Antiepileptic drugs

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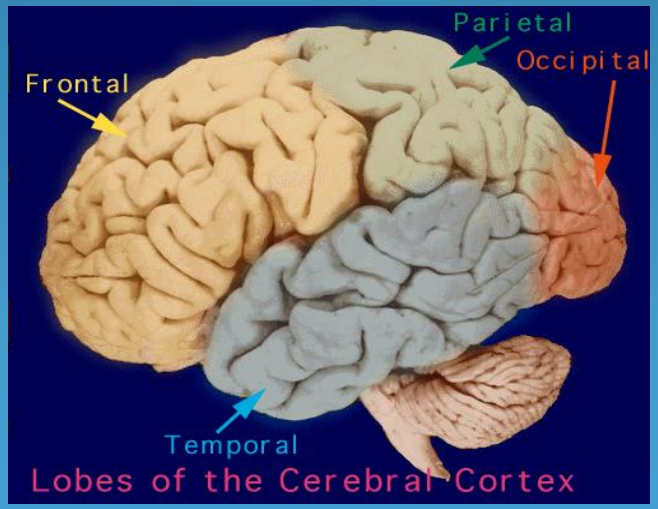


Objectives

- Epilepsy (1)
- Describe types of epilepsy
- Classify antiepileptic drugs according to the type of epilepsy treated and generation introduced
- Expand on pharmacokinetic and dynamic patterns of first generation antiepileptic drugs and specify their mechanism of action , therapeutic indications and adverse effects.

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

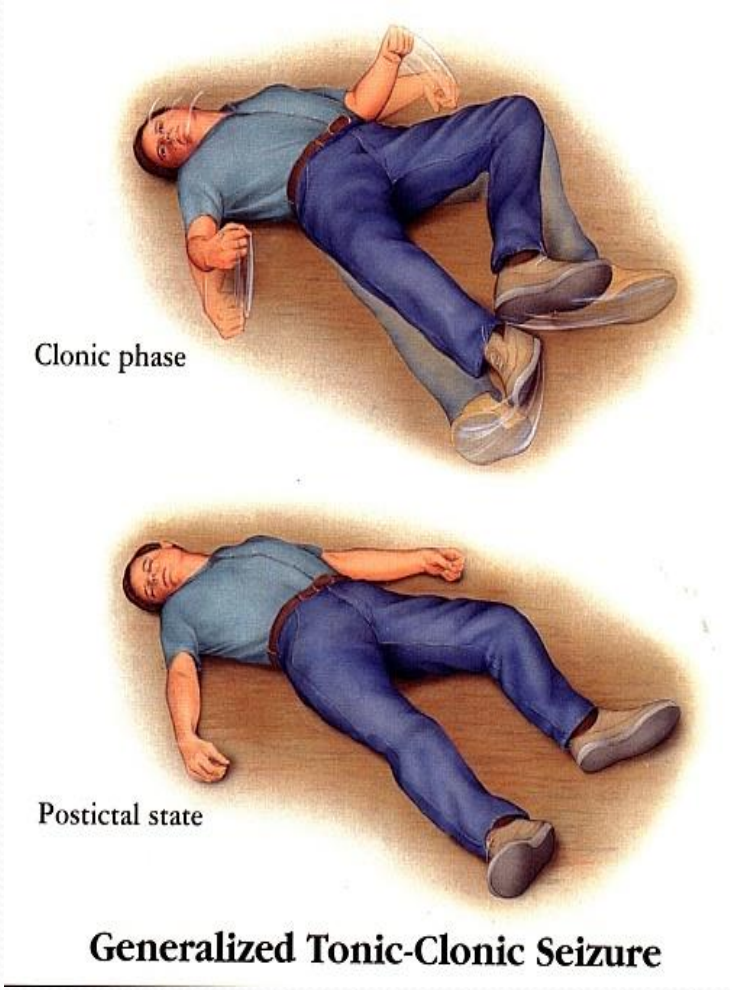
5- Describe the adverse effects of each antiepileptic drug

