3. Anti-seizure Drugs

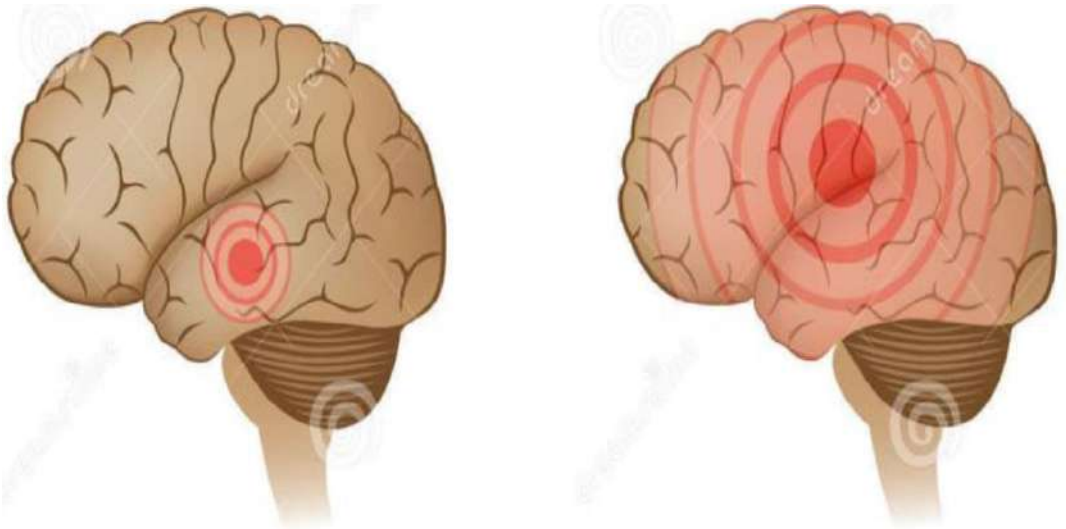
ANTICONVULSANT OR ANTIEPILEPTIC DRUGS

Epilepsy is a neurological condition affecting the nervous system in which clusters of nerve cells, in the brain signal abnormally,causing:

- Strange sensations, emotions and behavior.
- Convulsions.
- Muscle spasms.
- Loss of consciousness.

Introduction

- Seizures result from the ***sudden***, ***excessive*** firing of neurons.
- Seizures are broadly classified as:
  1. ***Partial*** (local, focal) seizures: the abnormal firing initially occurs in a small number of neurons, but spread to adjacent areas.
  2. ***Generalized*** seizures: the entire brain is affected simultaneously



Partial seizure

Generalized seizure

SEIZURE

Partial

Seizure activity starts in one part of the brain

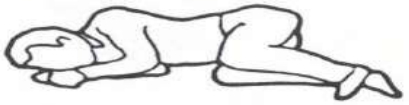
Simple

Seizure activity while the person is alert

Complex

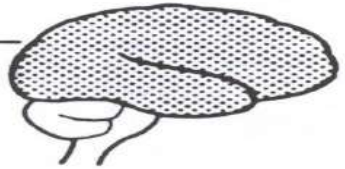
Seizure activity with change in awareness of surroundings

With secondary generalization



Seizure activity begins in one area and spreads

Generalized



Seizure activity involves the whole brain

Absence

Staring and blinking without falling

Myoclonic

Jerking movements of the body

Tonic–clonic

Stiffening, falling and jerking of the body

Tonic

Falling heavily to the ground

Atonic

TABLE 17.1 Classification of Epileptic Seizures

Classification	Subtypes
Partial (local, focal) seizures	Simple (consciousness not impaired)
	Complex partial seizures (psychomotor seizures) 1. Beginning as simple partial seizures, progressing to complex seizures 2. With impairment of consciousness at onset
	Partial seizures evolving to secondarily generalized tonic-clonic convulsions
Generalized seizures (convulsive or nonconvulsive)	Absence seizures: typical (petit mal) and atypical
	Myoclonic
	Clonic
	Tonic
	Tonic-clonic (grand mal)
	Atonic
Unclassified epileptic seizures (includes some neonatal seizures)	

Myoclonic seizure

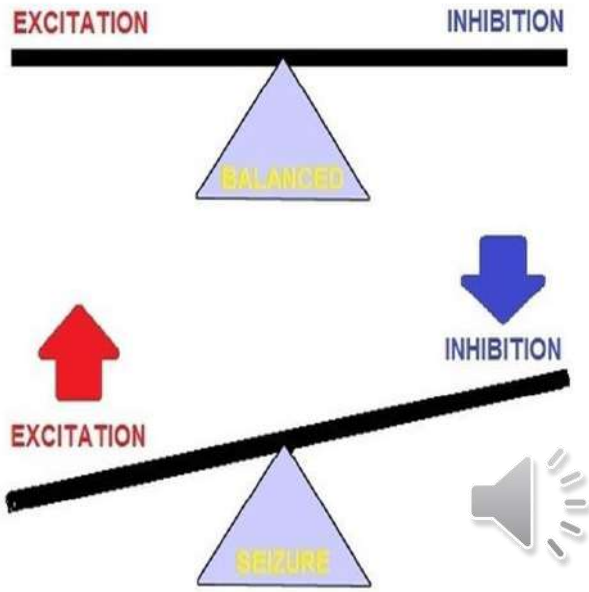
Major muscle groups contract quickly

Why does excessive firing of neurons happen?

1. ***Mutation*** in the ion channels will lead to seizures and epilepsy. K+, Na+ and Cl- ion channels play important role

2. ***Imbalance*** between synaptic inhibition and excitation:

- Normal brain physiology is the product of balanced interaction between excitatory and inhibitory processes.
- The predominant **inhibitory** neurotransmitter in brain is **GABA**.
- The predominant **excitatory** neurotransmitter is **glutamate.**
- Increased excitation or decreased inhibition may result in seizure activity.



Anti-seizure drugs

- The first agents used to treat epilepsy were KBr and phenobarbital, then phenytoin.
- Anti-seizure drugs are divided to two main lines: ***frontline*** and ***adjunct*** medications.

Frontline drugs:

Carbamazepine.

Benzodiazepine (Clonazepam & Diazepam).

Ethosuximide.

Phenytoin.

Phenobarbital.

Primidone.

Adjunct drugs:

Felbamate.
Gabapentin.
Lamotrigine.
Levetiracetam.
Oxcarbazepine

Tiagabine.
Topiramide.
Valproic acid.
Zonisamide.
Vigabatrin.

