# ANTICONVULSANT / ANTISEIZURE / ANTIEPILEPTIC DRUGS

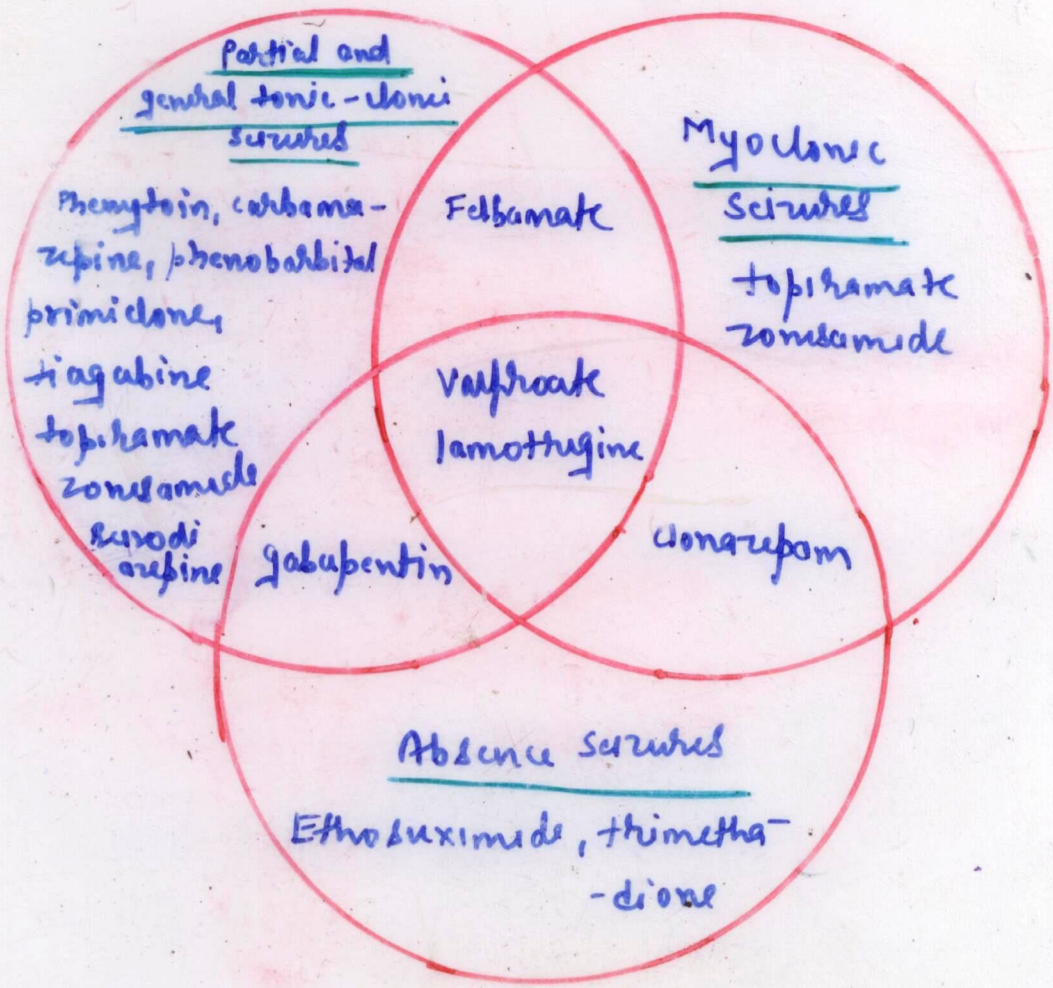
**Seizure** :- The term seizure refers to a transient alteration of behaviour due to the disordered, synchronous and rythmic firing of population of brain neurons.

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

## Classification of Epileptic Seizures

| Seizure Type | Features |
|---|---|
| Partial seizures<br>- Simple partial | lasting approximately 20-30 seconds.<br>(Key feature is preservation of consciousness) |
| - Complex partial | Impaired consciousness lasting 30 seconds to 2 minutes |
| - Partial with generalized tonic-clonic seizure. | loss of consciousness and sustained contractions (tonic) of muscles followed by periods of relaxation (clonic), 1-2 minutes. |

