Epilepsy & Seizures And Anti-Epileptic Drugs

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Introduction

The term "epilepsy," based on the Greek word epilambanein (meaning "to seize"), was first used by Hippocrates.

• Hippocrates provided the first classification of epilepsy, which is still used.

i) True (idiopathic) epilepsy: a disorder for which the cause is unknown.

ii) Symptomatic (organic) epilepsy: a disorder resulting from a physiologic abnormality, e.g., brain injury, tumour, infection, intoxication or metabolic disturbances.

"Epilepsy is a symptom complex characterized by recurrent paroxysmal aberrations of brain functions, usually brief and self -limited"

All forms of epilepsy originate in the brain and appear to be the result of changes in neuronal activity. These changes, such as an excessive neuronal discharge, may be brought about by a disturbance of physicochemical function and electrical activity of the brain.

The most important property of the nerve cell is its excitability. It responds to excitation by generating an action potential, which may lead to repeated discharges.

• All normal neurons may become epileptic if subjected to excessive excitation.

• There are two possible mechanisms for convulsive disorders: a loss of the normal inhibitory control mechanism, and a chemical super sensitivity that increases excitability of neuronal elements.

• **Epilepsy** is a disorder characterized by recurring seizures (also known as "seizure disorder")

• A **seizure** is a brief, temporary disturbance in the electrical activity of the brain

• **A seizure is a *symptom* of epilepsy**

The Brain Is the Source of Epilepsy

• All brain functions -- including feeling, seeing, thinking, and moving muscles -depend on electrical signals passed between nerve cells in the brain

• A seizure occurs when too many nerve cells in the brain “fire” too quickly causing an “electrical storm”

- **Generalized seizure:**

  Involves the whole brain and loss of consciousness

  - Absence: characterized by brief loss of consciousness
  - Tonic-Clonic: characterized by rhythmic jerking of muscles

- **Partial seizure:**

  Involves only part of the brain; may or may not include loss of consciousness

  - Symptoms relate to the part of the brain affected

Symptoms That May Indicate a Seizure Disorder

• Periods of blackout or confused memory

• Occasional “fainting spells”

• Episodes of blank staring in children

• Sudden falls for no apparent reason

• Episodes of blinking or chewing at inappropriate times

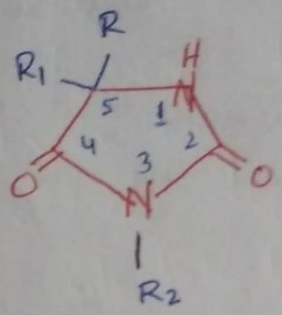
• A convulsion, with or without fever

• Clusters of swift jerking movements in babies

Classification of Anti-Epileptics

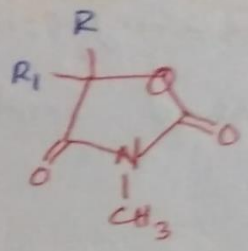
① **Barbiturates:** Phenobarbital, Mephobarbital, Methorbital — Sedatives & Hypnotics.

② **Hydantoin (Imidazolidine-2,4-dione) derivatives:**



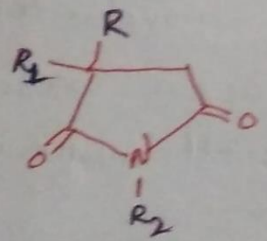
	R	R_1	R_2
*Phenytoin	C_6H_5-	C_6H_5	H
Phenylethyl hydantoin	C_6H_5	C_2H_5	H
Mephenytoin	C_6H_5	C_2H_5	CH_3
Ethotoin	C_6H_5	H	C_2H_5

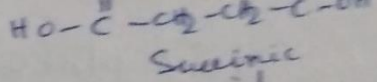
③ **Oxazolidinedione derivatives:**



	R	R_1
Trimethadione	CH_3	CH_3
Parmethadione	CH_3	C_2H_5
Aloxidone	CH_3	$CH_2=CHCH_2$-

④ **Succinimides**





Succinic acid.

