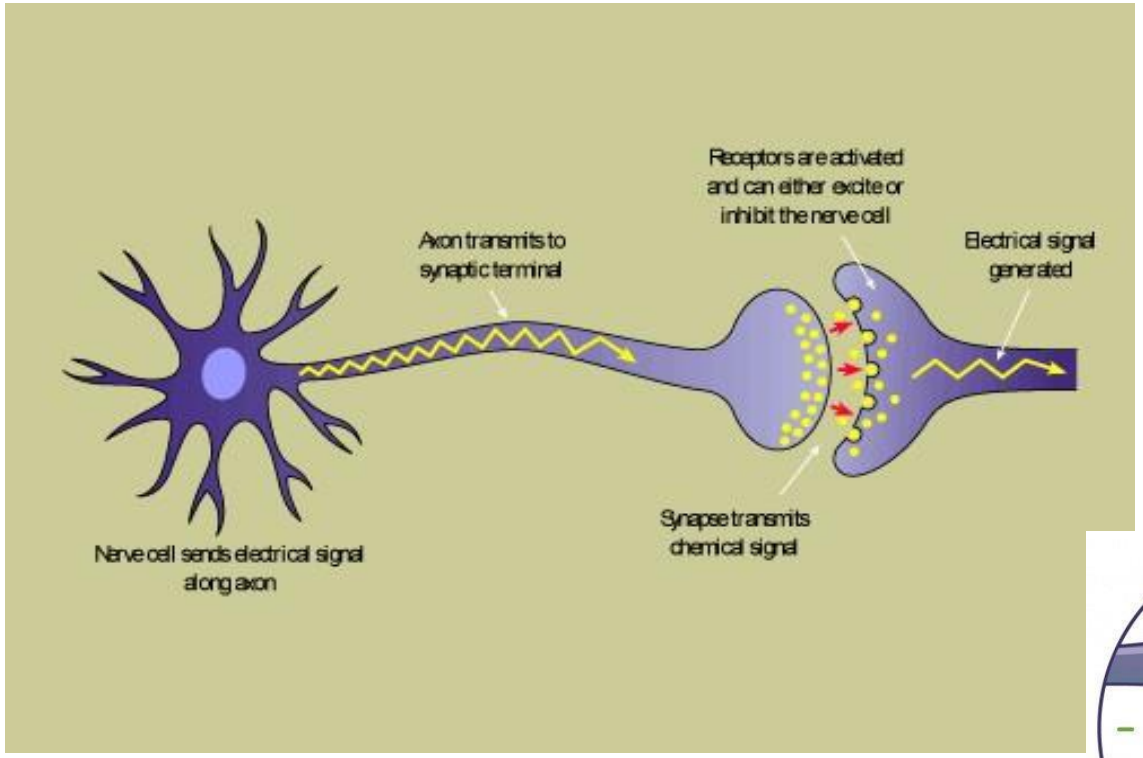
EPILEPSY

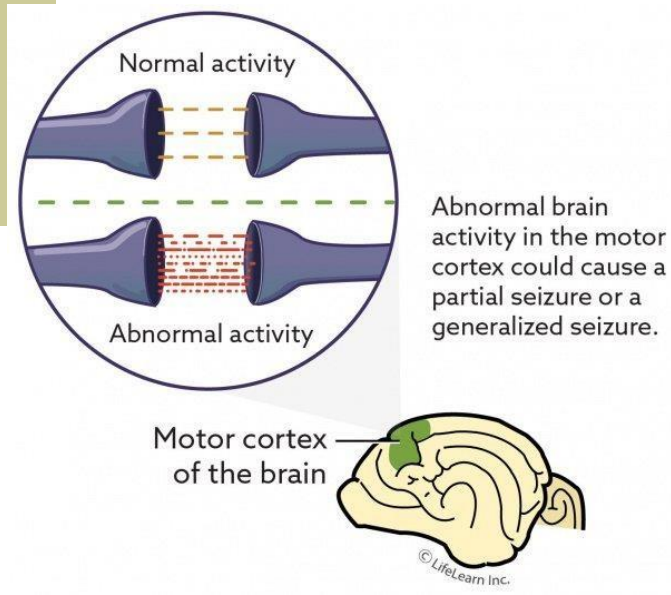
OSMOSIS.org

- *A **seizure** is a transient alteration of behavior due to the disordered, synchronous, and rhythmic firing of populations of brain neurons.*

- *Epilepsy refers to a disorder of brain function characterized by the periodic and unpredictable occurrence of seizures.*

