PHARMACOLOGY TEAM

Lecture : 2&3

Antiepileptic drugs

Done by: Abdullah AL-Anazi & Ali Alfuraydi

Revised by: Tuqa Alkaff, Sara Alabdulqader, Ahlam Almutairi

OBJECTIVES

At the end of the lectures, students should:

1-Describe types of epilepsy.

2-List the antiepileptic drugs.

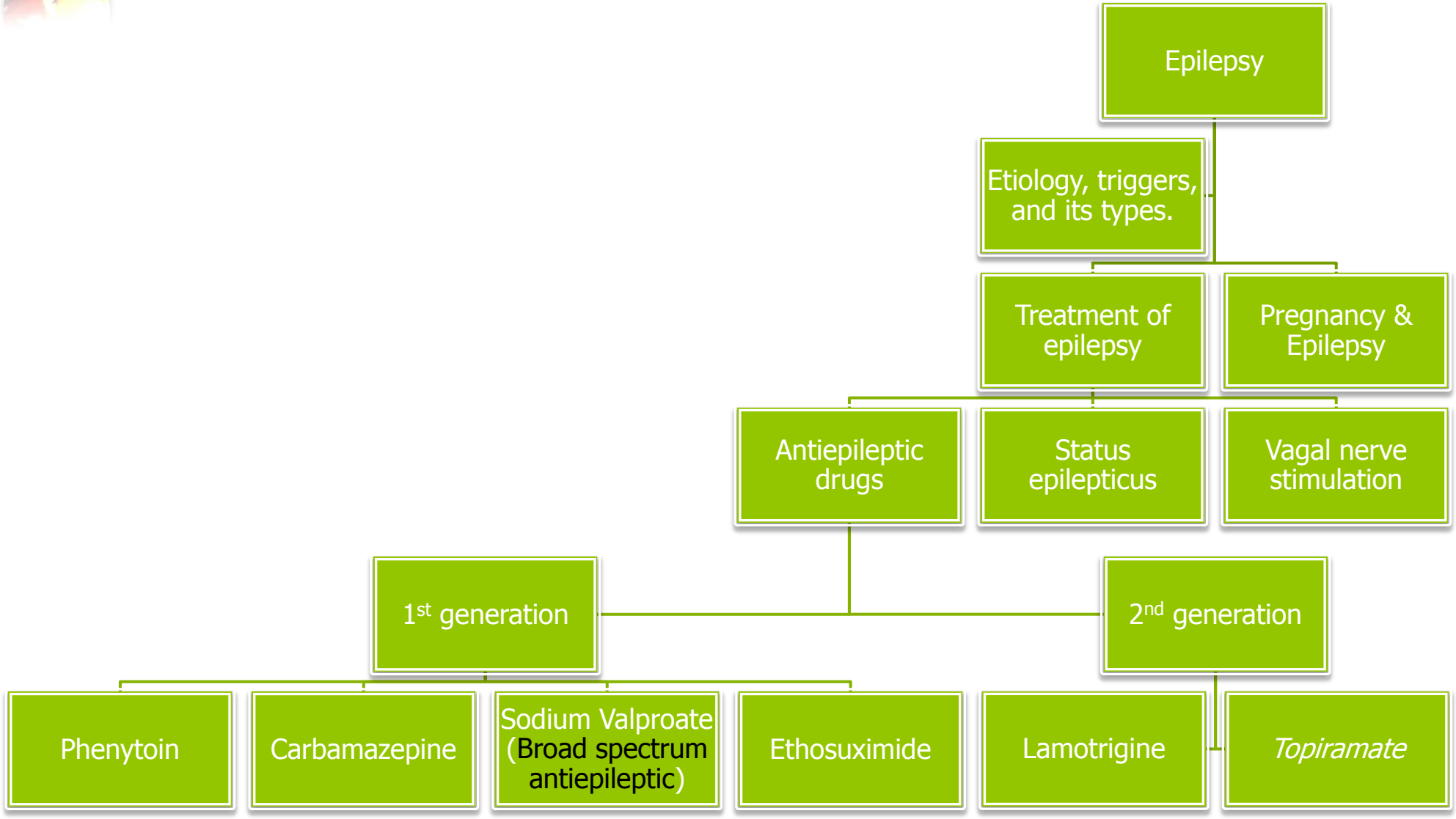
3-Describe briefly the mechanism of action of antiepileptic drugs.

