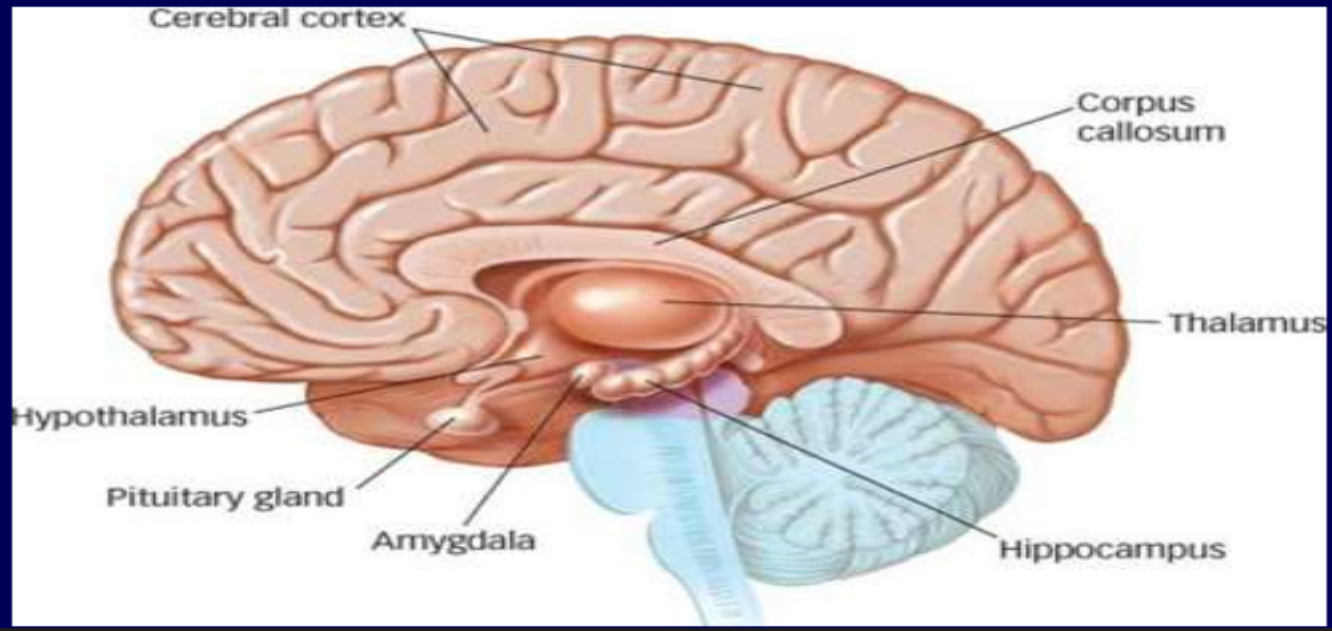
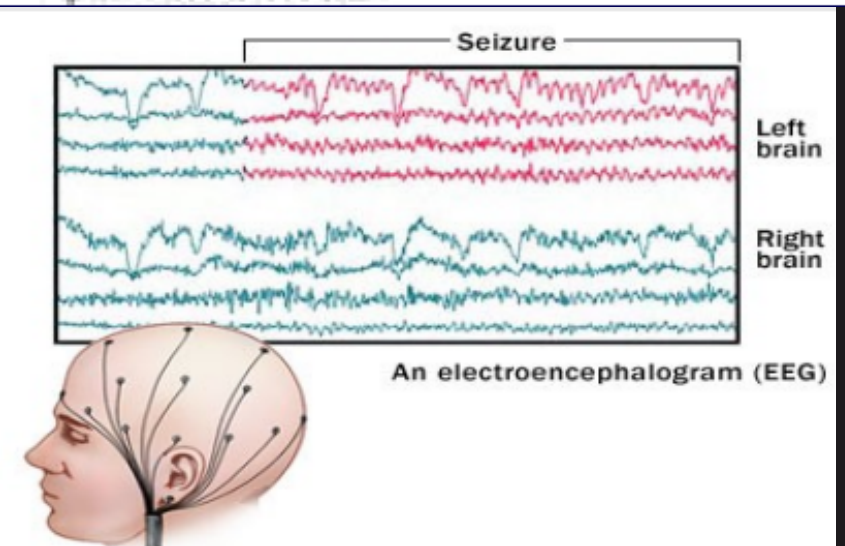
ANTICONVULSANTS





PREPARED BY:
NEETU SABARWAL
ASSISTANT PROFESSOR
DEPARTMENT OF PHARMACEUTICAL CHEMISTRY
SOS PHARMACEUTICAL SCIENCES
JIWAJI UNIVERSITY GWALIOR

Anticonvulsants

Anticonvulsants, sometimes also called **antiepileptic**, belong to a diverse group of pharmaceuticals used in prevention of the occurrence of epileptic seizures.

The goal of an anticonvulsant is to suppress the rapid and excessive firing of neurons that start a seizure. Anticonvulsant drug decreases the frequency and/or severity of seizures in people with epilepsy. They treat the symptom of seizures, not the underlying epileptic condition.

Definition:

Epilepsy is a common chronic neurological disorder characterized with occurrence of recurrent seizures

Seizures are transient brain dysfunctions induced by episodic high-frequency discharge of impulses by a group of neurons in the brain

Rather then single disease, epilepsy might viewed as a **family of brain disorders** sharing the common manifestation by seizures

Epidemiology: It affects 0.5-1%of the population.

Etiology:
-Often idiopathic, symptomatic eg. Brain damage(trauma, infection, stroke, intoxication or tumor growth)
-Inherited neurological syndromes or other kinds of neurological
Diagnosis–EEG, mri

WHAT ARE EPILEPSIES?

- **Definition:** These are Group of disorders of the CNS characterized by paroxysmal cerebral dysrhythmia, manifesting as brief episodes (seizure) of loss or disturbance of consciousness, with or without characteristic body movements (convulsions), sensory or psychiatric phenomena
  - **Focal origin and Disease of lightening (JH Jackson)**
- **What is a seizure?**
  - A seizure is a transient alteration of behaviour due to the disordered and synchronous firing of populations of brain neurons. Seizure can be non-epileptic and can be evoked in normal brain
  - A seizure is a paroxysmal behavioral spell generally caused by an excessive disorderly discharge of cortical nerve cells

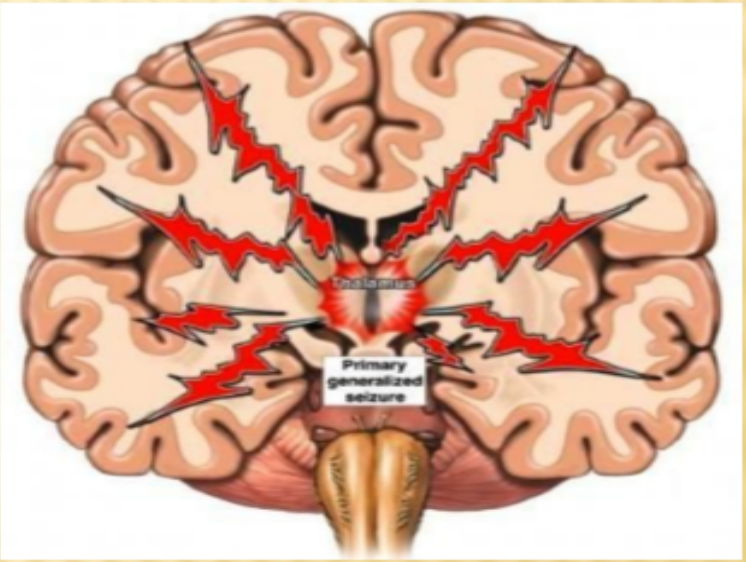
CAUSES OF EPILEPSY

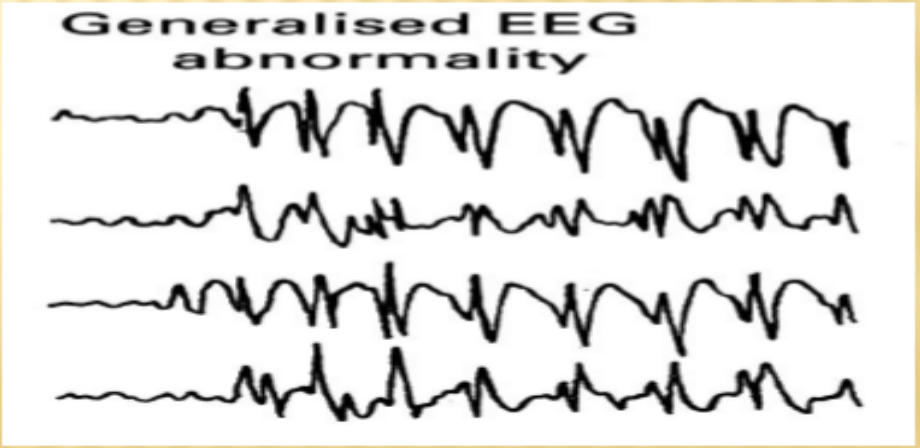
The cause of most cases of epilepsy is unknown.

- Brain injury (destruction of brain cells)
- Stroke (poor blood flow to the brain)
- Brain tumors (Abnormal cell growth-Cancer or benign)
- Infections of the brain
- Birth defects (brain damage at the time of birth).
- previous infections of the central nervous system(Bacterial, fungal, viral ...)
- Genetic mutations
- Sudden Discontinuation of CNS drugs(or) Noncompliance with the drug regimen.
- Hyperthermia(High fever in children)

CLASSIFICATION OF EPILEPTIC SEIZURES

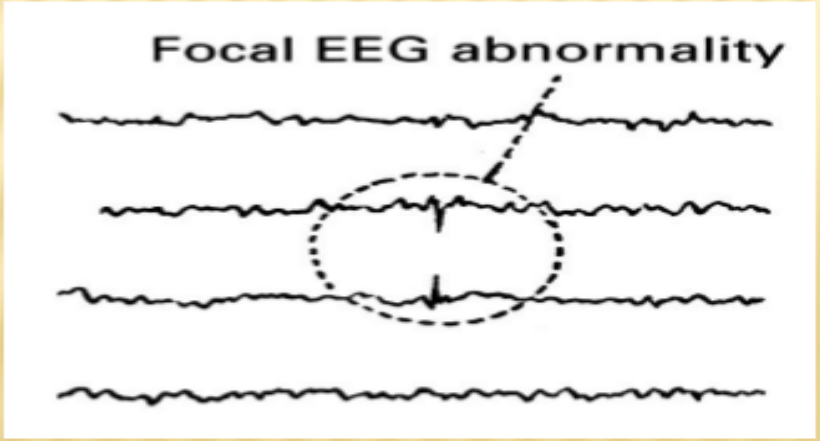
- Types: **Generalized** and **Partial (focal)** Seizures
- **Generalized:**
  1. Generalized tonic-clonic seizure
  2. Absence seizure
  3. Tonic seizures
  4. Atonic Seizure
  5. Myoclonic seizure
  6. Infantile spasm



