ANTIEPILEPTIC DRUGS (ANTICONVULSANT DRUGS)

- The term epilepsy, based on the Greek word epilambaein (meaning to seize), has been first mentioned by Hippocrates.
- It is characterised by abnormal and excessive electroencephalographic discharge and a disturbance or loss of consciousness.

**Types of epilepsy**

- There are three principal types of epilepsy are found-
  A) **Grandmal** => In which seizures last (continuous) from 2 to 5 minutes, being characterised by sudden loss of consciousness, tonic and clonic convulsions of all muscles.
  B) **Petitmal (Absence seizures)** => The seizures last from 5 to 30 seconds, being characterised by brief attack of unconsciousness, occurs in children at the age of 4 to 8 years.
  C) **Psychomotor seizures** => Characterised by attacks without convulsions lasting from 2 to 3 minutes.
- The primary use of anticonvulsant drug is in the prevention and control of epileptic seizures.
- The ideal antiepileptic drug should completely suppress seizures, do not cause sedation or other undesired CNS toxicity.
- The epileptic seizures have been classified into two category-
  a) **Generalised**
  b) **Partial**

**Mode of Action**

- Anticonvulsants are drugs which selectively depress the CNS.
- Anticonvulsant drugs inhibited the neuronal discharge or its spread and do so in one or more of the three ways-
  1) Reducing (altering) cell membrane permeability to ions (Na and Ca ion).
  2) Enhancing the activity of GABA (Gamma-amino butyric acid) the principal inhibitory transmitter of the brain the result is increased membrane permeability to Cl⁻ (ion), which reduces cell excitability.
  3) Inhibiting excitatory neurotransmitters (Glutamate).

**Classification**

- The different chemical classes of anticonvulsant agents are-
  - Most of the anticonvulsant drugs contain the **ureide** structure.
A) **Barbiturates**

<table>
<thead>
<tr>
<th>S.NO.</th>
<th>DRUG</th>
<th>R1</th>
<th>R2</th>
<th>R3</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Phenobarbital</td>
<td>-C₂H₅</td>
<td></td>
<td>-H</td>
</tr>
<tr>
<td>2.</td>
<td>Mephobarbital</td>
<td>-C₂H₅</td>
<td></td>
<td>-CH₃</td>
</tr>
<tr>
<td>3.</td>
<td>Methbarbital</td>
<td>-C₂H₅</td>
<td>-C₂H₅</td>
<td>-CH₃</td>
</tr>
</tbody>
</table>

B) **Hydantoin**

\[ \begin{array}{c}
\text{R1} \\
\text{R2} \\
\text{R3}
\end{array} \]
### C) Oxazolidinediones =>

![Oxazolidinediones diagram]

<table>
<thead>
<tr>
<th>S.NO.</th>
<th>GENERIC NAME</th>
<th>R1</th>
<th>R2</th>
<th>R3</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Trimethadione (Troxidone)</td>
<td>-CH₃</td>
<td>-CH₃</td>
<td>-CH₃</td>
</tr>
<tr>
<td>2.</td>
<td>Paramethadione</td>
<td>-CH₃</td>
<td>-C₂H₅</td>
<td>-CH₃</td>
</tr>
</tbody>
</table>

### D) Succinimides =>

![Succinimides diagram]

<table>
<thead>
<tr>
<th>S.NO.</th>
<th>GENERIC NAME</th>
<th>R1</th>
<th>R2</th>
<th>R3</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Phensuximide</td>
<td>-C₆H₅</td>
<td>-H</td>
<td>-CH₃</td>
</tr>
<tr>
<td>2.</td>
<td>Methsuximide</td>
<td>-C₆H₅</td>
<td>-CH₃</td>
<td>-CH₃</td>
</tr>
<tr>
<td>3.</td>
<td>Ethosuximide</td>
<td>-C₂H₅</td>
<td>-CH₃</td>
<td>-H</td>
</tr>
</tbody>
</table>
E) **Ureas and monoacylureas** =>

Ex.- Carbamazepine

\[
\begin{array}{c}
\text{H} \\
\text{N} \\
\text{O} \\
\end{array}
\]

F) **Benzodiazepines** =>

\[
\begin{array}{c}
\text{R} \\
\text{N} \\
\text{O} \\
\text{Cl} \\
\text{CH}_3
\end{array}
\]

<table>
<thead>
<tr>
<th>S.NO.</th>
<th>GENERIC NAME</th>
<th>R</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Nitrazepam</td>
<td>-H</td>
</tr>
<tr>
<td>2.</td>
<td>Clonazepam</td>
<td>-Cl</td>
</tr>
</tbody>
</table>

- Diazepam

G) **Miscellaneous type** =>

Ex.-
Phenytoin (5,5,-diphenylhydantoin) is the first anticonvulsant in which it was clearly demonstrated that anticonvulsant activity could definitely be separated from sedative-hypnotic activity. It is a prime example of an anticonvulsant acting as a sodium channel blocker. One effect of neuronal sodium channel block is to decreases presynaptic glutamic acid release, giving anticonvulsant activity.
Another consequence is to reduce glutamate-induced ischemic damage to neurons.

- The drug is useful against all seizure types except absence.

**SYNTHESIS OF CARBAMAZEPINE**

2-Chloromethylnitrobenzene → Styrene → 2-Chloromethyl nitrobenzene

\[ \text{CH}_2\text{Cl} + \text{NaOH} \rightarrow \text{SN/HCl} \rightarrow \text{Amylacohol} \]

\[ \text{N} \quad \text{H} \]

\[ \text{N} \quad \text{H} \]

\[ \triangle \rightarrow -\text{NH}_3 \]

\[ \text{Br} \]

\[ \text{Dehydrohalogenation} \]

\[ \text{COCl}_2 + \text{NH}_3 \]

\[ \text{CONH}_2 \]

Carbamazepine

**Note**
Overall shape of the molecule suggests the mode of action, **sodium channel block**.

- It is useful in generalized tonic-clonic and partial seizures.

**Synthesis of Ethosuximide**

- For anticonvulsant activity $R_1$ and $R_2$ should be both hydrocarbon radicals.
- If both $R_1$ and $R_2$ are lower alkyls, the tendency is to be active against Absence seizures (Petitmal) and not active against Generalized tonic-clonic (Grandmal) or Partial seizures.
  - Ex.- Metharbital, Trimethadione, Paramethadione, Valproic Acid
- If one of the hydrocarbon substituent’s ($R_1$ or $R_2$) is an aryl group, activity tends to be directed toward Generalized tonic-clonic and partial seizures and not antiabsence activity.
  - Ex.- Mephobarbital, Phenytoin, Carbamazepine
- A conformational analysis of the aryl-containing antigeneralized tonic-clonic agents indicates that the conformational arrangement of the hydrophobic groups is important.