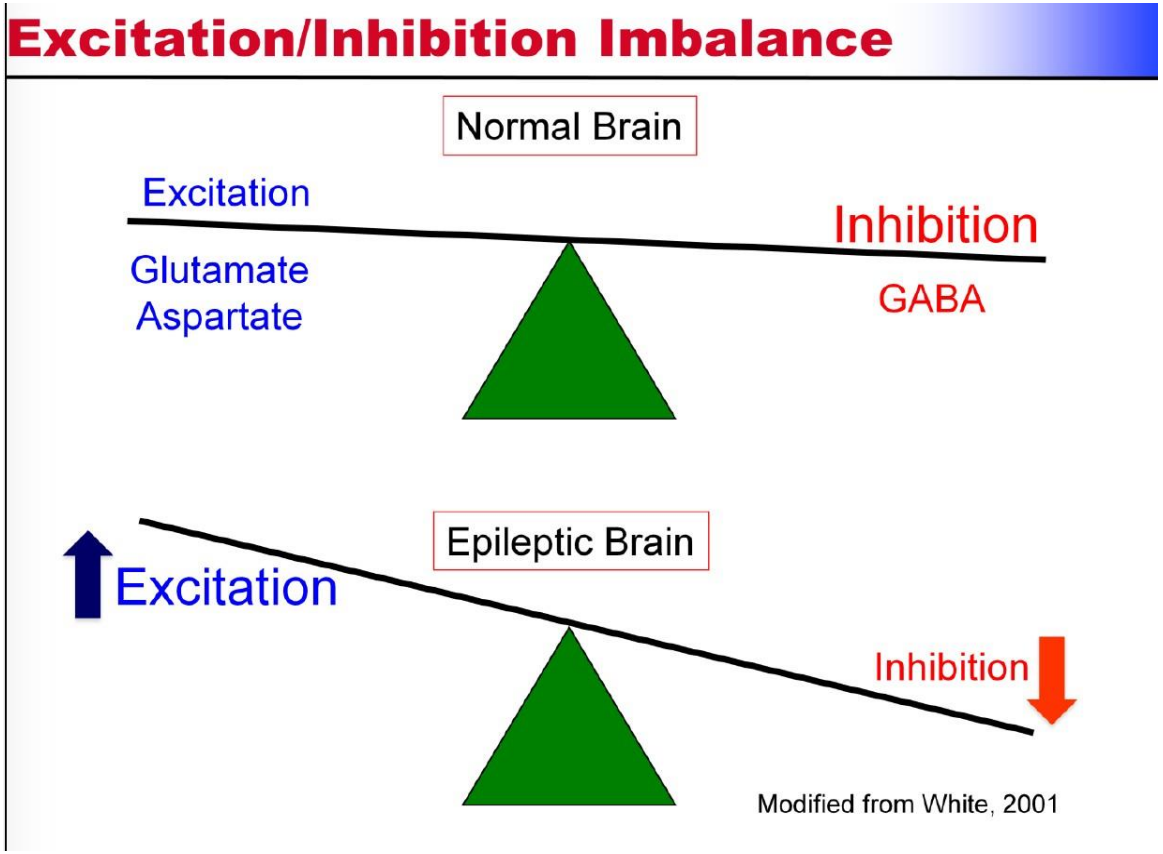


Abnormal excessive electronic activity

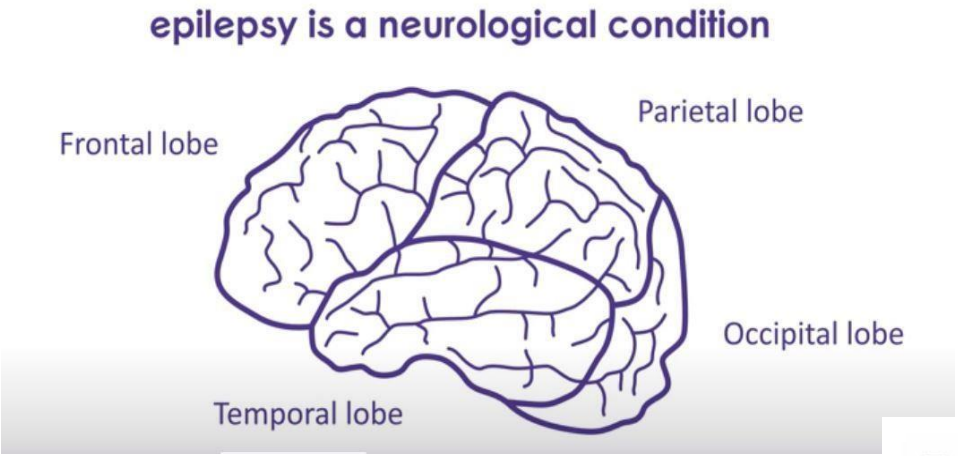


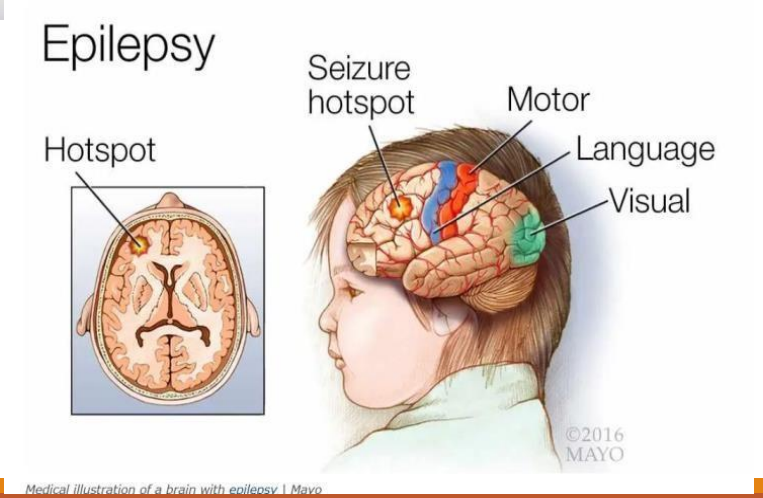
Epilepsy is caused by imbalance between

. GABA & Glutamate



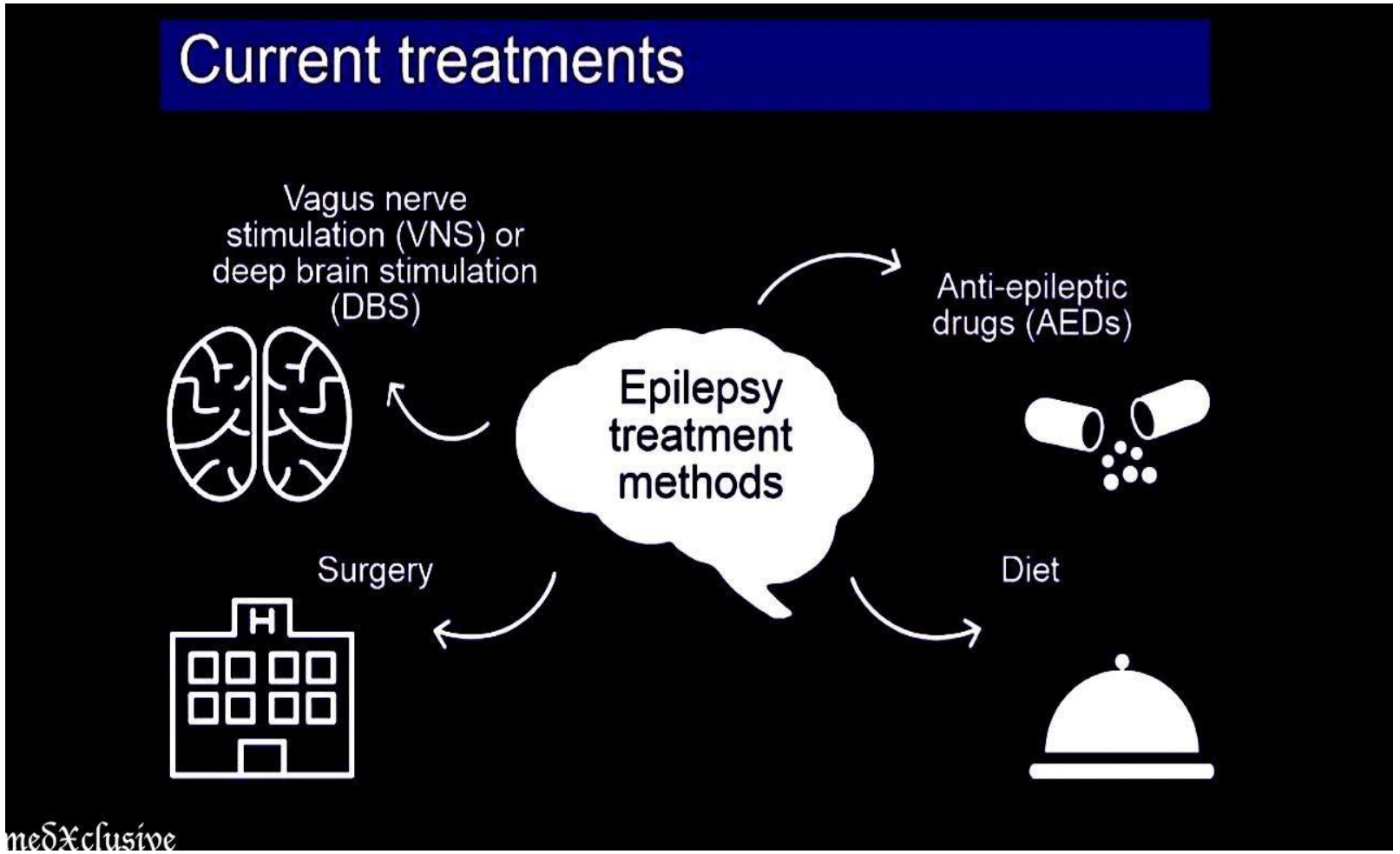
Symptoms depend upon site of origin of epileptic foci





Medical illustration of a brain with epilepsy | Mayo

CLASSIFICATION	CHARACTERIZATION
Partial (Focal) Seizures	Arise in one cerebral hemisphere
Simple partial seizure	No alteration of consciousness
Complex partial seizure	Altered consciousness, automatisms, and behavioral changes
Secondarily generalized seizure	Focal seizure becomes generalized and is accompanied by loss of consciousness
Generalized Seizures	Arise in both cerebral hemispheres and are accompanied by loss of consciousness
Tonic-clonic (grand mal) seizure	Increased muscle tone followed by spasms of muscle contraction and relaxation
Tonic seizure	Increased muscle tone
Clonic seizure	Spasms of muscle contraction and relaxation
Myoclonic seizure	Rhythmic, jerking spasms
Atonic seizure	Sudden loss of all muscle tone
Absence (petit mal) seizure	Brief loss of consciousness, with minor muscle twitches and eye blinking


Current treatments
Vagus nerve stimulation (VNS) or deep brain stimulation (DBS)
Anti-epileptic drugs (AEDs)
Epilepsy treatment methods
Surgery
Diet
H
medXclusive

Classification of AEDs

- Chemical classification
- Therapeutic classification
- On the basis of Mechanism of action

Antiepileptic Drugs

Conventional

Before 1993
Carbamazepine
Clonazepam
Diazepam
Ethosuccimide
Lorazepam
Phenobarbital
Phenytoin
Primidone
Valproic acid

New

1993-2005	2009-2011
Felbamate	Vigabatrin
Gabapentin	Rufinamide
Lamotrigine	Lacosamide
Levetiracetam	Clobazam
Oxcarbazepine	Ezogabine
Pregabalin	
Tiagabine	
Topiramate	
Vagus nerve stimulation	
Zonisamide	

Classification chemical

a) Hydantoin Derivatives:

Phenytoin, Fosphenytoin, Mephenytoin,

b). Iminostilbenes:

Carbamazepine, Oxcarbazepine.

c). Barbiturates:

Phenobarbitone, Primidone

d). GABA-/ Glycine - analog :

Vigabatrin, Gabapentin, Topiramate, Tiagabine; / Felbamate.

e). Sulfonamide derivative:

Zonisamid

f). Antifole:

Lamotrigine.

g). Succinimides:

Ethosuximide, Phensuximide, Methsuximide

h). Valproate Derivative:

Valproic Acid, Valproate Sodium.

I). Oxazolindindiones: (rarely used now)

Trimethadion, Paramethadion & Dimethadione.

J) Carbonic Anhydrase-Inhibitors:

Acetazolamide, Sulthiame.