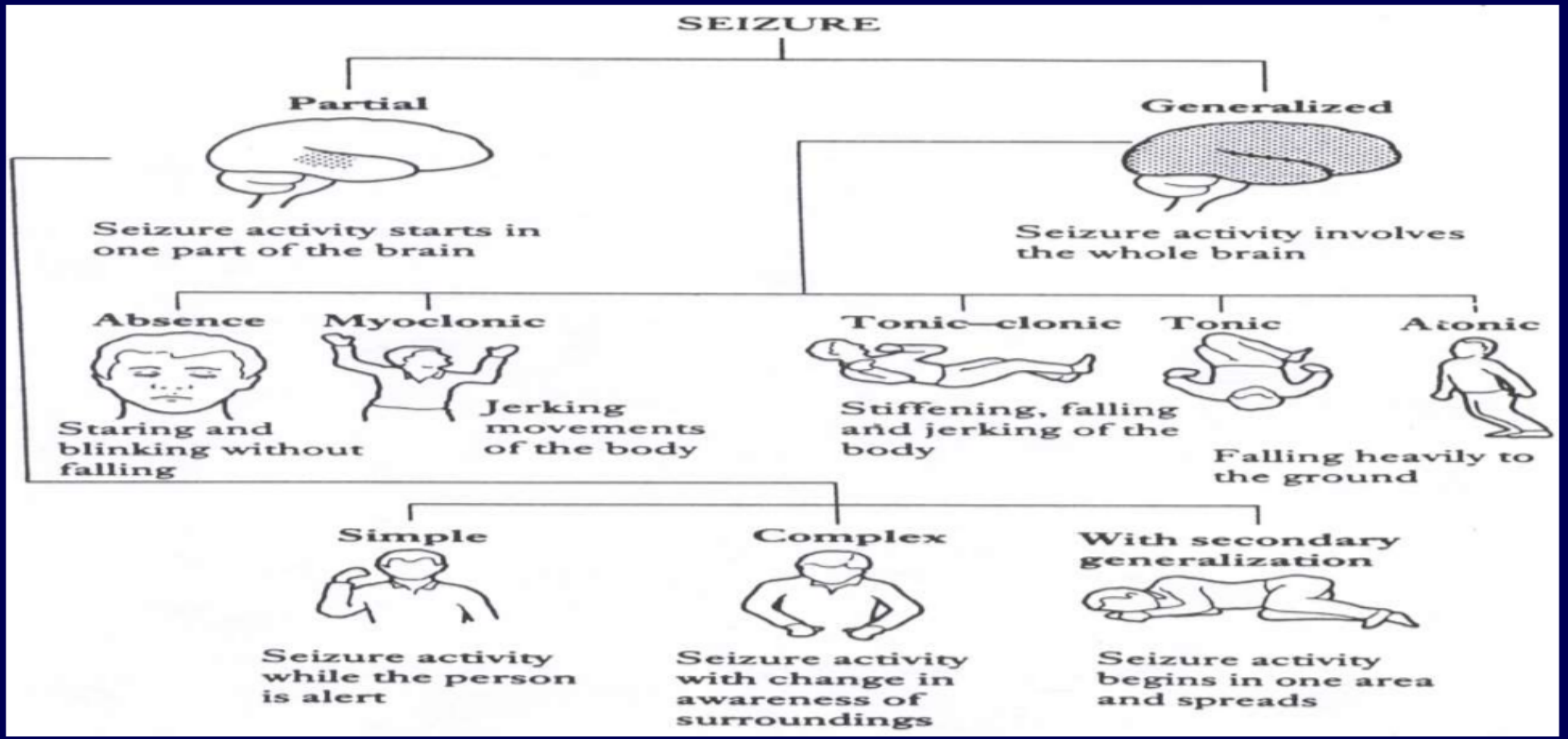


TYPES OF SEIZURES – CONTD.

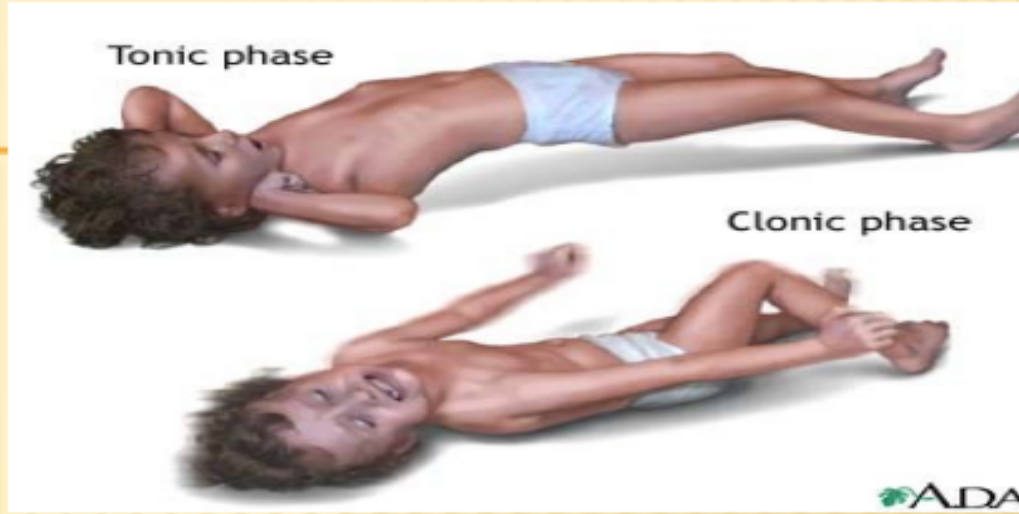
- **Partial (focal) Seizures: 80% of Adult epilepsies**
  - Simple Partial Seizures
  - Complex Partial Seizures
  - Simple partial or complex partial secondarily generalized



Classification of Epileptic Seizures



GENERALIZED SEIZURES

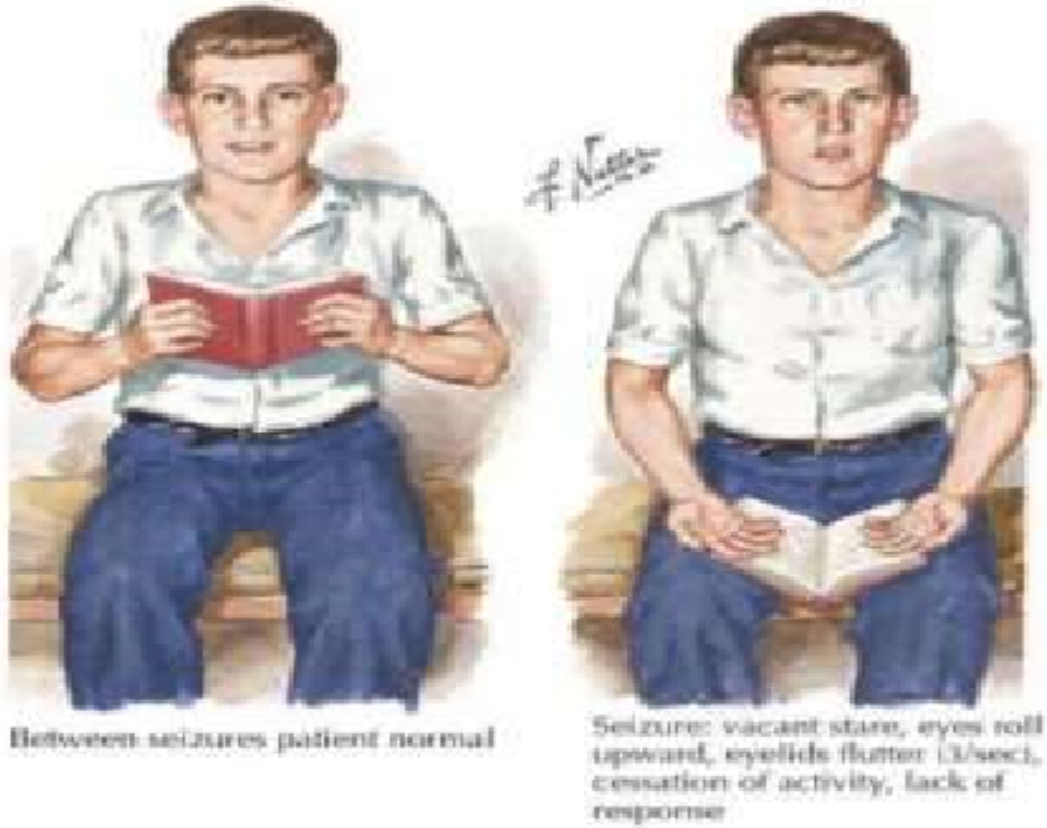


1. **Generalized tonic-clonic**
   - GTCS/major epilepsy/grand mal
   - Commonest of all
   - Lasts for 1-2 minutes
   - Aura-cry-unconsciousness-tonic phase-clonic phase
   - Usually occurs in both the hemispheres
   - Manifestations are determined by cortical site of seizure occurrence
- **2 phases:** tonic phase followed by clonic phase
- **Tonic phase:**
  - Sustained powerful muscle contraction (involving all body musculature) which arrests ventilation
- **Clonic phase**:
  - Alternating contraction and relaxation, causing a reciprocating movement which could be bilaterally symmetrical

GENERALIZED SEIZURES – CONTD.

- **Absence seizure:**
  - Also called minor epilepsy/petit mal
  - Usually in Children and lasts for 1-2 minutes
  - Typical generalized spike-and-wave type discharges at 3 per second (3 Hz)
  - Momentary loss of consciousness (not convulsion), patient stares at one direction
  - No motor (muscular component)
  - No convulsions
  - Minor muscular twitching restricted to eyelids (eyelid flutter) and face
  - No loss of postural control.

Absence Seizures
(Petit Mal)



Between seizures patient normal

Seizure: vacant stare, eyes roll upward, eyelids flutter (3/sec), cessation of activity, lack of response

Sudden & brief cessation in activity with rapid return to normality, may be frequent, 3Hz spike and wave

GENERALIZED SEIZURES – CONTD.

- **Atonic Seizures:**
  - Unconsciousness with relaxation of all muscles
  - Patient falls down
  - Loss of postural tone, with sagging of the head or falling
- **Myoclonic Seizures:**
  - Isolated clonic jerks associated with brief bursts of multiple spikes in the EEG
  - Momentary contractions of muscles of limbs or whole body
  - No loss of postural control
- **Infantile spasm:**
  - An epileptic syndrome
  - Characterized by brief recurrent myoclonic jerks (muscle spasm) of the body with sudden flexion or extension of the body and limbs
  - Progressive mental deterioration

GENERALIZED SEIZURE: OTHER TYPES

Myoclonic Seizure

- Non-rhythmic jerks resulting from involuntary muscle twitching that normally target the upper extremities, and after an episode, patients may describe the perceived sensation as momentary electrical shocks.

ATONIC SEIZURE

Atonic seizures

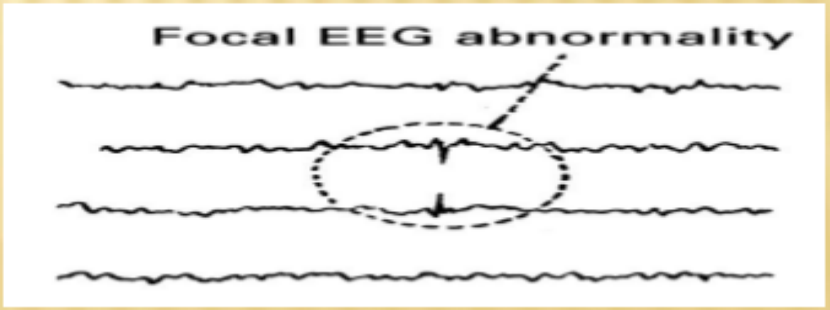
Sometimes known as a "drop attack," atonic seizures cause a sudden loss of muscle tone. This may result in the dropping of the head or a limb, or lead a student to fall to the ground. There also may be a brief loss of consciousness. Because the student may fall to the ground, there is a risk of injury.

PARTIAL (FOCAL) SEIZURES

- Simple partial seizure (Jacksonian)
  - Lasts for 20 – 60 seconds
  - Motor, sensory, vegetative or psychic symptomatology
  - *Typically consciousness is preserved*
  - Confined to a group of muscles or localized sensory disturbances depending on area of cortex involved
  - For example – if motor cortex of the left thumb then jerking movement of left thumb, and if it is sensory cortex then paresthesia of left thumb.
  - No alteration of consciousness
- EEG: Excessive synchronized discharge by a small group of neurons. Contralateral discharge

PARTIAL (FOCAL) SEIZURES – CONTD.