4-Enumerate the clinical uses of each drug.

5-Describe the adverse effects of each antiepileptic drug.

6-Describe treatment of status epilepticus.

OBJECTIVES



Slides Important Doctor's Notes Explanation Female's Slides

Definition

- **Epilepsy is a symptom of disturbed electrical activity(function) in the brain caused by a variety of disorders a chronic medical condition characterized by 2 or more unprovoked seizures(attacks) (within 6-12 months).**

seizure	**epileptic**
disease	**syndrome**
provoked cause	**Unprovoked cause**
cured	**controlled but not cured**

Notes:
Each epilepsy accompany seizures but not all seizures are symptom of epilepsy
Repetitive activation of electrical neurons in different brain areas>> attack
Epilepsy episode last for (2sec-5min) while status epilepticus last for (30min).

Epilepsy

- Epilepsy is a general name given to the wide range of symptoms that reflect functions of brain including 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 (with in 6 -12 months) are considered to have epilepsy.
- Etiology :
- Usually there is balance between excitatory neurotransmitters and inhibitory neurotransmitters, when (glutamate,asparate) increase in their level and (GABA) decreases >> epilepsy occurs.

Etiology

Idiopathic

- Inherited abnormality in the C.N.S.

Triggers

- Fatigue.
- Stress.
- Sleep deprivation.
- Poor nutrition.
- Alcohol.

Symptomatic

- Tumors
- Head injury & skull fractures
- Hypoglycemia
- Meningeal infections
- Drug withdrawal
- Photo epilepsy (by watching TV)
- PKU (phenylalanine $\xrightarrow{\text{Phenylalanine hydroxylase}}$ tyrosine)
- Fever in children (febrile convulsion).
- A poison, like lead

Classification of Epilepsy

A) Partial Arise in one cerebral hemisphere		
[1] Simple (consciousness is retained)		Features depend on part of brain affected
	Motor cortex (Jacksonian epilepsy)	Jerking, muscle rigidity, spasms, head-turning
	Sensory cortex	Unusual sensations
	Visual cortex	Flashing lights
	Autonomic	Defecation,micturation and salivation
	Psychologic	Memory or emotional disturbances
[2] Complex (Altered consciousness)		Automatisms (lip smacking, hand wringing) & behavioral changes, preceded by aura(aura meaning as we took it in miagrane lec)
[3] Secondarily generalized seizure		Begins as partial (simple or complex) and progress into(generalized) grand mal seizure, tonic and clonic of all limbs.

B)Primary Generalized Both hemispheres + loss of consciousness.	
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(sudden loss of muscle tone)	Pt's legs give under him &drop down
Myoclonic	Jerking movement of the body
Absence (Petit mal)	Brief loss of consciousness with minor muscle twitches
Status epilepticus	eye blinking Re-occuring seizure