K). Miscellaneous:

Bromides: KBr, NaBr ;

Acetylureas: Phenacemide,
Phenylacetylurea,

Others: Paraldehyde,
Aminoglutithimide

Antiepileptic drugs include:
remember of "ABCD SHIP"

Aliphatic carboxylic acid
Benzodiazepines/
Barbiturates
Cyclic GABA analogues
DeoxyBarbiturate
Succinimides
Hydantoin
Iminostilbenes
Phenyltriazine

Therapeutic classification

CLASSIFICATION OF ANTIEPILEPTIC DRUGS*

Drugs for Partial Seizures and Generalized Tonic-Clonic Seizures

- Carbamazepine (TEGRETOL)
- Oxcarbazepine (TRILEPTAL)
- Phenytoin (DILANTIN)
- Phenobarbital (LUMINAL)
- Primidone (MYSOLINE)
- Valproic acid (DEPAKENE)[a]

Adjunct Drugs for Partial Seizures

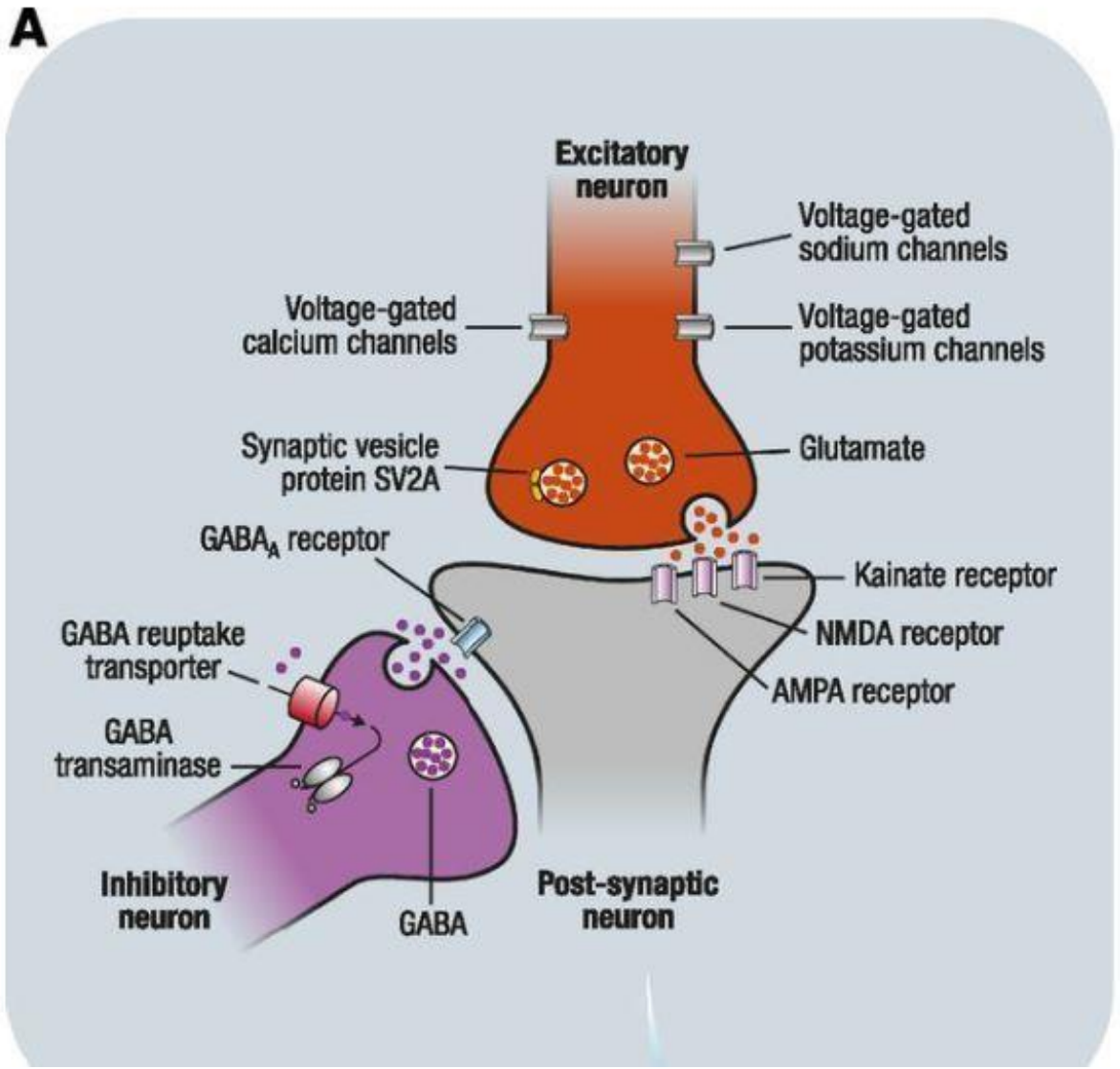
- Clorazepate (TRANXENE)
- Felbamate (FELBATOL)
- Gabapentin (NEURONTIN)
- Lamotrigine (LAMICTAL)
- Topiramate (TOPAMAX)[b]

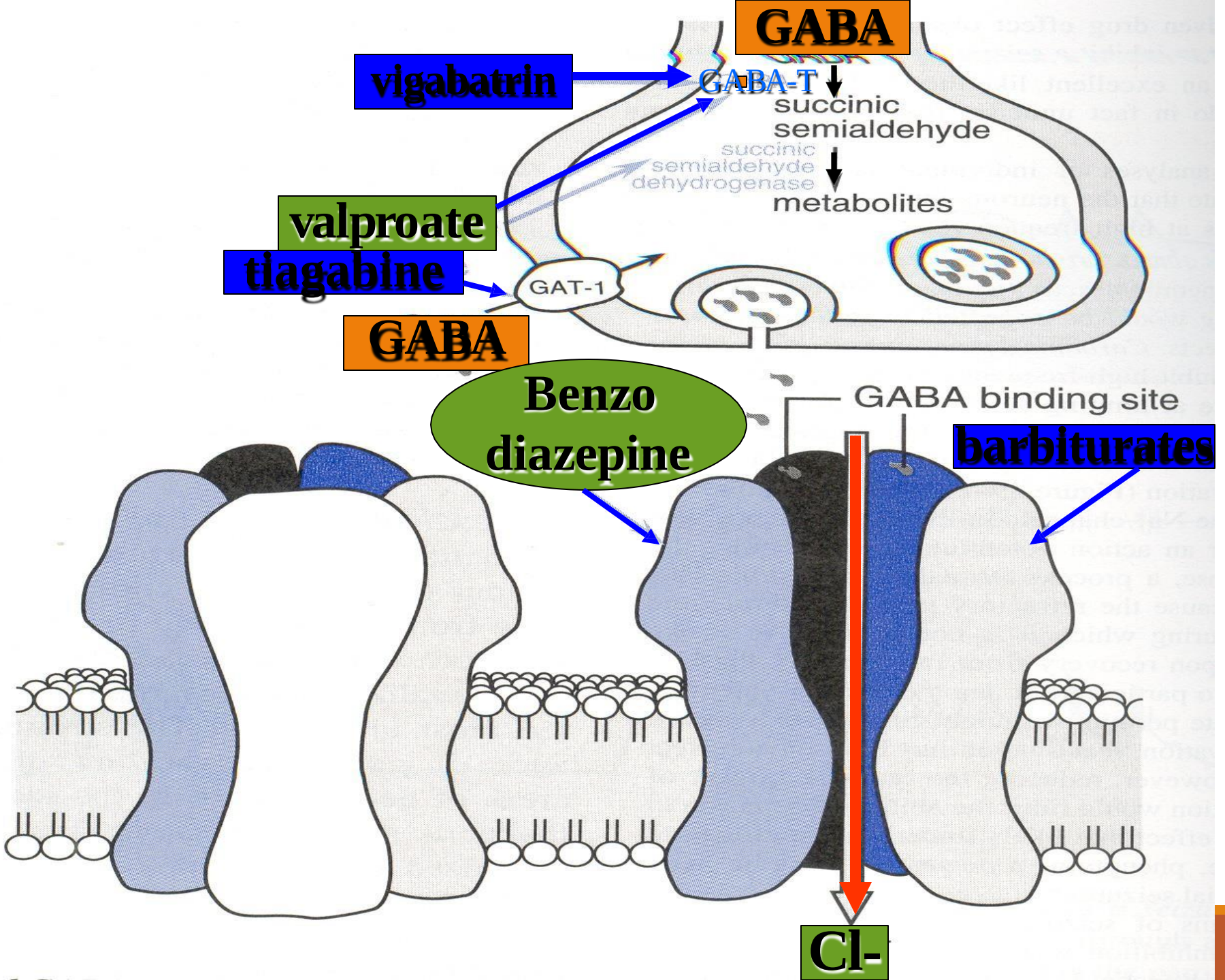
Drugs for Generalized Absence, Myoclonic, or Atonic Seizures

- Clonazepam (KLONOPIN)
- Ethosuximide (ZARONTIN)
- Lamotrigine (LAMICTAL)
- Valproic acid (DEPAKENE)