- **Complex partial seizure (temporal lobe/psychomotor epilepsy)**
  - Focus is located in temporal lobe
  - Confused behaviour and purposeless movements and emotional changes lasting for 30 seconds to 2 minutes
  - An aura often present
  - Automatisms (repetitive coordinated movements)
    - perioral and hand automatisms
  - Wide variety of clinical manifestations and Consciousness is impaired



Status epilepticus

- Continuous seizure activity for more than 30 minutes, or 2 or more seizures without recovery of consciousness.
- Emergency: Recurrent tonic-clonic convulsions without recovery in between.

classification

Barbiturates:- eg: phenobarbitone, mephobarbitone

Hydantoins:- eg: phenytoin, mephenytoin, ethotoin

Oxazolidinediones:- eg: trimethadione, paramethadione

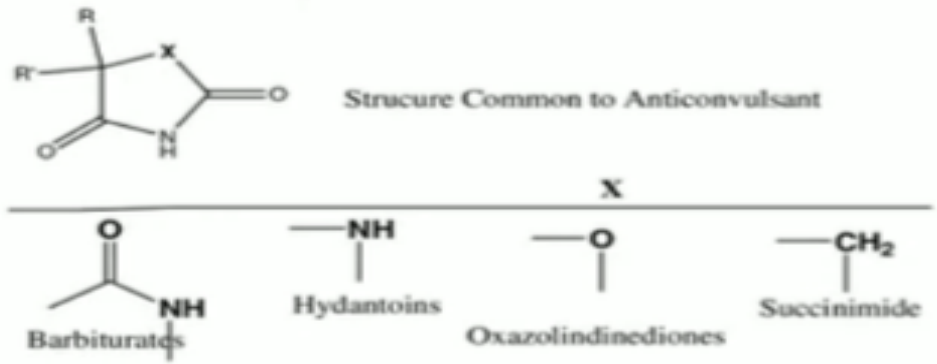
Succinimides:- eg: phensuximide, methsuximide, ethosuximide

Urea and monoacyl ureas:- eg: carbamazepine

Benzodiazepines:- eg: clonazepam, diazepam, chlorazepate

Miscellaneous:- eg: primidone, valproic acid, zonisamide, gabapentin, tiagabine, felbamate, phenacemide

Classification of antiepileptic drug



Chemical Class	Examples of antiepileptic drug
Barbiturates	Phenobarbitone, Mephobarbitone, Primidone
Hydantoins	Phenytoin Mephenytoin
Iminostilbene	Carbamazepine
Oxazolidinedione	Trimethadione (Troxidone)
Succinimide	Ethosuximide
Aliphatic Carboxylic acid	Valproic acid (Sodium valproate)
Benzodiazepines	Clonazepam, Diazepam
Acetyl urea	Phenacemide
Newer drugs	Progabide, Vigabatrin, Gabapentin Lamotrigine, Felbamate, Topiramate, Tiagabine
Miscellaneous	Acetazolamide, Dexamphetamine

Mechanism of action

- Seizures are electrical explosions of brain which are due to overactivity of **stimulatory neurotransmitters** like (Glutamate).
- Basic M.O.A. of anticonvulsant by=

  By enhancing **G.A.B.A.** mediated inhibitory neurotransmission.

  By terminating/attenuating the excitatory neurotransmission in Brain.

  By blocking the **Voltage gated sodium channel** (as influx of sodium cause **neuronal firing**).

Mechanism of action

Antiepileptics inhibit the neuronal discharge

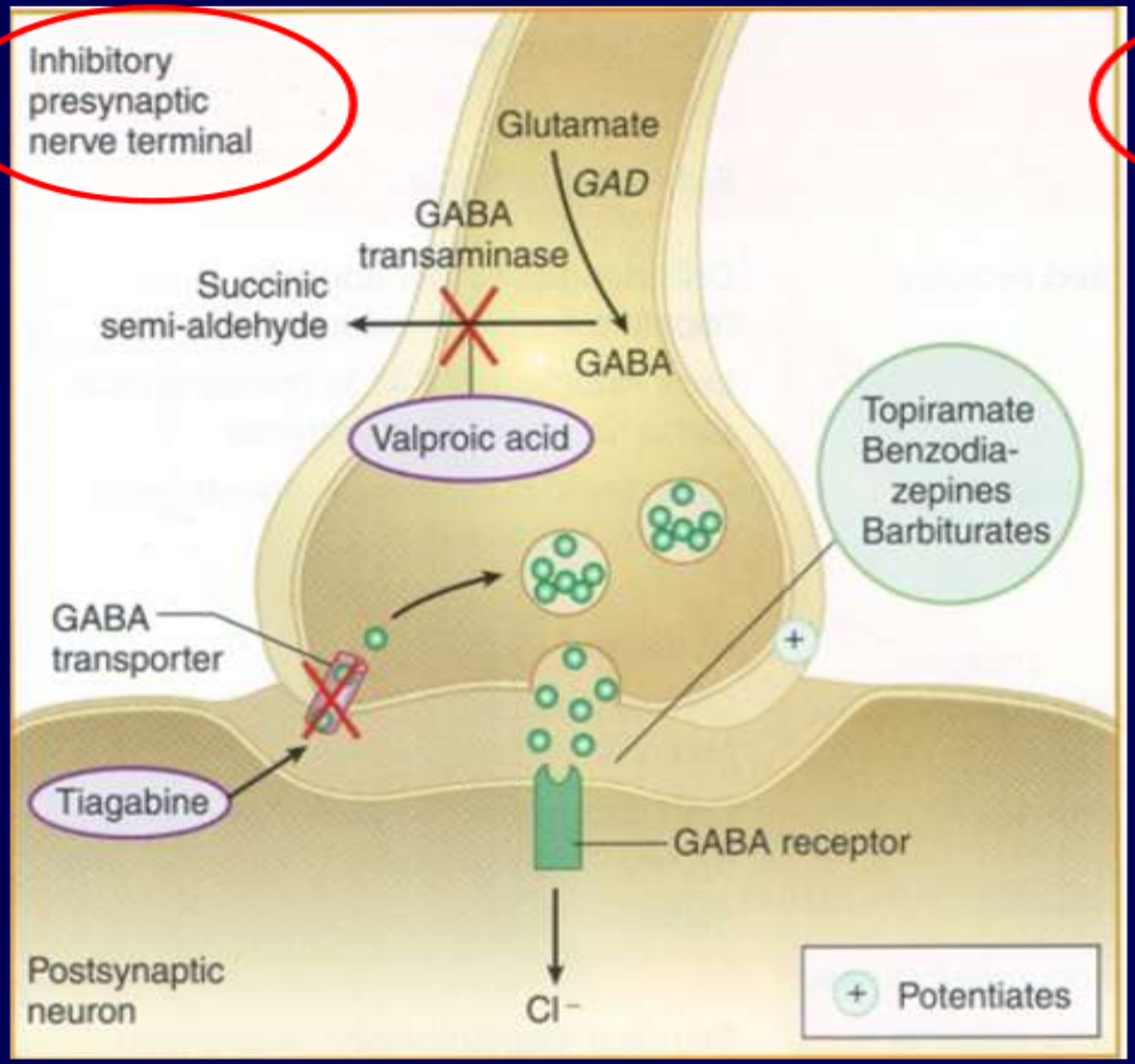
(1) Enhancing GABA synaptic transmission: barbiturates, benzodiazepines, gabapentin, levetiracetam, tiagabine, vigabatrin, topiramate, valproate; the result is increased permeability to chloride ion, which reduces neuronal excitability. Valproate and topiramate block GABA transaminase and tiagabine blocks reuptake of GABA.

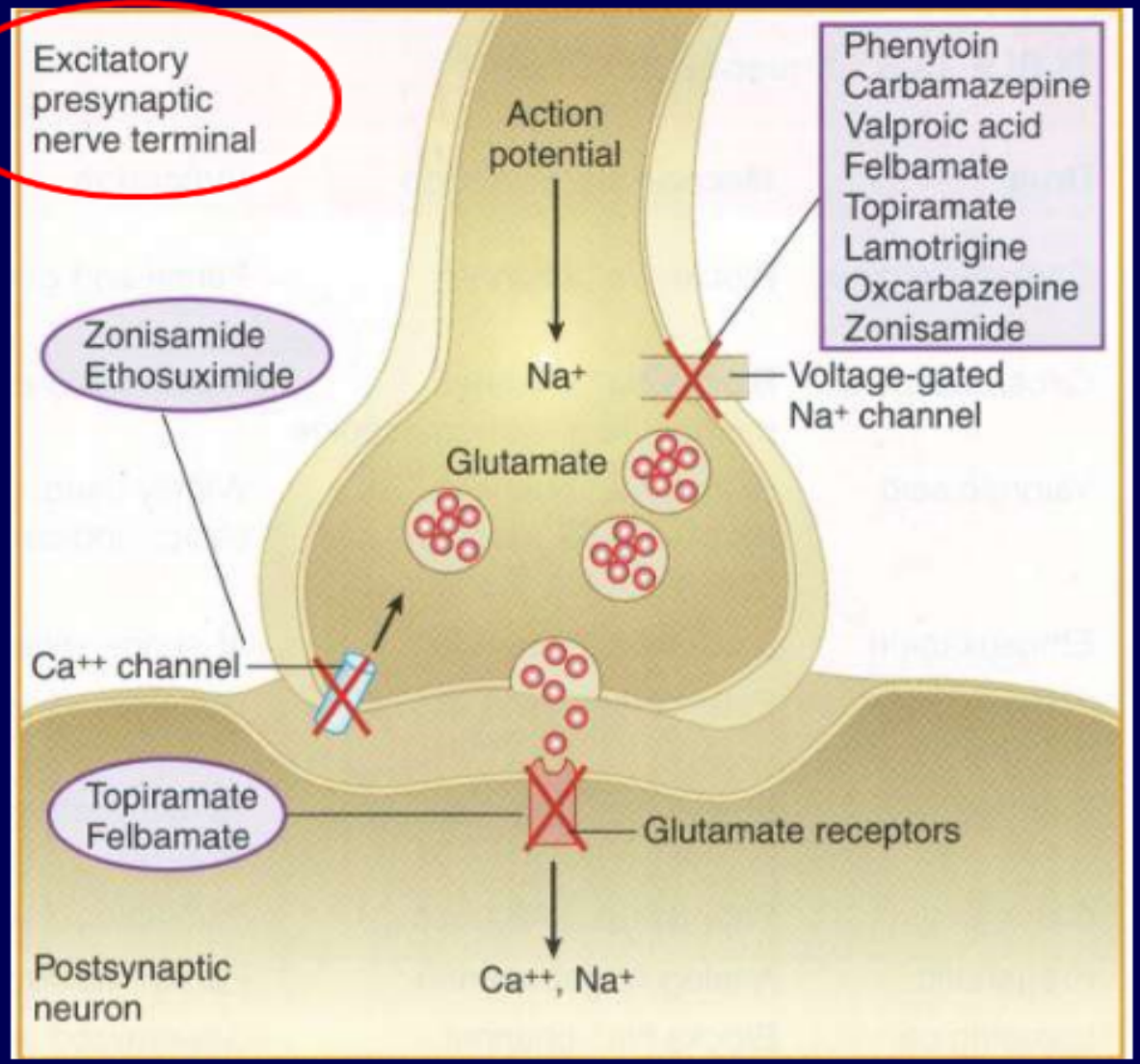
(2) Reducing cell membrane permeability to voltage-dependent sodium channels: carbamazepine, lamotrigine, oxcarbazepine, phenytoin, topiramate, valproate.

