ANTI- EPILEPTICS

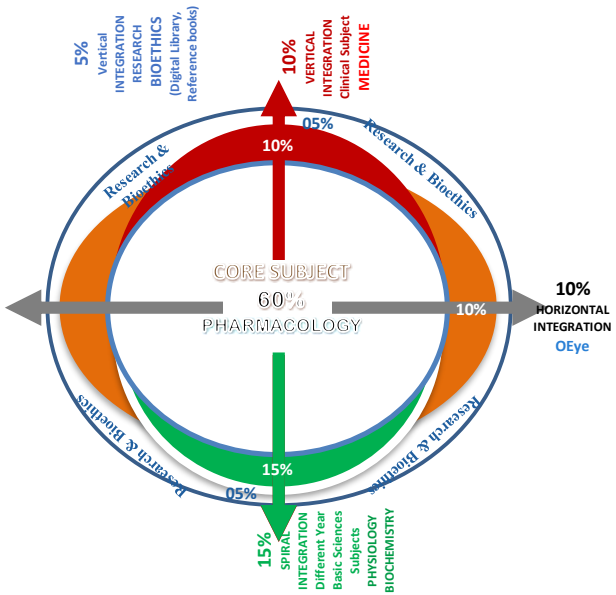
Sources

- 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

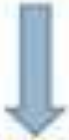
A seizure orignates from grey matter of any cortical or subcortical area