Standard AEDs

Phenytoin, carbamazepine, phenobarbital, primidone, valproate, ethosuximide, and the benzodiazepines

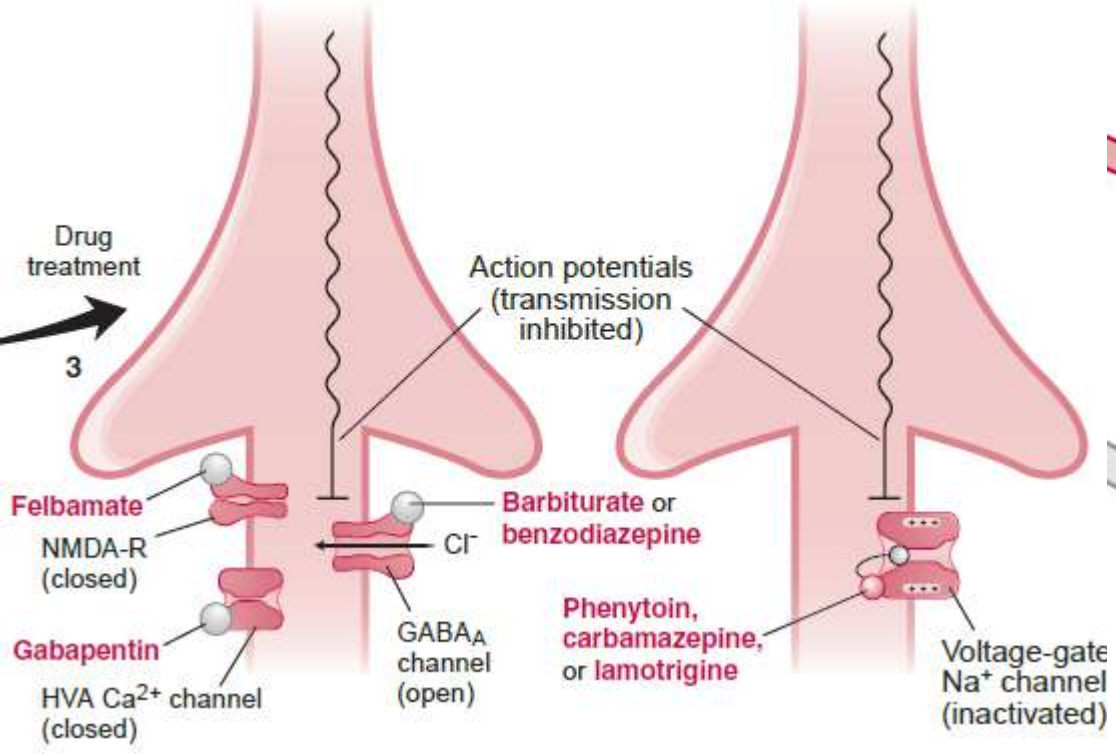
New generation of AEDs

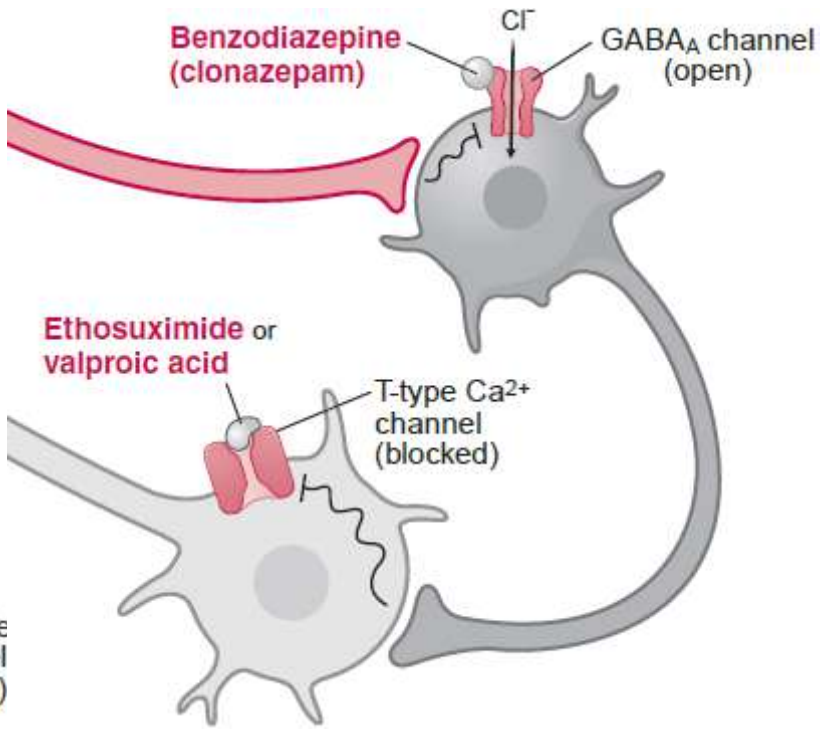
felbamate, gabapentin, lamotrigine, oxcarbazepine, Eslicarbazepine, levetiracetam, tiagabine, topiramate, zonisamide, and vigabatrin

Pharmacological targets of anti-seizure drugs

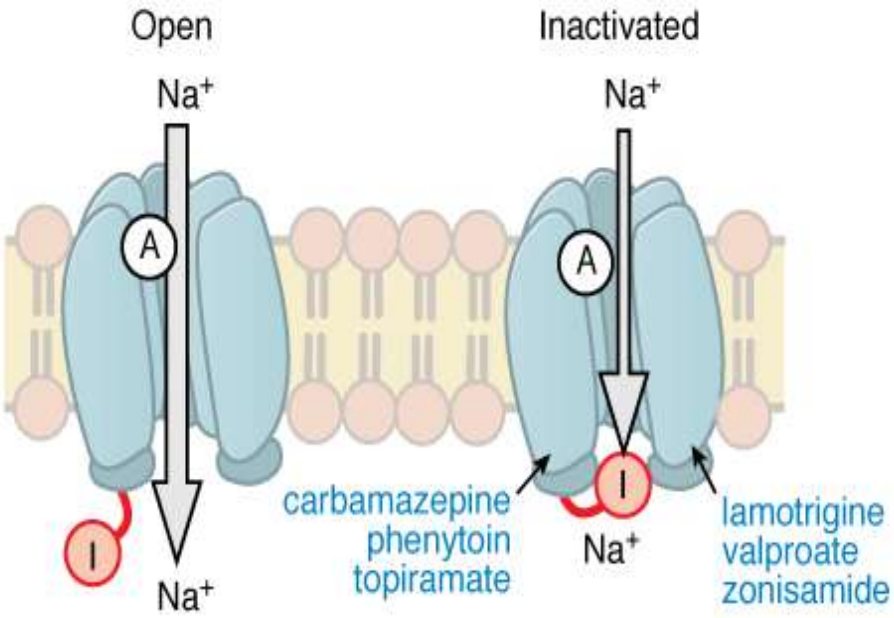
1. **GABA system**: Increase inhibitory neurotransmitter system
2. **Glutamate system**: Decrease excitatory neurotransmitter system
3. **Ion channels**: Block voltage-gated inward positive currents (Na^+ or Ca^{++}).