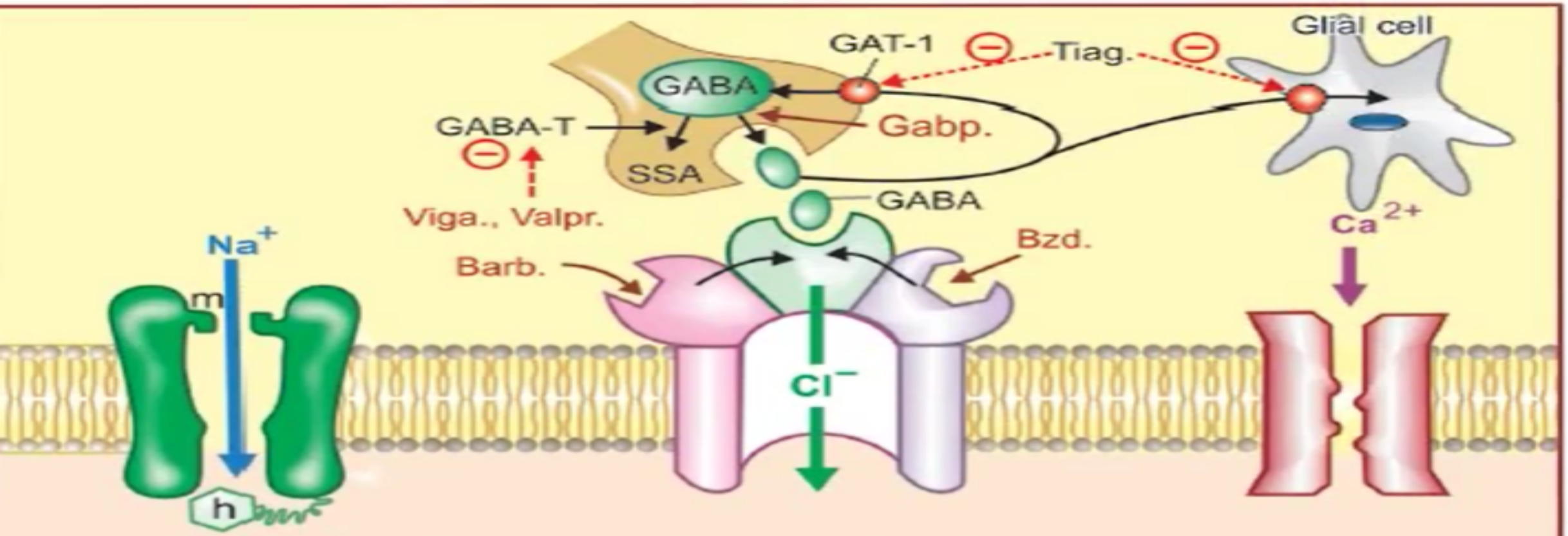
(3) Reducing cell membrane permeability to T-type calcium channels: valproate, ethosuximide; the result is diminishing of the generation of action potential.

(4) Inhibiting excitory neurotransmitter glutamate: lamotrigine.

Mechanism of action of AEDs







PROLONGATION OF Na^+ CHANNEL INACTIVATION

Phenytoin
Carbamazepine

FACILITATION OF GABA MEDIATED Cl^- CHANNEL OPENING
(high conc Phenytoin)

Barbiturate (Barb.)
Benzodiazepine (Bzd.)

INHIBITION OF 'T' TYPE Ca^{2+} CURRENT
(high conc Phenytoin)

Ethosuximide

Valproate — Valproate (Valpr.) · Valproate

Lamotrigine

MOA: Mechanism Of Action

- **Benzodiazepines (diazapam, clonazapam)**
  - Increase frequency of GABA-mediated chloride channel openings
- **Barbiturates (phenobarbital, primidone)**
  - Prolong GABA-mediated chloride channel openings
  - Some blockade of voltage-dependent sodium channels

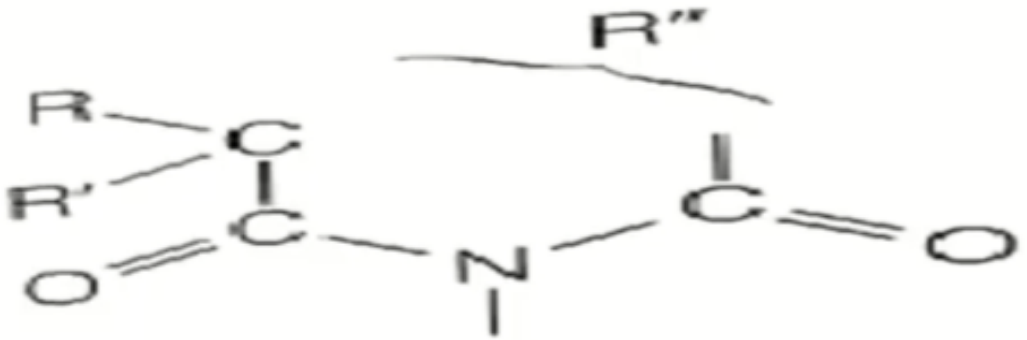
Phenytoin, Carbamazepine

- Block voltage-dependent sodium channels at high firing frequencies—use dependent

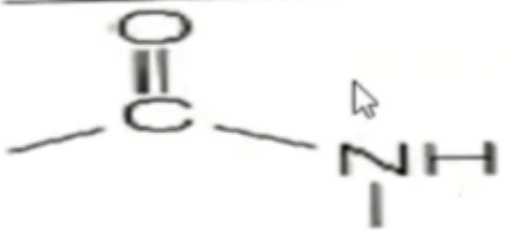
Valproate

- May enhance GABA transmission in specific circuits
- Blocks voltage-dependent sodium channels

SAR Of Anticonvulsants



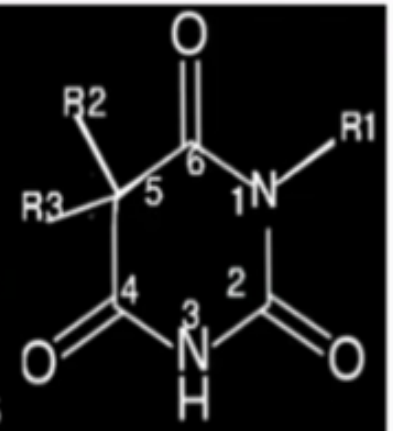
Structure common to anticonvulsant drugs.

R''	
	Barbiturates
— NH	Hydantoins
— O	Oxazolidinediones
— CH_2	Succinimides

Structure activity relationship of anticonvulsants

1.BARBITURATES

Phenobarbitone
$R_1 = H$ $R_2 = C_2H_5$ $R_3 = C_6H_5$
Mephobarbitone
$R_1 = CH_3$ $R_2 = C_2H_5$ $R_3 = C_6H_5$
Metharbital
$R_1 = CH_3$ $R_2 = C_2H_5$ $R_3 = C_2H_5$



Barbiturates

Structure-Activity Relationship :

(1) Optimum activity is observed when one of the substituents at C_5 is phenyl.

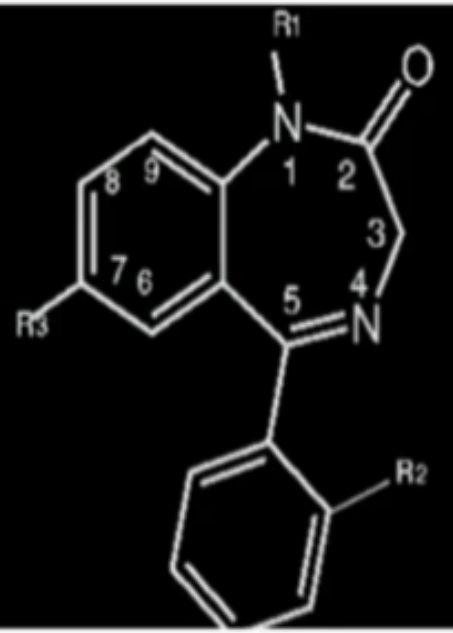
(2) The 5, 5 - diphenyl derivative has less activity than phenobarbitone.

(3) N_2 and N_3 substitutions, in some cases also resulted in an increased activity.

(4) 5, 5 - dibenzyl barbituric acid, causes convulsions.

2. BENZODIAZEPINES

- Diazepam
  $R_1 = CH_3$ $R_2 = H$ $R_3 = Cl$
- Nitrazepam
  $R_1 = H$ $R_2 = H$ $R_3 = NO_2$
- Clonazepam
  $R_1 = H$ $R_2 = Cl$ $R_3 = NO_2$



Structure-Activity Relationship :

(1) The electron withdrawing atom or group at position 7 increases the anti - epileptic activity while electron donating substituents at 7, 8 or 9 positions decrease it.

(2) A phenyl group at position 5 is necessary for activity. But only halogen substituents are allowed in the ortho position.

(3) The electron withdrawing groups at ortho or diortho positions at 5-phenyl increase the activity while any substituent on meta or para position at 5-phenyl decreases the activity.

(4) Methyl substitution at position 1 confirms high activity.

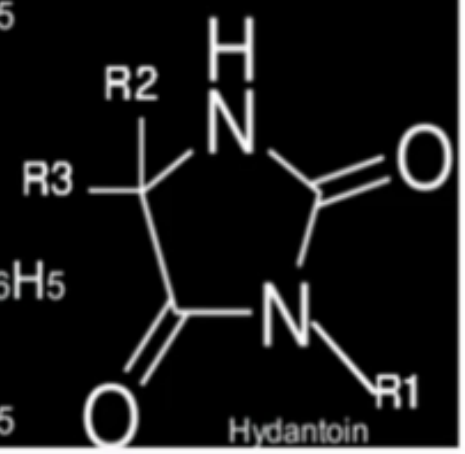
3.HYDANTOINS

Phenylethylhydation
$R_1 = H \quad R_2 = C_2H_5 \quad R_3 = C_6H_5$

Phenytoin
$R_1 = H \quad R_2 = R_3 = C_6H_5$

Mephenytoin
$R_1 = CH_3 \quad R_2 = C_2H_5 \quad R_3 = C_6H_5$

Ethotoin
$R_1 = C_2H_5 \quad R_5 = H \quad R_5 = C_6H_5$



Hydantoin

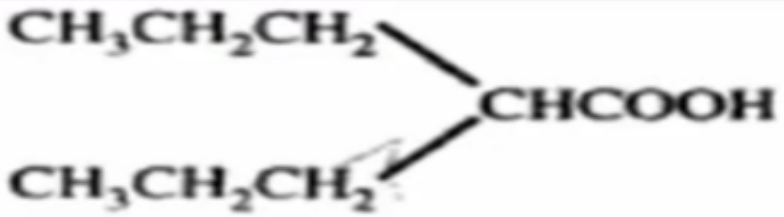
Structure-Activity Relationship :

(1) A 5-phenyl or other aromatic substituent is essential for the activity.

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

(3) Among other hydantoins, like spirohydantoins, thiohydantoins, dithiohydantoins and 1, 3-disubstituted hydantoins, some exhibit activity against chemically induced convulsions while remain ineffective against electroshock induced convulsions.

4.VALPROIC ACID



Valproic acid

Among other relatives of valproic acid, 3, 3, 4-trimethylpentanoic acid is also as active as valproic acid. In this series, [i.e. dialkylalkanoic acid having less than 14 carbon atoms]

(1) The anticonvulsant activity increases with increased chain length.

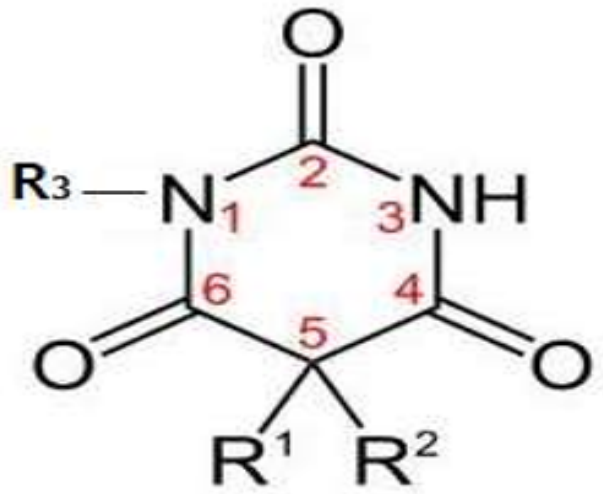
(2) Introduction of a double bond decreases the activity.