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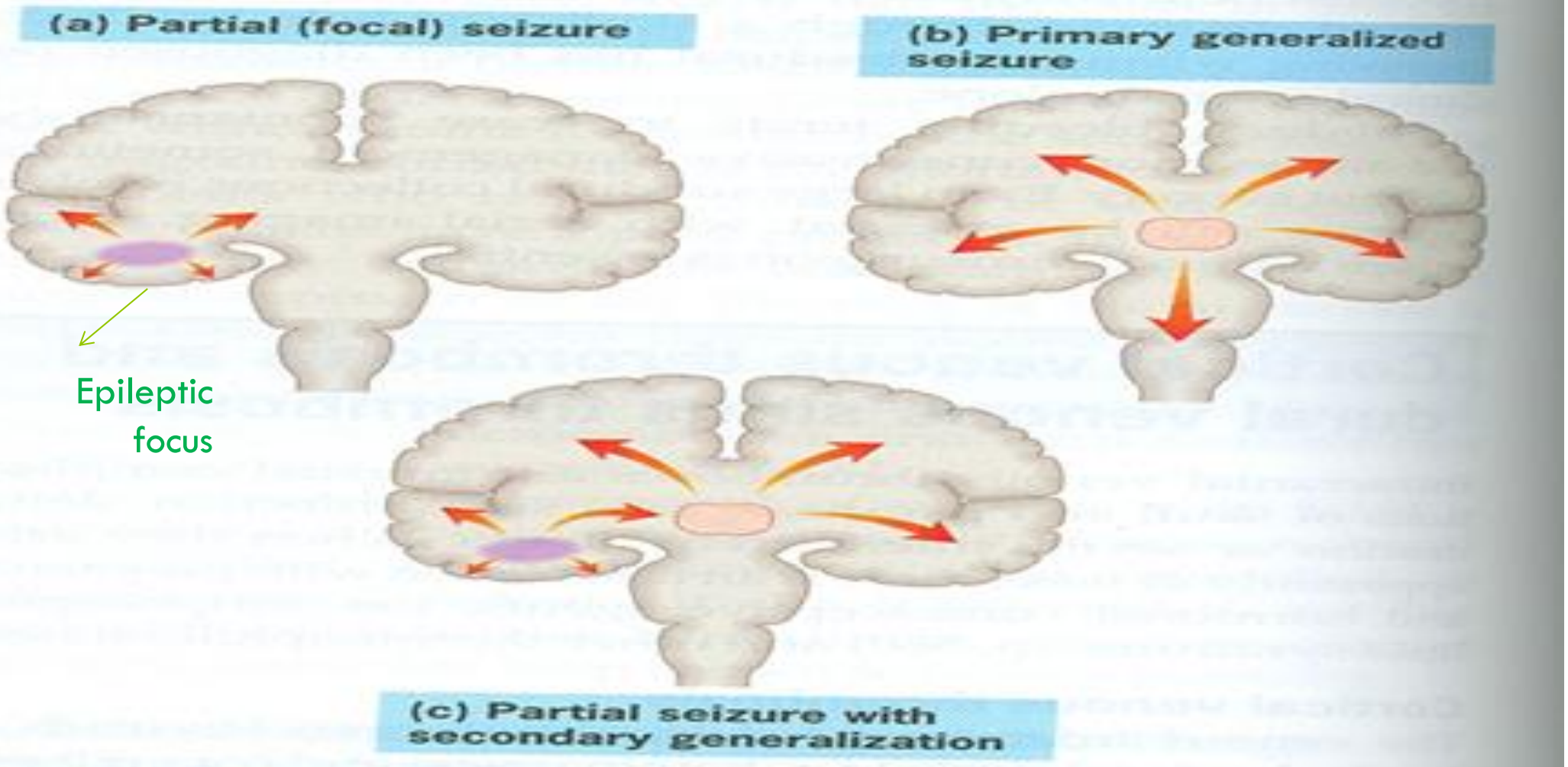


Fig. 20.23 **Seizure types.** **(a)** Partial (focal) seizure. **(b)** Primary generalized seizure. **(c)** Partial seizure with secondary generalization.

comparison

Absence seizures	Partial seizures
brief; loss of consciousness accompanied by minimal motor manifestations cessation of an ongoing behavior	Simple: consciousness is often preserved. (e.g.deviation of the head & eyes to one side)
full recovery is evident **after 5-15 sec.**	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

- Epilepsy is usually controlled but not cured with medication.
- Upto 80% of pts can expect partial or complete control of seizures with appropriate treatment.
- Antiepileptic drugs are indicated when there is two or more seizures occurred in short interval (6 m -1y).
- An initial therapeutic aim is to use only one drug (monotherapy).If it's complicated >> use politherapy
- Drugs are usually administered **orally**
- Monitoring plasma drug level is useful (not essential)
- Triggering factors can affect seizure control by drugs.
- Sudden withdrawal of drugs should be avoided causing status epilepticus

Withdrawal considered

- Seizure –free period of 2-3 up to 5 yrs or longer from the last fit
- Normal IQ
- Normal neurological examination , Normal EEG, Brain Scan (CT, MRI)
- Normal EEG prior to withdrawal
- NO juvenile myoclonic epilepsy

  - Relapse rate when antiepileptics are withdrawn is 20-40%.

