What is Epilepsy?

- Epilepsy is a collective term for a group of disorders characterised by paroxysmal cerebral dysrthmia, menifesting as brief episodes (seizures) of loss or disturbance of conciousness with or without characteristic body movements(convulsions)sensory or psychiatric phenomina

Convulsion – Involuntary spasmodic contractions of any or all voluntary muscles throughout the body, including skeletal and facial muscles.

Seizures – Brief episode of abnormal electrical activity in the nerve cells of the brain -- detected on EEG

Epilepsy – Chronic, recurrent pattern of seizures

Classification

- Generalized
- Partial

Generalised seizures

1.Generalised tonic clonic seizures (GTCS)
Grand mal epilepsy

- Major epilepsy1-2 min
- Commonest
- Aura –cry –unconciousness –tonic spasm of all body muscles-tonic jerking
- Prolongrd sleep and depression of all CNS functions

2.Absence Seizures

Minor epilepsy, petit mal

- ½ minute
- Children
- Apparent freezing
- EEG: 3 cycle per second spike and wave pattern

3. Atonic Seizures

Akinetic Epilepsy ,Drop Attack

- Sudden loss of postural tone
- Unconciousness
- Excessive inhibitory discharges

4.Myoclonic seizures

Shock like momentary contraction of muscles of a limb or the whole body

5. Infantile Spasms

Hypsarrhythmias

Partial seizures

1. Simple partial seizures

2. Complex Partial seizures

3. Simple Partial or complex partial seizures secondarily generalized

Clinical classification of antiepileptic drugs

- Tonic-clonic (grand mal) seizures:
  - Carbamazepine, Phenytoin, Valproate, Phenobarbitone
  - Newer agents: Lamotrigine, Gabapentin
- Partial (focal) seizures (Psychomotor epilepsy or temporal lobe epilepsy): Carbamazepine, Phenytoin, Primidone, Valproate
- Absence seizures (petit mal): Ethosuximide, Clonazepam
- Petitmal + Grandmal: Valproate
- Status epilepticus: Lorazepam, Diazepam, Phenytoin, Phenobarbitol, General anesthesia
- Febrile seizures: Diazepam, Phenobarbitone

MECHANISM OF ACTION OF ANTIEPILEPTIC DRUGS

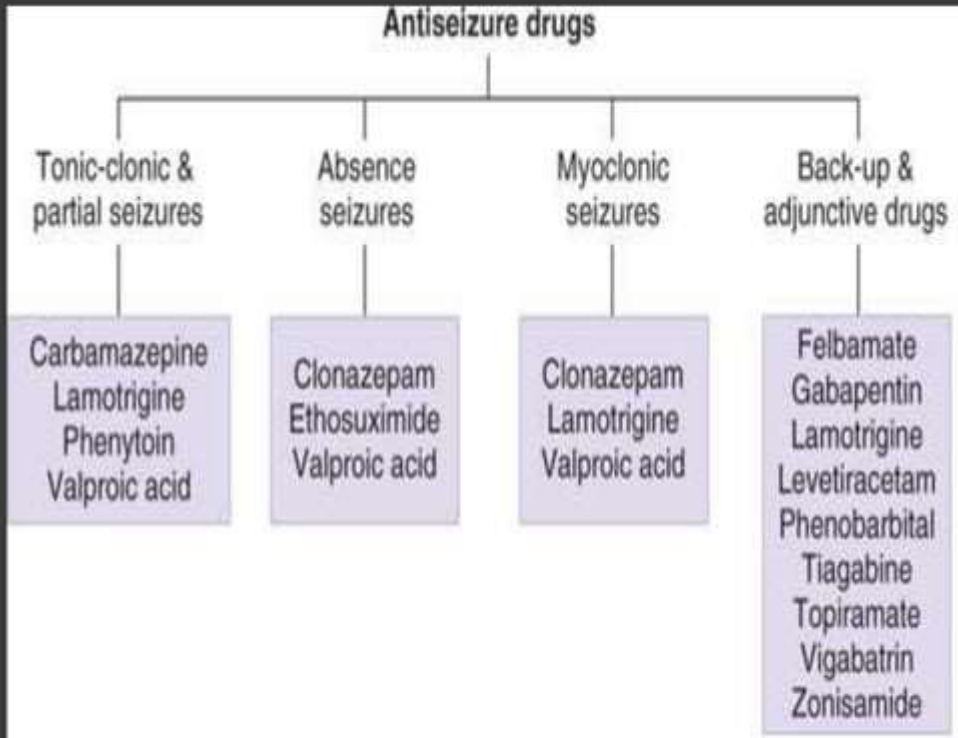
Antiepileptics inhibit the neuronal discharge or its spread in one or more of the following ways:

(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 calcium T-channels: valproate, ethosuximide; the result is diminishing of the generation of action potential.