(3) Introduction of a secondary or tertiary hydroxyl group or replacement of carboxyl by hydroxyl group has no effect.

barbiturates

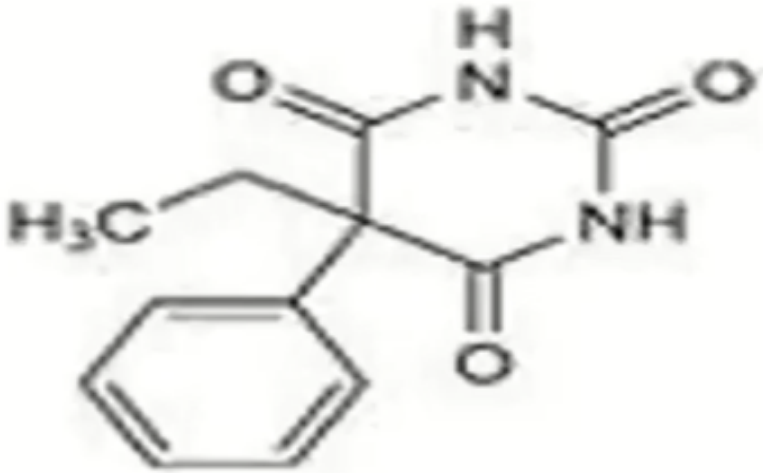
Most of the barbiturates are sedative and hypnotics, only few of them show anticonvulsant characters.

General structure



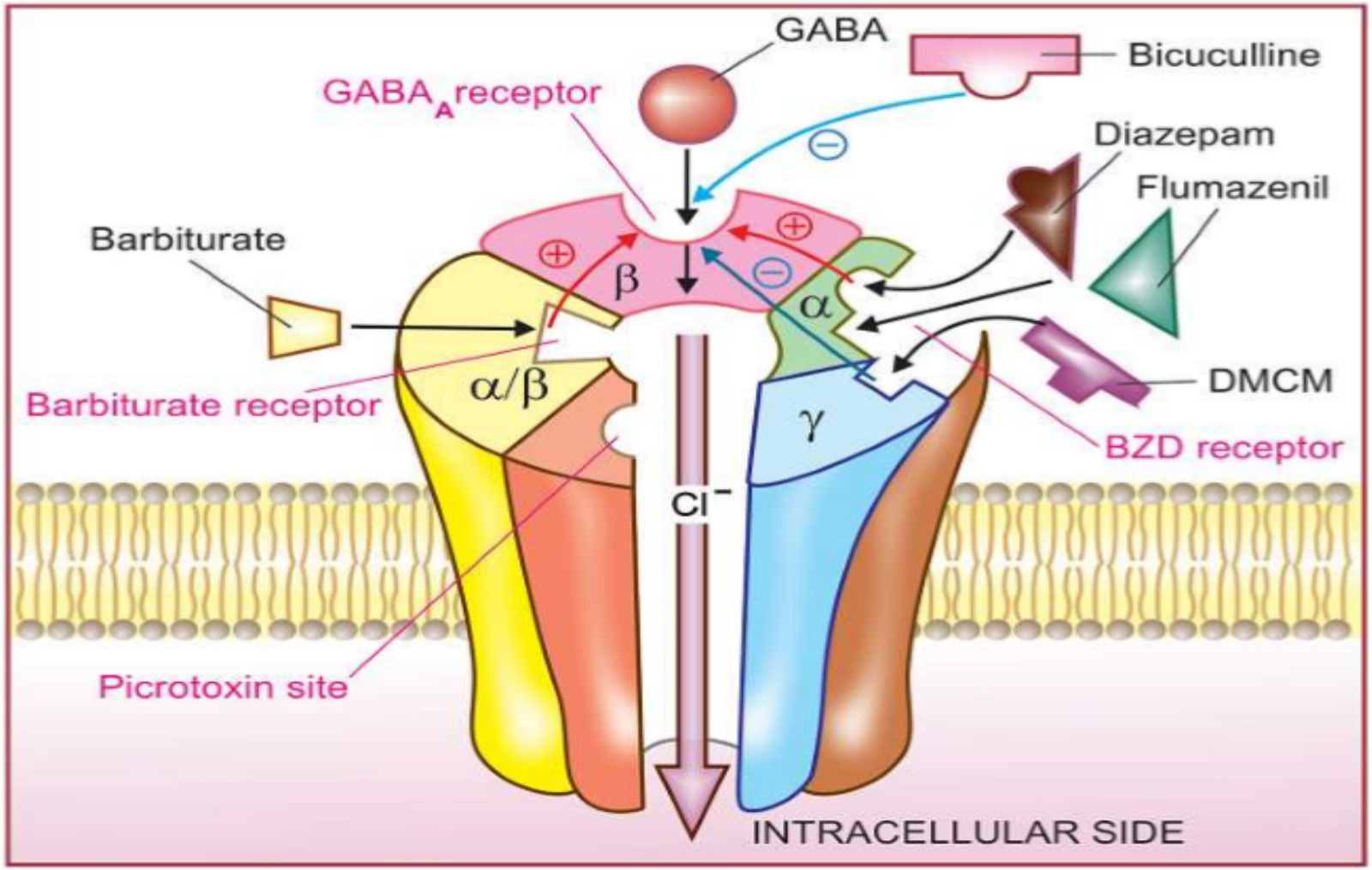
Name	R1	R2	R3
Phenobarbitone	C_2H_5	C_6H_5	H
Mephobarbitone	C_2H_5	C_6H_5	CH_3
Metharbital	CH_3	CH_3	CH_3

Phenobarbitone



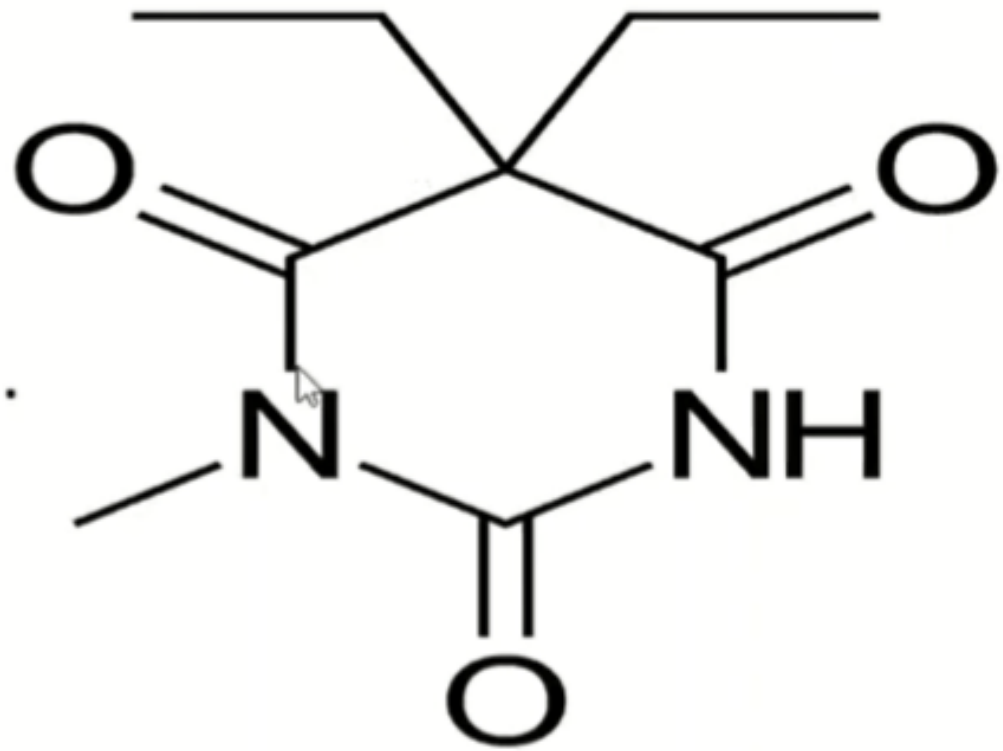
- Used in the treatment of all types of seizures, except absence seizures
- Is the first-line choice for the treatment of neonatal seizures(seizure in a baby younger than 4 weeks old.)
- Used to treat status epilepticus.
- Used to treat trouble sleeping, anxiety, and drug withdrawal.
- Used for alcohol detoxification and benzodiazepine detoxification for its sedative and anti-convulsant properties.
- Used for insomnia,not recommended due to the risk of addiction and other side affects
- Overdose may lead to pulmonary edema and acute renal failure, bradycardia, hypothermia, and hypotension.

Phenobarbitone : Mechanism of action



Methabarbital

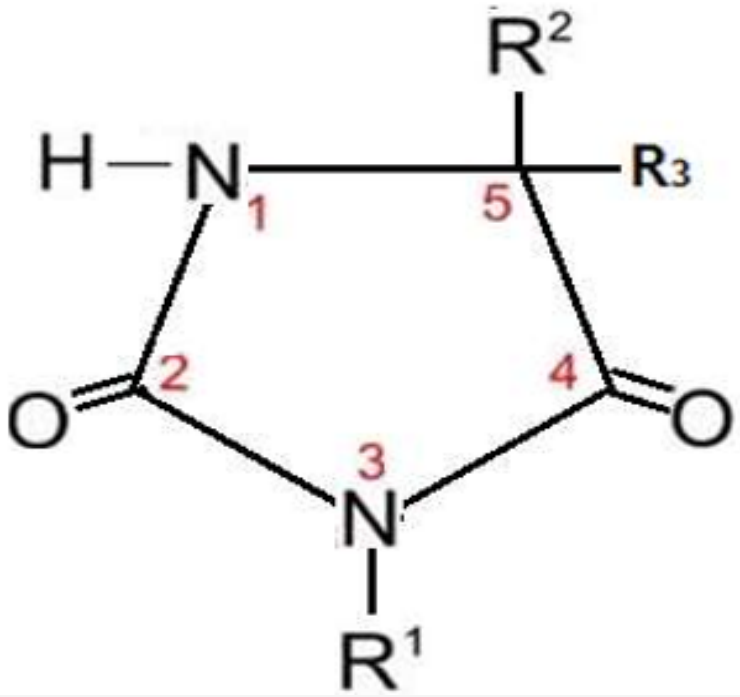
- It is a barbiturate derivative.
- Anticonvulsant, used in the treatment of epilepsy.
- It has similar properties to phenobarbital.



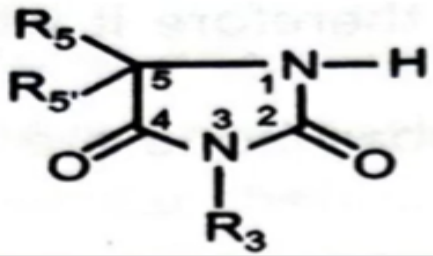
hydantoins

The hydantoins are close structural relatives of barbituric acid, differing in lacking of 6-oxo groups.

The lack of this carbonyl gp decreases the acidity, so it is weaker acid than that of barbiturates.

