nausea & vomiting)* • Drowsiness, fatigue , hiccups , headaches * so it should be taken after meals.

Lennox-Gastaut syndrome

Is a severe form of epilepsy. Seizures usually begin before 4 years of age.

Seizure types vary may include tonic , atonic and myoclonic (the child has more than one type of Seizure)

Most children with Lennox-Gastaut syndrome experience some degree of mental retardation along with behavioral disturbances.

So far !!

From all the **First-generation** drugs we can only use **Phenytoin** for status seizure because it can be given IV

Sodium valproate & Ethosuximide can use for **Absence seizures because it blocks ca channels + Ethosuximide is the best choice**

Second- generation

	Lamotrigine
Mechanism of action	• Blockade of Na^+ channels • Reduces the synthesis and release of glutamate & aspartate • *it works on exaitatory neurotransmitters.*
Therapeutic Use	• Adjunctive therapy for partial & generalized refractory seizures • Monotherapy in partial seizures • Lennox-Gastaut syndrome
Pharmacokinetics	*Rapidly absorbed, Oral bioavailability is 98% *Metabolized in liver, Less than 1% is excreted renally= (we can use it in case of renal failure or problems). *No difference in elderly from those younger subjects **We can give to epilepsy combined with renal failure or impairment.*
Side effects	*Diplopia, Ataxia, drowsiness, headache(most reported side effects) *Blurred vision *Influenza-like symptoms. *Severe skin rashes (Steven –Johnson reaction) (fatal) we should stop the drug Gradually if the patient complain from sensitivity or rashes on skin *Somnolence = النعاس

Second- generation

	Topiramate
Mechanism of action	• Blockade of Na^+ channels • Potentiates the action of GABA
Therapeutic Use	Adjunctive therapy for • refractory partial seizures • Secondary generalized seizures
Pharmacokinetics	*Well absorbed orally (80 %), Food has no effect on absorption. *Has no effect on microsomal enzymes, 9-17 % protein bound (minimal). *Mostly excreted unchanged in urine , Plasma t½ 18-24 hrs. *We tell the patient to take it at night because it has Somnolence Effect.
Side effects	*Ataxia , Dizziness , drowsiness *Somnolence , Weight loss *Renal stones(we usually ask the patient to drink a lot of water with the dose) *Decreases the effect of oral contraceptive (you should warn the patient so she change her preventing pregnancy method) *Psychological or cognitive dysfunction Sedation, Dizziness, Fatigue *Urolithiasis, Paresthesias (abnormal sensation)

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.

Antiepileptic drugs used in treatment of status epilepticus

Lorazepam (the drug of choice)

diazepam

Phenytoin Intravenous injection

fosphenytoin

Phenobarbital

Treatment of Epilepsy:

1. Drugs 2. Vagal nerve stimulation 3. Surgery 4. Ketogenic diet

Vagal nerve stimulation

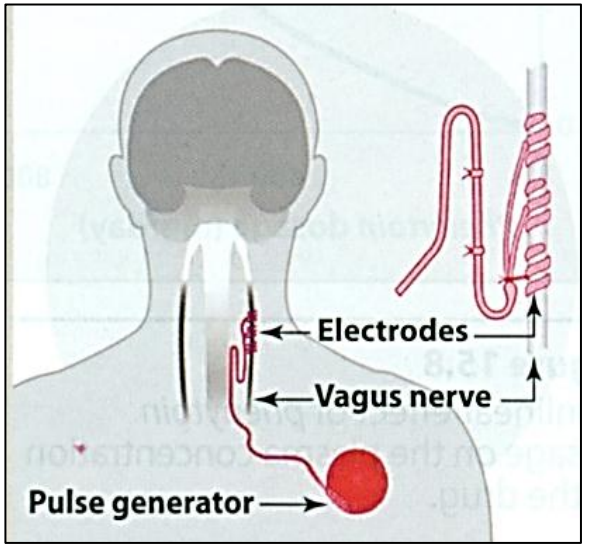
- **It is an alternative for patients**

who have been refractory to multiple drugs لم يستجيب لاي علاج.

Who are sensitive to the adverse effects

- **It is an expensive procedure**

1. An implanted pulse generator connects to electrodes that coil around the vagus nerve.
2. The vagal nerve stimulator generates an electrical pulse that stimulates the vagus nerve.
3. The electrical stimulation prevents the abnormal electrical activity that can causes a seizure.
4. The patient activates the stimulator when they anticipate a seizure .



Pregnancy & antiepileptic medications

NO antiepileptic drug is safe in pregnancy.