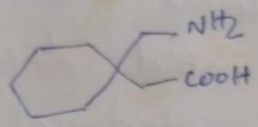
	R	R_1	R_2
Phensuximide	C_6H_5	H	CH_3
Methsuximide	C_6H_5	CH_3	CH_3
*Ethosuximide	C_2H_5	CH_3	H

⑤ Benzodiazepines : (Sedative & Hypnotics)

- Clobazam
- Clonazepam
- Diazepam
- Clorazepate

⑥ Gama-amino butyric acid (GABA) analogues :

- Progabide
- Tiagabin
- Vigabatrin
- Gabapentin →

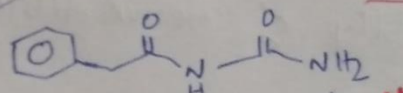


⑦ Misscellaneous

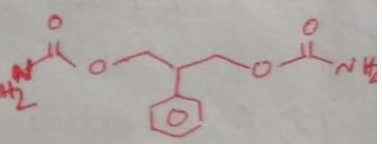
- Carbamazepine →
- Valproate
- Phenacemide →
- Primidone

* Urea & monoacyl ureas

- Phenacemide
- *Carbamazepine



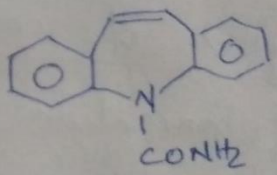
Phenacemide



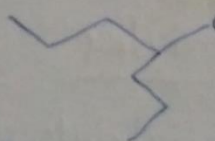
* • (Felbamate)

⑧ Newer drugs

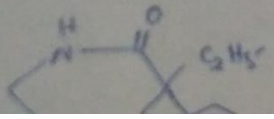
- Benzimol
- Dezinamide
- Fosphenytoin
- Lamotrigine
- Nafimidone
- Ralitoline
- Topiramate
- Zonisamide



(carbamazepine)



(Sod. Valporate)



Mechanism of Action

① **Hydantoins**: They block the voltage-gated sodium channels in the brain. Voltage-gated sodium channels are responsible for the generation of action potential of nerve fibres through selective transport of sodium ions across the cell membrane, leading to the rapid depolarisation of the cell network and on that to electrical excitability.

Hydantoin inhibits the influx of sodium ions, prevents depolarisation and decreases electrical excitability of nerve fibres.

② **Oxazolidinediones**:

These blocks T-type, voltage-dependent calcium channels in thalamic neurons and block the influx of calcium ions, thereby preventing the depolarisation of the membrane & decreases the electrical excitability of the neurons.

③ **Succinimides**:

They inhibits the T-type, volatage-dependent calcium channels in thalamic neurons.

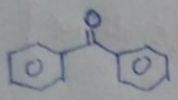
④ Benzodiazepines

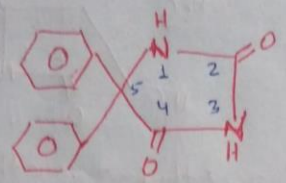
- Benzodiazepines receptors are present in brain & they form part of a $GABA_A$ receptor-chloride ion channel complex.
- Binding of benzodiazepines to these receptors activate $GABA_A$ receptor and increases chloride conductance by increasing the frequency of opening chloride ion channel. These in turn, inhibit neuronal activity by hyper polarisation and depolarisation block.

⑤ GABA Analogues :

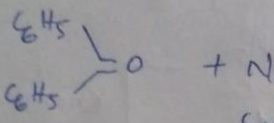
- GABA is an inhibitory neurotransmitter.
- It can't cross the blood-brain barrier. This problem is overcome by enhancing the lipid solubility by formation of Schiff's base of gabamide.
- The binding of GABA analogues to specific receptors in the neuronal membrane causes the opening of ion channels to allow the flow of either negatively charged chloride ions into the cell or positively charged potassium ions out of the cell. This action results in a negative change

Phenytoin :





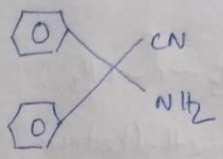
[5,5- diphenylimidazolidine-2,4-dione]



Diphenyl ketone
(Benzophenone)

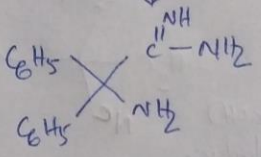
+ NaCN
Sod. cyanide

$(NH_4)_2CO_3$
Ammonium carbonate (Excess)



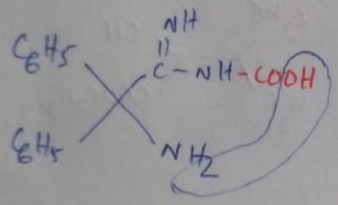
Amino nitrile derivative

NH_3 [from $(NH_4)_2CO_3$]

