Antipsychotic Agents “Neuroleptics”

Different Nomenclatures for antipsychotics:

- **Antipsychotic:** called so because they actually diminish the underlying thought disorders that is the chief characteristic of schizophrenia.
- **Major tranquilizers:** because they have a calming effect in agitated psychotic patients.
- **Neuroleptics:** because they induce lessening of reactivity of emotional stimuli, with little effect on consciousness.

Uses
They are used in manic disorders and schizophrenia.

- Schizophrenia is a neurological disorder characterized by altered thought patterns and social withdrawal. The etiology of schizophrenia is unknown although there may be a genetic component. Symptoms of schizophrenia fall into two main categories: **Positive symptoms and Negative symptoms.**

**NEGATIVE** symptoms are usually resistant to treatment. Drugs control symptoms rather than cure illness. These drugs are referred to as **NEUROLEPTICS.**
- Hypothesis behind schizophrenia states that there is an **EXCESS of DA tone to brain limbic centers that distorts objective reality.**

### Psychosis Symptoms

**Positive Symptoms**
- Delusion
- Hallucination
- Disorganized speech
- Disorganized behavior
- Agitation

**Negative Symptoms**
- Passivity
- Apathetic social withdrawal
- Stereotyped thinking
- Anhedonia
- Attentional impairment
- Emotional withdrawal

**Cognitive Symptoms**
- Impaired verbal fluency
- Problems with serial learning
- Problems with focusing attention
- Concentration

- **General principles:** There are two kinds of antypsychs. **Typical** = Treatment POSITIVE symptoms (“Noisy and abnoxious” Symptoms ie: paranoia, hallucinations, grandiosity, hostility, anxiety and agitation. and **ATYPICAL** = Treatment NEGATIVE symptoms of psychosis (“Quiet Symptoms” ie: Blunted affect, withdrawal, lethargy, lack of initiative)

- **Typical** antipsychotics act by blocking DA receptors.
• **Atypical** act by blocking H1, 5HT2 and Alpha adrenergic receptors and relatively low effect on DA receptors.

### Antipsychotics

**First generation**
- Chlorpromazine
- Acetophenazine
- Fluphenazine
- Haloperidol
- Trifluoperazine
- Triflupromazine

**Second generation**
- Clozapine
- Risperidone
- Olanzapine
- Quetiapine
- Ziprasidone
Typical Neuroleptics Side Effects:

- Extrapyramidal Side Effects (EPS): parkinsonism, due to the D2 blocking action in the striatum.
- Tardive dyskinesia: is related to prolonged and potent D2 striatal block, characterized by excessive striatal dopaminergic activity, symptoms include involuntary movements of the lips, tongue and mouth and with movement of the extremities.
- Many, but not all of these agents are strongly anticholinergic.
- An increase in prolactin levels by a block of Dopamine (DA) receptor in the hypothalamus (amenorrhea and gynecomastia).
- An antiemetic effect by a block of the Dopamine (DA) receptor in the trigger zone chemo-receptor.
• Postural hypotension due to peripheral α1adrenoreceptor block, specially among the N, N-dimethylamino group phenothiazines.

Drugs used in the treatment of psychosis, in the treatment of schizophrenia, organic psychosis, manic phase of manic depression illness, and other acute or chronic idiopathic illness are:

- Phenothiazines
- Thioxanthines
- Butyrophenones
- Dibenzazepines
- Benzaamides
- Others

**Phenothiazines**
- This is the most widely used class as neuroleptics, especially chlorpromazine and the class may be divided into 1) Aliphatic 2) piperydine 3) and piperazine derivatives.
- About 24 phenothiazines and thioxanthines are used as neuroleptics.

**Interaction of phenothiazines and thioxanthines with the dopamenergic receptor:**
- X-ray examination of structures of dopamine and chlorpromazine shows that these two structures “in the preferred conformation” are partly superimposed. In the preferred conformation of chlorpromazine its side chain tilts away from the med. line towards the chlorine substituent ring “Cisoid conformation”.