Abnormal firing of neurons

Breakdown of normal membrane conductance & inhibitory synaptic currents

Locally

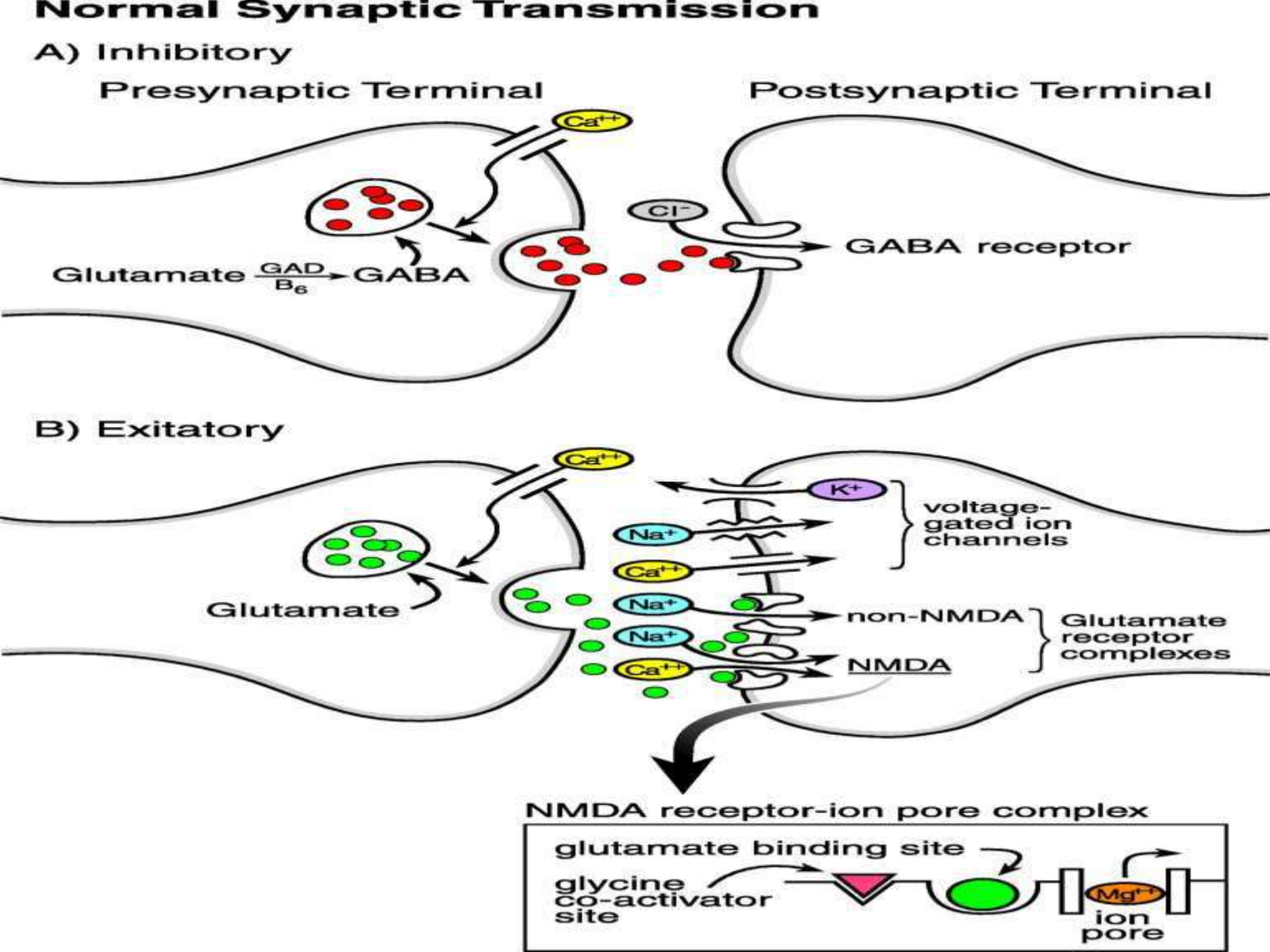
widely



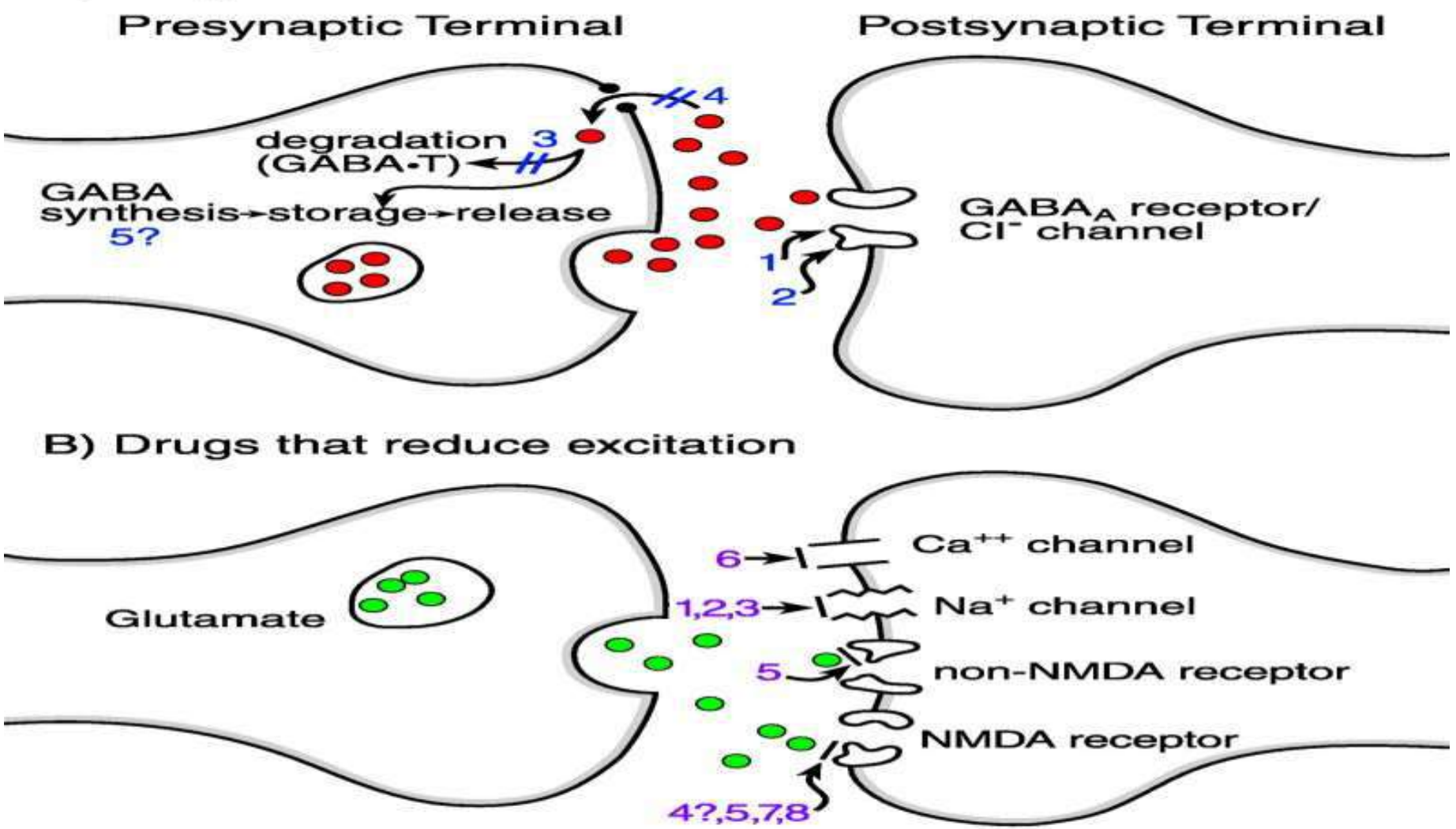
Focal seizure

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 — fosphenytoin
  - Carbamazepine — Oxcarbamazepine
  - Valproic acid — Na valproate
  - Topiramate — lamotrigine
  - Lacosamide — zonisamide