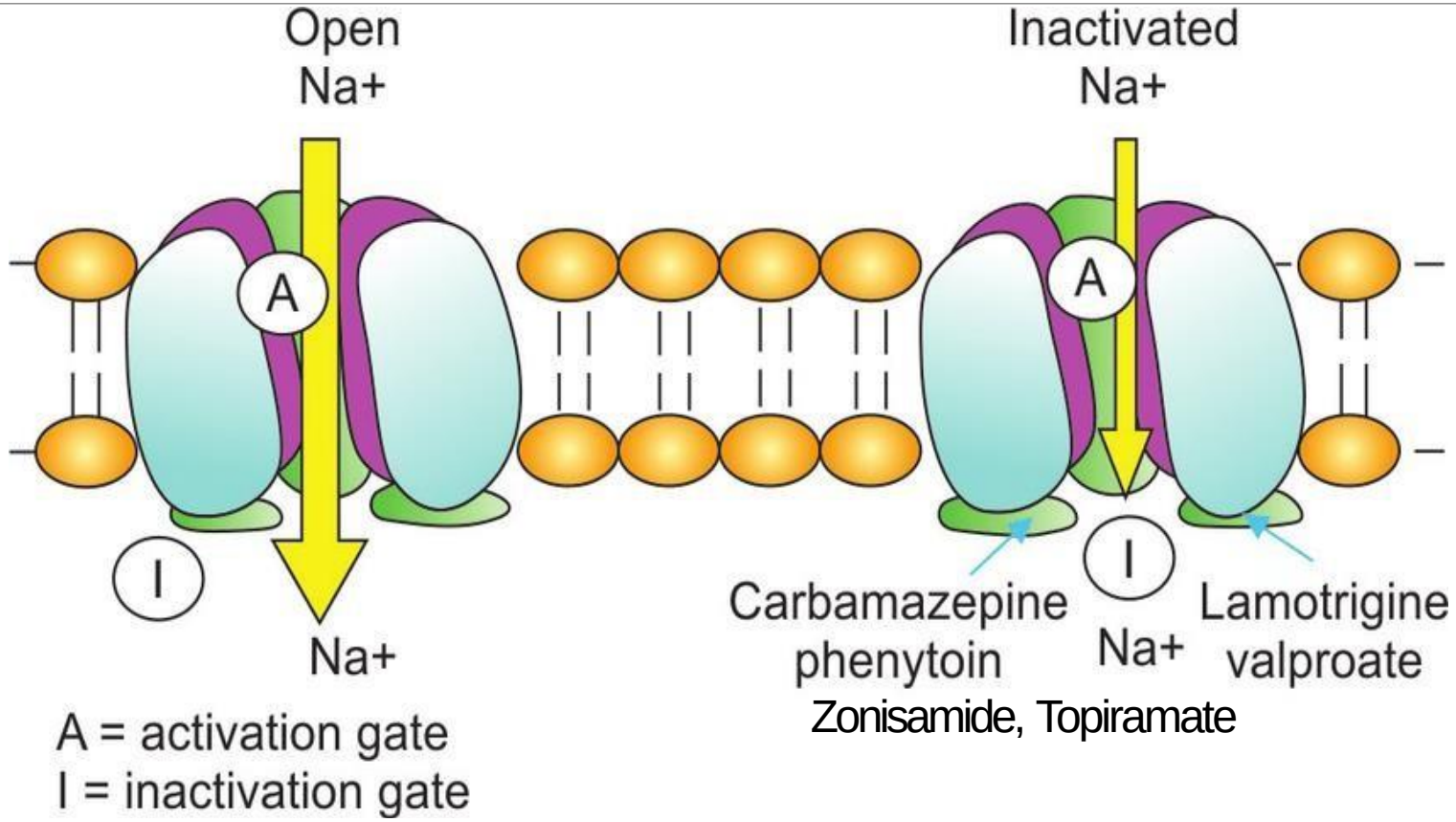
Drugs for Status Epilepticus

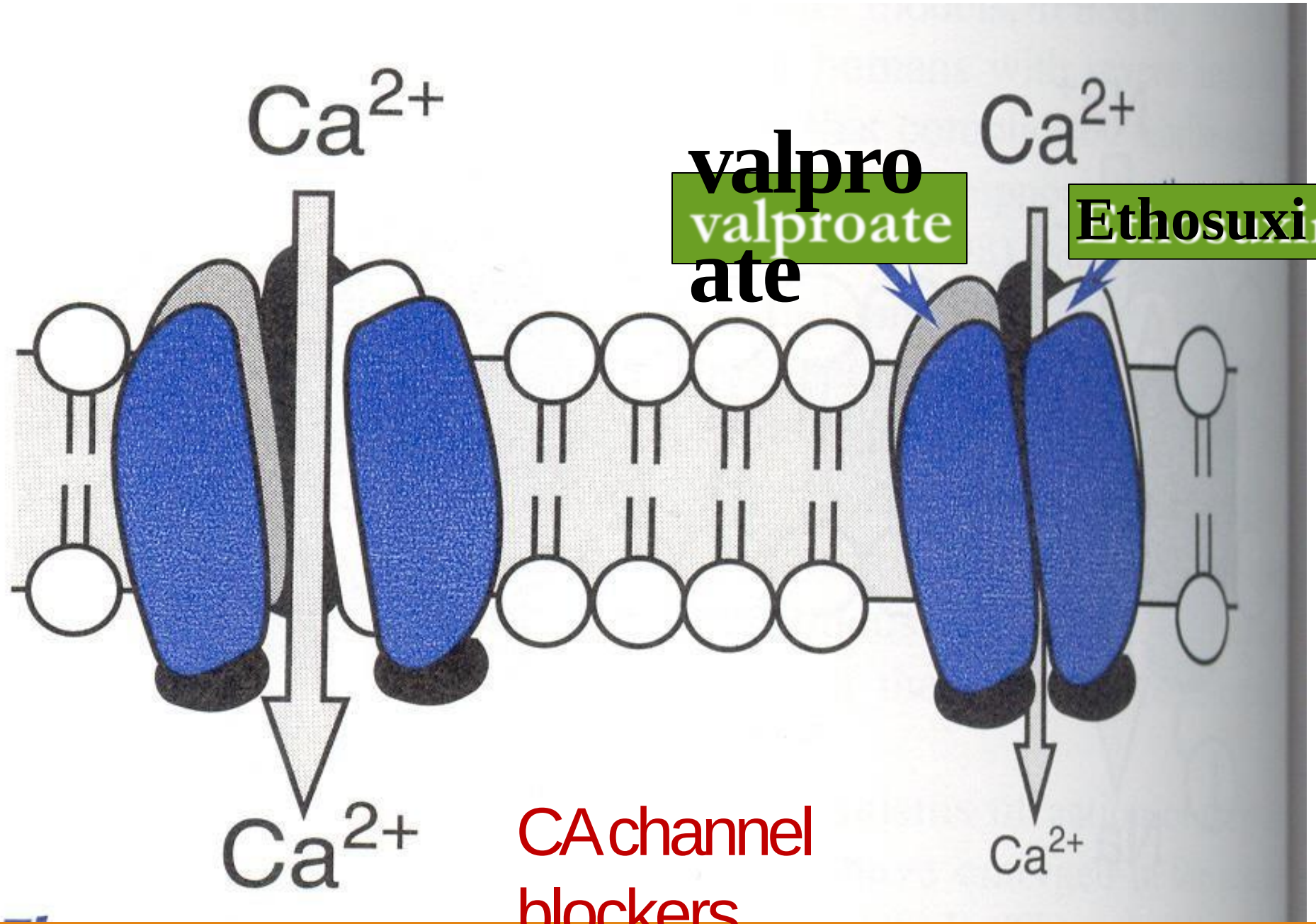
- Diazepam (VALIUM)
- Lorazepam (ATIVAN)
- Phenobarbital (LUMINAL)
- Fosphenytoin (CEREBYX)


A
Excitatory neuron
Voltage-gated sodium channels
Voltage-gated calcium channels
Voltage-gated potassium channels
Synaptic vesicle protein SV2A
Glutamate
GABA$_A$ receptor
Kainate receptor
NMDA receptor
AMPA receptor
GABA reuptake transporter
GABA transaminase
Inhibitory neuron
GABA
Post-synaptic neuron