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+)
  (Ca2+)
- Increase outward positive current
  (K+)
- Many anti-seizure drugs act via multiple mechanisms

In absence seizers
Block Ca Channel
Increase K outward>> Relaxation

If excitatory:
Decrease synthesis
Decrease release
Decrease action

If inhibitory:
Increase synthesis
Increase release
Increase action

Classification of antiepileptic drugs

First-generation	Second- generation
❖ Phenytoin	❖ Lamotrigine
❖ Carbamazepine	❖ Topiramate
❖ Valproic acid	
❖ Ethosuximide	

Notes:
Second generation is not used alone except in rare state and its advantage does not affect liver enzymes

First-generation

Drugs name	Pharmacokinetics	Mechanism of action	Therapeutic uses	Side effects
Phenytoin	❖ Given orally, well absorbed from GIT. ❖ Also available i.v. and i.m.(fosphenytoin) ❖ Enzyme inducer ❖ Metabolized by the liver to inactive metabolites ❖ Half life approx. 20 hr ❖ Excreted in urine	❖ Blockade of Na^+ channels. ❖ Inhibit the release of excitatory transmitters ❖ Potentiate the action of GABA	❖ Partial and generalized tonic-clonic seizures Not in absence seizure. ❖ In status epilepticus, IV .	❖ Acute: ❖ Nausea or vomiting ❖ Neurological like headache, vertigo, ataxia, diplopia , nystagmus ❖ Cardiac Arrythimas ❖ Sedation ❖ Chronic: ❖ Gum (gingival) hyperplasia (need good oral hyogene) ❖ Hirsutism, coarsining of facial features ❖ Acne ❖ **Better to be avoided in young women or adolescents .** ❖ Folic acid deficiency(megaloblastic anemia) ❖ Vit D deficiency (osteomalcia) ❖ Teratogenic effects ❖ **Induction of P450 enzymes**

Fosphenytoin is a Prodrug. Given i.v. or i.m. and rapidly converted to phenytoin in the body

❖Avoids local complications associated with phenytoin injection

Cont.

Drugs name	Pharmacokinetics	Mechanism of action	Therapeutic uses	Side effects
Carbamazepine	❖ Available only orally ❖ Well absorbed ❖ Strong enzyme inducer including its own metabolism(by chronic use T half will be reduced so we dose ❖ Metabolized by the liver to active & inactive metabolites ❖ Half life 18-35 hr ❖ Excreted in urine	**Mechanism of action** Blockade of Na^+ channels reduces cell excitability. Reduces propagation of abnormal impulses in brain Suppresses repetitive neuronal firing Attenuates action & release of glutamate	❖ Drug of choice in partial seizures espically complex type. ❖ Tonic-clonic seizures (1ry & 2ry generalized) **Not used in :** ○ **Myoclonic , absence seizures , status epilepticus**	❖ GIT upset.take it with food ❖ Hypersensitivity reactions (Skin Rashes) ❖ Drowziness , ataxia, headache & diplopia ❖ Hyponatremia & water intoxication ❖ Teratogenicity ❖ **Leucopenia , aplastic anemia & agranulocytosis** ❖ **Induction of hepatic P_{450}**

Notes:
It inhibits diuretic hormone so, it cause water intoxication that's lead to hypernatremia (ADH like effect)

Cont.

Drugs name	Pharmacokinetics	Mechanism of action	Therapeutic uses	Side effects
Sodium Valproate (valproic acid) : broad spectrum antiepileptic	❖ Available as capsules, Syrup , I.V ❖ Metabolized by the liver (inactive) ❖ Enzyme inhibitor (inhibit the metabolism of other drugs and this will increase their action so u decrease its dose) ❖ Half life 12-16 hr ❖ Excreted in urine	❖ Blocks activated Na+ channels. ❖ Enhances GABA synthesis & reduces degradation ❖ Suppress glutamate action. ❖ Blocks T-type Ca2+ channels	❖ Epilepsy: ❖ It is effective for all forms of epilepsy ❖ Generalized tonic-clonic seizures (1ry or 2ry). ❖ Absence seizures ❖ Complex partial seizures ❖ Myoclonic ❖ Atonic ❖ photosensitive epilepsy ❖ Not in status epilepticus (because absorption takes time)	❖ Weight gain (↑appetite). Used in anorexia ❖ Transient hair loss, with re-growth of curly hair ❖ Thrombocytopenia ❖ Hepatotoxicity ❖ Teratogenicity (spina bifida) (high incidence of birth defects, so never used in pregnancy) ❖ Alopecia (temporary) ❖ Enzyme inhibitor of P -450

[II] Other uses:

- ❖ **Bipolar disorder and mania (mood stablizer)**
- ❖ **Prophylaxis of migraine**
- ❖ **Lennox-Gastaut syndrome**

Lennox-Gastaut syndrome

- Is a severe form of epilepsy. Seizures usually begin before 4 years of age.
- Seizure types vary may includetonic , atonic and myoclonic
- Most children with Lennox-Gastaut syndrome experience some degree of mental retardation along with behavioral disturbances.