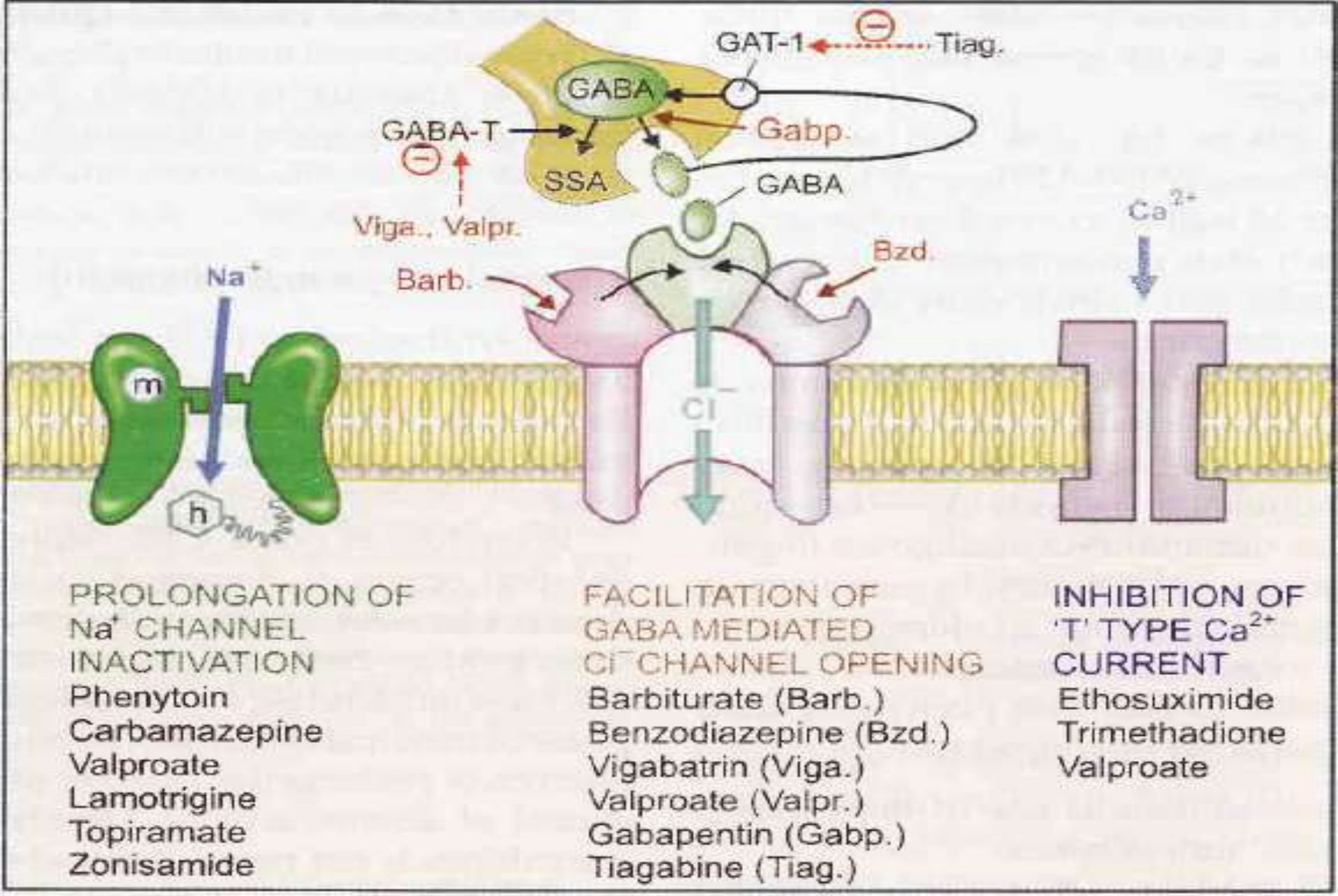
- **Ca channel blocker**
  - Phenytoin — valproic acid
  - Ethosuxamide — barbiturates
  - Lamotrigine — zonisamide

• 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



PROLONGATION OF Na^+ CHANNEL INACTIVATION
Phenytoin
Carbamazepine
Valproate
Lamotrigine
Topiramate
Zonisamide

FACILITATION OF GABA MEDIATED Cl^- CHANNEL OPENING
Barbiturate (Barb.)
Benzodiazepine (Bzd.)
Vigabatrin (Viga.)
Valproate (Valpr.)
Gabapentin (Gabp.)
Tiagabine (Tiag.)

INHIBITION OF 'T' TYPE Ca^{2+} CURRENT
Ethosuximide
Trimethadione
Valproate

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

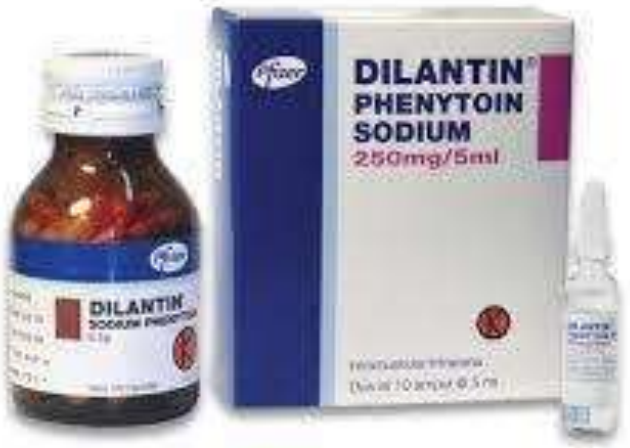
(3) Inhibiting calcium-induced secretory processes, including release of neurotransmitters(NE, SEROTININ)