- When the thioxanthine derivatives, that contain a double bond, are examined, it is evident that the Cis isomer is several times more active than the Trans one, and from compounds lacking the double bond.
- The chlorine atom is responsible for imparting asymmetry to the molecule. Compounds lacking of a chlorine atom are in most cases inactive as neuroleptic drugs.
Another major requirement for the therapeutic efficacy is that the side chain contains three-carbon atom bridge separating the two nitrogen atoms, allowing, in this manner, the most likely active conformation. In fact compounds possessing only two-carbon atom bridge act as antihistaminic.

**SAR (Structure Activity relationship)**
- The best position for substitution is the 2 position, generally activity increases with the increase of the electron withdrawing nature of the substituent.
- Substitution on position 1 or 4 produces less active compounds. On the other hand substitution in position 3 produces active compounds but not as substitution in position 2.
- Sulfur in position 5 corresponds to the dopamine p-hydroxyl group. Therefore it represents a receptor-binding function. Thus any substitution in position 4 may interfere with this binding function.
- The three-atom chain “bridge” between position 10 and the amino nitrogen is required. Shortening or lengthening the chain decreases drastically the activity.
- Branching the Carbon Bridge with large groups, such as phenyl or other, decreases activity. Branching the Carbon Bridge with polar groups decreases the activity also.
- Monomethylamine side chain derivatives are less active than the dimethylamino derivatives.
- Size increase as in N,N-diethylamino groups decreases activity. However, maintaining the effective size of about the equivalent to a dimethylamino, as in fusing N,N-diethyl substituents to produce a pyrrolidine group, activity can increase with the increasing of chain length. The critical size about the amino nitrogen indicates the importance of the protonated amino group for the receptor attachment once the size requirement is met, the effect of the added chain length could be to add receptor-binding forces.

**Products**
- **Aliphatic phenothiazines** (propyldialkylamino side chain): Promazine, Chlorpromazine, Triflupromazine.
- **Alkylpiperidyl phenothiazines**: Piperacetizine, Thioredazine, Mesoridazine.
- **Propylpiperazine phenothiazines**: Prochlorperazine, Trifluperazine, Triethylperazine, and Carphenazine The
**Aliphatic phenothiazines are characterized by:**
- Sedative properties due to $\alpha_1$ central antagonism.
- Hypotensive properties due to peripheral $\alpha_1$ antagonism.
- Peripheral anticholinergic activity is common.
- EPS “Extrapyramidal Side Effects” are also observed, especially for Triflupromazine.

**TABLE 14-3 Phenothiazine Derivatives**

<table>
<thead>
<tr>
<th>Generic Name</th>
<th>Proprietary Name</th>
<th>$R_{10}$</th>
<th>$R_2$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Propyl Dialkylamino Side Chain</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Promazine hydrochloride, USP</td>
<td>Sparine</td>
<td>$(\text{CH}_2)_3\text{N(CH}_3_2\text{)} \cdot \text{HCl}$</td>
<td>H</td>
</tr>
<tr>
<td>Chlorpromazine hydrochloride, USP</td>
<td>Thorazine</td>
<td>$(\text{CH}_2)_3\text{N(CH}_3_2\text{)} \cdot \text{HCl}$</td>
<td>Cl</td>
</tr>
<tr>
<td>Triflupromazine hydrochloride, USP</td>
<td>Vesprin</td>
<td>$(\text{CH}_2)_3\text{N(CH}_3_2\text{)} \cdot \text{HCl}$</td>
<td>CF$_3$</td>
</tr>
</tbody>
</table>

**alkylpiperidyl phenothiazines are characterized by:**
- Low tendency to produce EPS.
- High central anticholinergic activity, through which counterbalances the Dopamnergic block at the striatum.
- Decreased antemetic effect with respect to the other phenothiazines.

**The propylpiperazine phenothiazines are characterized by:**
- High potency.
- High prevalence of EPS.
- Low sedative and low side effects upon the autonomic nervous system.
**Metabolism**

- **Metabolic pathways for phenothiazines and thioxanthines**
  - Metabolism of neuroleptics has a major significance in the effect of these drugs; therefore, it is becoming more important to understand the metabolic fate of neuroleptics and to measure the level of both parent drugs and active metabolites.
  - The metabolic pathways of neuroleptics are similar to those for many other drugs “general metabolism”
  - It should be kept in mind that during metabolism, several processes can and do occur for the same molecule. For example, chlorpromazine can be demethylated, sulfoxidized, hydroxylated and glucuronidated. The combination of such processes leads to more than 100 identified metabolites for chlorpromazine.
  - Metabolic pathways are significantly altered quantitatively and qualitatively by a number of factors including species, age, sex, interaction with other drugs & the administration route.
  - There is evidence that the 7-hydroxylated derivatives and possibly other hydroxylated derivatives as well as the mono- and di-desmethylated metabolites are also active., whereas the sulfoxide in position 5 is inactive.
Thioxanthines differ from phenothiazines in metabolism in that they don’t suffer ring hydroxylations.