Cont.

Drugs name	Pharmacokinetics	Mechanism of action	Therapeutic uses	Side effects
Ethosuximide	❖ Absorption is complete ❖ Syrup & capsule forms ❖ Not bound to plasma proteins or tissues ❖ Metabolized in liver ❖ Half life 52-56 hr ❖ 10-20% of a dose is excreted unchanged the urine ❖ No effect on hepatic enzymes not inducer nor inhibitor	❖ Inhibits T- type Ca^{2+} channels in thalamo-cortical neurons. ❖ Inhibits NADPH-linked aldehyde reductase necessary for the formation of ý- hydroxybutyrate which has been associated with the induction of absence seizures	❖ Absence seizures. It is the drug of choice in absence seizure	❖ Gastric distress ❖ nausea ❖ vomiting ❖ Drowsiness, fatigue , hiccups, headaches

Second- generation

Drugs name	Pharmacokinetics	Mechanism of action	Therapeutic uses	Side effects
Lamotrigine	❖ Available as oral tablets ❖ Well absorbed from GIT ❖ Metabolized primarily by glucuronidation ❖ Does not induce or inhibit C. P-450 isozymes ❖ Half life approx. 24 hr ❖ No effect on hepatic enzymes	❖ Blockade of Na^+ channels ❖ Inhibits excitatory amino acid release and synthesis (glutamate & aspartate)	❖ As add-on therapy (Adjunctive) therapy for partial & generalized refractory(not responding to mono drug) seizures or as monotherapy in partial seizures ❖ Lennox-Gastaut syndrome	❖ Influenza-like symptoms. ❖ Skin rashes (may progress to Steven – Johnson syndrome) ❖ Somnolence نعاس ❖ (dose at bed)contrandicated in a driver or student ❖ Blurred vision ❖ Diplopia ❖ Ataxia When the 2nd & 3rd side effects happen we have to stop the drug

Cont.

Drugs name	Pharmacokinetics	Mechanism of action	Therapeutic uses	Side effects
Topiramate	❖ 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 t1l2: 18-24 hrs	❖ Blocks sodium channels (membrane stabilization) and also potentiates the inhibitory effect of GABA.	❖ Can be used alone for partial, generalized tonic-clonic, and absence seizures. ❖ Lennox- Gastaut syndrome (or lamotrigine, or valproate). ❖ Adjunctive therapy for refractory partial seizure and Secondary generalized seizures (female slides)	❖ Psychological or cognitive dysfunction ❖ Weight loss (can be desirable side effect) ❖ Sedation/somnolence ❖ Dizziness ❖ Fatigue ❖ Urolithiasis (renal stones) ❖ Paresthesias (abnormal sensation) ❖ Teratogenecity (in animal but not in human)

cont.

Type of seizure	Choice among drugs
Partial seizures: Carbamazepine or phenytoin or valproate or lamotrigine.	
Generalized seizures:	
Tonic-clonic (grand mal)	Valproate or carbamazepine or phenytoin or lamotrigine
Myoclonic	Valproate, clonazepam
Absence	Valproate, ethosuximide (drug of choice), clonazepam
Atonic	Valproate
Status epilepticus	lorazepam/diazepam. Fosphenytoin
refractory seizures	-**Lamotrigine:** Adjunctive therapy for partial & generalized refractory seizures -**Topiramate:** Adjunctive therapy for refractory partial seizures