Many AEDs act via multiple mechanisms on different targets.





PROLONGATION OF Na+ CHANNEL INACTIVATION

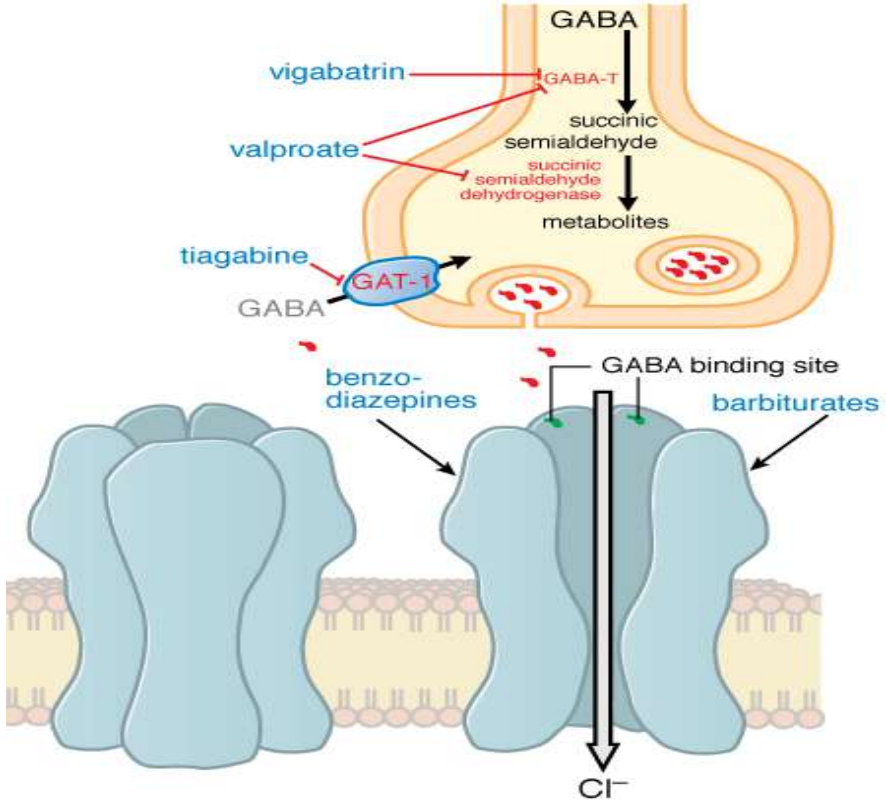


INHIBITION OF 'T' TYPE Ca^{2+} CURRENT

- Ethosuximide
- Trimethadione
- Valproate

FACILITATION OF GABA MEDIATED Cl CHANNEL OPENING

- Barbiturate (Barb.)
- Benzodiazepine (Bzd.)
- Vigabatrin (Viga.)
- Valproate (Valpr.)
- Gabapentin (Gabp.)
- Tiagabine (Tiag.)



1. GABA system

The potential targets for AED's action on the GABAergic inhibitory synapses include:

1. GABA-modulating agents (e.g. barbiturates, BZDs)
2. Drugs that inhibit GABA degradation (vigabatrin)
3. Drugs that inhibit the reuptake of GABA (tiagabine)
4. Drugs that enhance the biosynthesis of GABA (gabapentin, pregabalin, and VPA)

Benzodiazepines

The benzodiazepines produce their anti-seizure effects by enhancing the effect of the inhibitory neurotransmitter GABA on the GABAA chloride channel.

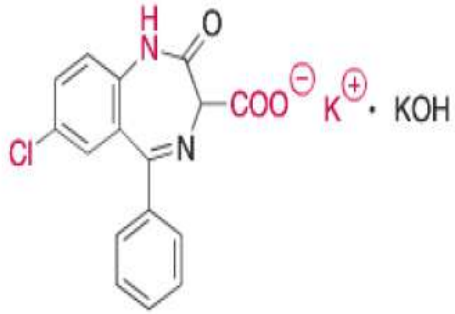
Diazepam administrated IV or IM is the drug of choice for rapid control of status epilepticus (emergency case).

Clorazepate dipotassium will undergo decarboxylation at the acidic pH of the stomach. The importance of COOH at C3 of ring B is to form salt to increase water solubility of the drug.

Diazepam

Clonazepam

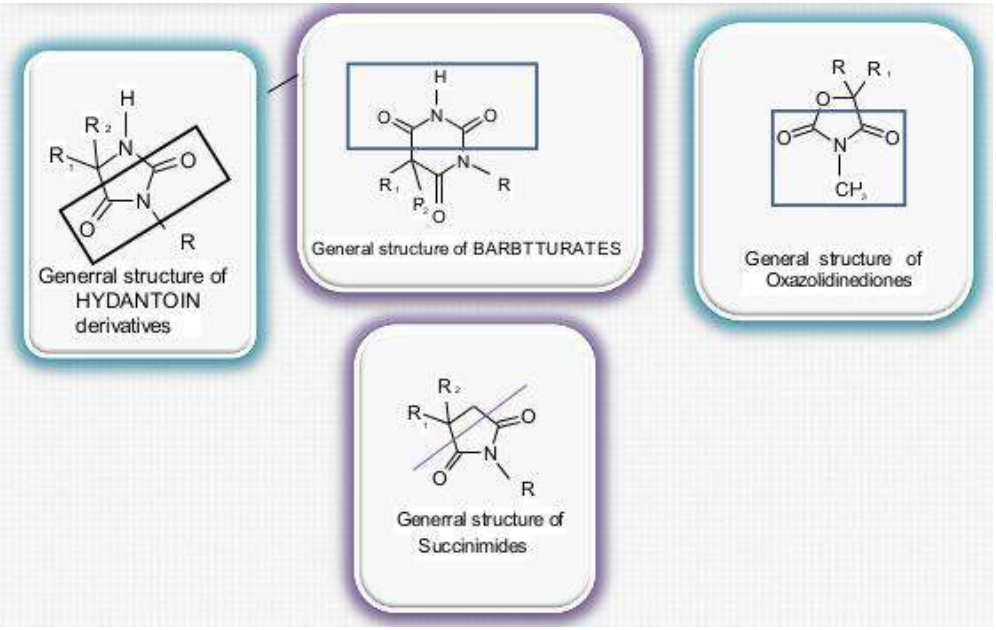
Lorazepam

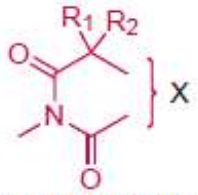


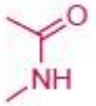
Clorazepate dipotassium

Midazolam

Urea derivatives





Class of Compounds	X
Barbiturates	
Hydantoins	
Oxazolidinediones	
Succinimides	

R and R1**:** both should be hydrocarbon.