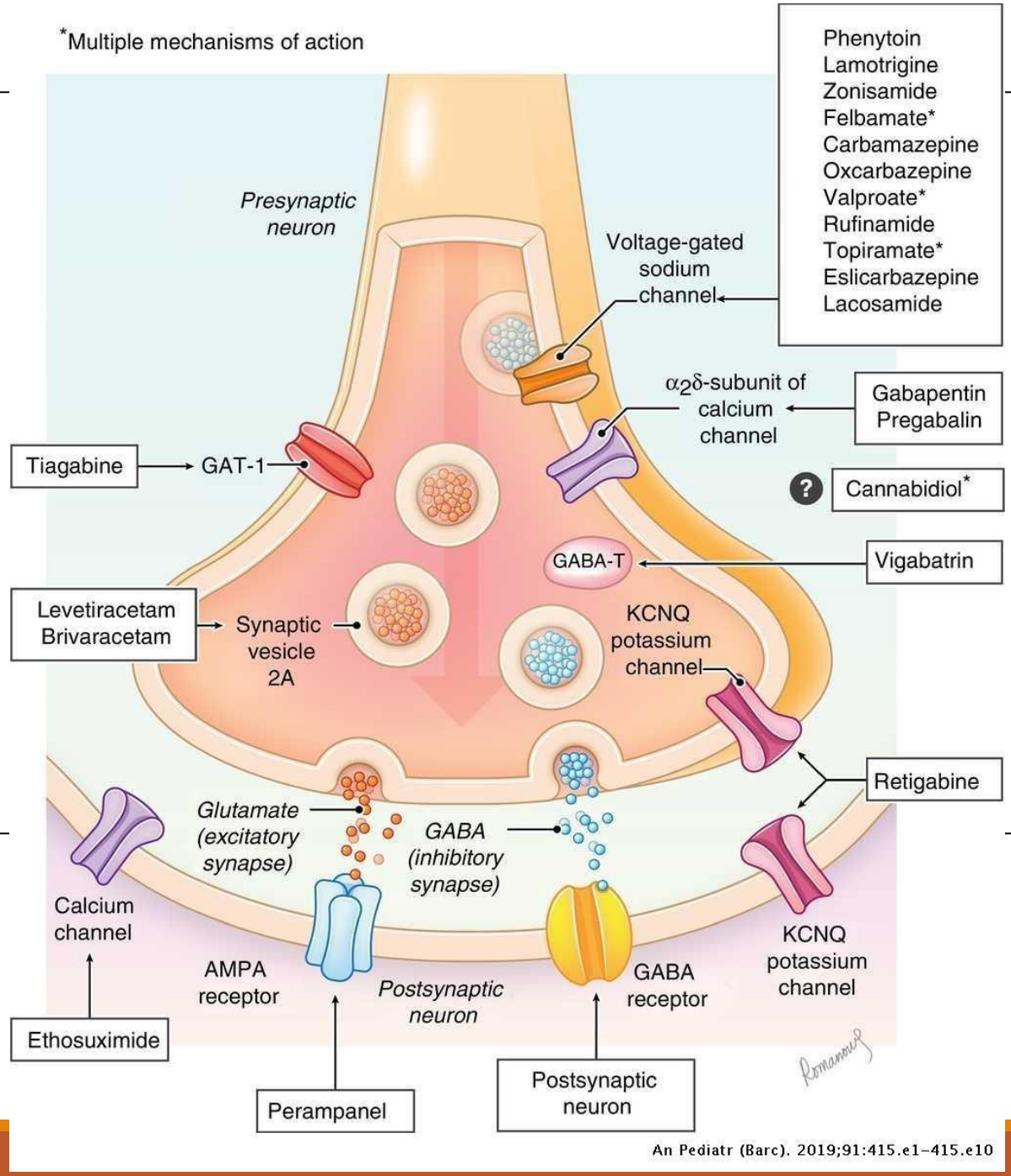

GABA
vigabatrin
GABA-T
succinic
semialdehyde
succinic
semialdehyde
dehydrogenase
metabolites
valproate
tiagabine
GAT-1
GABA
Benzo
diazepine
GABA binding site
barbiturates
Cl-

Na channel
Na channel blockers
blockers





CA channel blockers

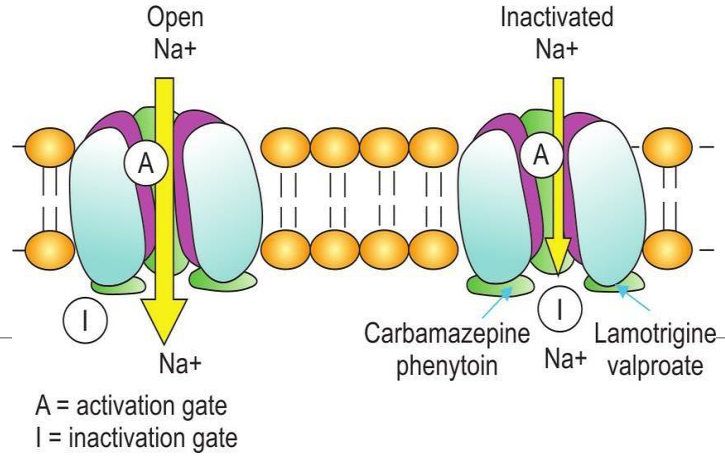

*Multiple mechanisms of action
Phenytoin
Lamotrigine
Zonisamide
Felbamate*
Carbamazepine
Oxcarbazepine
Valproate*
Rufinamide
Topiramate*
Eslicarbazepine
Lacosamide
Presynaptic neuron
Voltage-gated sodium channel
α2δ-subunit of calcium channel
Gabapentin
Pregabalin
Tiagabine
GAT-1
?
Cannabidiol*
GABA-T
Vigabatrin
Levetiracetam
Brivaracetam
Synaptic vesicle 2A
KCNQ potassium channel
Retigabine
Glutamate (excitatory synapse)
GABA (inhibitory synapse)
Calcium channel
AMPA receptor
Postsynaptic neuron
GABA receptor
KCNQ potassium channel
Ethosuximide
Perampanel
Postsynaptic neuron
An Pediatr (Barc). 2019;91:415.e1–415.e10

INDIVIDUAL DRUGS

PHENYTOIN


Phenytoin
Sodium Inj., USP
100 mg/2 mL
NDC 0641-0493-21
NDC 0641-2555-41
Phenytoin
Sodium Inj., USP
250 mg/5 mL
℞ only
(50 mg/mL)
FOR IV OR IM USE
5 mL Single Dose Vial

Mechanism of Action:



it produces changes in:

- Conductance of Na^+, K^+ & Ca^{++}
- Membrane potential (i.e., stabilization)

- It blocks Na^+ channels & thus the action potential esp. when sustained, high frequency & repetitive firing is there.

- There is prolongation of inactivated state of Na^+ conductance by binding with membrane lipids

Uses:

1. Partial Seizures,
2. Generalized Tonic-Clonic Seizures,
3. Status Epilepticus,
4. Neuralgias (Carbamezepine is preferred)
5. Cardiac Arrhythmias (Chronic & Acute Ventricular Arrhythmias & Digoxin-induced arrhythmias)

Toxicity:

Early:

- **Cerebellum & vestibular system:**

  Nystagmus, Diplopia, Ataxias;

- **GIT :**

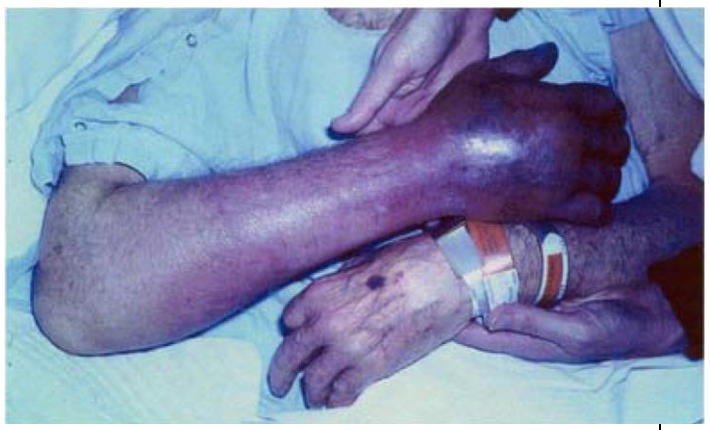
  Nausea, vomiting

- **CNS:**

  Behavioral Changes – sedation, confusion, hallucination, etc.