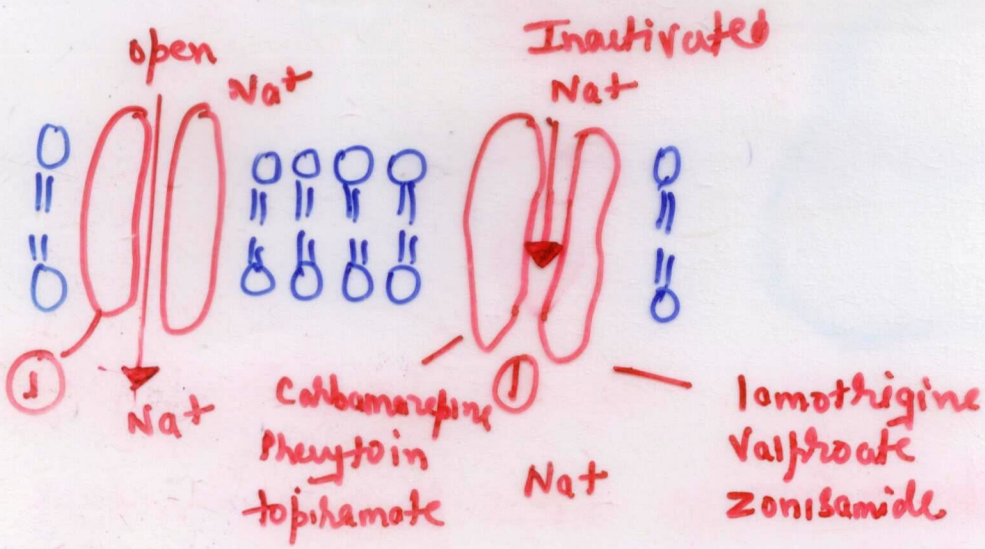
| | |
|---|---|
| - Generalized Seizures | |
| - Absence Seizures | Abrupt onset of impaired consciousness with starting and cessation of ongoing activities (last 30 seconds). |
| - Myoclonic Seizures | - A brief shock like contraction of muscles to part of one extremity & generalized. |
| (grand mal) Tonic - clonic Seizures | Represents a maximal epileptic response of the brain |