(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

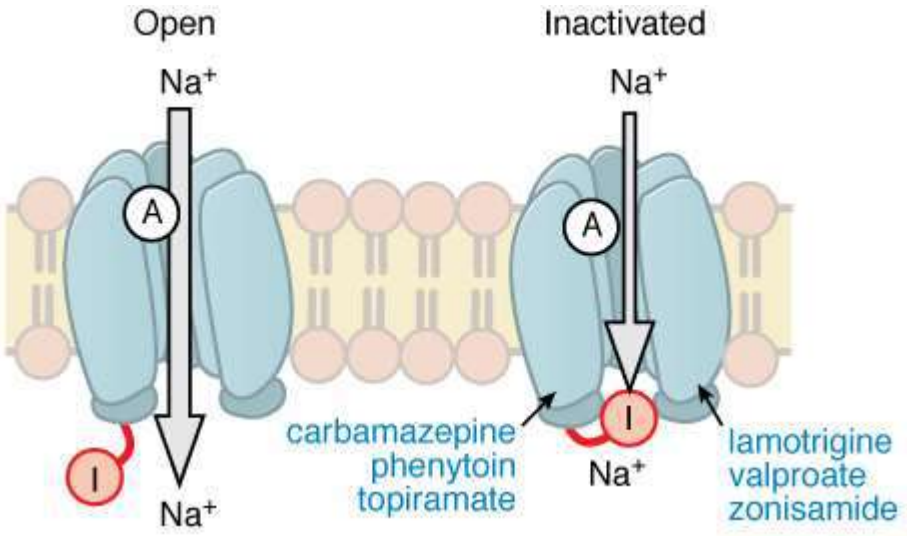
Drug interactions of phenytoin:

- 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)

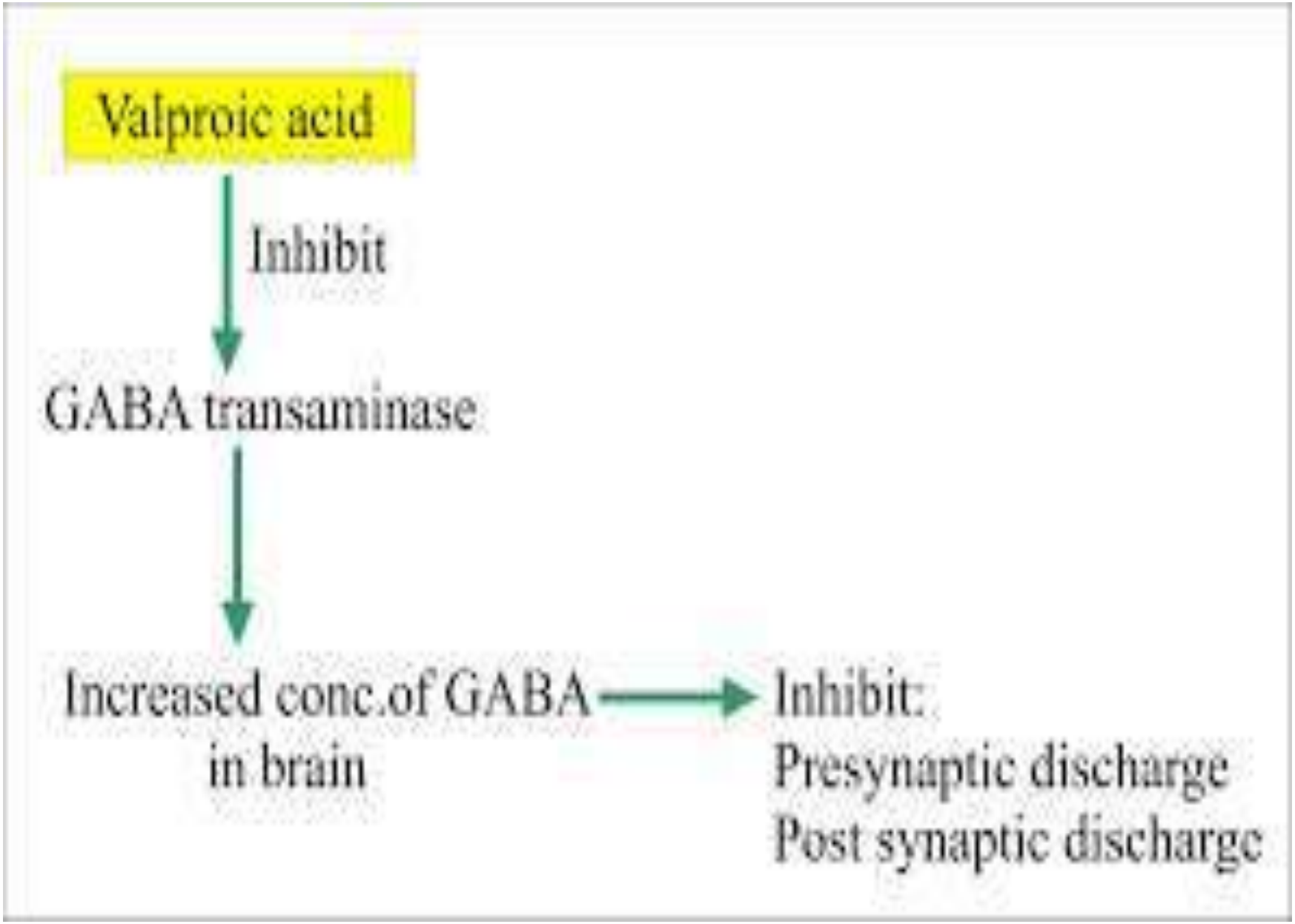


Carbamazepine-adverse effects & interactions

- 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

Valproic acid-broad spectrum

- **Mechanismof action:**
  - Prolongs Na channel inactivation
  - Decrease Ca mediated current
  - facilitate glutamic acid decarboxylase
  - inhibit GABA-transaminase , inhibit GAT-1
  - Increase K conductance


Valproic acid
Inhibit
GABA transaminase
Increased conc.of GABA in brain
Inhibit:
Presynaptic discharge
Post synaptic discharge