**Thioxanthines**
- Close structural relatives of phenothiazines and do share many of their clinical properties with them. Examples of products are Chlorprothixene, which displays activity similar to chlorpromazine and Thiothixen that displays activity similar of piperazine subgroup of phenothiazines. In all cases the Z “cis” isomer is much more active than the E “trans” isomer. Why?

**Butyrophenones**
- A number of mepiridine (narcotic analgesic) analogs were prepared, including the propiophenone and butyrophenone analogs. The propiophenone analogs possess 200 times the analgesic potency of meperidine, but the butyrophenon analog, displays also activity resembling that of chlorpromazine, in addition to the morphine like activity. Janssen revealed that it is possible to eliminate the morphine type activity and simultaneously to accentuate the chlorpromazine type activity, provided that certain structural changes are made.

**Products:**

*Haloperidol (Haldol®)*
Effective in manic phase or manic illness and in Schizophrenia, Haloperidol decanoate “Ester of Haloperidol with decanoic acid” is used as a depot maintenance therapy when injected every 4 weeks.

- The pharmacological effects of Haloperidol differ in degree but not in kind from those of the piperazine phenothiazines in that blocking the effect of dopamine.

*Drproperidol*
This agent could be used alone as pre-anesthetic neuroleptic or as antiemetic. Its most frequent use is in combination with the narcotic agent fentanyl preanesthetically.

Dr. Majdi Bkhaitan
Side effects

- EPS
- Less sedation than chlorpromazine
- Antiemetic
- Less autonomic side effects, only mild hypotension.

Atypical Neuroleptics

In recent years, several new compounds have been developed with unique properties. Collectively, these compounds are referred to as atypical neuroleptics. Atypical neuroleptics are generally effective in treating both the positive and negative symptoms of schizophrenia. Clozapine was the first dopamine antagonist identified with a relatively low incidence of extrapyramidal side effects. The lack of extrapyramidal side effects may be due in part to its potent anticholinergic effects, in addition to a high affinity for 5-HT2 (serotonin) receptors. Agranulocytosis is a major side effect associated with clozapine, necessitating the routine monitoring of blood to avoid a dangerous loss of granulocytes. In recent years, other atypical neuroleptics, including olanzepine and quetiapine, have been identified with fewer unwanted side effects. Atypical neuroleptics generally have high affinity for 5-HT2, D2, M1, and H1 receptors.

Dibenzazepines

- Dibenzoxazepine: Loxapine
- Dibenzothiazepine: Methiapine, Clothiapine
- Dibenzodiazepine: Clozapine Olanzepine
Benzisoxazole and benzisothiazole derivatives

Risperidone (Risperdal®)
- It is a structural hybrid of a butyrophenone antipsychotic and trazodone-like antidepressants. It is considered as 5HT2 and D2 receptors antagonist with both antidepressant and antipsychotic activities. This compound is reported to benefit all symptoms of schizophrenia “positive and negative ones”. This compound can be considered in a class derived from the development of butyrophenones possessing also the same side effects. And because of its high hydrophobicity it is also considered as long acting.
**Benzamides**

- Metchlorpropamide has antiemetic activity due to central dopamenergic antagonism. This had suggested the development of related compounds to produce neuroleptics with less EPS. This had led to the development of derivatives such as sulpiride, sultopride and remoxipride.

- These agents are of low potency, especially sulpiride because of their high lipophilicity, they present low EPS, may be due to their action upon the limbic system rather than above striatal tissue.