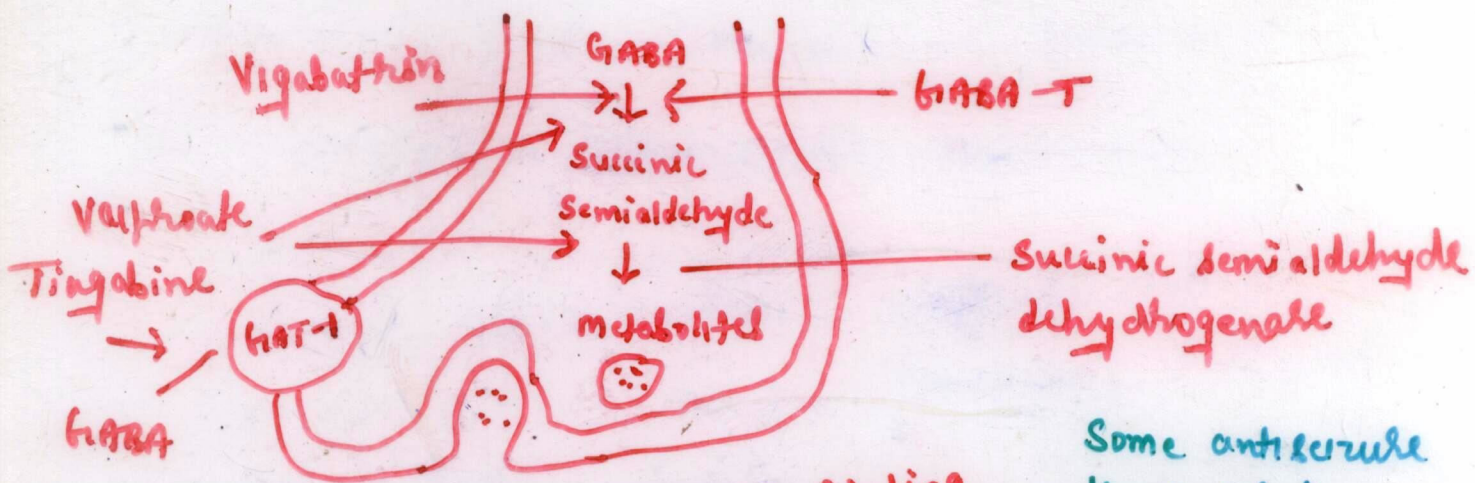

The antiseizure drugs used in various seizures

# Mechanism of action of Antiseizure drugs

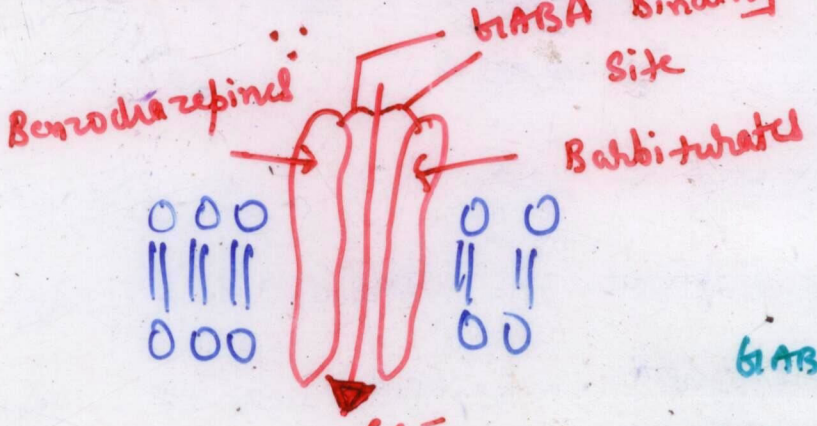
- Insights into mechanism of seizures suggest that enhancing GABA - mediated synaptic inhibition would reduce neuronal excitability.




Antiseizure drug - enhanced $Na^+$ channel inactivation

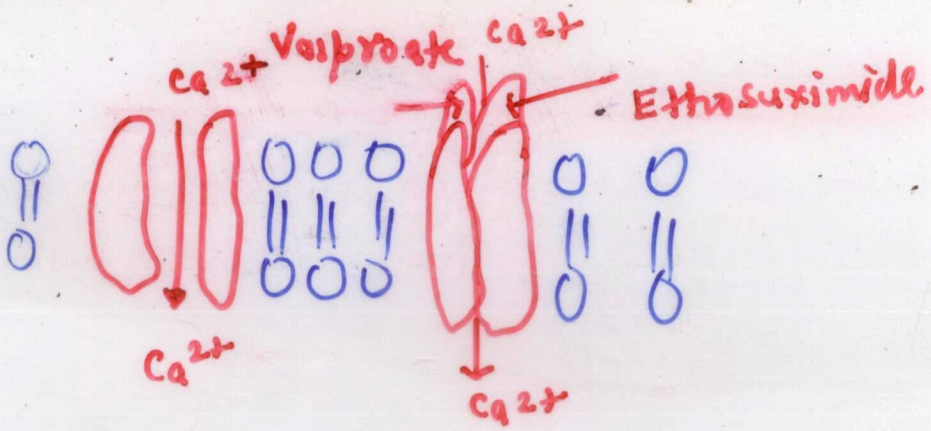



Some antiseizure drugs act by reducing the metabolism of GABA




Others act by the $GABA_A$ receptor, enhancing $Cl^-$ influx in response to GABA.

Enhanced GABA Synaptic transmission.




Antiseizure drug induced reduction of current through T-type $Ca^{2+}$ channels.