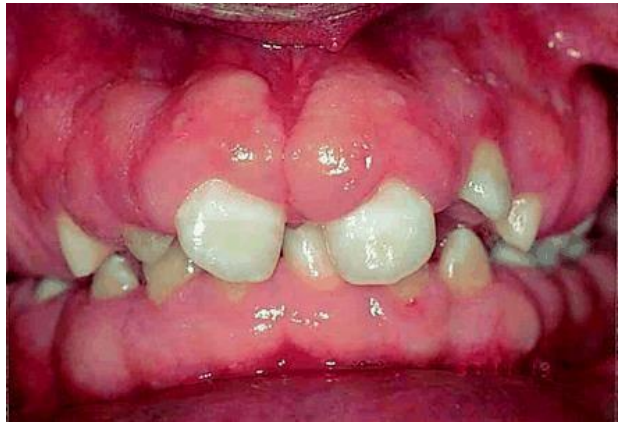
- **Intravenous Infusion:**

  hypotension, ventricular fibrillation
  purple glove syndrome



Later::

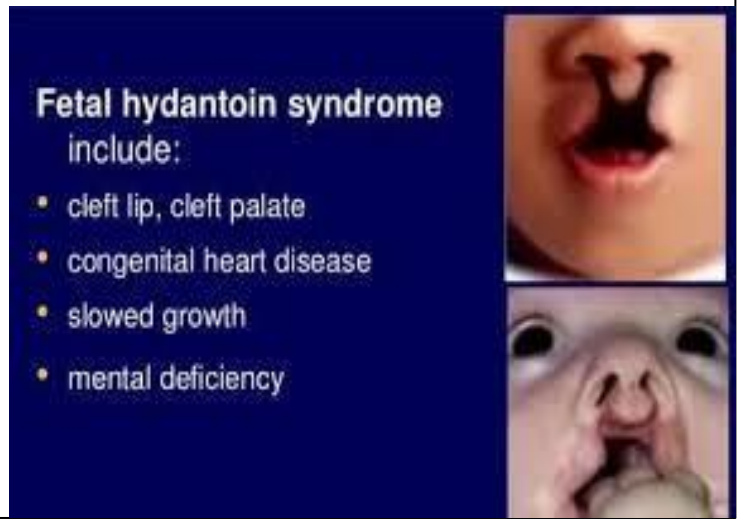
- esp. in children: Gingival hyperplasia, Hirsutism coarsening of facial features
- Vit. B_{12} metabolism interference: Megaloblastic Anemia



Rare:

Hypersensitivity, fever, lymphedenopathy, agranulocytosis, hypoprothrombinemia & hemorrhages esp. in newborns.

Fetal hydantoin syndrome



CARBAMAZEPINE

MOA

Mechanism of Action: (autoinduction)

(similar to phenytoin)

At Therapeutic conc. It blocks Na+ channels & inhibits high frequency repetitive firing of action potential.

It also act pre-synaptically to decrease synaptic transmission

It potentiates post-synaptic actions of GABA.

Uses:

Partial and Generalized Tonic-Clonic Seizures.

Trigeminal Neuralgias

. Bipolar Affective Disorders & mania.

Toxicity:

Early: Diplopia, Ataxia, Nausea, Vomiting.

Later:

- High Doses: Drowsiness, coma, blurred vision.
- Idiosyncrasy: Aplastic anemia,

agranulocytosis, Thrombocytopenia,

Persistant Leukopenia, Eryhtmatous rash.

Serious (Rare): Hepatic dysfunction.

Hyponatremia

VALPROIC ACID

- Mechanism multiple. Broadest spectrum AED
- (GABA enhance: GABA T–ve: Na, CA blockers;
- K channel opener)

- Absorption affected by food,BA 80%
- PPB increased, Enzyme inhibitor

- T/U.All seizure types, bipolar disorder, migraine

- Adverse effects
- GIT disturbance,hepatic dysfunction,
  ,thrombocytopenia, teratogenic (sb), wt gain,

ETHOSUCCIMIDE

- T-Type Ca current inhibits
- Na and K channels

- No PPB

A/E

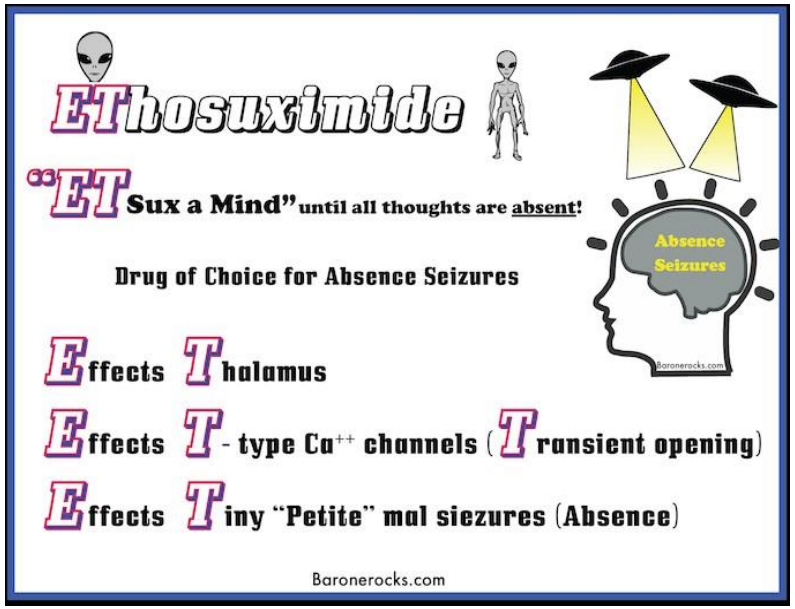
- GIT distress, lethargy, headache

T/U

- Absence seizure
- GTC

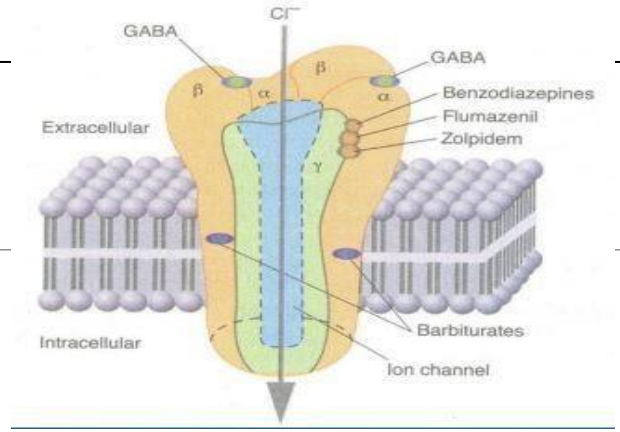
Ethosuccimide

Ethosuximide is Administered to treat Absence Seizures



BARBITURATES

Mechanism of Action:



i. Enhancement of inhibition
ii. Inhibition of excitation

1. Therapeutic conc..... GABA mimetic
2. Therapeutic conc.....blocks release of glutamate

3. High conc.....Suppress high-frequency repetitive firingin neurons in culture through an action on N conductance

4. High conc.....barbiturates block some Ca^{2+} currents (L-type and N-type).

Clinical Uses

- partial seizures
- generalized tonic-clonic seizures

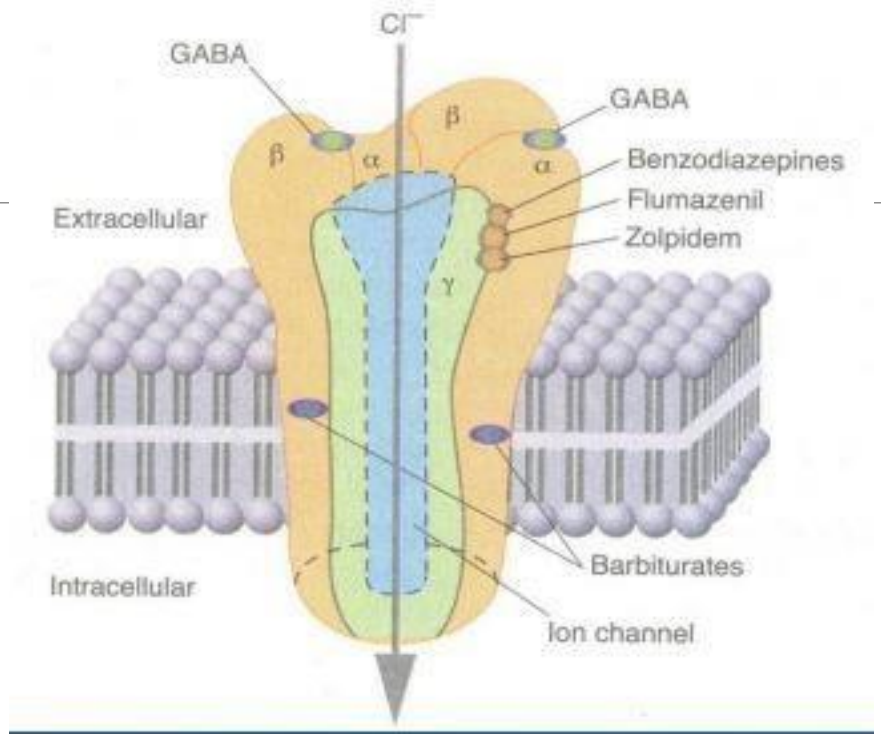
- Kernicterus
- Sedative &Hypnotic
- General Anaesthetic

BENZODIAZEPINES

Benzodiazepines

- Diazepam, Lorazepam
- GABAergic

- Status epilepticus, febrile convulsions, GTC, partial
- Limitations.. Sedation and tolerance



Newer drugs/Add-on /Adjuvant drugs

Vigabatrin:

MOA

- Irreversible inhibitor of GABA aminotransaminase (GABA-T), the enzyme responsible for the degradation of GABA.

- It may also inhibit the vesicular GABA transporter.

Typical toxicities

- drowsiness, dizziness, and weight gain. Visual loss

- agitation, confusion, and psychosis;

Contraindication.

- preexisting mental illness

***Uses*:**

- treatment of partial seizures and West's syndrome.

