ANTI- EPILEPTICS

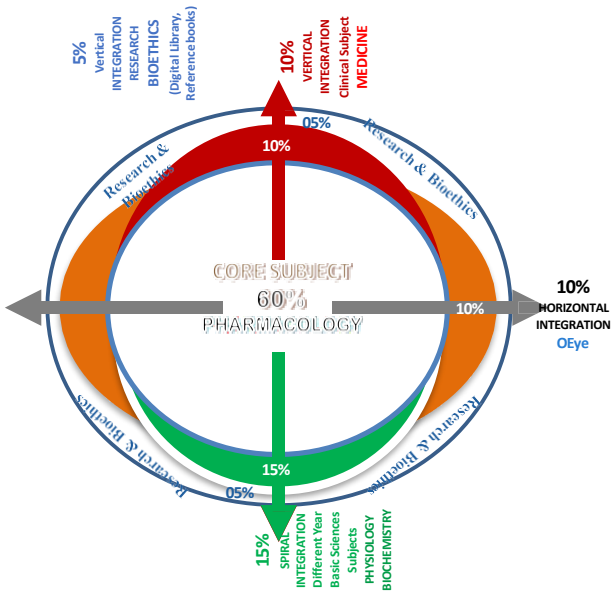
Sources

- Bertram G. katzung Basic & Clinical Pharmacology 15th Edition
- Goodman and Gilman's The Pharmacological Basis of Therapeutics 13th edition

MOTTO AND VISION

- To impart evidence based research oriented medical education
- To provide best possible patient care
- To inculcate the values of mutual respect and ethical practice of medicine

Prof. Umar's Clinically Oriented Integration Model
For Basic Sciences Interactive Lectures



4rd Year Pharmacology LGIS	
Core Subject – 60%	
Pharmacology	
Horizontal Integration – 10%	
Same Year Subjects	• Eye • Pathology
Vertical Integration – 10%	
Clinical Subjects	• Medicine • Surgery
Spiral Integration – 15%	
Different Year Basic Sciences Subjects	• Physiology (10%) • Biochemistry (5%)
Research & Bioethics, Digital library – 05%	

HORIZONTAL INTEGERATION-PATHOLOGY

Definition of Epilepsy

Epilepsy is a chronic neurological disorder characterized by recurrent seizures, which are finite episodes of brain dysfunction resulting from abnormal discharge of cerebral neurons.

Epilepsy

- Epilepsy affects 0.5-1 % of the population
- The characteristic event is the **seizure**
- The seizure is caused by an **abnormal high-frequency discharge of a group of neurons** and spreading to a varying extent to affect other parts of the brain.
- No specific cause
- 1/3rd cases--- familial, involve genetic mutation