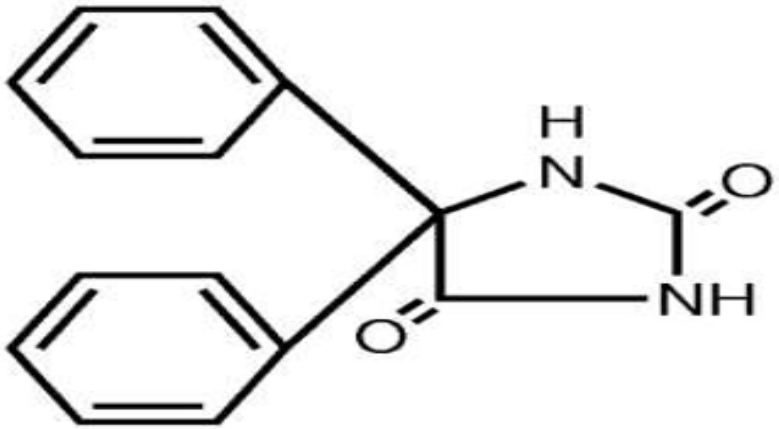


- Hydantoins with lower alkyl substituents are not active against absence seizure.

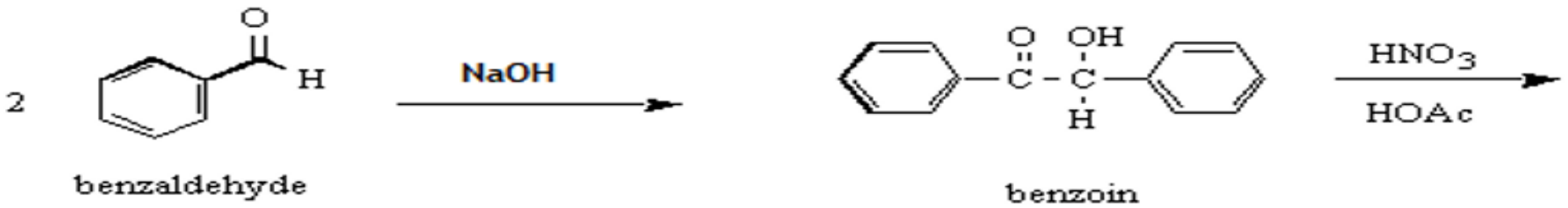


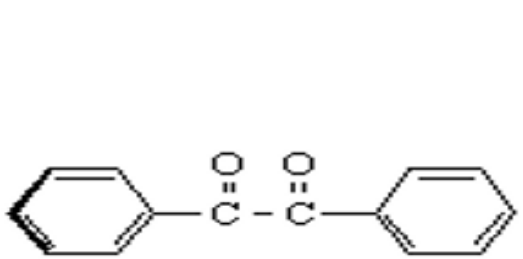
Generic name	Substituents		
	R1	R2	R3
PHENYTOIN	C_6H_5	C_6H_5	H
MEPHENYTOIN	C_6H_5	C_2H_5	CH_3
ETHOTOIN	C_6H_5	H	C_2H_5

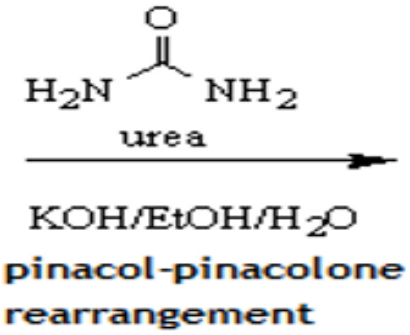
1) PHENYTOIN

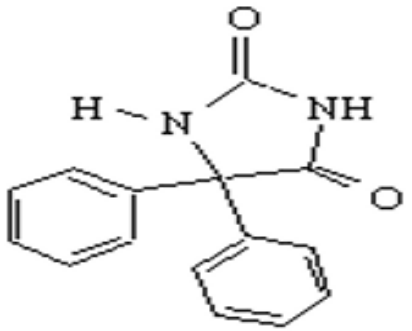


Synthesis









Mechanism of action

It is a sodium channel blocker.

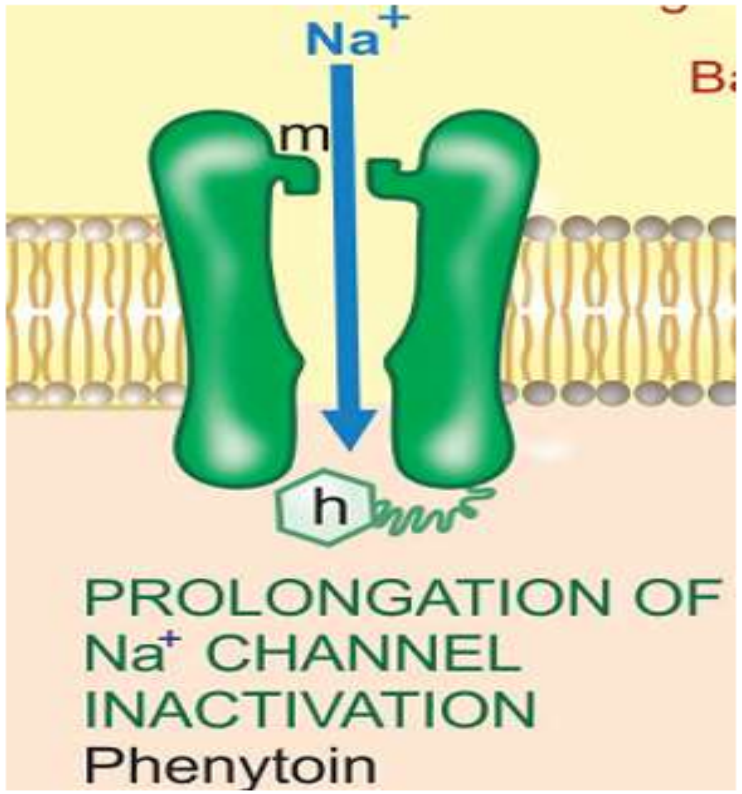
Both the Na+ and Cl- ions are invariably present at much higher concentration outside the cell, whereas K+ charged proteins and organic cations are more abundantly available inside the cell.

Epileptic seizures causes Na+ ion accumulation within the central neuron, which initiates enhanced synaptic nerve transmissions following presynaptic stimulation.

Phenytoin decreases Na+ intracellular ion by activating biochemical process that normally extrudes Na+ ion from neurons.

Phenytoin

- Prolonging the inactivated state of voltage sensitive neuronal Na+ channel.



USES

Phenytoin is used in the treatment of;

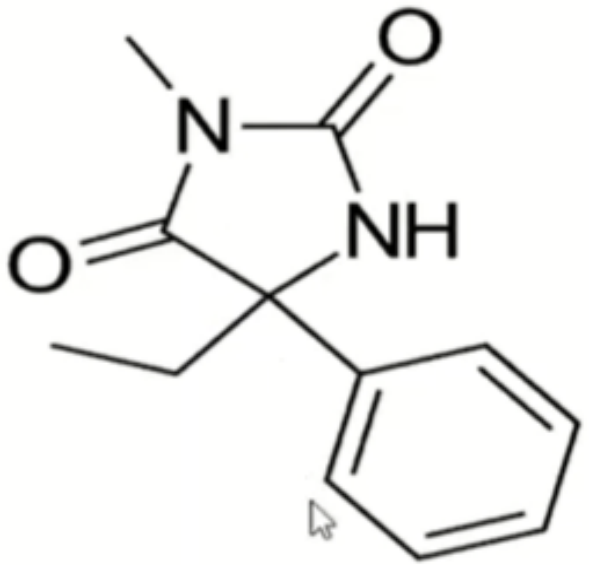
1. Generalized tonic-clonic seizures.
2. Partial seizures.
3. Trigeminal and other neuralgias.
4. Status epilepticus ; phenytoin is administered intravenously in normal saline.

DOSE

100-200 mg twice daily oral, 25 mg/min slow i.v injection.

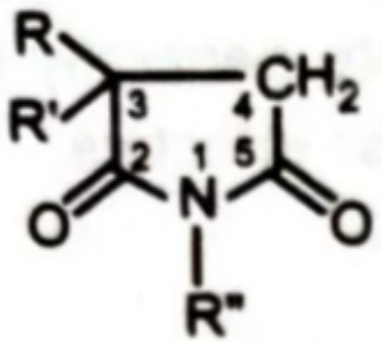
Mephenytoin

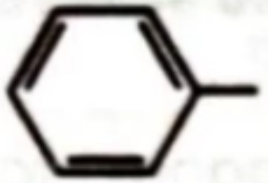
- **Mephenytoin** is a hydantoin
- used as an anticonvulsant.
- The significant metabolite of mephenytoin is nirvanol (5-ethyl-5-phenylhydantoin),
- which was the first hydantoin (briefly used as a hypnotic).



[redacted] Succinimides

As oxazolidine diones are toxic, an extensive search was carried out to replace them with less toxic drugs. Substitution of ring oxygen in the oxazolidine diones with a $-CH_2$ group gave the antiseizure succinimides. The precise mechanism of action of succinimides is unknown, but it is proposed to act by decreasing the activity of T- type calcium channel. These drugs are used in the treatment of absence (petit mal epilepsy) seizure.



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

Phensuximide:

- Phensuximide is chemically 1-methyl-3-phenylpyrrolidine-2,5-dione.
- It suppresses the paroxysmal three cycles per second spike and wave EEG pattern associated with lapses of consciousness in absence (petit mal) seizures.
- N-demethylation occurs to yield the putative active metabolite.

Uses:

- Phensuximide occasionally is used for the treatment of absence seizures.
- The phenyl substituent leads to be active against generalized tonic-clonic and partial seizures.
- It also had some activity against maximal electroshock seizure.

Methsuximide:

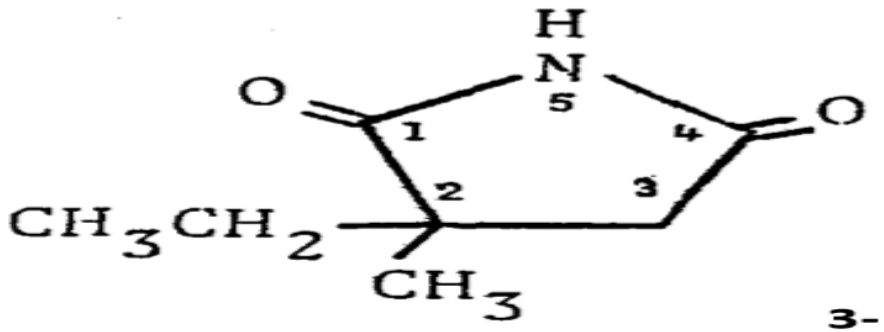
- Methsuximide is chemically, 1,3-dimethyl-3-phenylpyrrolidine-2,5-dione.
- It increases the seizure threshold and suppresses the paroxysmal three cycles per second spike and wave ECG pattern seen with absence (petit mal) seizures.
- It is generally considered as more toxic than ethosuximide.

Uses:

- Methsuximide is used primarily for the treatment of absence seizures and complex partial seizure.
- It also had some activity against maximal electroshock seizure.