![Chemical structures of Metchlorpropamide and Sulpride](image-url)
SEDATIVE/HYPNOTICS/ANXIOLYTICS

Anxiety

**feeling of helplessness, difficulty in concentrating, irritability & insomnia, GI disturbances, muscle tension, excessive perspiration, palpitations, dry mouth, impending doom, dread**

Clinical Disorders

- Panic disorder
- Obsessive-compulsive disorder
- Post-traumatic stress disorder
- Social phobia
- Social anxiety disorder
- Generalized anxiety disorder
- Specific phobias

Anxiolytic sedative, minor tranquilizers, antianxiety, tensiolytics, are used to control neuroses and stress. Strategy for treatment: Reduce anxiety without causing sedation

Chemical classes of Anxiolytics

1) Benzodiazepines (BZDs).
2) Barbiturates (BARBs).
3) 5-HT<sub>1A</sub> receptor agonists.
4) 5-HT<sub>2A</sub>, 5-HT<sub>2C</sub> & 5-HT<sub>3</sub> receptor antagonists.

If ANS symptoms are prominent:

- β-Adrenoreceptor antagonists.
- α<sub>2</sub>-AR agonists (clonidine).

Other Drugs with anxiolytic activity.

- TCAs (Fluvoxamine). Used for Obsessive compulsive Disorder.
- MAOIs. Used in panic attacks.
- Antihistaminic agents. Present in over the counter medications.
• Antipsychotics (Ziprasidone).

Sedative/Hypnotics
A hypnotic should produce, as much as possible, a state of sleep that resembles normal sleep.

Physiology of sleep
States of life: three life states can be distinguished:

1st. Wakefulness: one is fully aware of one self and environment.
2nd. Slow wave sleep (SWS): non rapid eye movement (NREM)
3rd. Paradoxic sleep (PS): rapid eye movement (REM)

Sleep cycle: under normal circumstances, normal young adults at night display a regular pattern of sleep; 20-25% of which is REM sleep, and 75-80% of which is NREM sleep.

NREM sleep precedes REM sleep. After about 90 minutes of NREM sleep, the first REM sleep occurs, with duration of 20 minutes, afterwards, REM occurs cyclically at intervals of 90min. Throughout a night, four to five periods of dreaming (REM) take place, accounting for about 20% of total sleep time.

In case of deprivation of REM sleep (either physically be awakening the sleeper, or using hypnotics that reduce or suppress REM sleep), we can observe what is called a “rebound effect” in case of drug withdrawal that is characterized by a REM sleep period longer than the usual. This occurs in case of withdrawal of addicting hypnotics. Effect of drugs on the sleep cycle: most CNS acting drugs affect REM sleep after the first dose. Repeated administrations lead to tolerance and the REM sleep returns to normal, occupying 20-25% of the night. This however doesn’t inhibit the rebound effect upon REM after withdrawal. Because most available hypnotics suppress REM it is considered bad practice their prolonged administration.

Oswald says: “drugs capable of causing dependence are drugs that both suppress paradoxical sleep (REM) and provoke a rebound enhancement of paradoxical sleep when withdrawn”

Drug Choices
Older:
- Barbiturates (drugs ending in “barbital”)
- Alcohols / Choral Hydrate

Newer:
- Benzodiazepines (drugs name ending in “lam” or “pam”)**
- Benzodiazepine “Like” (zolpidem & zaleplon)
- 5-HT1A partial agonist (buspirone)

** The most commonly used anxiolytics
**Mechanism of Action**
Most sedative-hypnotics exert effects on GABA_\textsubscript{A} R’s

GABA - the major inhibitory NT in the CNS

- GABA_\textsubscript{A} receptors - heteromultimeric structure
  - 5 transmembrane polypeptide subunits per receptor/channel complex
  - \( \alpha, \beta, \delta, \epsilon, \gamma, \pi \) polypeptide subtypes
  - multiple isoforms for each (e.g. \( \alpha_{1-6} \))

- GABA binding stimulates Cl\(^-\) current
  - hyperpolarizing effect
  - inhibitory effect on neuronal excitability

**GABAergic SYNAPSE**

**Barbiturates**
Multiple mechanisms

1) Bind to GABA\textsubscript{A} receptors at different site

Don’t compete for BNZ binding & are not blocked by flumazenil and they *increase the duration of Cl\(^-\) channel openings*

1. Increase GABA effect (increased duration of openings)
2. Directly activate GABA\textsubscript{A} channels at high concentrations
3. Block glutamate NT\(^*\) effects
4. Block Na channels
Barbiturates modify the mechanism of synaptic transmission; they reduce the excitability of post-synaptic cell by altering the permeability of the cell membrane. They exert their action on the central synaptic transmission process of the reticular activating system, and the cerebral cortex becomes deactivated (antidepolarizing blocking agents). Barbiturates act also upon the limbic, hypothalamic, and thalamic synaptic system.