PATHOPHYSIOLOGY

Paroxysmal discharges in cortical neurons

A seizure orignates from grey matter of any cortical or subcortical area

Abnormal firing of neurons

Breakdown of normal membrane conductance & inhibitory synaptic currents

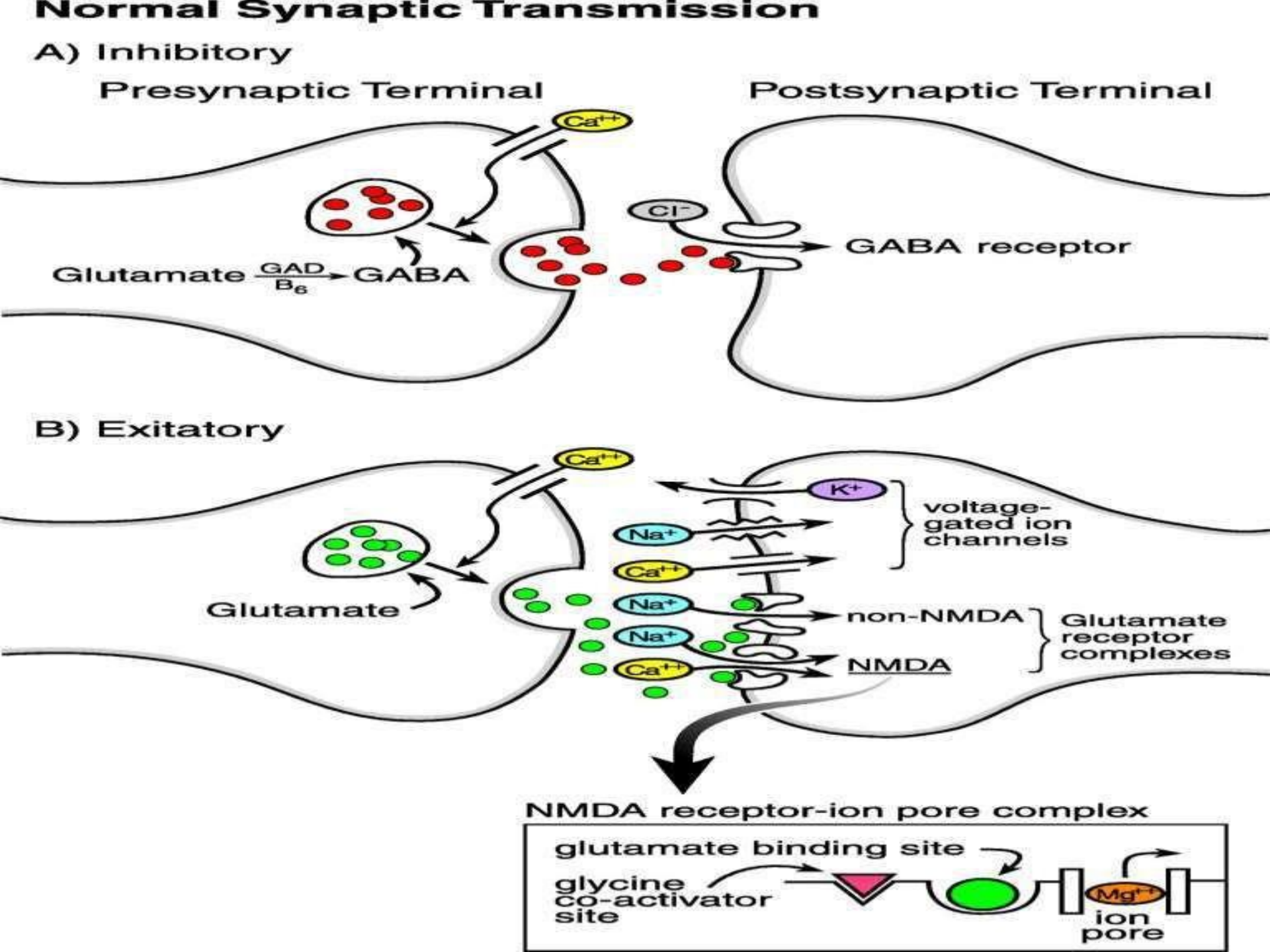
Locally

widely

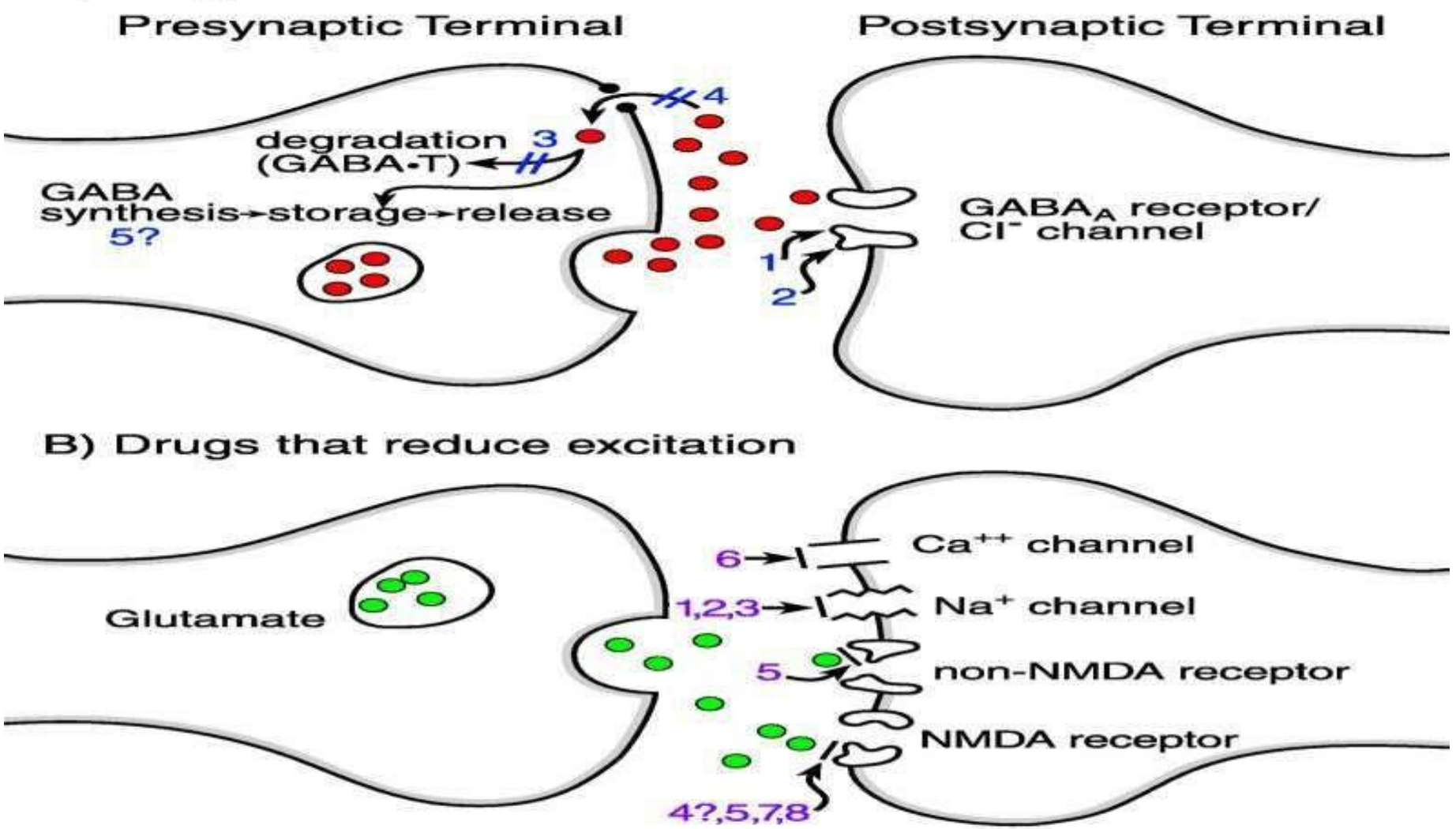
Focal seizure

Generalized seizure

Normal Synaptic Transmission



Actions of Antiepileptic Drugs



A) Drugs that enhance inhibition
1. phenobarbital
2. benzodiazepines
3. vigbatrin
4. tiagabine
5. gabapentin

B) Drugs that reduce excitation
1. phenytoin
2. carbamazepine
3. lamotrigine
4. felbamate
5. topiramate
6. ethosuximide
7. ketamine
8. Mg^{++}

CORE SUBJECT

Strategies for treatment

- **Inhibit repetitive activity**
  - Blocking voltage gated Na channels (inhibition of high frequency firing is thought to be mediated by reducing ability of Na channels to recover from inactivation)
  - Blocking voltage gated Ca channels (Drugs effective against absence seizure work by inhibition of voltage-activated Ca^{2+} channels responsible for T-type Ca^{2+} currents.)

- **Stabilizing membrane**
  - Increased conductance through K conductance

- **Increasing inhibitory output (GABA enhancers)**
  - Increasing synthesis of GABA
  - Decreasing the degradation of GABA
  - Decreasing GABA uptake
  - GABA facilitators (GABAmimetics)

- **Decreasing excitatory output (glutamic acid)**
  - Antagonism at Glutamic acid receptors

- **Other non-specific mechanisms:**
  - Inhibition of release of NE , serotinin
  - Increase uptake of dopamine
  - Inhibiton of Na /K ATPase

- **Carbonic anhydrase inhibition**

Classification

- On basis of their Chemistry
- On basis of therapeutic uses
- On basis of their mechanism of action