6- Describe treatment of status epilepticus

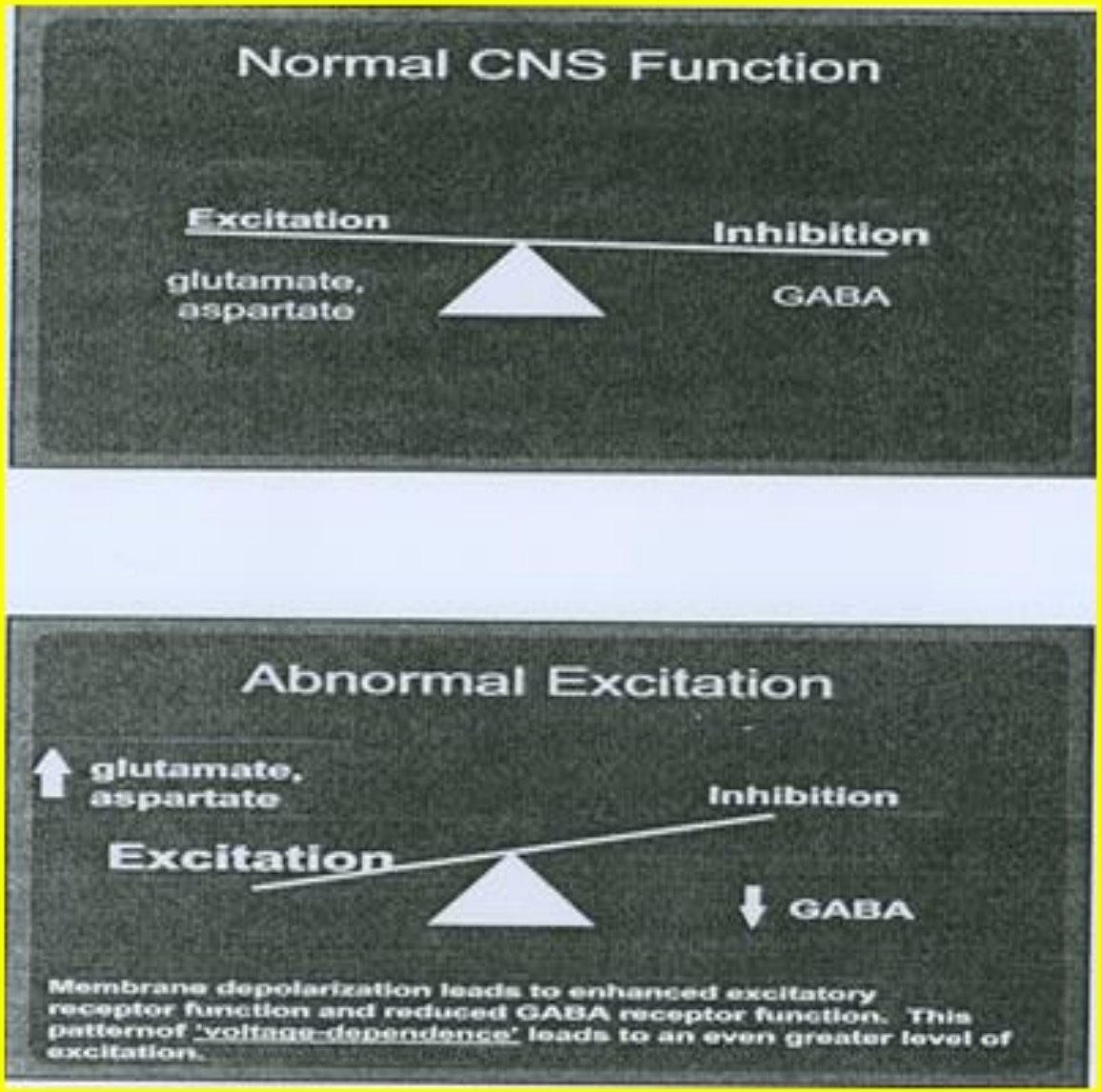
Definition

- *Epilepsy is a chronic medical condition characterized by 2 or more unprovoked seizures(within 6-12 months).*
- *What is the difference between seizure & epileptic syndrome?*
- *It is not a disease, it is a syndrome*

  (what is the difference ?)