** If they are lower alkyls: active against absence seizures and not active against generalized tonic-clonic or partial seizures.

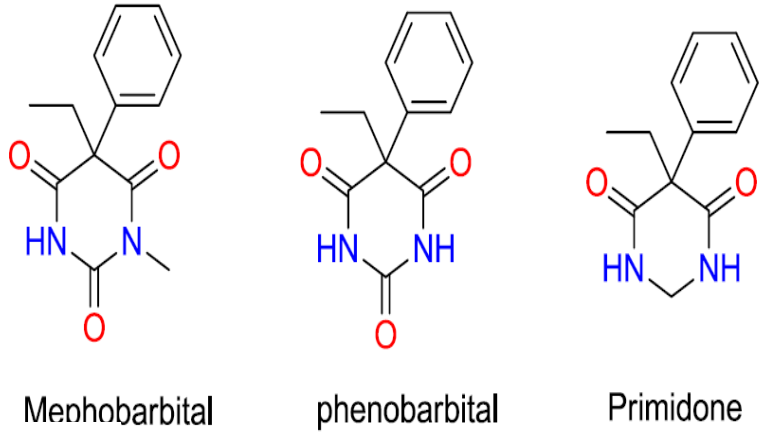
If one of the hydrocarbon substituents is an aryl group: the activity will be directed toward generalized tonic-clonic and partial seizures, and not toward antiabsence activity.

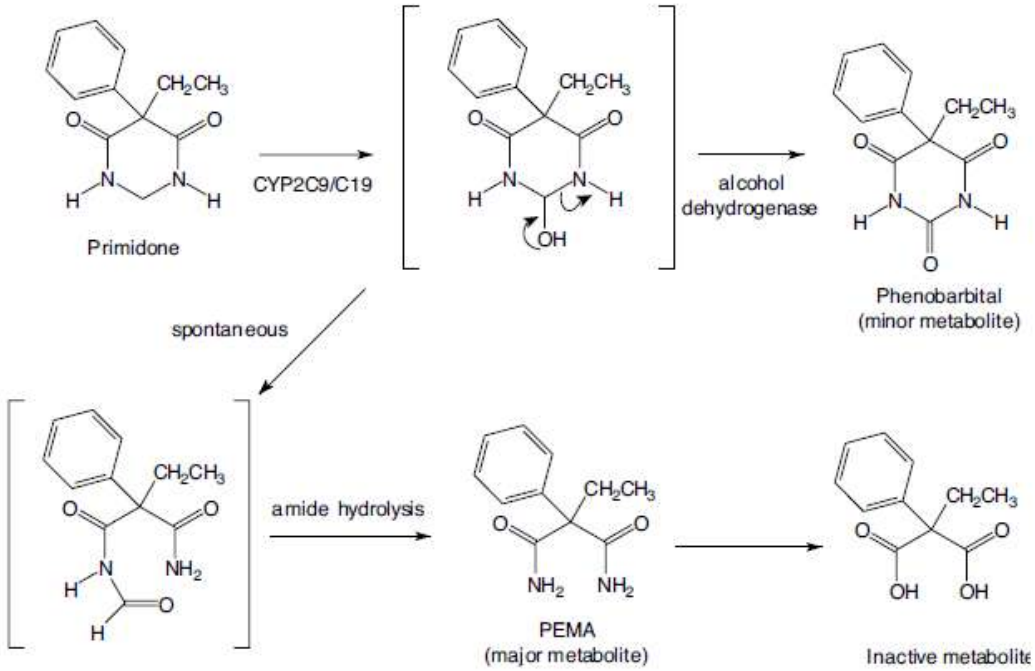
Anticonvulsant groups:

A. Barbiturates.
B. Hydantoins.
C. Oxazolidinediones.
D. Succinimides.
E. Ureas and monoacylureas.

A. Barbiturates

The mechanism of anti-seizure action for the barbiturates is thought to involve blockade of sodium channels and enhancement of GABA-mediated inhibitory transmission.

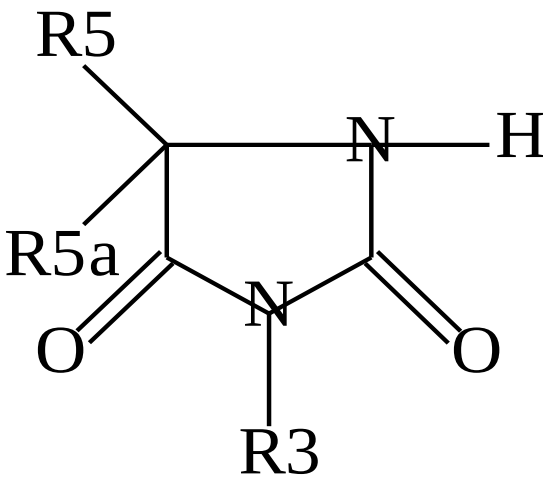


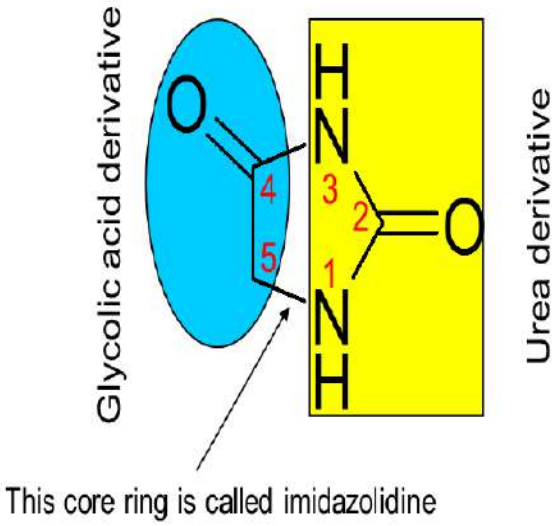


Phenobarbital is enzyme inducer

B. Hydantoins (Sodium ion channels)

Also called glycolylurea; a compound that is formed from condensation of urea with glycolic acid.