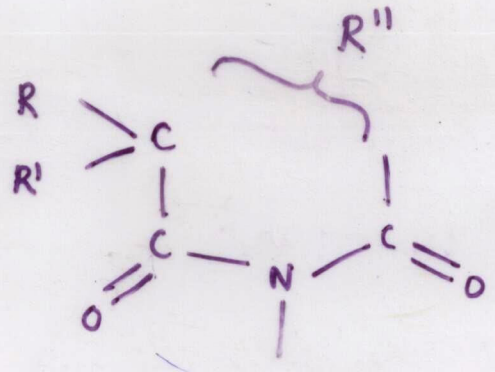
## Classification of Drugs

The different chemical classes of anticonvulsant agents are,

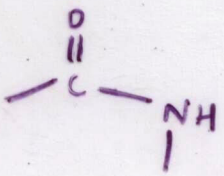
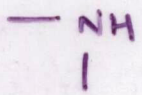
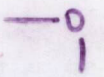
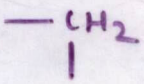
1) Barbiturates :- Phenobarbital, Mephobarbital
2) Hydantoins :- Phenytoin, mephenytoin.
3) oxazolidinediones :- Trimethadione, paramethadione
4) Succinimides :- Ethosuximide, Phensuximide, methsuximide
5) Sulfonamides :- Zonisamide
6) Carboxylic acid derivatives :- Valproic acid
7) Benzodiazepines :- Diazepam, clonazepam, clobazepate
8) GABA analogs :- Gabapentin
9) Iminostilbenes :- Carbamazepine, oxcarbazepam
10) Phenyltriazine derivative :- Lamotrigine
11) Pyrrolidone derivative :- Levetiracetam
12) Nipecotic acid derivative :- Tiagabine
13) Sulfamate-substituted monosaccharide :- Topiramate
14) Dicarbamate derivative :- Felbamate

# SARS Among Anticonvulsants

Several major groups of drugs have the common structure given below



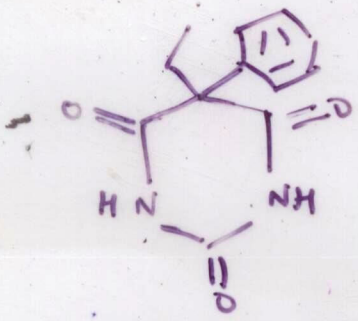

ureide structure

| Class of Compounds | R'' |
|---|---|
| Barbiturates |  |
| Hydantoins |  |
| Oxazolidinediones |  |
| Succinimides |  |

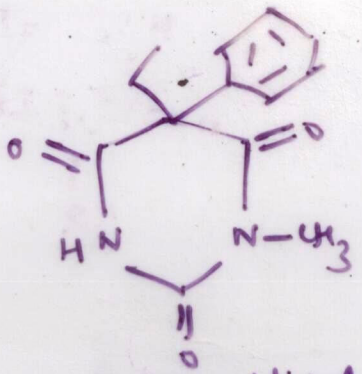
Structure of anticonvulsant drugs containing the ureide structure.

## 1. Barbiturates

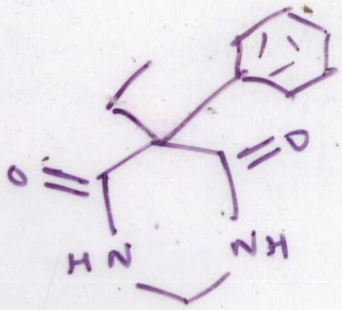
- The barbiturates are substituted pyrimidine derivatives with an ureide structure
- They are lipophilic weak acids that are well distributed into brain.
- Clinically useful barbiturates as antiseizure drugs are phenobarbital, mephobarbital and Primidone.



Phenobarbital



Mephobarbital



Primidone

Barbiturates

**Phenobarbital** :- It is a drug of choice for infants upto 2 months old.
Indicated for partial generalized tonic - clonic seizures
Metabolism to P- Hydroxylation followed by glucuronidation.

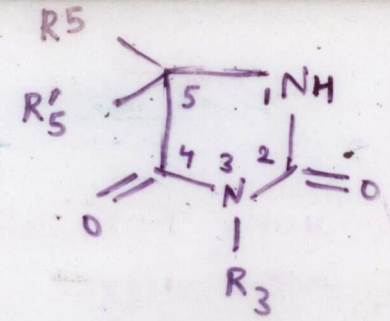
**Mephobarbital** :- classified as long acting barbiturate
Mephobarbital is N- demethylated to phenobarbital.
Most of its activity is due to metabolite phenobarbital.

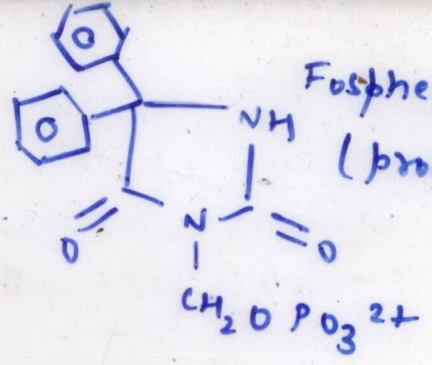
**Primidone** :- Primidone is the 2- deoxyderivative of phenobarbital
- For simple partial, complex partial and tonic - clonic seizures.