Generalized Tonic-Clonic Seizure


Normal CNS Function
Excitation
Inhibition
glutamate,
aspartate
GABA
Abnormal Excitation
glutamate,
aspartate
Inhibition
Excitation
GABA
Membrane depolarization leads to enhanced excitatory receptor function and reduced GABA receptor function. This patternof 'voltage-dependence' leads to an even greater level of excitation.

Etiology

- **Congenital defects, head injuries, trauma, hypoxia**
- **Infection (bacteria or virus) e.g. meningitis, brain abscess, viral encephalitis.**
- **Concussion, depressed skull, fractures.**
- **Brain tumors (including tuberculoma), vascular occlusion, stroke.**
- **Drug withdrawal, e.g. CNS depressants,alcohol or drug abuse or drug overdose,e.g. penicillin.**
- **A poison, like lead**
- **Fever in children (febrile convulsion).**
- **Hypoglycemia**
- **PKU(** phenylalanine $\xrightarrow{\text{Phenylalanine hydroxylase}}$ tyrosine)
- **Photo epilepsy**

Triggers

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

Classification of Epilepsy

A)Partial(focal) ***Arise in one cerebral hemisphere***	
[1] Simple partial	***consciousness is retained***
[2] Complex partial	***Altered consciousness***

Partial with secondary generalization

Begins as partial (simple or complex) and progress into generalized seizure(tonic-clonic seizure).

B)Primary Generalized Both hemispheres + loss of consciousness.	
Tonic-clonic (grand mal)	***Stiffness followed by violent contractions & relaxation (1-2 min).***
Status epilepticus(Dangerous)	**Re-occuring tonic-clonic seizure(30 min or more)**
Tonic	***Muscle stiffness***
Clonic	***Spasms of contraction & relaxation***
Atonic(loss of 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. Eye blinking(no fall down).***