Chemical classification

- **Hydantoins-** phenytoin , mephenytoin , ethotin
- **Barbiturates -** phenobarbitone , primidone
- **Benzodiazepines –** diazepam , lorazepam , clonazepam , nitrazepam
- **Succinamides-** ethosuxamide , phensuxamide , methosuxamide
- **Carboxylic acid-** valproic acid , Na valproate
- **Imminostilbenes-** carbamazepine , oxcarbamazepine
- **Sulfonamide derivatives-** zonisamide , rufinamide
- **Oxazolindinediones-** dimethadione , trimethadione
- **CA inhibitors-** acetazolamide , sulthiame
- **GABA inhibitors-** vigabatrin , gabapentin , pregablin
- **Misc.-** tiagabine , lamotrigine

Classification-mechanism of action

- **Na channel blockers**
  - Phenytoin
  - Carbamazepine
  - Valproic acid
  - Topiramate
  - Lacosamide

  fosphenytoin

  Oxcarbamazepine

  Na valproate

  lamotrigine

  zonisamide

- **Ca channel blocker**
  - Phenytoin
  - Ethosuxamide
  - Lamotrigine

  valproic acid

  barbiturates

  zonisamide

• GABA enhancers

- **Increase synthesis**
  - Valproic acid gabapentin
- **Decrease degradation**
  - Valproic acid vigabatrin gabapentin tiagabine
- **Decrease uptake**
  - Tiagabine gabapentin valproic acid
- **Increase release/ GABA facilitators**
  - Phenytoin phenobarbitone topiramate BZD

- **Glutamate antagonists**
  - Phenobarbitone
  - Phenytoin
  - Lamotirigine
  - Topiramate
  - Felbamate