SUCCINIMIDES

4) ETHOSUXIMIDE[zarontin]



3- Ethyl-3-methyl pyrrolidin-2,5-dione

USE:- It is effective in the cure of petit mal epilepsy

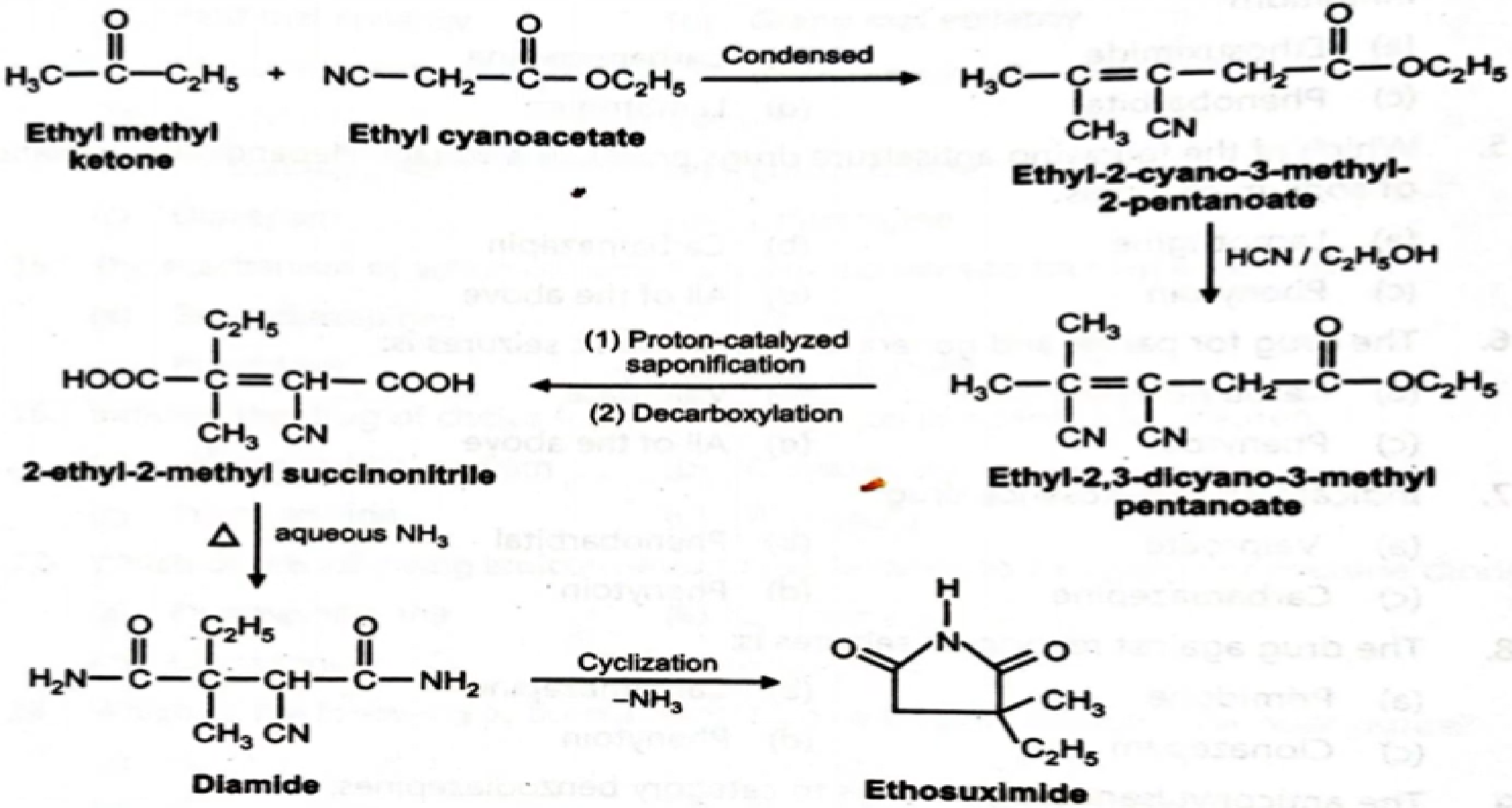
Ethosuximide:

- Ethosuximide is chemically, 3-ethyl-3-methylpyrrolidine-2,5-dione.
- It acts by blocking calcium T channel of the thalamic neurons. This results in decrease in burst firing of thalamocortical neurons, which stabilize the nerve activity in the brain and prevents seizures.
- It is more active and less toxic than trimethadione.

Uses:

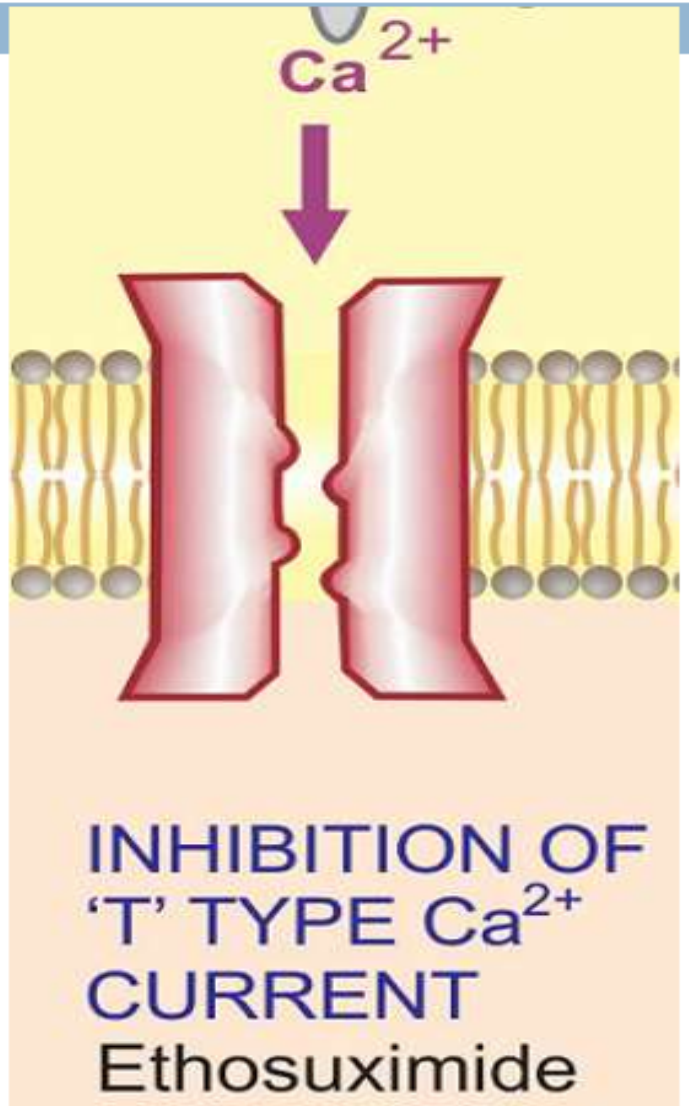
- Ethosuximide is used in the treatment of absence (petit mal) seizures.
- With other antiepileptic drugs it can be used to treat other types of epilepsy.

ETHOSUXIMIDE



Ethosuximide

- Ethosuximide selectively suppresses T current.
- Thalamic neurones exhibit prominent ‘T’ (transient) current which is low threshold Ca2+ current (due to inward flow of Ca2+ through T type Ca2+ channels).
- Use: Absence seizures;



OXAZOLIDINEDIONES

Replacement of the NH group at position 1 of the hydantoin systems with oxygen atoms yields the oxazolidine-2,4-dione system.

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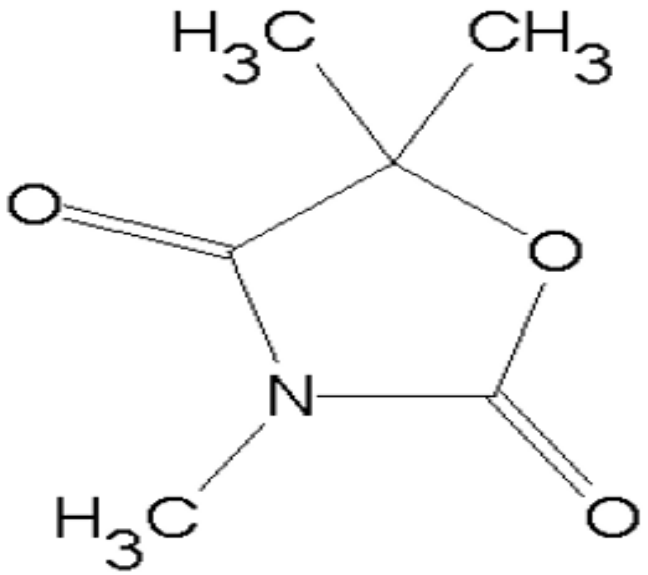
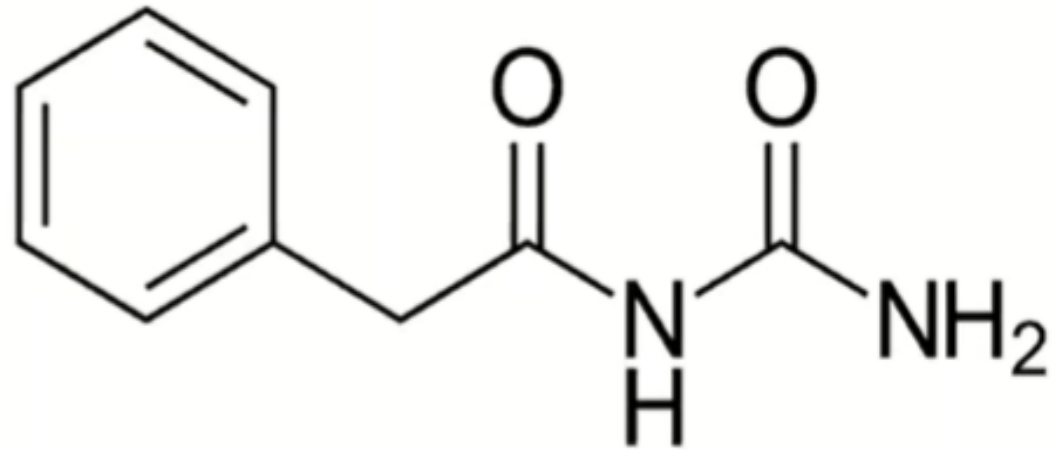
3) **TRIMETHADIONE**



3,5,5-trimethyl oxazolidin-2,4-dione

USE:- It is used in the treatment of petit mal epilepsy. Dermatological and hematological toxicities limit its clinical use.

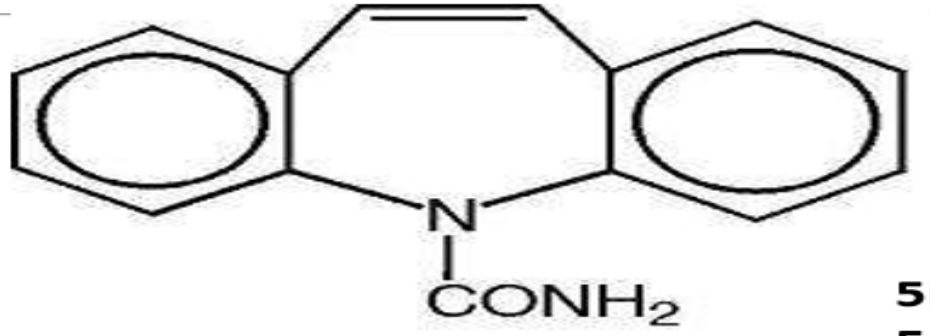
Urea and monoacylureas: Phenacemide



- Also known as **phenylacetylurea**
- Is an anticonvulsant of the ureide (acetylurea) class.
- It is a congener and ring opened analogue of phenytoin (a hydantoin), and is structurally related to the barbiturates and to other hydantoins.
- Phenacemide used for the treatment of epilepsy, but was eventually withdrawn due to toxicity.