## 2. Hydantoin derivatives

The hydantoins are close structural relatives of the barbiturates differing in lacking the 6- oxo group

They are cyclic monoacylureas rather than cyclic diacylureas
As a consequence of losing a carbonyl group, they are weaker organic acids than barbiturates.
(eg Phenytoin ($P_{Ka} = 8.3$)




Fosphenytoin (prodrug)

| Generic Name | $R_5$ | $R_5'$ | $R_3$ |
|---|---|---|---|
| Phenytoin |  |  | H |
| Mephenytoin |  | $CH_3-CH_2-$ | $CH_3-$ |
| Etothoin |  | H | $CH_3-CH_2-$ |

## Hydantoins

(Alkyl substituents at position – 5 contribute to sedation, a property absent in phenytoin.

**Phenytoin :–** (5, 5 – diphenylhydantoin)

Phenytoin binds to and stabilizes the inactivated state of sodium channels producing a use dependent blockade of repititive firing and inhibition of the spread of the seizure activity.

**Mephenytoin :–** (3 – Methyl – 5- ethyl – 5- Phenylhydantoin)

- N-methylated at position 3 with an ethyl group replacing one of the phenyl substituents at position 5.
- Indicated for focal and Jaksonian seizures.

**Etothoin :–** (3- Ethyl – 5- phenylhydantoin)

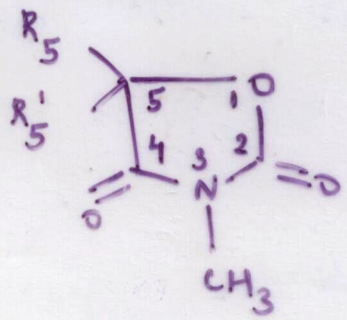
less toxic but produces greater sedation than phenytoin.

**Fosphenytoin** (Prodrug of Phenytoin) :– It is a soluble prodrug phosphate ester of phenytoin developed to circumvent PH and solubility of phenytoin sodium as

## 3. oxazolidinediones

Replacement of the N-H group at position 1' of the hydantoin system with an oxygen atom yields the oxazolidine-2,4-dione system.

Example :- Trimethadione



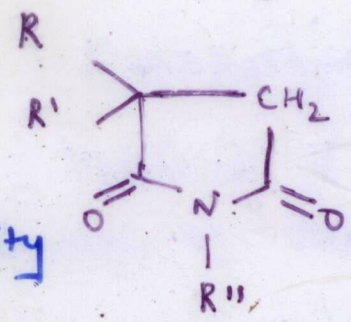

$R_5 = R_5' = CH_3$

Trimethadione

- First drug to treat absence seizures
- The drug is metabolized to active metabolite dimethadione by N- demethylation.
- Dimethadione is a calcium T- channel blocker.

## 4. Succinimide derivatives

Alkylation of imide NH is important for activity




At C-5 lower alkyl substituents tend towards anti-petit mal.

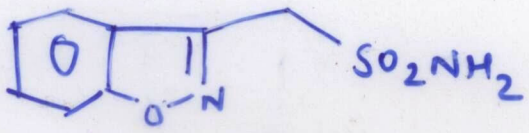
aryl substituents towards grand mal.

Phensuximide R =  R' = H R'' = $CH_3$

Methsuximide R =  R' = $CH_3$ R'' = $CH_3$

Ethosuximide R = $C_2H_5$— R' = $CH_3$ R'' = H

5. Sulfonamides :- Zonisamide

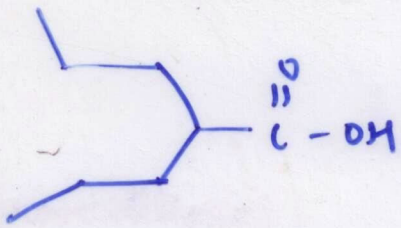


M.O.A :- Produces blockade of both Sodium and T-type calcium channels.

useful for partial seizures.

6. Carboxylic acid derivatives

Valproic acid



(Mechanistically the drug is Sodium channel blocker)

Valproic acid

(dipropylacetic acid)

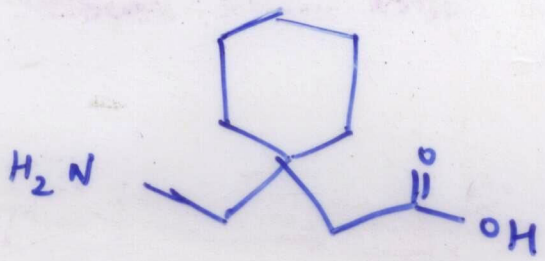
M.O.A :- Valproate is known to produce a blockade of high frequency of Repititive firing in neurons.