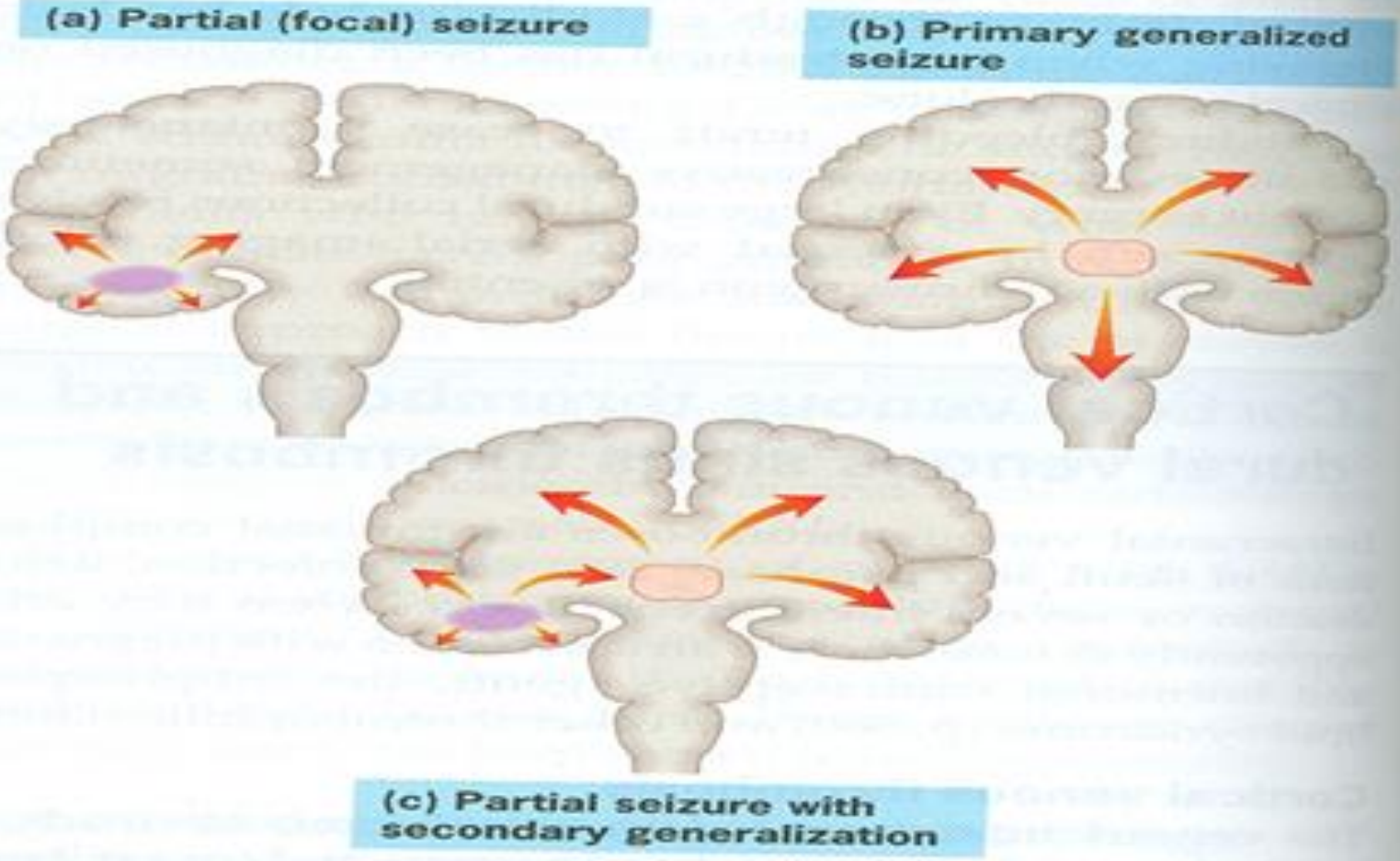


Fig. 20.23 **Seizure types.** **(a)** Partial (focal) seizure. **(b)** Primary generalized seizure. **(c)** Partial seizure with secondary generalization.

Treatment of Epilepsy

- **Drugs*****
- **Surgery**
- **Ketogenic diet**
- **Vagal nerve stimulation**

General rules for treatment of epilepsy

- Epilepsy is usually controlled but not cured with medication.
- Up to 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(mono therapy).

- Drugs are usually administered **orally**
- Monitoring plasma drug level is useful
- **Triggering factors can affect seizure control by drugs.**
- Sudden withdrawal of drugs should be avoided

Withdrawal considered

Seizure –free period of 2-5 yrs or longer

Normal IQ

Normal EEG prior to withdrawal

NO juvenile myoclonic epilepsy

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

Mechanism of Anti-Epileptic Drugs

- Antiepileptic 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^{+})

Classification of antiepileptic drugs

First-generation

- **Phenytoin****
- **Carbamazepine****
- **Valproate****
- **Ethosuximide****
- *Phenobarbital and Primidone*
- *Benzodiazepines (e.g.Clonazepam, lorazepam and diazepam)*

Second- generation

- **Lamotrigine****
- **Topiramate ****
- Levetiracetam
- Gabapentin
- Felbamate
- Zonisamide
- Pregabalin

Phenytoin

Pharmacokinetics :

- Available as capsules & i.v.
- Given orally, well absorbed from GIT.
- Enzyme inducer
- Metabolized by the liver to inactive metabolites
- Half life approx. 20 hr
- Excreted in urine

Fosphenytoin

- Parenteral form of phenytoin(i.v. & i.m.)
- **A Prodrug**.
- Rapidly converted to phenytoin in the body

Advantages over phenytoin:

- More rapid i.v. administration than phenytoin.
- May be administered by i.m. injection.
- Lower local tissue and cardiac toxicity than phenytoin.
- Less pain and phlebitis at injection site than phenytoin

Phenytoin

Mechanism of action

- Blockade of Na^+ & Ca + + influx into neuronal axon.
- Inhibit the release of excitatory transmitters
- Potentiate the action of GABA