- *The half-life is approximately 6–8 hours, but considerable evidence suggests that the pharmacodynamic activity of the drug is more prolonged and not well correlated with the plasma half-life.*

Lamotrigine:

MOA

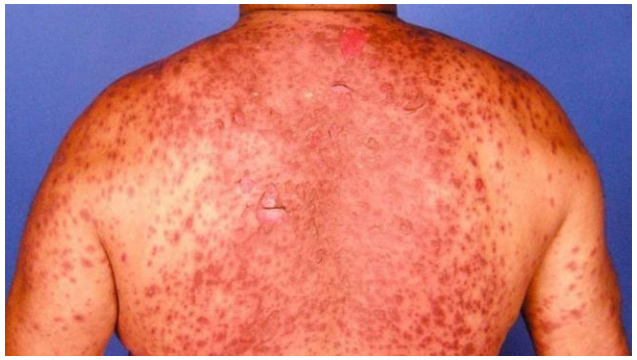
- Suppresses sustained rapid firing of neurons and produces a *voltage- and use-dependent inactivation of Na channels*.
- inhibits voltage-gated Ca^{2+} channels,
- decreases the synaptic release of glutamate.

Uses

- Add-on/monotherapy for partial seizures
- absence and myoclonic seizures in children.
- bipolar disorder.

Adverse effects

- dizziness, headache, diplopia
- nausea, somnolence, skin rash.
- The rash is a typical hypersensitivity reaction; its risk may be diminished by introducing the drug slowly, pediatric patients are at high risk; some studies suggest that a potentially life-threatening dermatitis will develop in 1–2% of pediatric patients.



Gabapentin / Pregabalin:

- Gabapentin is an amino acid, an analog of GABA, that is effective against partial seizures.
- Pregabalin is another GABA analog, closely related to gabapentin.
- This drug has been approved for both antiseizure activity, analgesic properties & muscle relaxant.

Mechanism of Action

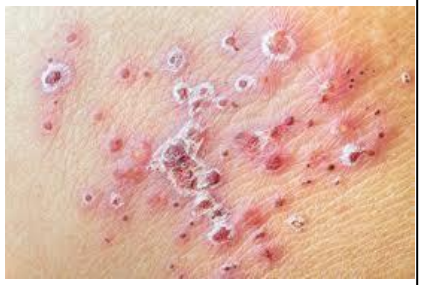
- In spite of their close structural resemblance to GABA, gabapentin and pregabalin do not act directly on GABA receptors.

- Binds to $\alpha 2\delta$ subunit of Ca channels
- Modify release of glutamate

Gabapentin follows saturation kinetics… absorption by L amino acid transport is saturated… bioavailability is decreased

Uses:

- Gabapentin & Pregablin both are effective as an adjunct against
- partial seizures
- generalized tonic-clonic seizures in larger doses.
- neuropathic pain



Adverse effects (No DDI)

- somnolence, dizziness, ataxia, headache, and tremor.

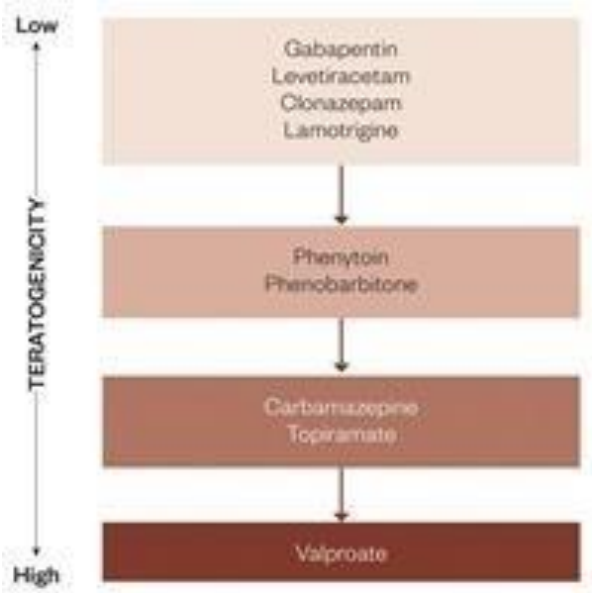
Status epilepticus

- IV benzodiazepines…lorazepam is preferred
- IV phenytoin/Phenobarbitals /valproic acid
- General anaesthetics

Teratogenicity

- Valproic acid, phenobarbital, phenytoin, topiramate ,carbamazepine are teratogenic

- Lamotrigine n levetiracetam are safe



Mechanism of Action

TABLE 20-2 Mechanisms of Selected Antiepileptic Drugs

DRUG	EFFECTS ON ION FLUX	EFFECTS ON GABA	EFFECTS ON GLUTAMATE
Carbamazepine	Blocks voltage-sensitive sodium channels	—	—
Clonazepam	—	Enhances GABA-mediated chloride flux	—
Clorazepate	—	Enhances GABA-mediated chloride flux	—
Diazepam	—	Enhances GABA-mediated chloride flux	—
Ethosuximide	Blocks T-type calcium channels	—	—
Felbamate	—	—	Blocks glycine activation of NMDA receptors
Gabapentin	—	Increases GABA release	—
Lamotrigine	Blocks voltage-sensitive sodium channels	—	—
Lorazepam	—	Enhances GABA-mediated chloride flux	—
Phenobarbital	—	Enhances GABA-mediated chloride flux	—
Phenytoin	Blocks voltage-sensitive sodium channels	—	—
Primidone	Possibly blocks voltage-sensitive sodium channels	Enhances GABA-mediated chloride flux	—
Topiramate	Blocks voltage-sensitive sodium channels	Increases GABA activation of $GABA_A$ receptors	Blocks kainate and AMPA receptors
Valproate	Possibly blocks voltage-sensitive sodium channels and T-type calcium channels	Increases GABA synthesis and inhibits GABA degradation	Possibly decreases glutamate synthesis