- Also appears to increase the inhibitory effect of GABA possibly by inhibition of GABA-T.
- For absence seizures and generalized tonic-clonic seizures.

7. Benzodiazepines :- Diazepam, Clonazepam, Clobazepate, Lorazepam

(Covered under antianxiety agents)

## 8) GABA analogs Gabapentin

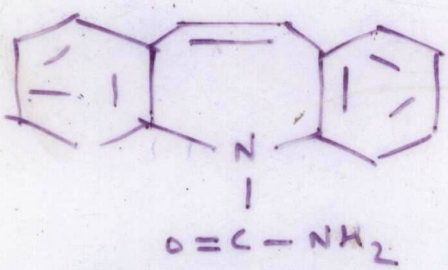


M.O.A :- Gabapentin may alter the metabolism & release of GABA.
(Its mechanism of action does not appear to involve an interaction with $GABA_A$ receptors.

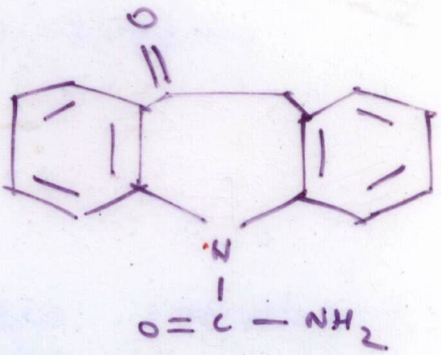
- Effective against partial seizure and secondary generalized tonic clonic seizures.

## 9. Iminostilbenes

Carbamazepine [ 5H - dibenz[b, f] azepine - 5 - carboxamide.



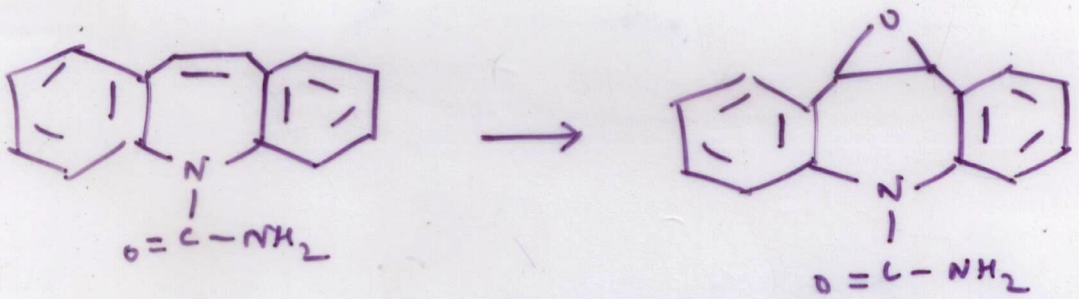
Carbamazepine



oxcarbazepine

- The two phenyls substituted on the urea nitrogen fit the pattern of antigeneralized tonic activity.
- Blocks Sodium channel activity thus preventing seizures.

- Metabolism proceeds largely through the epoxide formed at the (Z) cis-stilbene double bond.



Carbamazepine

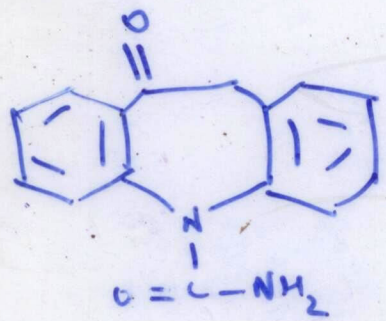
Carbamazepine 10, 11 epoxide

(The epoxide is suspect in idiosyncratic reactions ie aplastic anemia).

To avoid epoxide formation oxcarbazepine was developed.

- M.O.A :- Carbamazepine acts by blocking sodium channel oxcarbazepine is less potent than carbamazepine

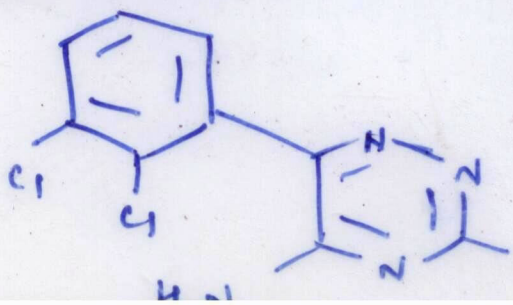
- useful for generalized tonic-clonic and partial seizures.



oxcarbazepine

## 10. Phenyltriazine derivative Lamotrigine

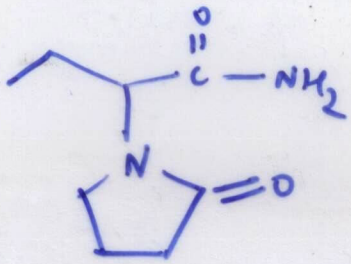
For partial seizures.