Uses of valproic acid

- Generalized tonic clonic attacks
- Certain types of infantile epilepsy
- Absence seizures
- Migraine prophylaxis
- Mania & bipolar illness

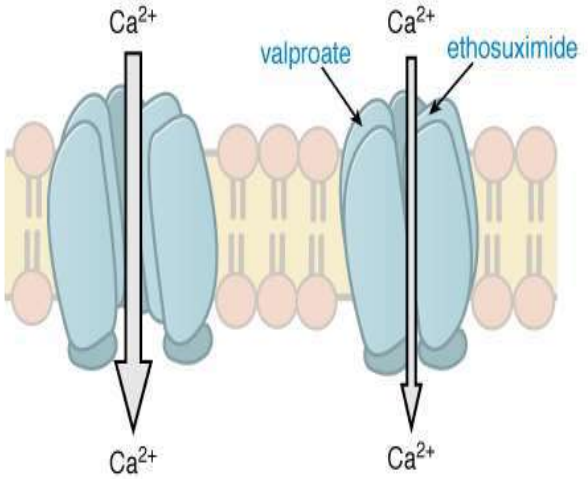
Adverse effects

- Relatively few unwanted effects:
- Commonly GIT symptoms like anorexia, nausea
- Teratogenicity –spina bifida
- Alopecia , increased appetite , increased weight
- liver damage (rare, but serious)
- Valproate undergo auto metabolism
- Its an enzyme inhibitor

Ethosuximide

- The main drug used to treat absence seizures
- Also called pure petit mal drug

- **Mechanism of action**
  - Acts by blocking T-type Ca^{2+}-channels



- **Adverse effects**

➢ mainly nausea and anorexia.

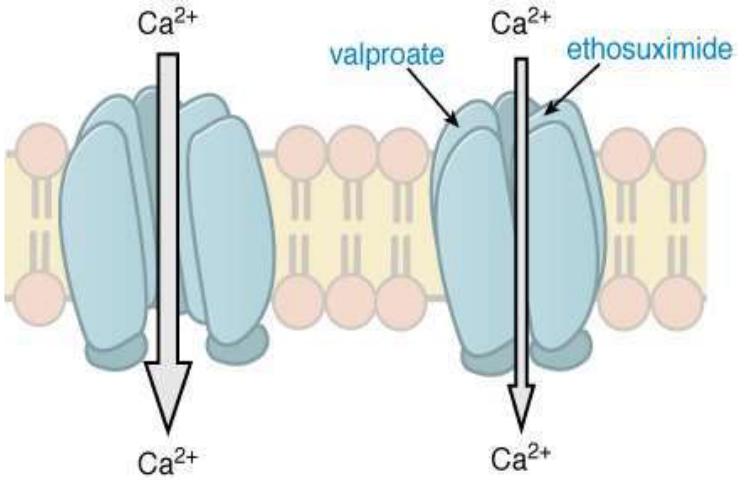
➢ fatique , drowsiness

- **Drug interactions**

➢ Valporic acid decreases ethosuximide clearance

Lamotrigine

- Prolong Na channel inactivation
- Blocks voltage gated Ca channels particularly N and P/Q type channels
- Decrease release of glutamate
- **Use:**
  - All types of seizure except infantile seizures
  - **Adverse effects:**
  - Dizziness, diplopia
  - HSV
  - vomiting



Gabapentin & Pregabalin

- **Mechanism of action:**
  - GABA analogs
  - Modify synaptic or non synaptic release of GABA
  - Bind avidly to α2δ subunit of voltage gated Ca channels
  - Decrease Ca entry with predominant effect on presynaptic N type channels
  - Decrease in synaptic release of glutamate