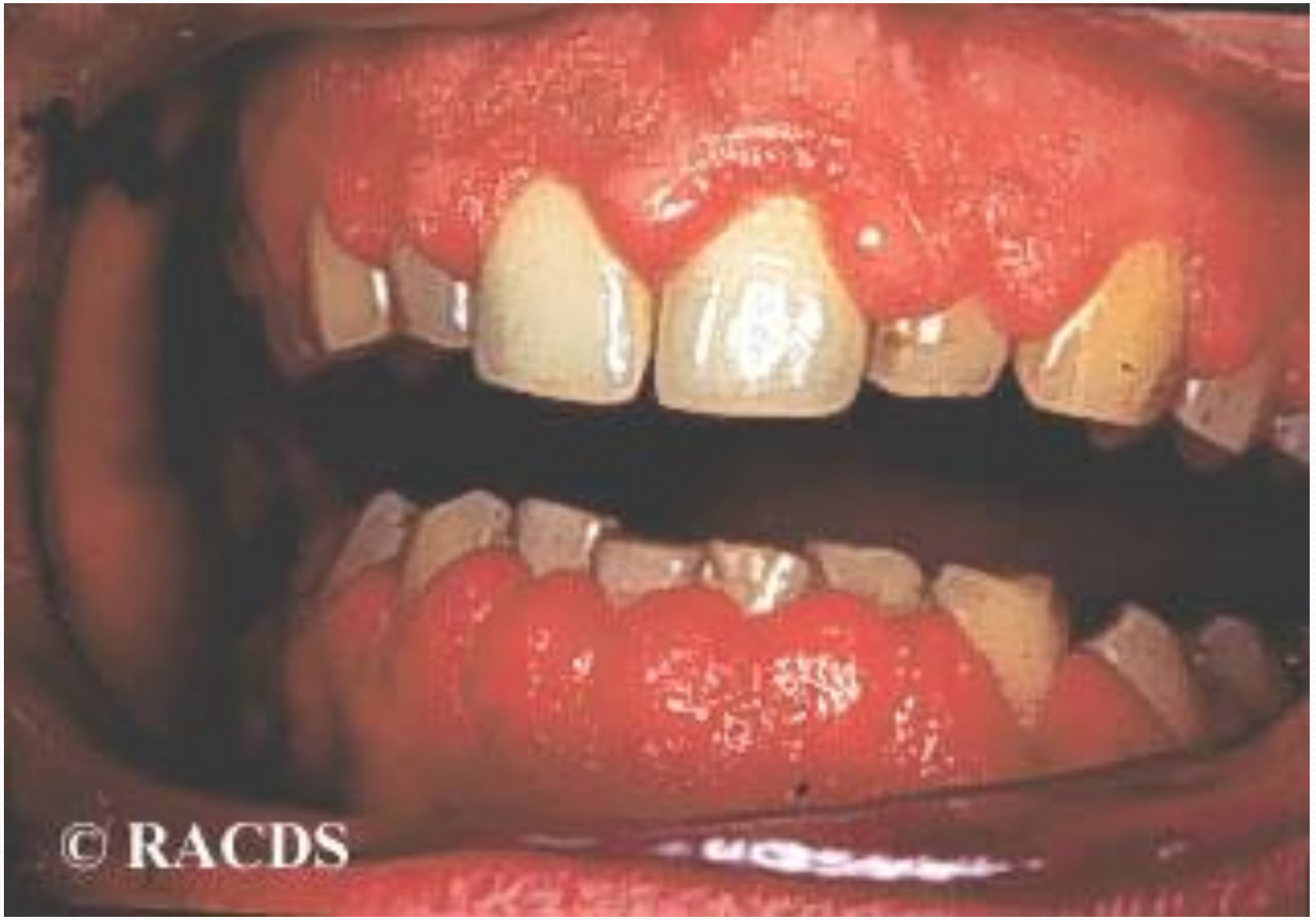
Therapeutic uses:

- Partial and generalized tonic-clonic seizures **Not** in **absence seizure**.
- In status epilepticus, IV .