- **Carbonic anhydrase inhibitors**
  - Acetazolamide
  - Topiramate

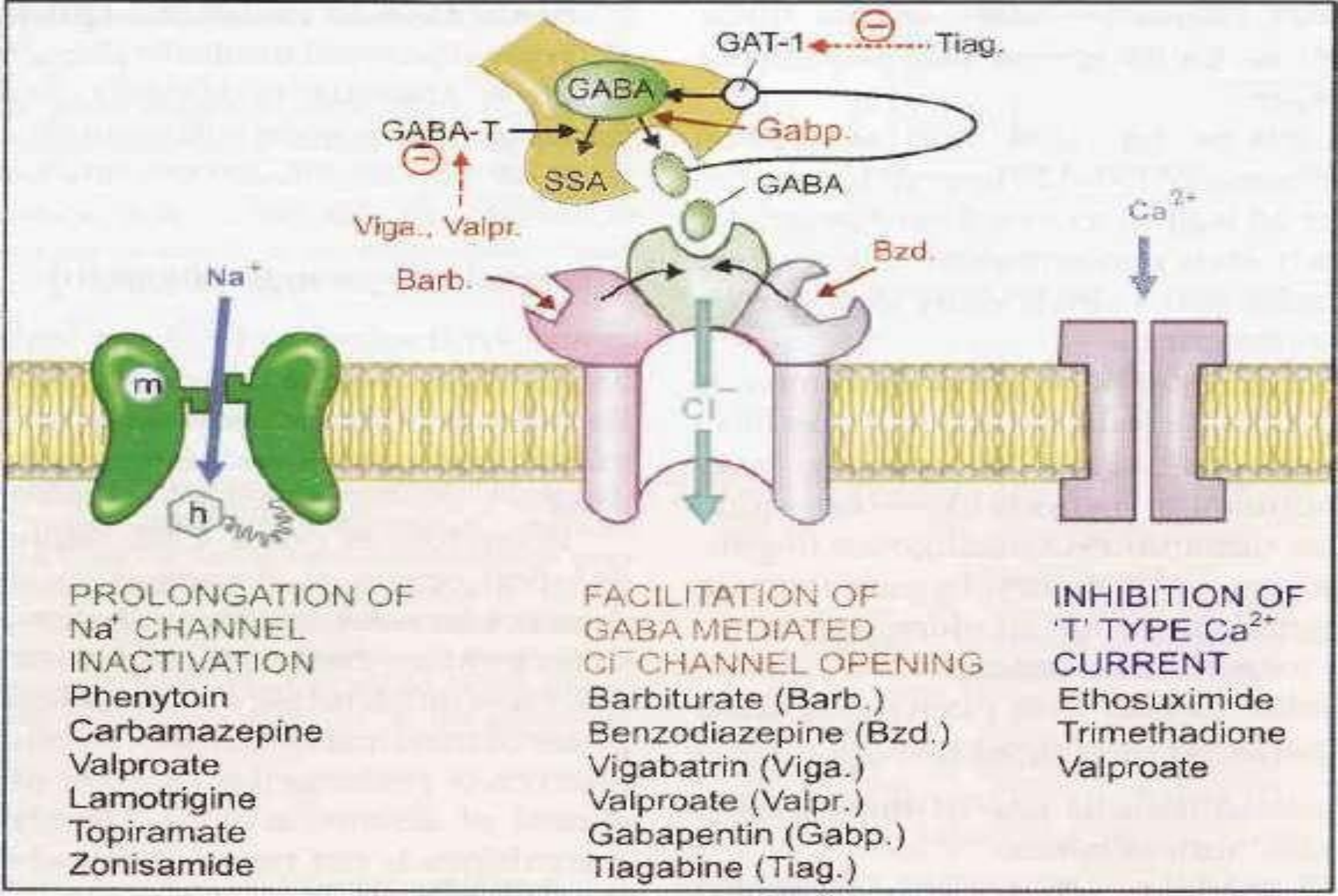


Fig. 30.2: Major mechanisms of anticonvulsant action
m: Activation gate; h: Inactivation gate; GABA-T: GABA transaminase; SSA: Succinic semialdehyde; GAT-1: GABA transporter

Pharmacokinetics of anti-seizure drugs – (in general)

- Most have oral activity
- All enter CNS
- 80-100% bioavailability
- Cleared chiefly by liver
- Many drugs are potent inducers of hepatic enzymes
- Mostly Administered in O.D / B.D doses

Phenytoin

Mechanism of Action:

(1) Blocking voltage-dependence Na^+ channel

(2) Blocking voltage-dependence Ca^{2+} channel

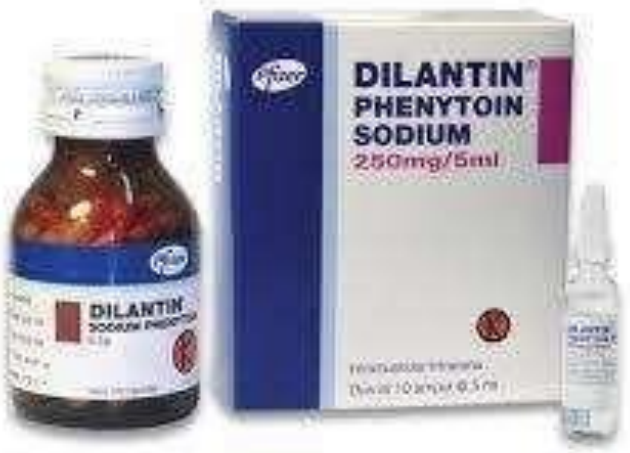
(3) Inhibiting calcium-induced secretory processes, including release of neurotransmitters(NE, SEROTININ)

(4) Inhibiting GLUTAMATE action & potentiates GABA

Also promotes uptake of dopamine

Therapeutic uses

- Antiseizure:
  - grand mal epilepsy
  - tonic-clonic seizure disorders
  - Status epilepticus



- Can Treat trigeminal neuralgia

- Antiarrhythmic class IB- digitalis induced

Adverse effects of Phenytoin

- Nystagmus, Diplopia, Ataxia
- Gingival hyperplasia
- Hirsutism
- Increased collagen proliferation
- Hepatitis
- Fetal malformations: fetal hydantion syndrome
- Megaloblastic anemia
- Osteomalacia