Physical dependence may be induced by various doses of the drugs. As a rule, drug dependence is followed by tolerance, in which increased doses are required to obtain the same pharmacological effect. Barbiturates don’t induce natural sleep.

**SAR**

- In order to possess good hypnotic activity, a barbiturate must be a weak acid and must have a lipid /water partition coefficient between certain limits.

**Acidity:** In order to possess good hypnotic activity, a barbiturate must be a weak acid and must have a lipid /water partition coefficient between certain limits. pKa of unsubstituted barbituric acid equals 4.12, while pKa of 5,5 disubstituted barbituric acid equals 7.1-8.1. So, salts of the 5,5 disubstituted barbituric acid can be obtained with bases such NaH. A second ionization can occur with pKa values 11.7-12.7. It is possible to assume that dialkali metal salts could be prepared.
Products

Long duration barbiturates

- barbital (5,5-diethylbarbituric acid), phenobarbital (5-ethyl-5-phenyl barbituric acid).

Intermediate duration of action

- Amobarbital (5-ethyl 5-isopentile barbituric acid), butabarbital (5-secbutyl 5-ethylbarbituric acid)

Short duration barbiturates

- pentobarbital (5-ethyl 5-secpentyl barbituric acid), secobarbital (5-allyl5-secpentyl barbituric acid)
Metabolism:

- Occurs primarily in the liver, where through metabolism the lipophilic nature decreases through:
  - Oxidation of substituents at C5 (ω,ω-1, hydroxylation)
  - Hydrolytic cleavage of barbituric ring, with the formation of acetamide and acetyl urea derivatives
  - Desulferation of 2-thiobarbiturates
  - N-dealkylation in case of 1-substituent comp’s, which proceed slowly however.
- Benzodiazapines

Many derivatives of the 1,4-benzodiazapine series display:

- Tranquilizing
- Muscle relaxant
- Anticonvulsant and
- Sedative effects.

No 1,4-benzodiazepin can be selected exclusively as a hypnotic agent in preference to other benzodiazepins.

Benzodiazepins that are rapidly metabolized and eliminated (e.g. temazepam) have gained popularity as sleep inducers, because of lack of toxicity neither through accumulation nor hangover.

Benzodiazapine Mechanism of action

CNS BNZ receptors: thalamus, limbic system, cerebral cortex.

BNZs - increase the frequency of Cl⁻ channel openings in presence of GABA, GABAₐ receptor composition varies in different regions, BNZs bind to receptors with alpha & gamma subunits.
- BNZ binding “enhances” the effect of GABA on the Cl⁻ current
- BNZs exert no effect in the absence of GABA.
- BNZ effect & binding blocked by flumazenil (BNZ antagonist)
- Not all BNZs are identical (may be due to differences in effects on different GABAₐ R isoforms)
Receptor Characterization and Drug Classification

Several receptors have been described for benzodiazepine agonists. The benzodiazepine receptor is part of the GABA$_A$ protein. As stated above, this protein is a pentamer composed of combinations of structurally related subunit families ($\alpha$, $\beta$, $\gamma$, $\delta$, $\rho$), some of which exist in multiple isoforms. The $\alpha$-subunit bears the benzodiazepine (BDZ) binding site. The Type I BDZ receptor, which displays high affinity for a wide range of benzodiazepine analogs, contains an $\alpha_1$ subunit, whereas the Type II BDZ receptor, which has a lower affinity for such agents, contains $\alpha_2$ or $\alpha_3$ subunits. Since an increasing number of compounds with affinity for these receptors are not benzodiazepines, it may be more acceptable to employ the alternative nomenclature: $\omega_1$ for Type I BDZ and $\omega_2$ for Type II BDZ. The $\omega_1$ receptor is located in brain areas involved with sedation; $\omega_2$ receptors are highly concentrated in areas responsible for cognition, memory, and psychomotor functioning. Zolpidem was the first non-benzodiazepine $\omega_1$ agonist marketed; it is a hypnotic agent with minimal anticonvulsant and anxiolytic effects. Zaleplon is another $\omega_1$ agonist used in the treatment of insomnia.