Side effects

- Nausea or vomiting
- Headache, vertigo, ataxia, diplopia , nystagmus
- Sedation
- Gum(gingival) hyperplasia
- Hirsutism
- Acne
- Folic acid deficiency(megaloblastic anemia)
- Vit D deficiency (osteomalcia)
- Teratogenic effects

Phenytoin- induced gum hyperplasia



Carbamazepine

- **Pharmacokinetics :**

- **Available as capsules &Syrup only orally**
- **Well absorbed**
- **Strong enzyme inducer including its own metabolism**
- **Metabolized by the liver to active & inactive metabolites**
- **Half life 18-35 hr**
- **Excreted in urine**

Carbamazepine

Mechanism of action

- Blockade of Na^+ & Ca + + influx into neuronal axon.
- Inhibit the release of excitatory transmitters
- Potentiate the action of GABA

Therapeutic uses:

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

Other uses:

- **Bipolar depression.**
- **Trigeminal neuralgia**

Side effects

- GIT upset.
- Hypersensitivity reactions
- Drowziness , ataxia, headache & diplopia
- Hyponatremia & water intoxication
- Teratogenicity

Sodium Valproate

Broad spectrum antiepileptic

- **Pharmacokinetics :**
  - **Available as capsules, Syrup , I.V**
  - **Metabolized by the liver (inactive)**
  - **Enzyme inhibitor**
  - **Half life 12-16 hr**
  - **Excreted in urine**

Sodium valproate

Mechanism of action

- Blocks activated Na^+ channels.
- **Enhances GABA synthesis & reduces degradation**
- Suppress glutamate action.
- **Blocks T-type Ca^{2+} channels**

[II] Other uses:

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

Therapeutic Uses

[I] Epilepsy:

It is effective for all forms of epilepsy

- Generalized tonic-clonic seizures (1^{ry} or 2^{ry}).
- Absence seizures
- Complex partial seizures
- Myoclonic
- Atonic
- photosensitive epilepsy

Side effects:

GI(nausea, vomiting , heart burn).

Weight gain (↑appetite).

Transient hair loss, with re-growth of curly hair

Thrombocytopenia(not used with aspirin or coumadin

Transient increase in liver enzymes & hepatotoxicity

Teratogenicity(neural tube defect)

Ethosuximide

- **Mechanism of action**

Inhibits T- type Ca^{2+} channels in thalamo-cortical neurons.

Pharmacokinetics

- 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

Therapeutic uses

- Absence seizures

Adverse effects

- Gastric distress

  nausea

  vomiting
- Drowsiness, fatigue , hiccups, headaches

Lamotrigine

Mechanism of action

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

Therapeutic Use

- As **add-on** therapy or as **monotherapy** in partial &generalized tonic-clonic seizures.
- Lennox-Gastaut syndrome.
- Bipolar depression.