Patient has to continue therapy.

use the lowest effective doses

Carbamazepine has the least teratogenic effect so we can use it for a pregnant lady.

Seizure is very harmful for pregnant woman. .

Monotherapy usually better than drug combination.

Valproate & phenytoin are contraindicated during pregnancy.

		Mechanism of action	Uses	AE	Comments
1st Generation	Phenytoin	-Blockade of Na^+ channels. -Interferes with the release of excitatory transmitters -Increase the action of GABA	-Partial seizures - Generalized tonic-clonic seizures.	*Chronic :* -connective tissue effects(gum hyperplasia) -Teratogenecity -Folic acid deficiency -Vitamin D deficiency -Induction of P450 enzymes	Fosphenytoin: Given I.V. used for treatment of status epilepticus
	Carbamazepine	-Blockade of Na^+ channels -Decrease action & release of glutamate .	-Partial seizures especially complex type. -Generalized tonic-clonic seizures.	-Leucopenia , aplastic anemia & agranulocytosis -Hyponatremia & water intoxication. -Induction of hepatic P_{450}	Carbamazepine has the least teratogenic effect.
	Valproic acid	-Blockade of Na^+ channels. -Enhances GABA synthesis &reduces degradation -Decrease glutamate action. -Blocks T-type Ca^{2+} channels	-Generalized tonic-clonic seizures (1ry or 2ry). -Absence seizures -Complex partial seizures -Myoclonic	-Weight gain -Alopecia (temporary) Thrombocytopenia -Hepatotoxicity -Enzyme inhibitor of P -450	Broad spectrum antiepileptic drug used in mixed seizures.
	Ethosuximide	-Inhibits NADPH-linked aldehyde reductase necessary for the formation of ý-hydroxybutyrate . - Inhibits T- type Ca^{2+} channels	-Absence seizures	-Nausea & vomiting	
2nd Generation	Lamotrigine	-Blockade of Na+ channels -Reduces the synthesis and release of glutamate & aspartate	Adjunctive therapy for partial & generalized refractory seizures Monotherapy in partial seizures	-Severe skin rashes (Steven – Johnson reaction) -Somnolence	Used as monotherapy or adjunctive therapy in refractory cases
	Topiramate	-Blockade of Na+ channels -Potentiates the action of GABA	Adjunctive therapy for -Refractory partial seizures -Secondary generalized seizures	-Somnolence -Weight loss -Renal stones	

Quiz yourself

1- 35 years old , pregnant women came to you as first time , she has partial seizures complex type , which one of the antiepileptic drugs should you give her

A. Topiramate
B. Carbamazepine
C. Valproate
D. phenytoin

2- The drug of choice for myoclonic epilepsy :

A. Carbamazepine
B. Phenobarbital
C. Phenytoin sodium
D. Valproate acid

3- The following measures may be helpful in status epilepticus , except:

A. IM diazepam
B. Rectal paraldehyde
C. IV phenytoin
D. IV phenobarbital

4-which of the following has an impotent effect on the T-type calcium channels in thalamic neurons?

A. Carbamazepine
B. Lamotrigine
C. Ethosuximide
D. Phenytoin

5- **The drug which is used for absence seizures is :**

A. Sodium valproate
B. Phenobarbital
C. Carbamazepine
D. Phenytoin .

6- which of the following does not induce hepatic microsomal enzymes ?

A. Carbamazepine
B. Phenytoin
C. Phenobarbital
D. Sodium valproate .

7- young lady came to you complain from hirsutism and acne in her face as side effect of antiepileptic drug, which one of the following antiepileptic drugs can cause such side effect ?

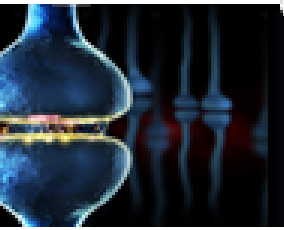
A. Phenytoin
B. Carbamazepine
C. Topiramate
D. Lamotrigine

8- Patient get pregnant after she take one of antiepileptic drugs, she was taking oral contraceptive, which one of the following antiepileptic drugs you think she take ?

A. Topiramate
B. Carbamazepine
C. Lamotrigine
D. Phenytoin

Answers:

1-B, 2-D, 3-A, 4-C, 5-A, 6-D, 7-A, 8-A



CNS Block

PHARMACOLOGY 433

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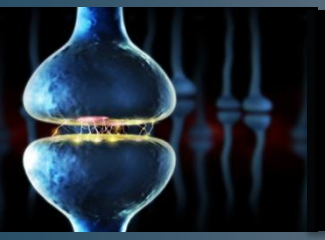
We hope that we made this lecture easier for you
Good Luck !



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