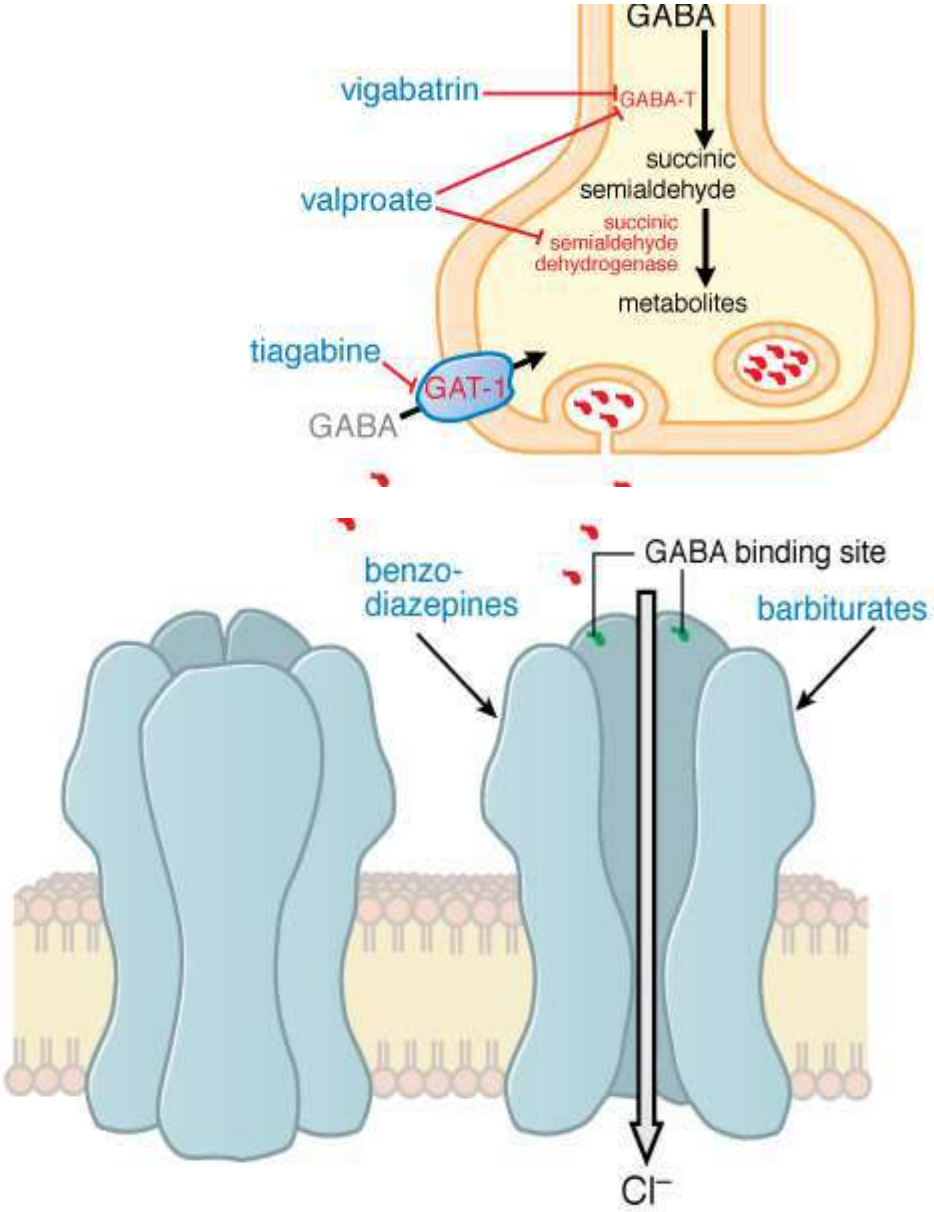
Uses of gabapentin

- Partial seizures
- Generalized tonic clonic seizures
- Neuropathic pain
- Post herpetic neuralgia
- Painful diabetic neuropathies

Adverse effect

- Sedation
- Dizziness
- Ataxia

Vigabatrin


GABA
vigabatrin
GABA-T
succinic
semialdehyde
valproate
succinic
semialdehyde
dehydrogenase
metabolites
tiagabine
GAT-1
GABA
benzo-
diazepines
GABA binding site
barbiturates
Cl⁻

Vigabatrin

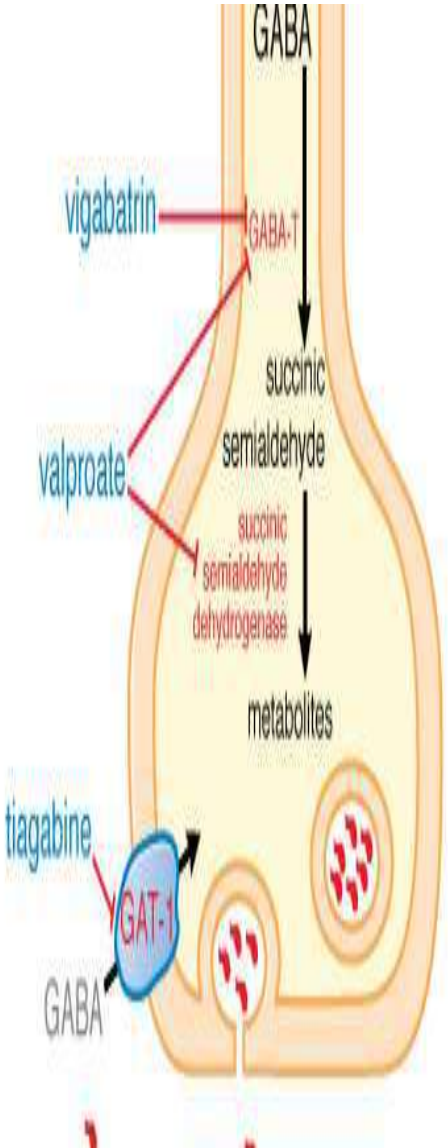
- **Uses**
  - Partial seizures
  - Infantile spasm (DOC)

Adverse effects:

- Drowziness
- Weight gain
- Visual field defects

Tiagabine

- **MOA:**
  - GABA reuptake inhibitor
- **Use:**
  - Partial seizures
- **Adverse effects:**
  - Dizziness, confusion
  - Tremors
  - Ataxia



LEVETIRACETAM

- Levetiracetam binds selectively to a synaptic vesicular protein SV2A.

- The function of this protein is not understood but it is likely that levetiracetam modifies the synaptic release of glutamate and GABA through an action on vesicular function.

- USES

➢ Partial seizures

➢ Primary generalized tonic clonic seizures

- ADVERSE EFFECT

➢ somnolence, asthenia, and dizziness.

FELBAMATE

- MOA

➢ It produces a use-dependent block of the NMDA receptor, with selectivity for the NR1-2B subtype.

➢ It also potentiates $GABA_A$ receptor responses.

USES

- Partial seizures

S/E

- Aplastic anemia
- Severe hepatitis

D/I

- Felbamate increases plasma phenytoin and valproic acid levels but decreases levels of carbamazepine.