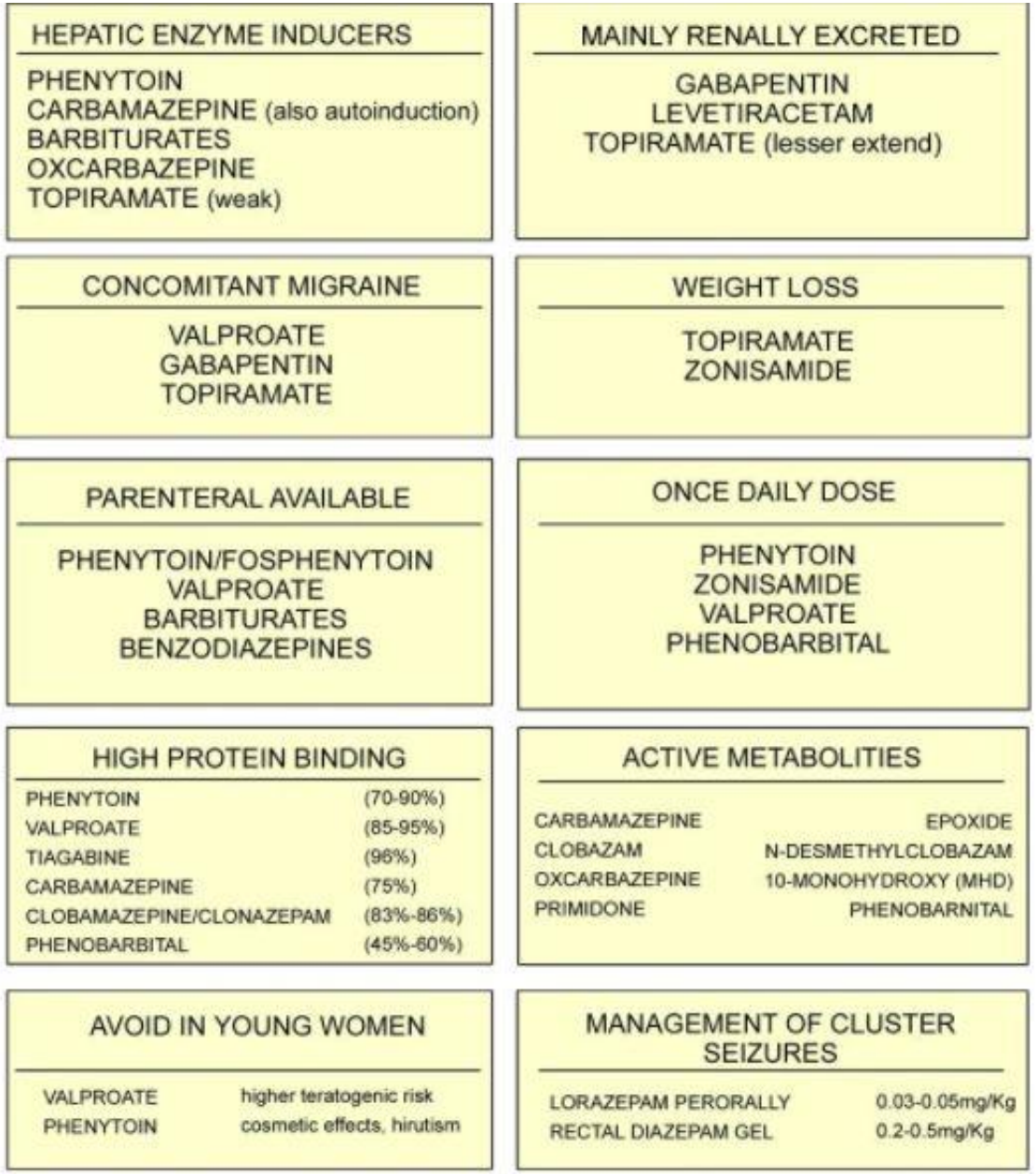
ADVERSE EFFECTS

Antiepileptic Drug	Adverse Effects
Benzodiazepines	Sedation, tolerance, dependence
Carbamazepine	Diplopia, cognitive dysfunction, drowsiness, ataxia; rare occurrence of severe blood dyscrasias and Stevens-Johnson syndrome; induces hepatic drug metabolism; teratogenic potential
Ethosuximide	Gastrointestinal distress, lethargy, headache, behavioral changes
Felbamate	Aplastic anemia, hepatic failure
Gabapentin	Dizziness, sedation, ataxia, nystagmus; does not affect drug metabolism (pregabalin is similar)
Lamotrigine	Dizziness, ataxia, nausea, rash, rare Stevens-Johnson syndrome
Levetiracetam	Dizziness, sedation, weakness, irritability, hallucinations, and psychosis
Oxcarbazepine	Similar to carbamazepine, but hyponatremia is more common; unlike carbamazepine, does not induce drug metabolism
Perampanel	Dizziness, somnolence, headache; behavioral hostility, anger. Drug interactions with CYP inducers (carbamazepine, oxcarbazepine, phenytoin)
Phenobarbital	Sedation, cognitive dysfunction, tolerance, dependence, induction of hepatic drug metabolism; primidone is similar
Phenytoin	Nystagmus, diplopia, sedation, gingival hyperplasia, hirsutism, anemias, peripheral neuropathy, osteoporosis, induction of hepatic drug metabolism
Retigabine (ezogabine)	Dizziness, somnolence, confusion, dysarthria, pigment discoloration of retina and skin
Tiagabine	Abdominal pain, nausea, dizziness, tremor, asthenia; drug metabolism is not induced
Topiramate	Drowsiness, dizziness, ataxia, psychomotor slowing and memory impairment; paresthesias, weight loss, acute myopia
Valproic acid	Drowsiness, nausea, tremor, hair loss, weight gain, hepatotoxicity (infants), inhibition of hepatic drug metabolism
Vigabatrin	Sedation, dizziness, weight gain; visual field defects with long-term use, which may not be reversible
Zonisamide	Dizziness, confusion, agitation, diarrhea, weight loss, rash, Stevens-Johnson syndrome

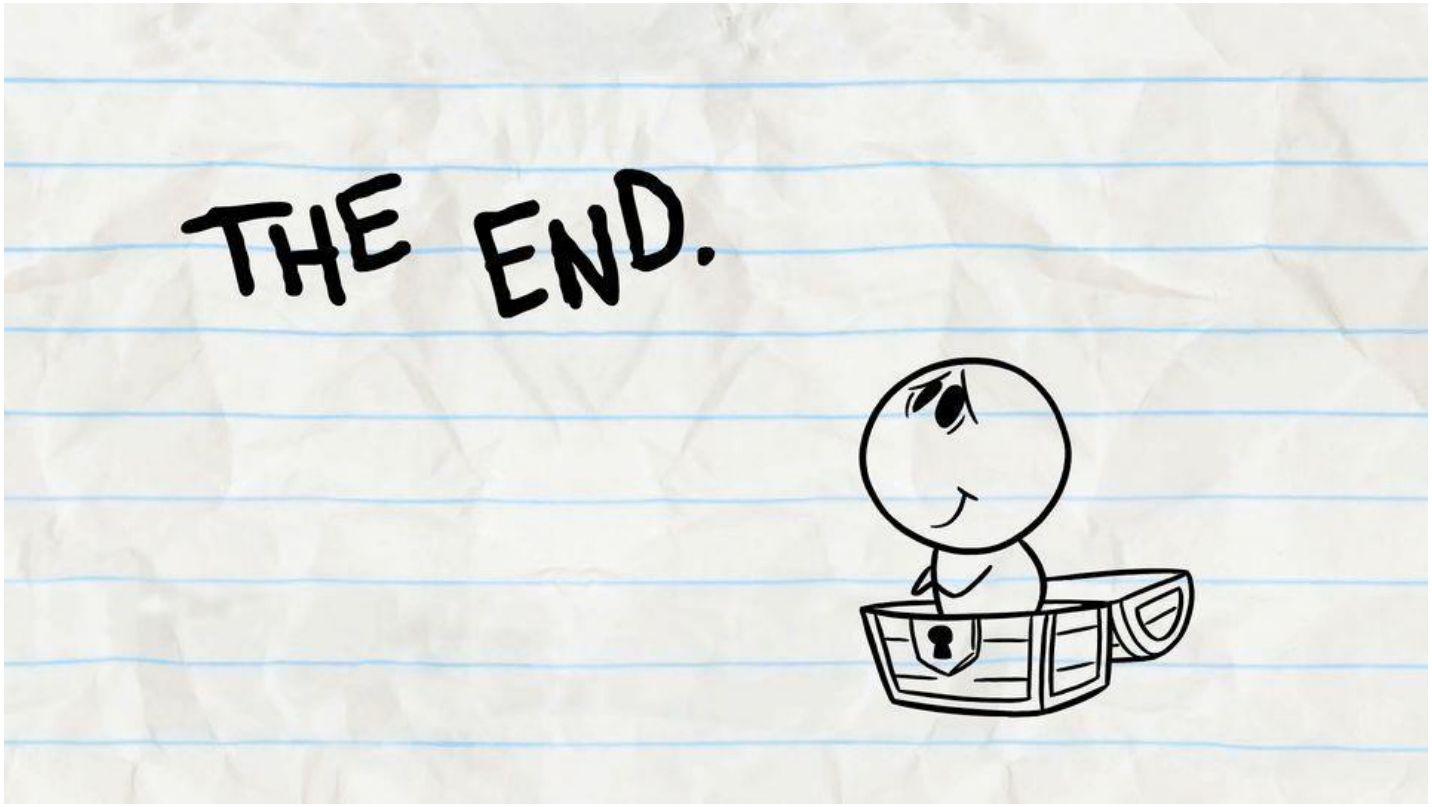
Drug drug interaction (DDI)

TABLE 20-4 Interactions of Antiepileptic Drugs

ANTIEPILEPTIC DRUG	INTERACTING DRUGS THAT INCREASE SERUM LEVELS*	INTERACTING DRUGS THAT DECREASE SERUM LEVELS†	INTERACTIONS THAT CAUSE OTHER EFFECTS
Carbamazepine	Cimetidine, diltiazem, erythromycin, fluoxetine, isoniazid, and propoxyphene	Carbamazepine	Decreases serum levels of calcium channel blockers, clozapine, haloperidol, steroids, theophylline, thyroid, and warfarin Increases lithium toxicity.
Clonazepam	Cimetidine and disulfiram	Rifampin	Increases central nervous system (CNS) depression if alcohol is ingested
Clorazepate	Cimetidine and disulfiram	Rifampin	Increases CNS depression if alcohol is ingested.
Diazepam	Cimetidine	Rifampin	Increases CNS depression if alcohol is ingested
Ethosuximide	Valproate	—	May alter seizure pattern if taken in combination with haloperidol
Felbamate	—	Carbamazepine and phenytoin	Increases CNS depression if alcohol is ingested
Gabapentin	—	Antacids	—
Lamotrigine	Valproate	Carbamazepine, phenobarbital, and phenytoin	Decreases serum levels of valproate
Lorazepam	—	Rifampin	Increases CNS depression if alcohol is ingested
Phenobarbital	Valproate	Phenobarbital	Decreases serum levels of many drugs; increases meperidine toxicity
Phenytoin	Chloramphenicol, cimetidine, isoniazid, and sulfonamides	Carbamazepine	Decreases serum levels of amiodarone, digoxin, quinidine, steroids, theophylline, vitamin K, and other agents
Primidone	Valproate	Phenobarbital	—
Topiramate	—	Carbamazepine and phenytoin	Decreases serum levels of oral contraceptives
Valproate	Salicylates	Carbamazepine, lamotrigine, and phenytoin	May increase or decrease serum levels of carbamazepine and phenytoin



Pearls of antiepileptic drug use and management.


THE END.