Urea and monoacyl urea

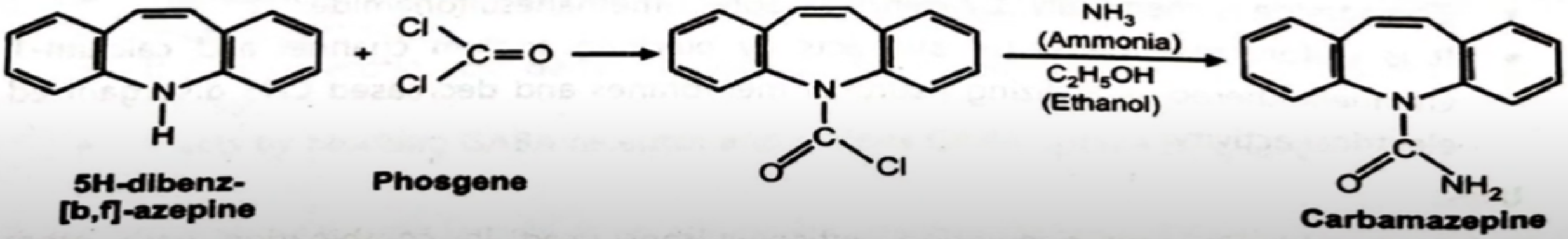
5) CARBAMAZEPINE[Tegretol]



5H –Dibenz-[b,f]-azepin-5-carboxamide

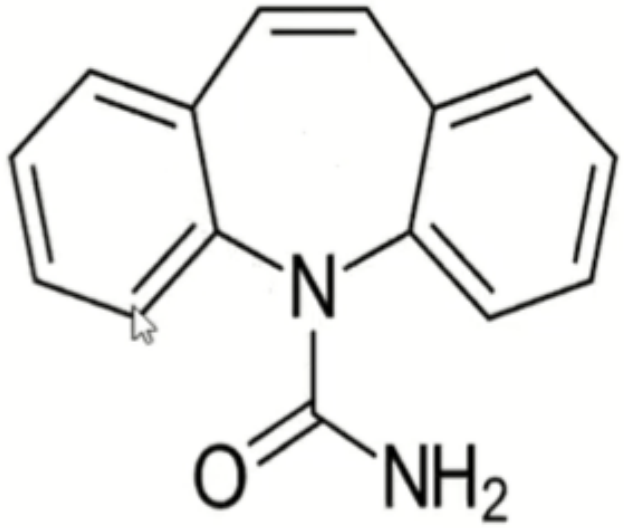
USE:- It is used to control grand mal and focal seizures. It is used in the treatment of trigeminal neuralgia and treatment of manic depression.

2. CARBAMAZEPINE



5H-dibenz-[b,f]-azepine + **Phosgene** → **Carbamazepine**

Urea and monoacylureas: **Carbamazepine**



- Is an anticonvulsant and mood stabilizing drug.
- Used primarily in the treatment of epilepsy

in partial seizures, generalized tonic-clonic seizures and mixed seizures)

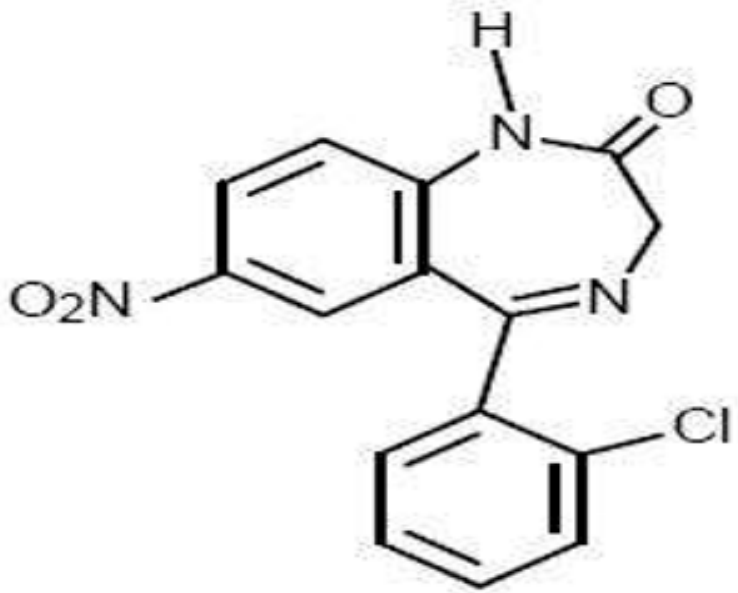
Used in bipolar disorder, as well as trigeminal neuralgia

- It is also used for a variety of indications,

including attention-deficit hyperactivity disorder (ADHD), schizophrenia, and post-traumatic stress disorder.

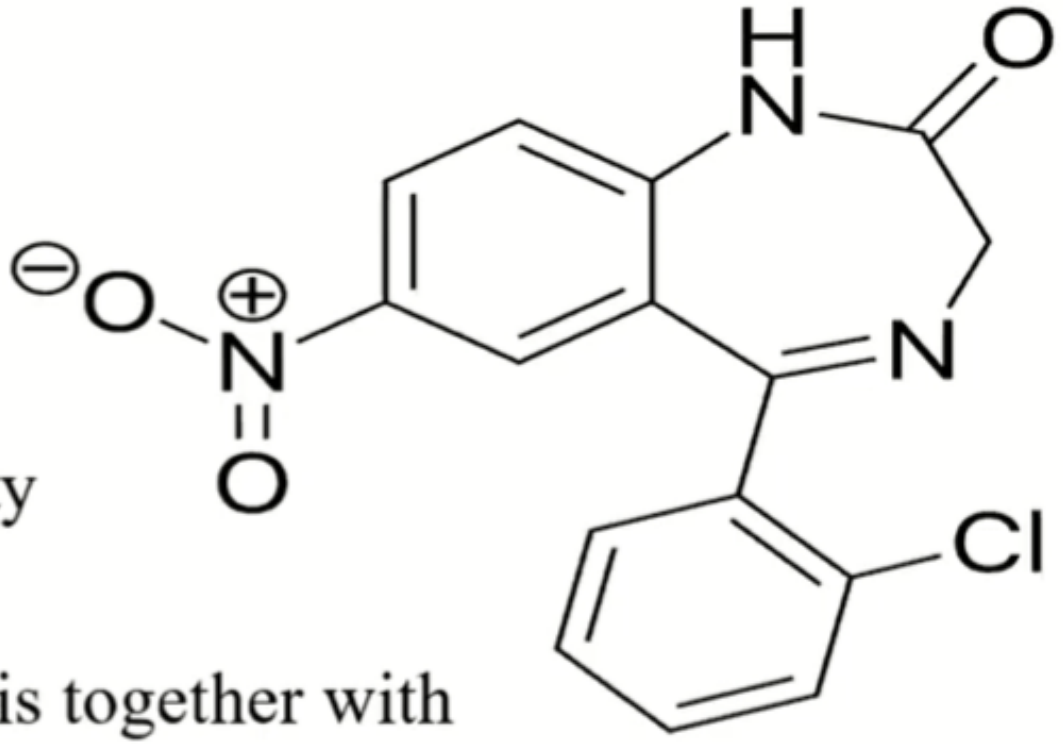
BENZODIAZEPINES

6) CLONAZEPAM



USE:- It is effective in all type of epilepsy i.e. grand mal, psychomotor, petit mal, myoclonic and status epilepsy.

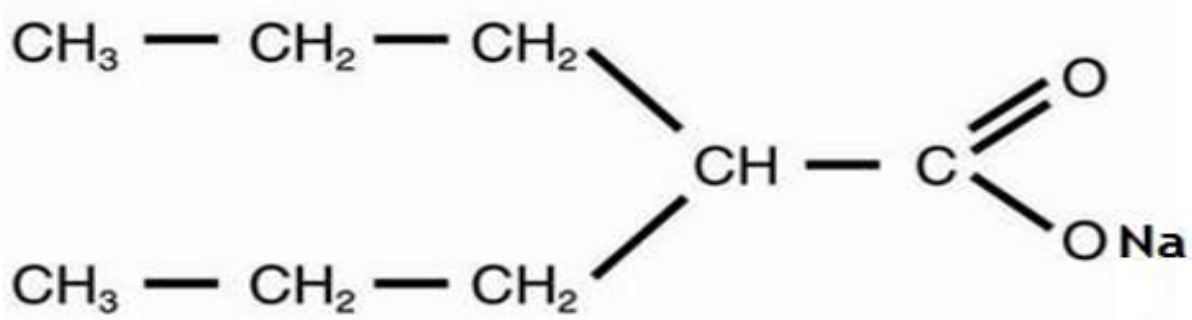
Clonazepam

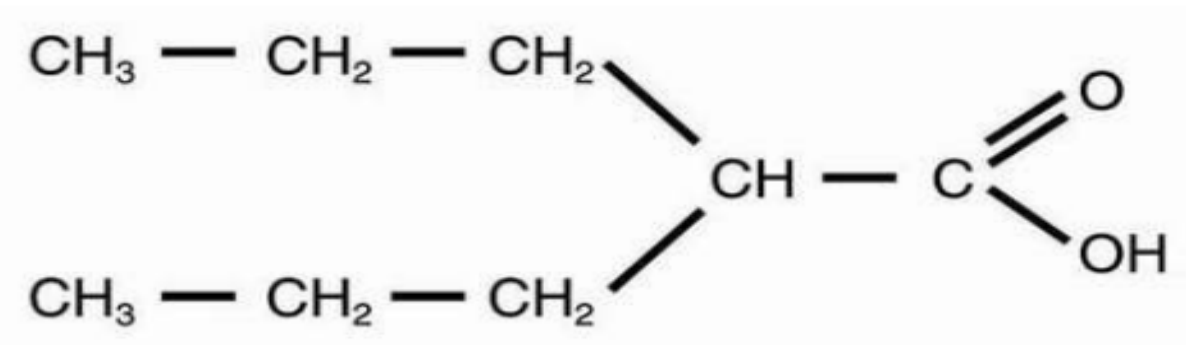


- Is a benzodiazepine derivative having anticonvulsant, muscle relaxant, and very potent anxiolytic properties (Used in Anxiety disorders , Panic disorder)
- Initial treatment of mania or acute psychosis together with
- first line drugs such as lithium, haloperidol or risperidone.
- Long-acting benzodiazepine.
- Clonazepam is a chlorinated derivative of nitrazepam and therefore a nitrobenzodiazepine.
- MOA: Enhancement of the neurotransmitter GABA via modulation of the $GABA_A$ receptor.

MISCELLANEOUS

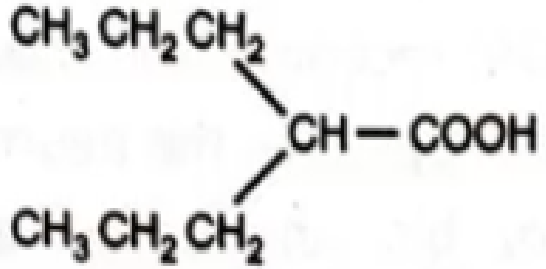
7) SODIUM VALPROATE





VALPROIC ACID

Valproic acid:



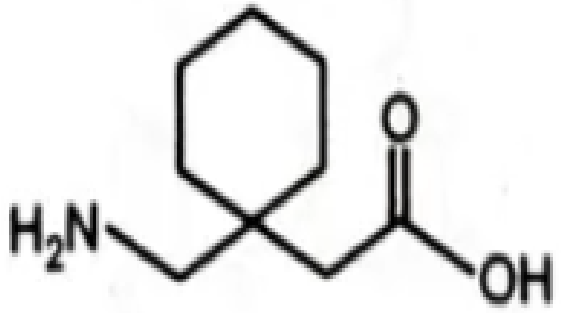
Valproic acid

- Valproic acid is chemically, 2-propylpentanoic acid.
- It is synthetic derivative of propylpentanoic acid.
- It may act by increasing GABA levels in the brain or by blocking voltage dependent sodium channels and disorganized electrical activity.
- As this drug undergoes extensive dissociation at physiological pH produce poor partitioning across BBB, hence less potent compared to other drugs.

Uses:

- Valproic acid has anticonvulsant properties and is used in the treatment of grand mal epilepsy, petit mal epilepsy and complex partial seizure.
- It is also used as a mood stabilizer.
- It possesses antineoplastic and antiangiogenesis activities.

Gabapentin:



Gabapentin

- Gabapentin is chemically, 1-(aminomethyl) cyclohexaneacetic acid.
- It is synthetic GABA-mimetic analogue capable of penetrating the CNS.
- It is a water-soluble amino acid, act by altering the metabolism or release of GABA and decreased CNS disorganized electrical activity.
- It raises brain GABA levels in patients with epilepsy.
- It also acts by binding with calcium channels.

Uses:

- Gabapentin is used in refractory partial seizures and generalized tonic-clonic seizures.
- It also approved for the treatment of postherpetic neuralgia.

THANK YOU