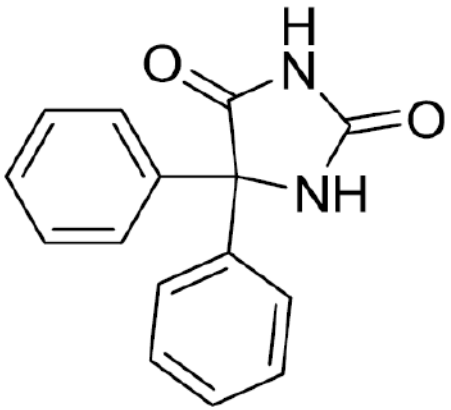


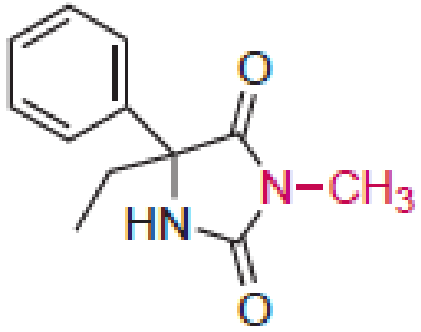
They have antigeneralized tonic-clonic activity rather than antiabsence activity.

EXAMPLES: A. **Phenytoin.** B. **Mephenytoin.** C. **Ethotoin.**

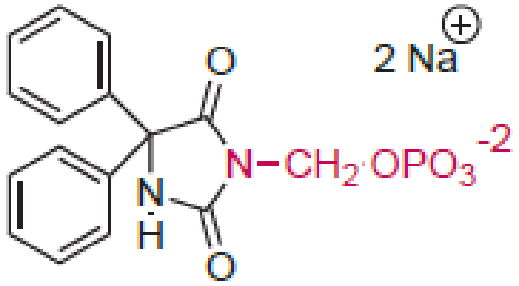
Phenytoin:(Dilantin)

- 5,5-diphenyl hydantoin.
- ***Insoluble*** in water, so prepared as sodium salts for being suitable for injection.
- Useful against all types of seizures EXCEPT absence seizures.
- Fosphenytoin sodium is a soluble prodrug disodium phosphate ester of phenytoin (142 mg/mL)
- is rapidly absorbed by the IM route (37). It is rapidly metabolized to phenytoin by in vivo phosphatases.





Mephenytoin



Phosphenytoin

Phenytoin is Enzyme inducer and lead to drug interactions
SE: include gingival hyperplasia

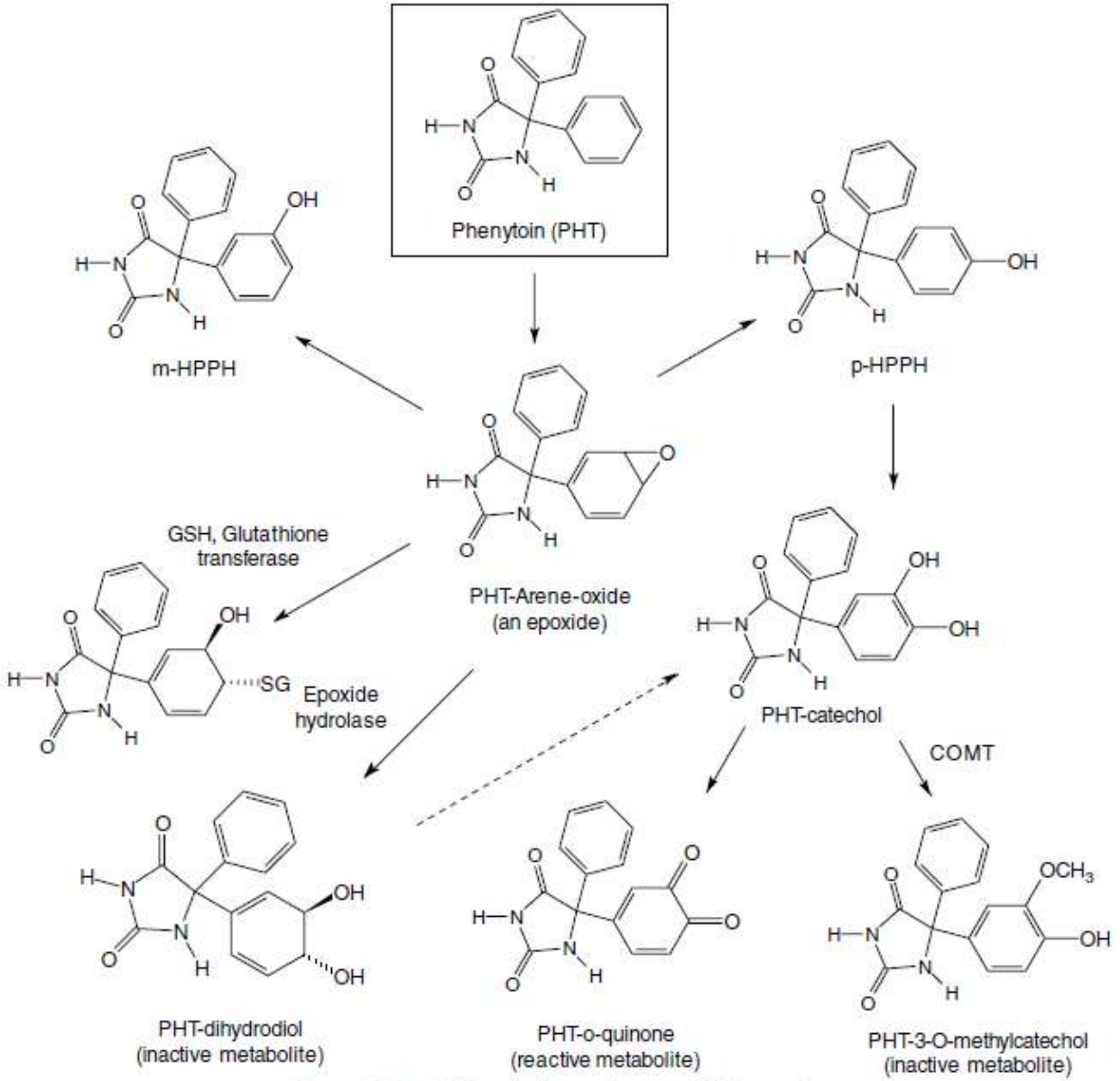
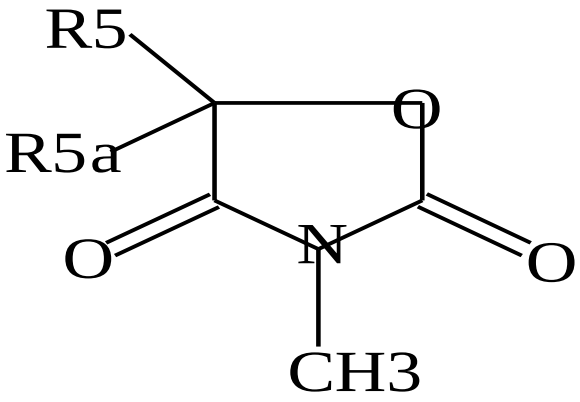
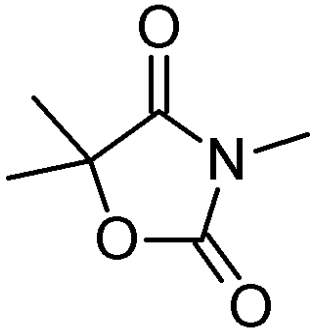


Figure 14.6 • Metabolic pathways of phenytoin.