M.O.A :- The drug is said to act by blocking sodium channels and preventing glutamate release, thus reducing neuronal cell death in ischemia.

## 11. Pyrrolidine derivative

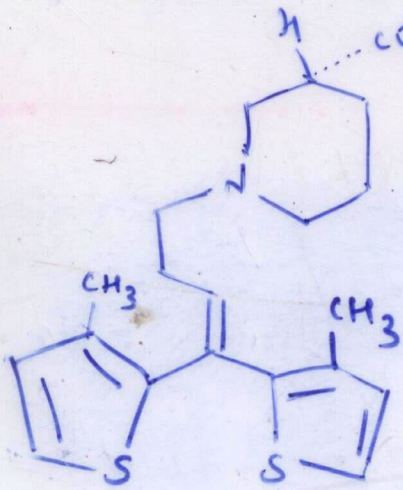
S(-) Levetiracetam



It is indicated as an adjunct in the treatment of partial onset seizures in adults.

## 12. Nipecotic acid derivative

Tiagabine (GABA reuptake blocker)

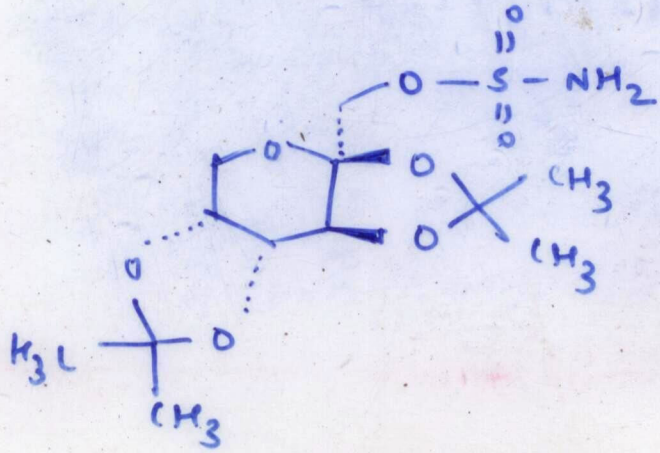


M.O.A :- It blocks GABA reuptake as a major Mode of its anticonvulsant activity.

use against partial seizures

## 13. Sulfamate substituted monosaccharide

Topiramate

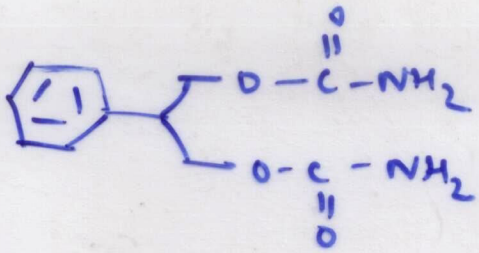


M.O.A :- It acts by blocking sodium channels in neurons
Also acts by blocking calcium T- channels

Effective for partial seizures

14. Dicarbamate derivative

## Felbamate

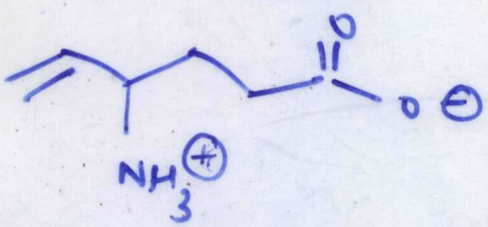


- Felbamate is a dicarbamate that is structurally similar to meprobamate.

M.O.A :- Felbamate antagonizes the NMDA receptor by binding to a glycine recognition site, and lowers voltage gated calcium channels.

## Investigational Antiseizure drug

## — Vigabatrin



- Vigabatrin is structural analog of the inhibitory neurotransmitter GABA.
- It is actively transported into the brain to produce its antiseizure effect by irreversibly inhibiting the degenerative enzyme GABA-transaminase (GABA-T) which produces an increase in CNS GABA levels.
- The effect may exacerbate myoclonic seizures.