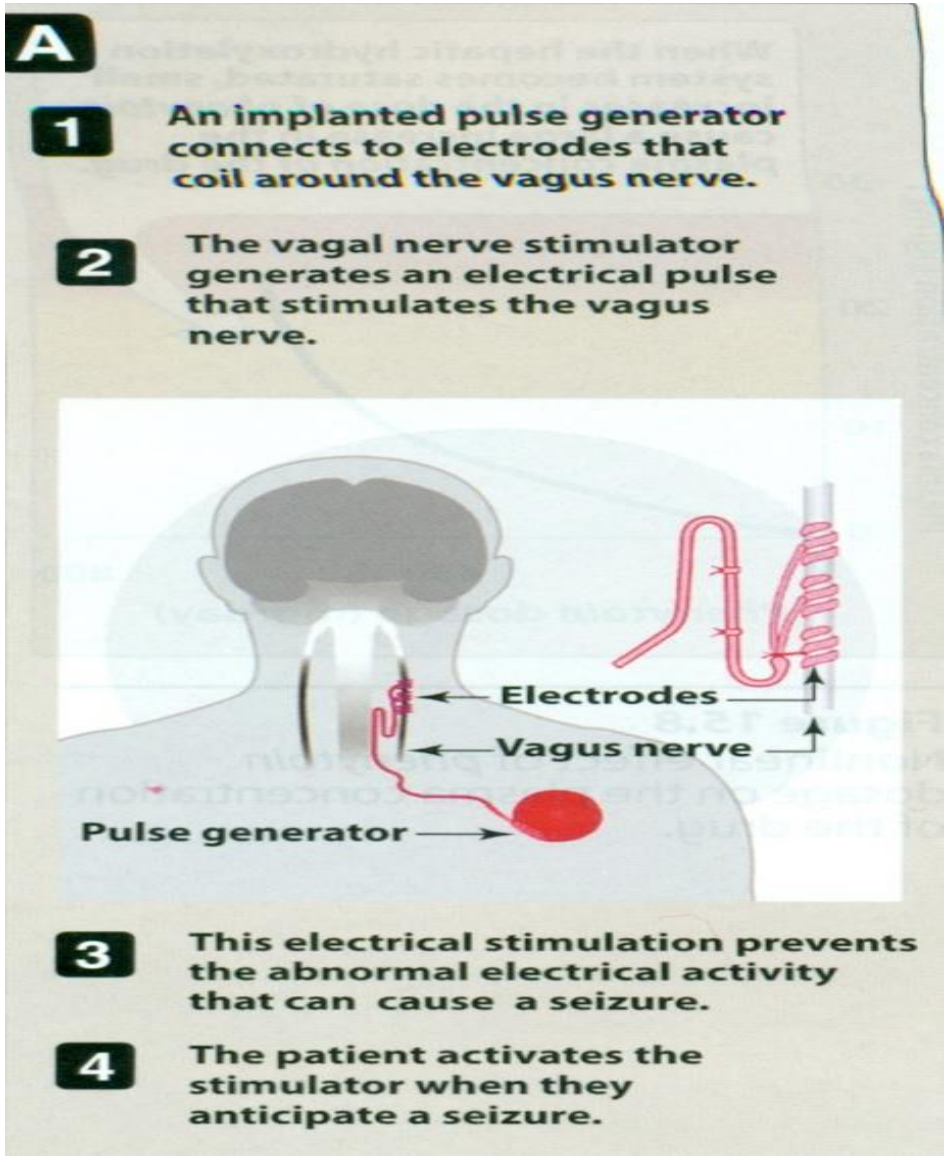
Drugs used for treatment of Status Epilepticus

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.

- Intravenous injection of :
  - Lorazepam is the drug of choice
  - Diazepam.
  - Phenytoin.
  - Fosphenytoin.
  - Phenobarbital .

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 anti epileptic drugs .
- It is an expensive procedure.



Pregnancy & antiepileptics

- Seizure is very harmful for pregnant woman.
- NO antiepileptic drug is safe in pregnancy.
- Monotherapy usually better than drug combination.
- Valproate & phenytoin are contraindicated during pregnancy.
- Patient has to continue therapy.
- Use the lowest effective doses.

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.
- 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.

QUESTIONS

1) 20 year-old man who known to have epilepsy for last 10 months, present to dental clinic suffering from gum hyperplasia, which one of the following antiepileptic drug have been prescribed to the patient?
   - A- Ethosuxemide
   - B- Phenytoin
   - C- Lamotrigine
2) 55 year-old patient under antiepileptic drug for last 25 years present to clinic with impairment in his liver enzymes which of the following drugs is the best to prescribe to the pateint:
   - A- Topiramate
   - B- Carbamazebine
   - C- Fosphenytoin
3) Which one of the following drugs is the best in status epilepticus:
   - A- sodium valproate
   - B- Lorazepam
   - C- Phenytoin

1-B, 2-A, 3-B

THE END

Leaders

Abullah AL-Anazi & Tuqa Alkaff

E-Mail

pharmacologyteam1@gmail.com