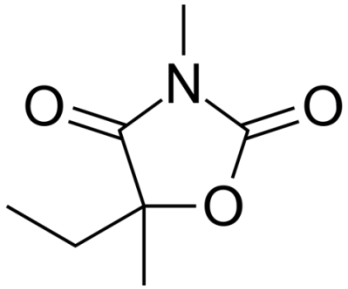
C. Oxazolidinediones



- Structurally similar to hydantoins with replacement of the N-H at position 1of the hydantoin system with an oxygen atom.
- Active against absence seizures.
- They reduce T-type ***calcium*** currents in thalamic neurons



Trimethadione



Paramethadione

D. Succinimides:

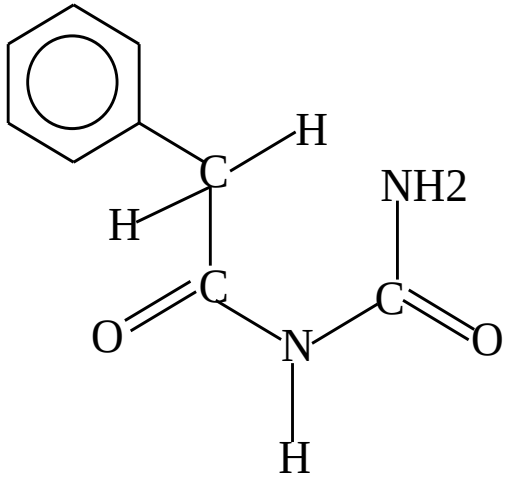
- ureide derivatives, X=CH_2. they were designed to replace toxic oxazolidinones by isosterically replacing the O into CH_2.

Ethosuximide is the drug of choice for treatment of simple absence seizures

E. Ureas and monoacylureas:

A. **Phenacemide {Phenurone}:**

- It is a phenylacetylurea.
- Broad spectrum agent.
- It has **severe side effects** including: personality changes, blood, renal and skin disorders.

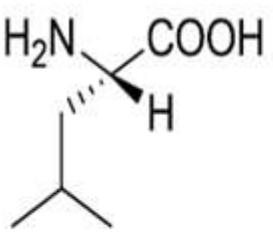


3. Anti-seizure Drugs

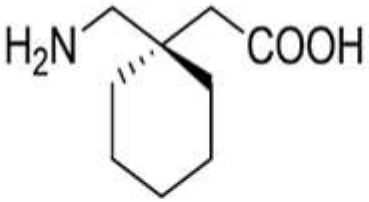
2. GABA analogues

Calcium channels blockers/ Drugs that enhance the biosynthesis of GABA

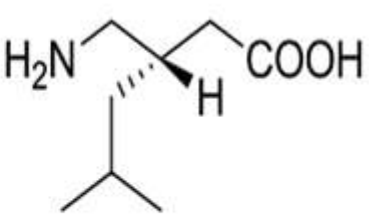
- ***Gabapentin*** (Neurontin) and its second generation derivative ***Pregabalin*** (S-3-isobutyl-GABA) are broad-spectrum anticonvulsants which is a lipophilic GABA ***analogue*** for partial seizures.
- Gabapentin is water soluble amino acid designed firstly as ***GABA-mimetic***
- Act specifically on calcium channel (VDCC) subunits called α2δ, It is unclear how this action leads to their antiepileptic effects, but ***inhibition*** of neurotransmitter release may be one mechanism.
- Gabapentin is ***absorbed*** from intestine using ***L-Leucine*** transport protein.



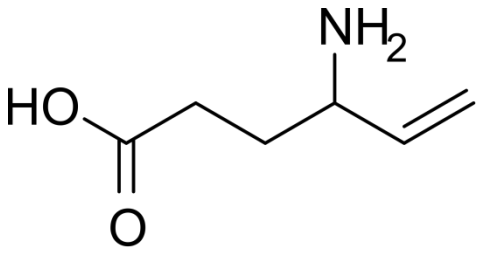
L-Leucine



Gabapentin



Pregabalin



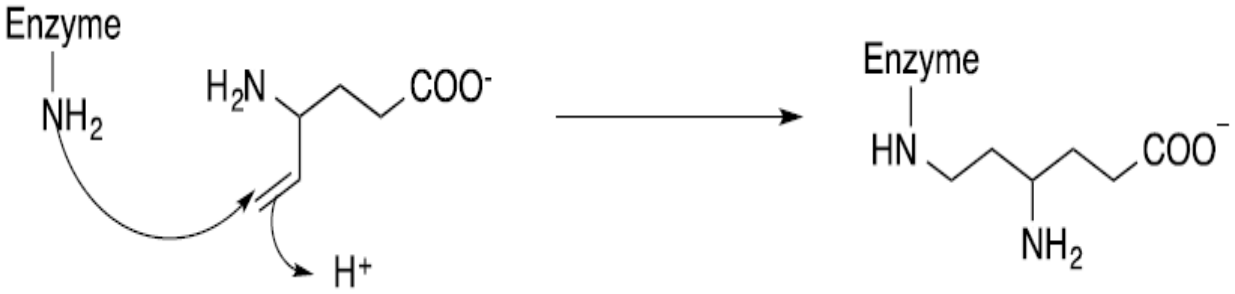
Vigabatrin

3. Inhibition of GABA degradation

Vigabatrin elevates GABA levels by irreversibly inhibiting GABA-transaminase as a result GABA levels will be elevated. GABA-transaminase is the main enzyme in the degradation of GABA.