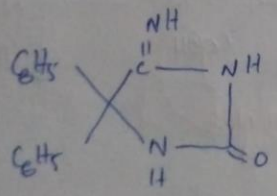


Amidine

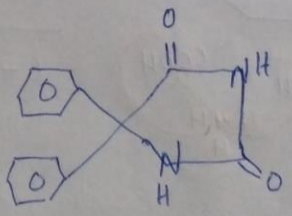
CO_2 from $(NH_4)_2CO_3$



$-H_2O$ | Cyclisation



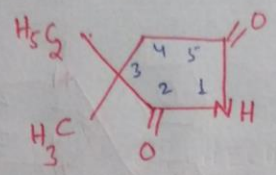
H^+/H_2O



(Phenytoin)

MOA: (Refer Hydantoins)

Ethosuximide

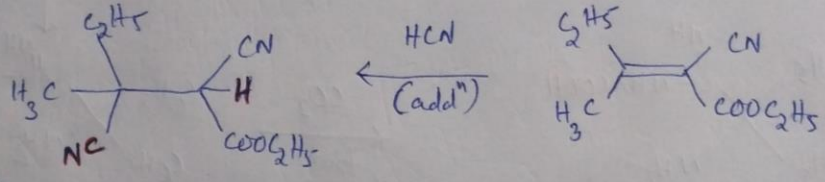


[3-Ethyl-3-methylpyrrolidine-2,5-dione]

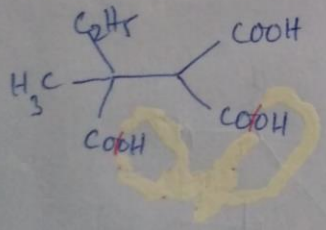
$C_2H_5-\overset{O}{\overset{\|}{C}}-CH_3$ + $NC-CH_2-COOC_2H_5$

Ethylmethylketone (2-Butanone) — Ethylcyanoacetate

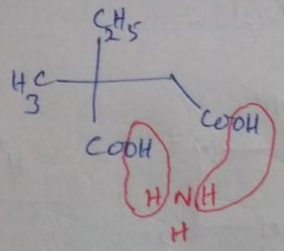
↓ Knoevenagel Cond^n



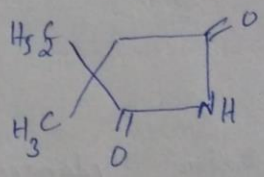
(NaOH) Hydrolysis ↓



$\xrightarrow[(-CO_2)]{\Delta}$

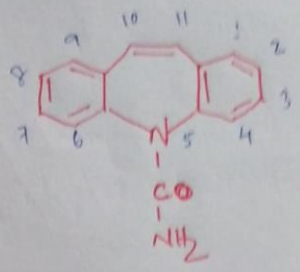


↓ NH_3 (Amination)

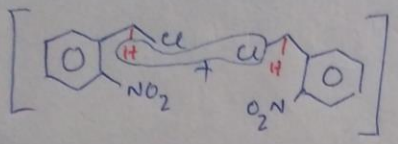


(Ethosuximide)

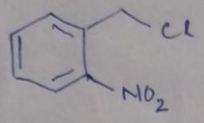
Carbamazepine :



[Dibenzazepine - 5 - carboxamide]



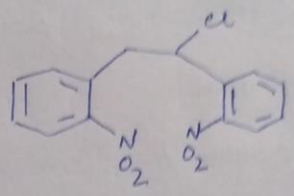
(HCl)

2 

$NaNH_2$

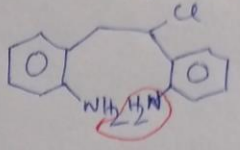
(Self-alkylation)

2-Nitro benzyl chloride

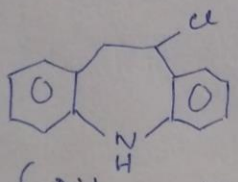


[H]

Redⁿ

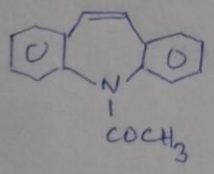


$\xrightarrow{\Delta}$ $-NH_3$



(Dibenzazepine)

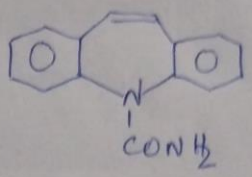
$-HCl$ $\downarrow (CH_3CO)_2O$



i) NaOH

ii) $COCl_2$

iii) NH_3



Carbamazepine.

MAD : Inhibits voltage-dependent sodium channels and is used to treat partial seizure & grand mal seizure.