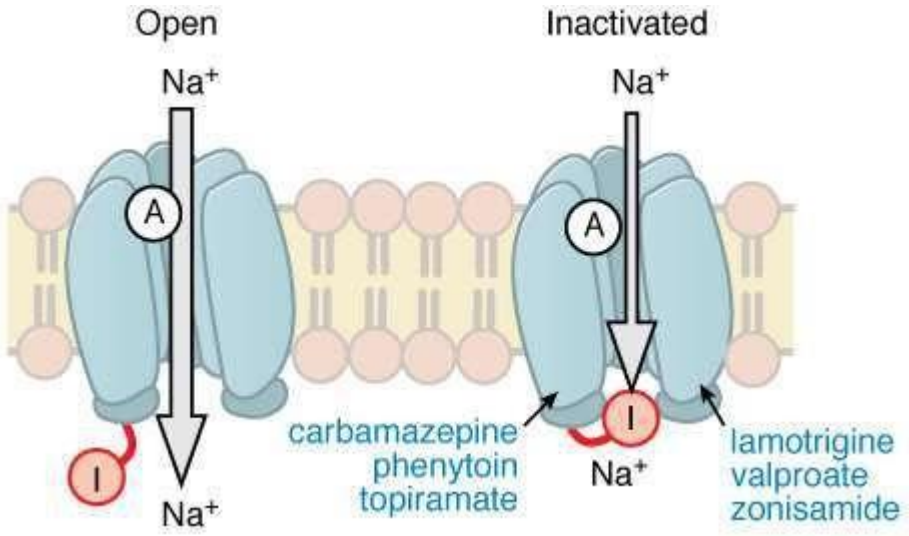
Drug interactions of phenytoin:

- Phenobarbitone & carbamazepine increased plasma concentrations of phenytoin
- Izoniazide inhibit its metabolism
- Sulphonamide, phenylbutazone & valproic acid displace phenytoin from plasma protein binding
- Sucralfate binds phenytoin , decrease absorption

Carbamazepine

- **MOA:**
  - blocks Na channels
  - Potentiation of voltage gated K current

- **Uses:**
- Drug of choice in-
  - complex partial seizures (psychomotor epilepsy)
  - trigeminal neuralgia
  - Mania (alternative to lithium)



Carbamazepine-adverse effects & interactions

- GIT disturbances
- Sedation and drowsiness
- Diplopia and ataxia
- Hyponatremia and water retention
- Aplastic anemia and agranulocytosis
- Increased rate of metabolism of phenytoin, ethosuximide, valporic acid and clonazepam
- Valporic acid may inhibit carbamazepine clearance

RESEARCH/ AI/BIOETHICS

- Mobed A, Shirafkan M, Charsouei S, Sadeghzadeh J, Ahmadalipour A. Biosensors technology for anti-epileptic drugs. Clinica Chimica Acta. 2022 Aug 1;533:175-82.

- Obaidullah AJ, Almehizia AA. Analysis experimental and modeling of the solubility of an antiepileptic drug, Levetiracetam, in supercritical solvent. Journal of Molecular Liquids. 2023 Nov 15;390:123065.

- Ammendolia I, Mannucci C, Cardia L, Calapai G, Gangemi S, Esposito E, Calapai F. Pharmacovigilance on cannabidiol as an antiepileptic agent. Frontiers in Pharmacology. 2023 Feb 10;14:1091978.

How to use HEC Digital Library

1. Go to the website of HEC National Digital Library

   http://www.digitallibrary.edu.pk

2. On Home Page, click on the INSTITUTES.

3. A page will appear showing the universities from Public and Private Sector and other Institutes which have access to HEC National Digital Library (HNDL).

4. Select your desired Institute.

5. A page will appear showing the resources of the institution

6. Journals and Researches will appear

7. You can find a Journal by clicking on JOURNALS AND DATABASE and enter a keyword to search for your desired journal.

EOLA

- A patient with epilepsy is started on Phenytoin and experiences a rash, fever, and lymphadenopathy. What is the suspected diagnosis?

A) Hypersensitivity reaction

B) Toxic epidermal necrolysis

C) Stevens-Johnson syndrome

D) Drug-induced lupus

E) Viral infection

EOLA

- A patient with epilepsy is taking Phenytoin and warfarin concurrently. What is the expected effect on warfarin's anticoagulant activity?

A) Increased

B) Decreased

C) Unchanged

D) Variable

E) Reversible


Thank
you!!