Pharmacokinetics

Available as oral tablets

Well absorbed from GIT

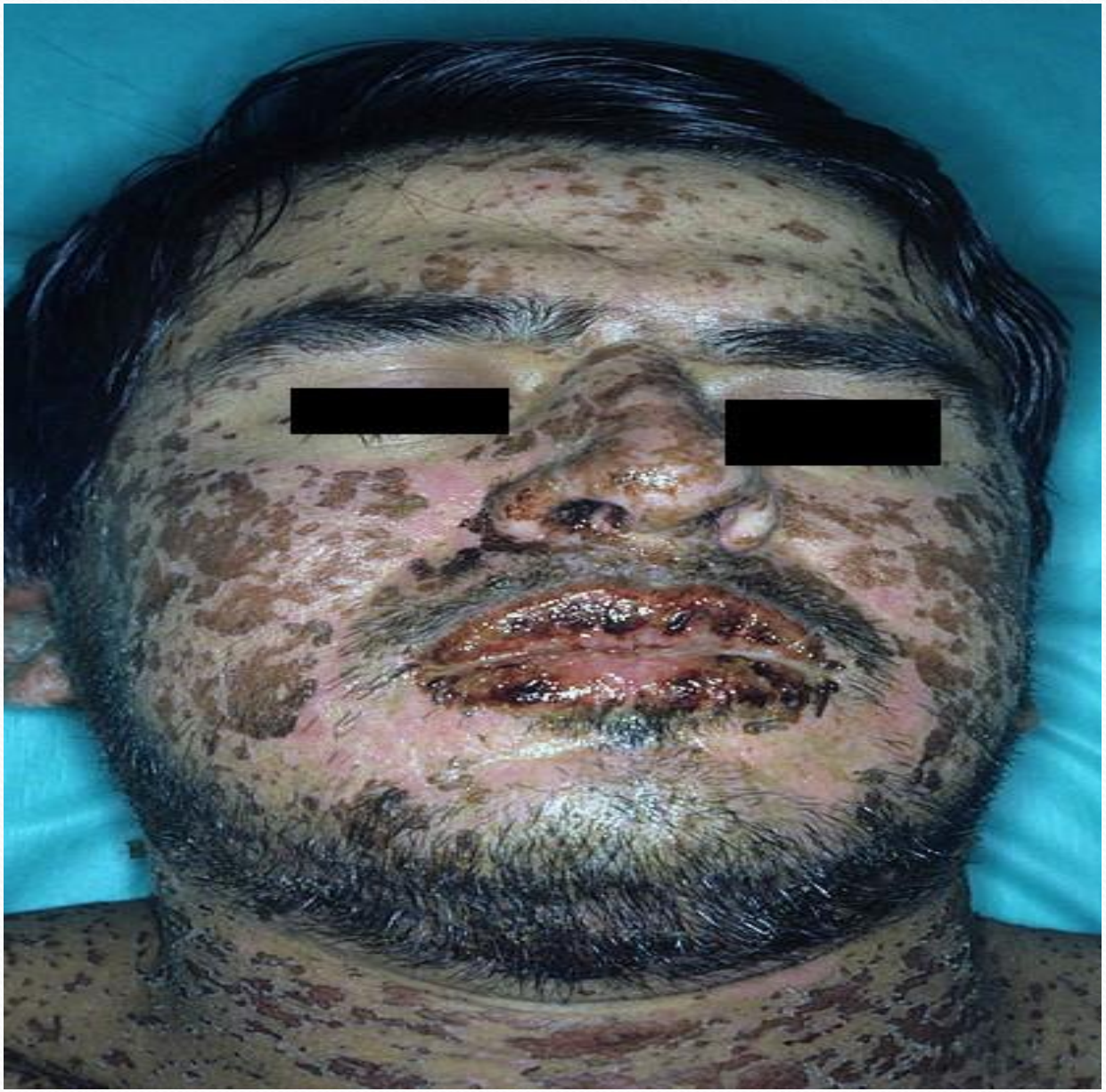
Metabolized primarily by glucuronidation

Does not induce or inhibit C. P-450 isozymes

Half life approx. 24 hr

Side effects

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



Topiramate

Pharmacological Effects:

- *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*

Mechanism of Action:

- *Blocks sodium channels (membrane stabilization) and also potentiates the inhibitory effect of GABA.*

Topiramate (Cont.)

Clinical Uses:

- ***Can be used alone for partial, generalized tonic-clonic, and absence seizures.***
- ***Lennox- Gastaut syndrome (or lamotrigine, or valproate).***

Side effects:

- ***Psychological or cognitive dysfunction***
- ***Weight loss*** *(can be desirable side effect)*
- *Sedation*
- *Dizziness*
- *Fatigue*
- *Urolithiasis*
- *Paresthesias (abnormal sensation)*
- *Teratogenecity*