LACOSAMIDE

- Enhances slow inactivation of voltage gated Na channels.

- It also binds to the collapsin response mediator protein CRMP-2, thereby blocking the effect of neurotrophic factors such as BDNF and NT3 on axonal and dendritic growth

- Use in Partial seizures

➢ Adverse effects include

- Dizziness, headache
- Diplopia
- Nausea

PRIMIDONE

- Converted into phenobarbital and phenylethylmalonamide
- May be more like that of phenytoin
- Partial seizures
- Generalized tonic clonic seizures

Topiramate

- Prolongation of Na channels
- Act on L type Ca channel
- GABA potentiator
- Depresses excitatory action of kainate on glutamate receptors

- Uses:
  - Partial and generalized tonic clonic seizures
  - Lennox Gastaut syndrome
  - Infantile spasms
  - Migraine

- Adverse effects:

✓Dizziness

✓Fatique

✓Acute myopia and glaucoma

✓urolithiasis

Zonisamide

- **MOA:**
  - Na channel blocker
  - T type Ca channel blocker
- **Uses**
  - Generalized
  - Complex partial
  - Infantile spasm
- **Adverse effects**
  - same

Benzodiazepine

- Diazepam: preferred drug for Status epilepticus
- Nitrazepam: myoclonic seizures and infantile spasms.
- Clonazepam: is one of the effective drug in absence seizure.

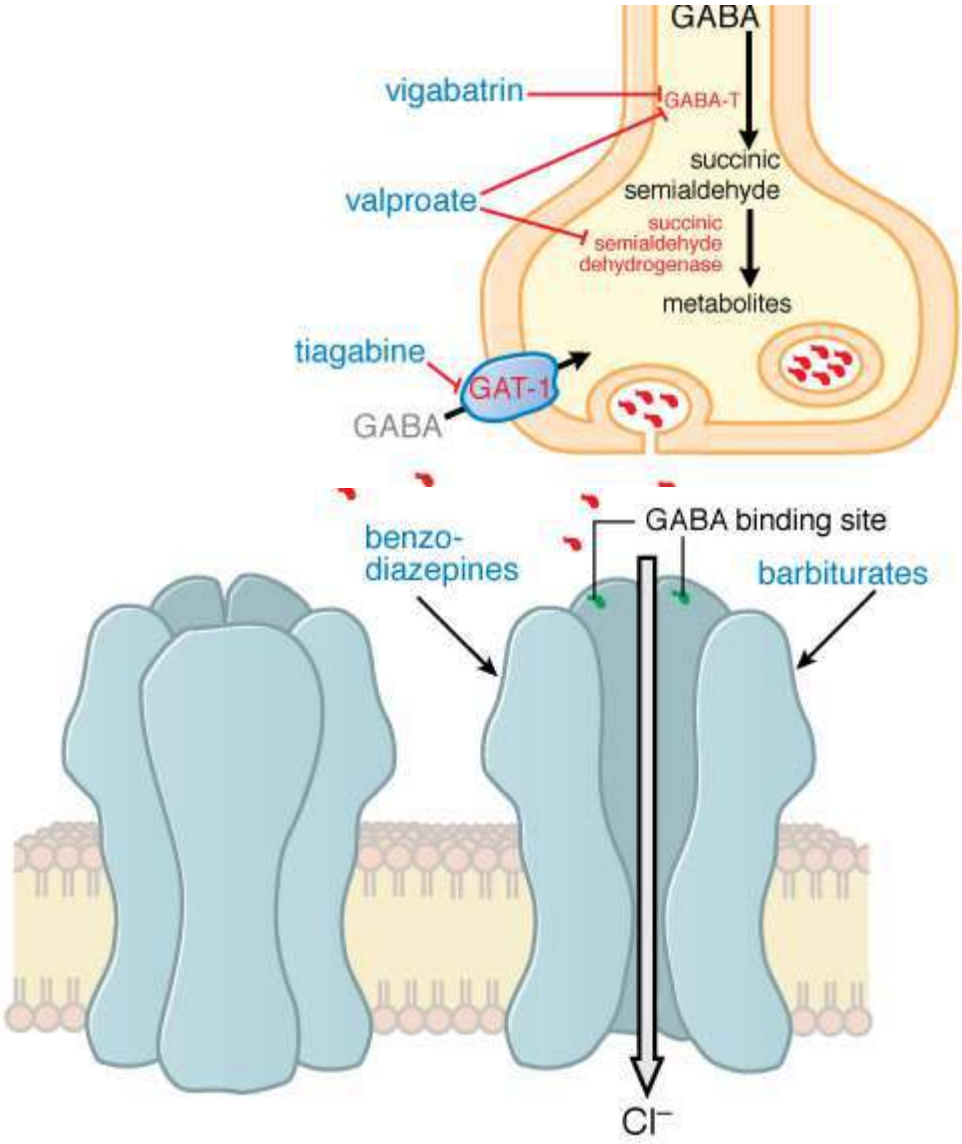
Barbiturates

- **Phenobarbital:**
  - useful in the treatment of generalized tonic-clonic seizures and statue epilepticus.

- **Mechanism:**
  - (1) block Ca^{2+} currents presynaptic membrane and decrease neurotransmitter release.
  - (2) prolong the openings of the Cl^- channel in postsynaptic membrane and decrease it's response.