(4) Inhibiting excitory neurotransmitter glutamate: lamotrigine.



Source: A.J. Trevor, B.G. Katzung, M. Kruidering-Hall: Katzung & Trevor's Pharmacology: Examination & Board Review, 11th Ed.
www.accesspharmacy.com

CLASSIFICATION OF ANTIEPILEPTIC DRUGS

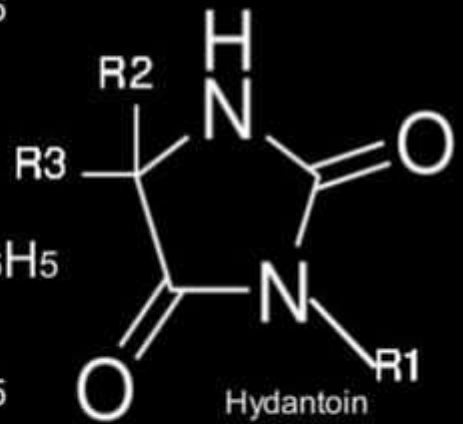
- **Hydantoins:** phenytoin, phosphenytoin
- **Barbiturates:** phenobarbitone
- **Iminostilbenes:** carbamazepine, oxcarbazepine
- **Succinimides:** ethosuximide
- **Aliphatic carboxylic acid:** Valproic acid, divalproex
- **Benzodiazepines:** clonazepam, diazepam, lorazepam
- **New compounds:** gabapentin, lamotrigine, tiagabine, topiramate, vigabatrin, zonisamide, felbamate

Structural activity relationship of:

1. Hydantoin
2. Barbiturates
3. Benzodiazepines
4. Valproic Acid
5. Succinimides

1. 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
  $R_1 = C_2H_5 \quad R_5 = H \quad R_5 = C_6H_5$



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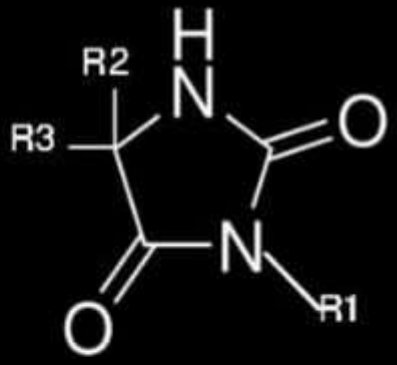
- A phenyl or other aromatic substituents at C_5 is essential for the activity.
- Alkyl substituents at position 5 may contribute to sedation, a property absent in phenytoin. Hydantoin



Hydantoin

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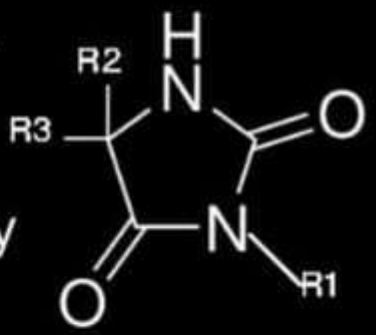
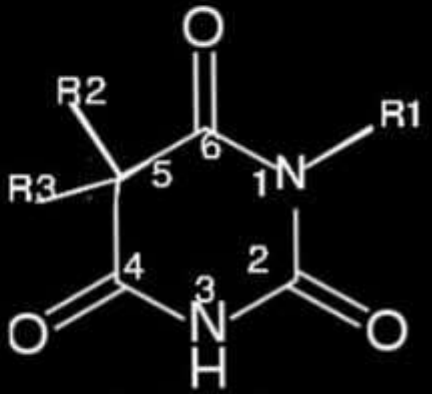
- Among other hydantoins, like spirohydantoins, thiohydantoins, dithiohydantoins, and 1, 3-disubstituted hydantoins, some exhibit activity against chemically induced convulsions.
- While remaining are ineffective against electroshock induced convulsions.