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
Atonic	Valproate

Drugs used for treatment of Status Epilepticus

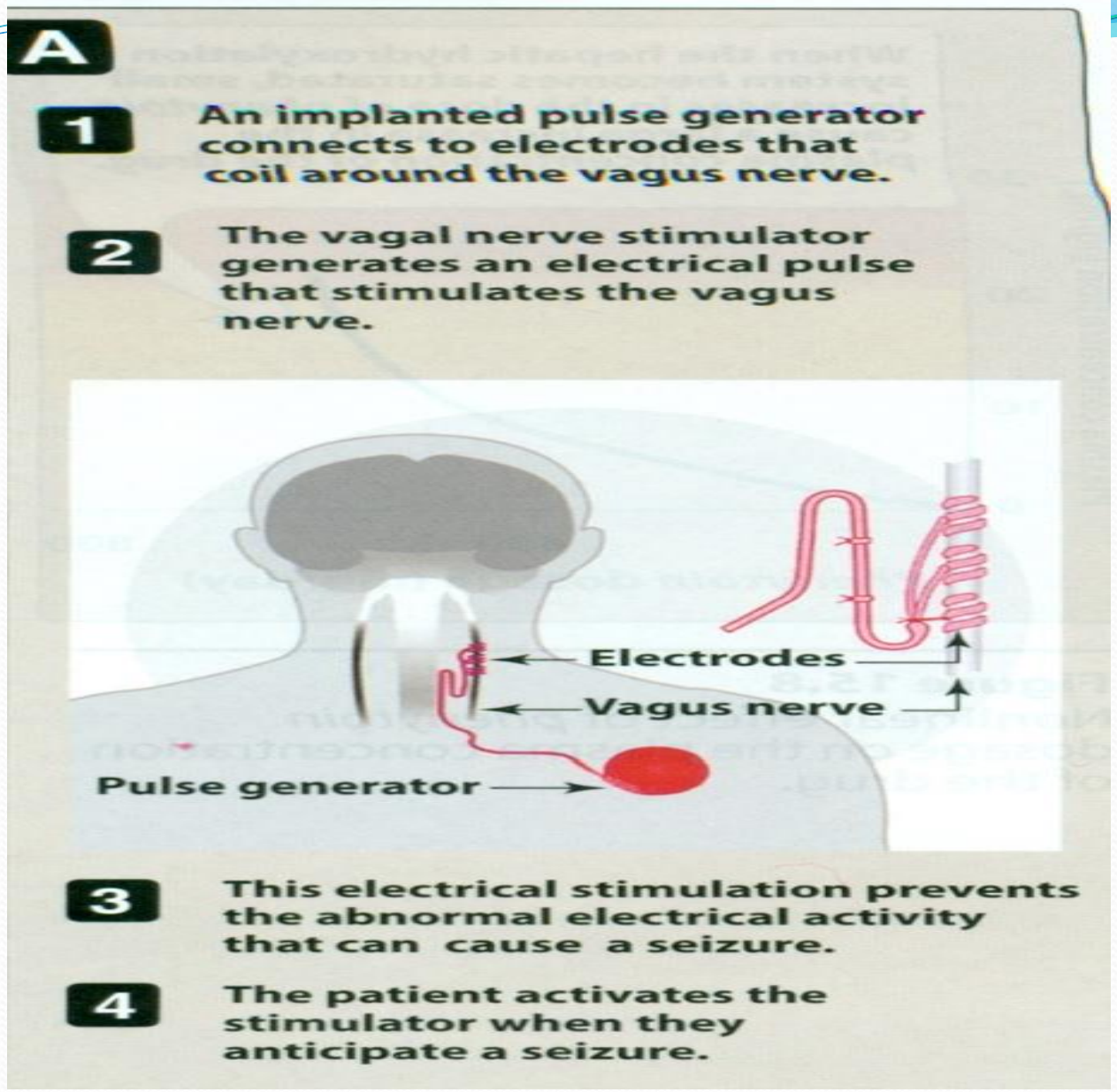
- Most seizures last from few seconds to few minutes. When seizures follow one another without recovery of consciousness, it is called “status epilepticus”. It has a high mortality rate . Death is from cardiorespiratory failure.

- **Antiepileptics used in status epilepticus**

  Intravenous injection of :
- **Lorazepam, Diazepam (drugs of choice)**
- **Phenytoin**
- **Fosphenytoin**
- **Phenobarbital**
- **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 anti epileptic drugs
- It is an expensive procedure


A
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.
Electrodes
Vagus nerve
Pulse generator
3
This electrical stimulation prevents the abnormal electrical activity that can cause a seizure.
4
The patient activates the stimulator when they anticipate a seizure.

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.

Summary

- - Epilepsy is classified into partial or generalized according to the site of lesion.
- The exact mechanism of action of antiepileptics is not known.
- Phenytoin is mainly used for treatment of generalized tonic-clonic seizures .

Carbamazepine is mainly used for treatment of partial seizures

Summary (con.)

- Sodium valproate is a broad spectrum antiepileptic drug.
- Lamotrigine & levetiracetam are used as monotherapy or adjunctive therapy in refractory cases.
- Lorazepam , diazepam , phenytoin are used intravenously for treatment of status epilepticus.