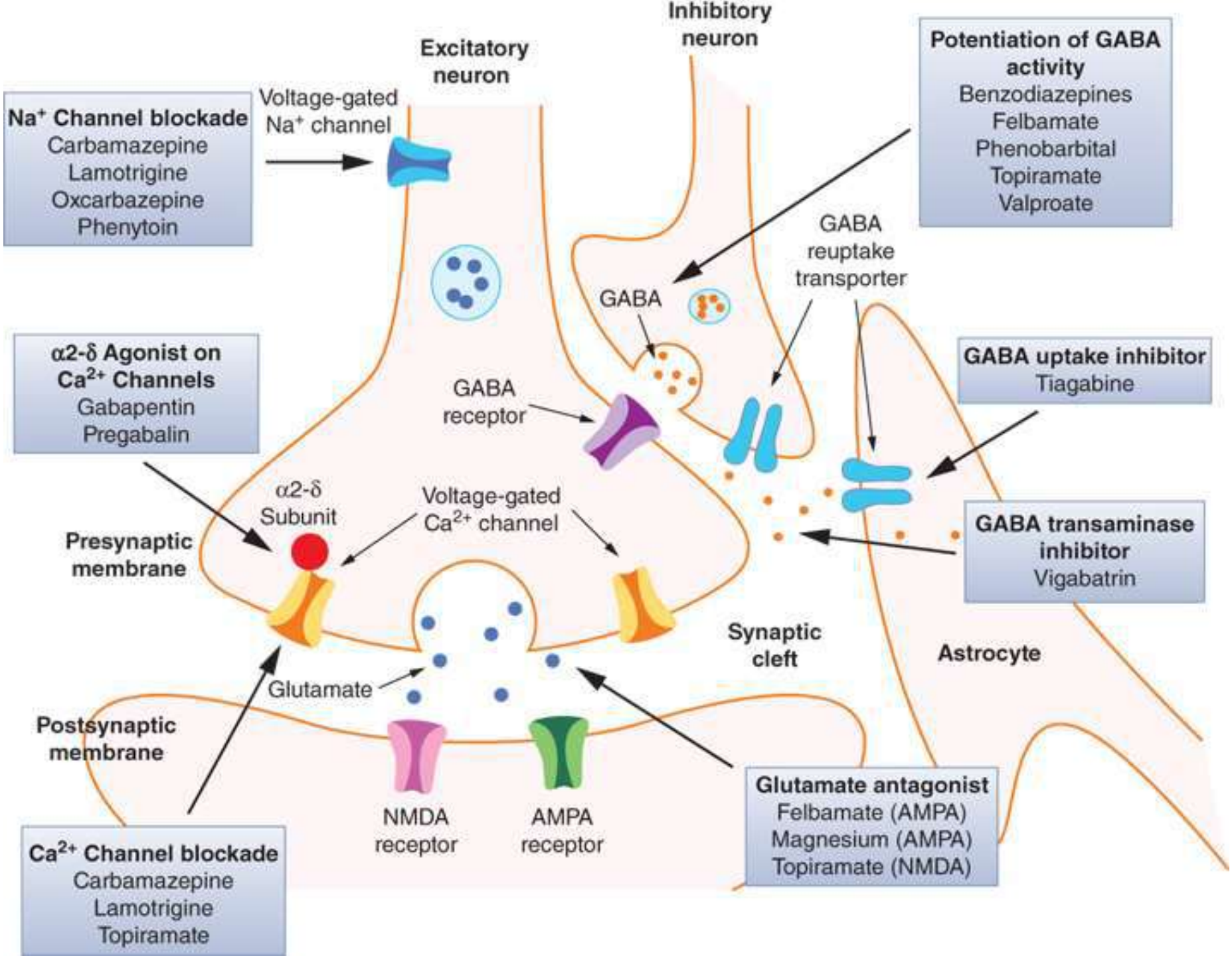
- **Adverse effects:**
  - sedation, depression, drug interaction.

GABAergic synapse



STATUS EPILEPTICUS

- Diazepam I/V
- Lorazepam (relativ. Longer acting than diazepam0
- Phenytoin (I/V)
- Fosphenytoin (I/V Safer)
- Phenobaritone (I/V)
- Lignocaine for generalized tonic-clonic seizures
- Gene. Anesthesia for resistant cases
- Neuromuscular blocker


Inhibitory neuron
Excitatory neuron
Potentiation of GABA activity
Benzodiazepines
Felbamate
Phenobarbital
Topiramate
Valproate
Na+ Channel blockade
Carbamazepine
Lamotrigine
Oxcarbazepine
Phenytoin
Voltage-gated Na+ channel
GABA reuptake transporter
GABA
α2-δ Agonist on Ca2+ Channels
Gabapentin
Pregabalin
GABA uptake inhibitor
Tiagabine
GABA receptor
α2-δ Subunit
Voltage-gated Ca2+ channel
Presynaptic membrane
GABA transaminase inhibitor
Vigabatrin
Synaptic cleft
Astrocyte
Glutamate
Postsynaptic membrane
NMDA receptor
AMPA receptor
Glutamate antagonist
Felbamate (AMPA)
Magnesium (AMPA)
Topiramate (NMDA)
Ca2+ Channel blockade
Carbamazepine
Lamotrigine
Topiramate

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!!