GABA-degradation:

GABA-transaminase in the presence of ***vigabatrin:***

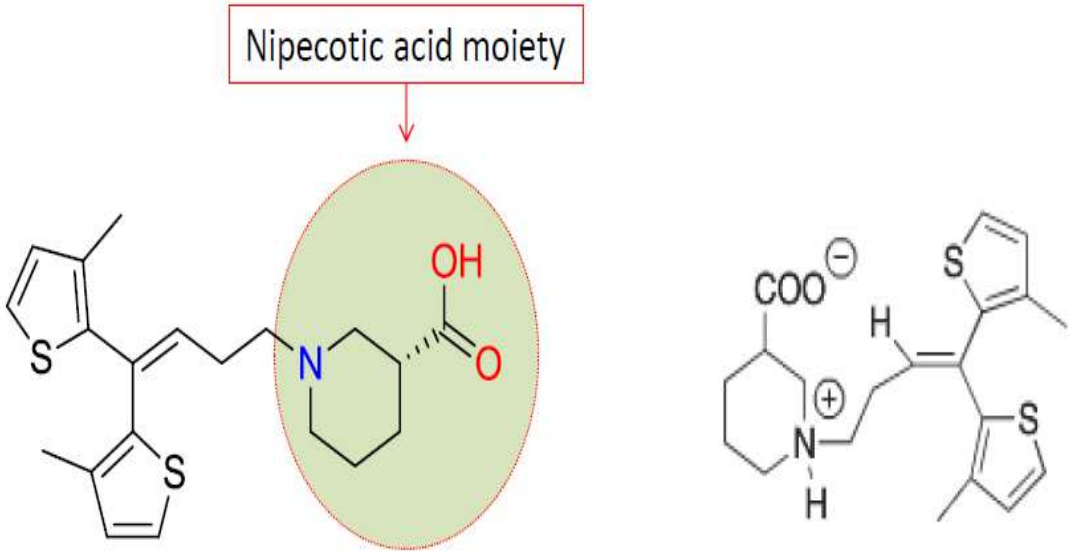


4. GABA re-uptake inhibitors

• ***Tiagabine*** acts on specific protein found in pre-synaptic neuron and inhibits re-uptake of GABA

• Tiagabine is nipecotic acid derivative

• Tiagabine can cross BBB, but nipecotic acid cannot



Tiagabine

R(-)-enantiomer, a potent GAT-1 inhibitor

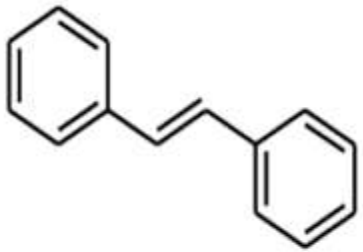
Iminostilbenes /dibenzazepine (*Sodium ion channels blockers as hydantoins)*

Carbamazepine (Tegretol® Novartis***)***

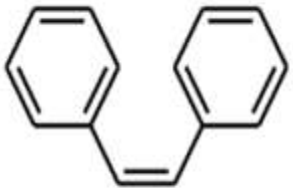
• It is ***autoinducer***: induces its metabolism by CYP450.

• Forms ***toxic*** metabolites: epoxide (highly electrophilic) and aromatic hydroxylation resulting in the formation of electrophilic imidoquinone

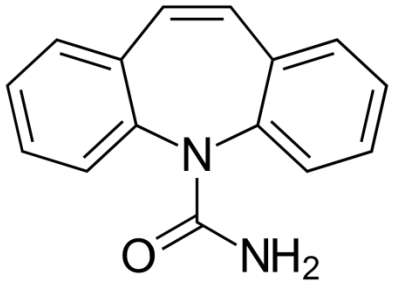
DOC in generalized tonic- clonic and partial seizures



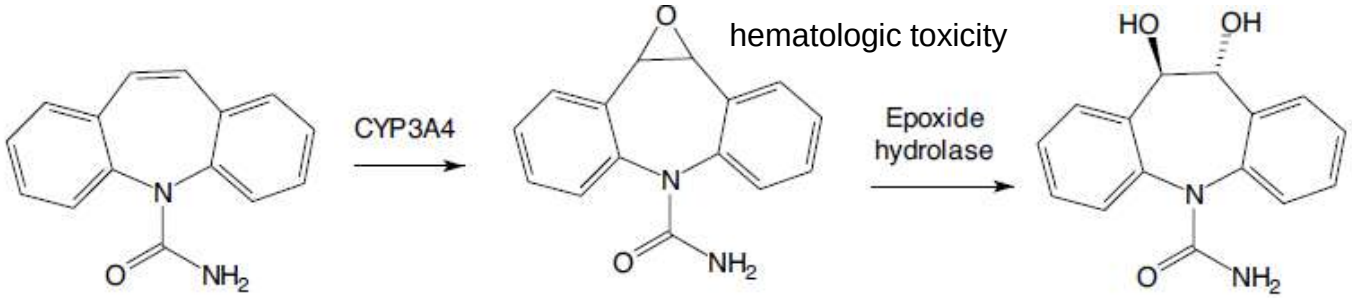
E-stilbene



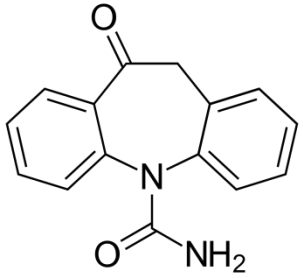
Z-stilbene



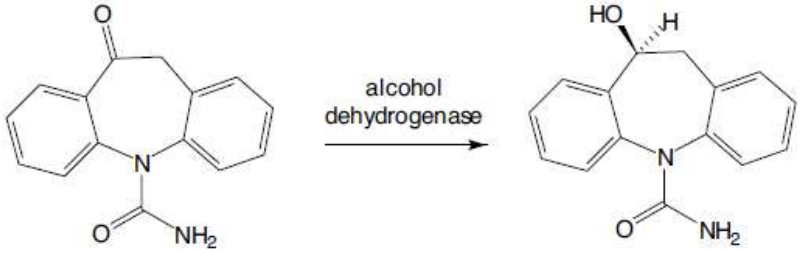
• Useful in generalized tonic–clonic and partial seizures.



Oxcarbazepine **trigeminal neuralgia**



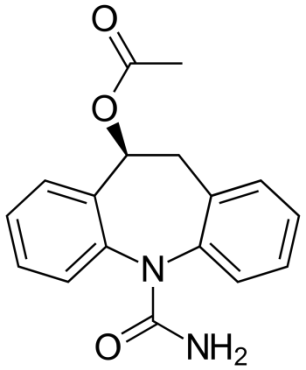
- 10-keto analog of carbamazepine (twice daily)
- It <u>is ***not*** autoinducer</u>
- ***No*** epoxide formation or aromatic hydroxylation



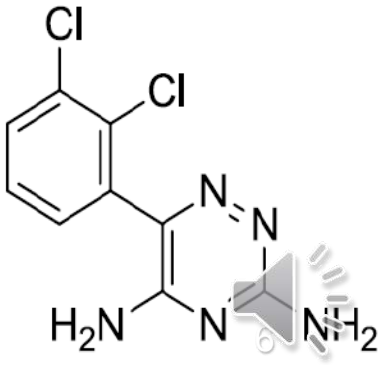
Oxcarbazepine (OXC) (S)-CBZ-10-ol (active metabolite)

Eslicarbazepine

Is a prodrug converted to S-licarbazepine, an active metabolite of oxcarbazepine (once-daily)



Lamotrigine ***(Lamictal® GSK)***



- 5-phenyl-1,2,4-triazine derivative
- Its ***action*** as AED is correlated with its ability to block sodium ion channels, reduce glutaminergic excitatory transmission and inhibits nicotinic acetylcholine receptors.