Hydantoin

2. Barbiturates

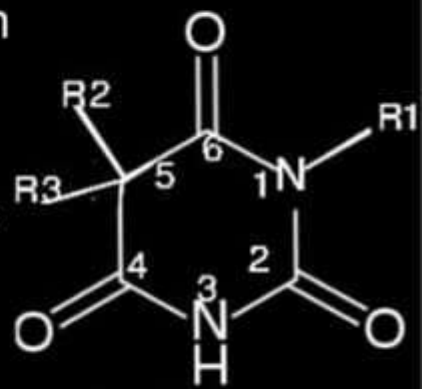
- Phenobarbitone
  $R_1 = H \quad R_2 = C_2H_5 \quad R_3 = C_6H_5$
- Mephobarbitone
  $R_1 = CH_3 \quad R_2 = C_2H_5 \quad R_3 = C_6H_5$
- Metharbital
  $R_1 = CH_3 \quad R_2 = C_2H_5 \quad R_3 = C_2H_5$



Barbiturates

Contd..

- Optimum activity is observed when one of the substituents at C_5 is phenyl.
- The 5, 5-diphenyl derivatives have less activity than phenobarbitone.
- N2 and N3 substituents, in some cases also results in an increased activity.
- 5, 5-dibenzyl barbituric acid causes convulsions.



Barbiturates

3. Benzodiazepines

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

Benzodiazepines

Contd..

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

Benzodiazepines

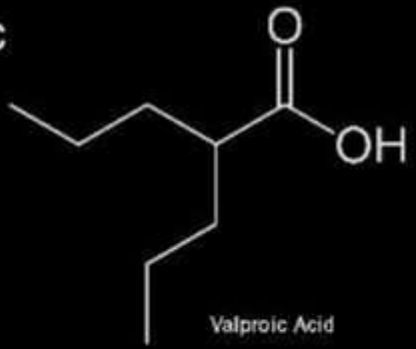
Contd..

- The electron withdrawing groups at ortho or diortho positions at 5-phenyl increase the activity while any substituents on meta or para position at 5-phenyl decreases the activity.
- Methyl substitution at position 1 confirms high activity.

Benzodiazepines

4. Valproic Acid

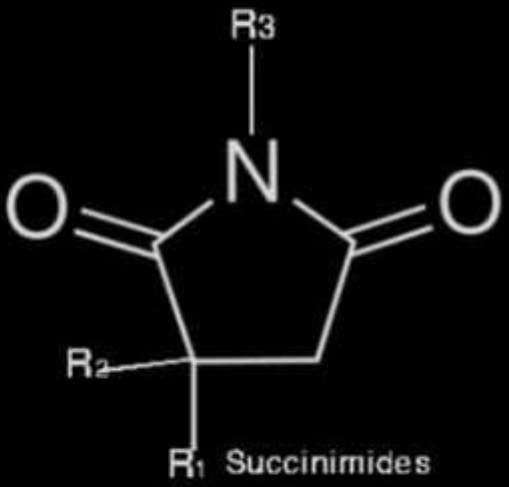
- Among other relatives of valproic acid, 3, 3, 4-trimethylpentanoic acid is also as active as valproic acid.
- The anticonvulsant activity increases with increased chain length.
- Introduction of a double bond decreases the activity.



Valproic Acid

5. Succinimides

- Phensuximide
  $R_1 = C_6H_5$ $R_2 = H$ $R_3 = CH_3$
- Methsuximide
  $R_1 = C_6H_5$ $R_2 = R_3 = CH_3$
- Ethosuximide
  $R = C_2H_5$ $R_2 = CH_3$ $R_3 = H$



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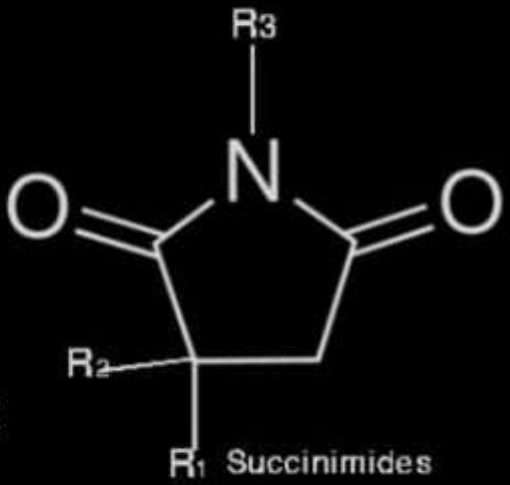
- Methsuximide and phensuximide have phenyl substituents which makes them active against electrically induced convulsion.
- N-Methylation decreases activity against electroshock seizures and impart more activity against chemically induced convulsion.



Succinimides