Broad-Spectrum Anticonvulsants *(acting on multiple targets)*

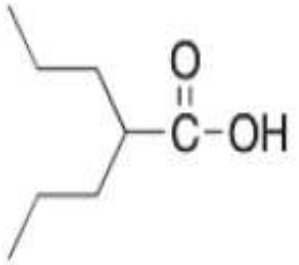
1- Valproic acid ***(***Depakene) and its derivatives

• Increase the inhibitory effect of GABA, possibly by activation of glutamic acid decarboxylase or inhibition of GABA-transaminase.

• Decrease GABA re-uptake

• Blockage of T-type calcium channels

DOC for typical and atypical absence seizures and in absence seizure with generalized tonic clonic seizure. (broad spectrum of action)

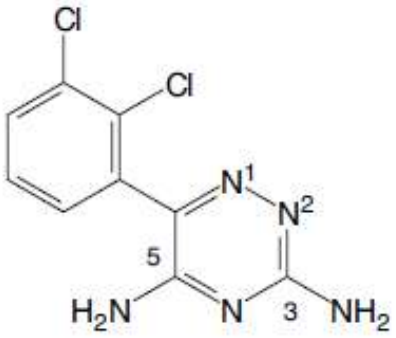


Dipropylacetic acid
2-propylpentanoic acid.

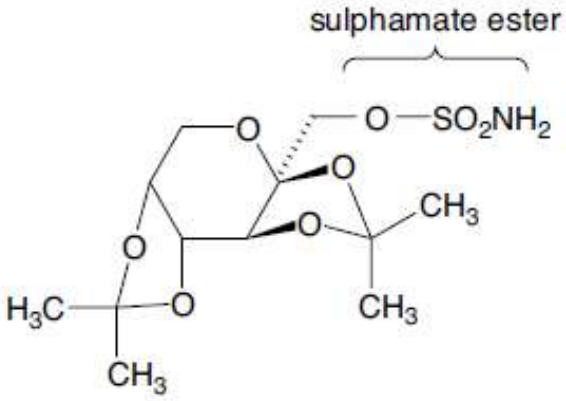
The newer AEDs

2- Topiramate is a sulphamate-substituted monosaccharide, a derivative of the naturally occurring sugar D-fructose that exhibits broad and potent AED actions at both glutamate and GABA receptors

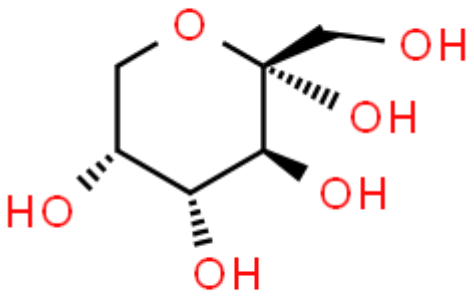
It has good oral bioavailability of 85% to 95%, most likely resulting from its structural similarity to monosaccharides.



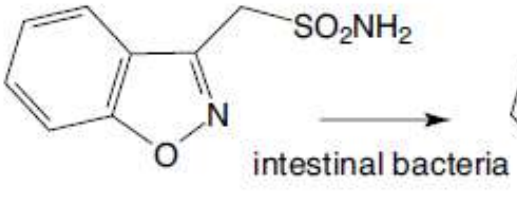
Lamotrigine



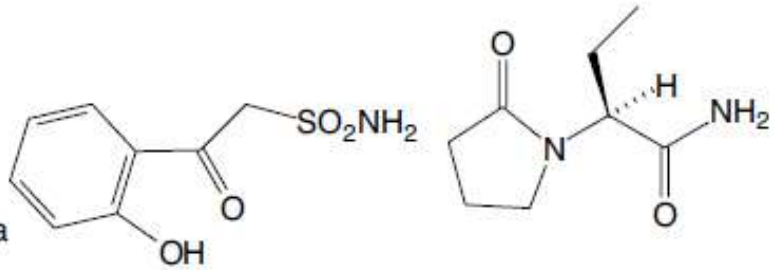
Topiramate



α-D-Fructopyranose



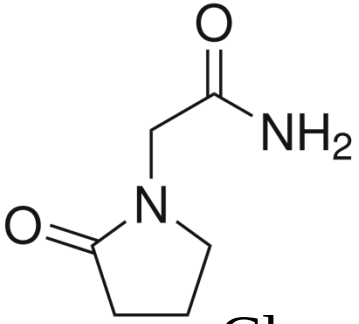
Zonisamide



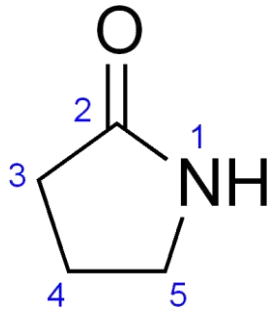
Levetiracetam

3- Zonisamide, a sulfonamide-type AED. produce blockade of both sodium and T-type calcium, indicated for partial seizures

4- LEV: appears to exert its antiepileptic action by modulating kainite/AMPA-induced excitatory synaptic currents, thus decreasing membrane conductance



Racetams



- Class of drugs that share a pyrrolidone nucleus.

1- Nootropics: such as piracetam, aniracetam, oxiracetam, pramiracetam and phenylpiracetam. Piracetam and aniracetam are positive allosteric modulators of the AMPA receptor (activating glutamate receptors Racetams are suggested to enhance memory through interaction with cholinergic and glutamate receptors in the central nervous system.

Nootropic is a compound that increases mental functions including memory, motivation, concentration, and attention

2- Anticonvulsants: levetiracetam and seletracetam.

A) Focal or partial

1) Simple partial(Jacksonian)- The electrical discharge is cofined to the **motor area.**

2)Complex partial(psychomotor)- The electrical discharge is confined in certain parts of the temporal lobe concerned with **mood** as well as **muscle.**

B) Primary generalized

1) **Tonic- clonic**. Pt fall in convulsion & may bite his tongue & may lose control of his bladder or bowel.

2) **Tonic**. Some pts, after dropping unconscious experience only the tonic phase of seizure.

3) **Atonic (akinetic)**. Unconsciousness and relaxation of pt's muscles & he drops down.

4) **Myoclonic**. Sudden, brief shock like contraction which may involve the entire body or be confined to the face, trunk or extremities.

5) **Absence (petit mall)** .momentary loss of consciousness without involving motor area. Most common in children (4-12 yrs).

EEG-symmetric 3 Hz spikes and wave pattern.

6) **Status epileptics (re-occuring seizure).** Continuous seizure (>30 min) without intervening return of consciousness.