BNZs - high doses commonly produce anterograde amnesia
more common with BNZs vs. other hypnotics)
Diazepam
Chlordiazepoxide
Flurazepam
Desmethyldiazepam
Oxazepam
Lorazepam
Nitrazepam
Triazolam
Alprazolam
SAR “Structure Activity relationship of Benzodiazepine”

- Presence of an electron-withdrawing group in position 7 is required for activity. More the electron-withdrawing more will be the activity.

- Position 6,8 and 9 should not be substituted

- A phenyl ring in position 5 promotes activity. Activity is increased when the phenyl is ortho or diortho substituted with electron-withdrawing groups. Substitution in para position brings about decrease in activity.

- Saturation of the N4-C5 double bond or its shifting to other positions decreases activity.

- Substitution with alkyl group at position 3 decreases activity, substitution with OH group doesn’t. This hydroxyl affects the pharmacokinetic of the drug, truly, compounds that doesn’t posses OH in 3 are non-polar, and have long duration of action, and undergo hepatic oxidation, whereas, compounds possessing the 3-OH group are more polar and are readily conjugated and excreted.

- 2-carbonyl function is optimal for the activity, as is the nitrogen atom at position 1, the N- substituent should be small. On the other hand there were obtained compounds with a fused triazole ring represented by “triazolam” and alprazolam, also midazolam, with a fused imidazole ring. In these latter mentioned cases the presence of the 7- electron-withdrawing group is not required for the activity.

Pharmacokinetics of Benzodiazepines

- Hepatic metabolism. Almost all BDZs undergo microsomal oxidation (N-dealkylation and aliphatic hydroxylation) and conjugation (to glucuronides).
- Rapid tissue redistribution ➔ long acting ➔ long half-lives and elimination half-lives (from 10 to >100 hrs).
- All BDZs cross the placenta ➔ detectable in breast milk ➔ may exert depressant effects on the CNS of the lactating infant.
- Many have active metabolites with half-lives greater than the parent drug.
- Prototype drug is diazepam (Valium), which has active metabolites (desmethyldiazepam and oxazepam) and is long acting (t½ = 20-80 hr).
- Differing times of onset and elimination half-lives (long half-life => daytime sedation).
- Estazolam, oxazepam, and lorazepam, which are directly metabolized to glucuronides have the least residual (drowsiness) effects.
- All of these drugs and their metabolites are excreted in urine.
Biotransformation of Benzodiazepines

Dr. Majdi Bkhaitan
### Sedative-Hypnotics-I
(Treatment for Insomnia)

<table>
<thead>
<tr>
<th>Benzodiazepines:</th>
<th>Nonbenzodiazepines:</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Rapid onset, short acting</td>
<td>• Rapid-onset, short acting</td>
</tr>
<tr>
<td>triazolam</td>
<td>Zaleplon</td>
</tr>
<tr>
<td>• Delayed onset, intermediate acting</td>
<td>Zolpidem</td>
</tr>
<tr>
<td>temazepam, estazolam</td>
<td>Zopiclone</td>
</tr>
<tr>
<td>• Rapid onset, long acting</td>
<td></td>
</tr>
<tr>
<td>flurazepam</td>
<td></td>
</tr>
<tr>
<td>quazepam</td>
<td></td>
</tr>
<tr>
<td>• Act at benzodiazepine receptors</td>
<td>• Binds to omega-1 but not</td>
</tr>
<tr>
<td>and increase the inhibitory action</td>
<td>to omega-2 benzodiazepine</td>
</tr>
<tr>
<td>of GABA</td>
<td>receptor subtype</td>
</tr>
<tr>
<td>• High doses required</td>
<td>• Less cognitive, memory and</td>
</tr>
<tr>
<td>• Develop tolerance</td>
<td>motor side effects</td>
</tr>
<tr>
<td></td>
<td>• Shorter half life</td>
</tr>
<tr>
<td></td>
<td>• No dependence, tolerance</td>
</tr>
<tr>
<td></td>
<td>or withdrawal symptoms</td>
</tr>
</tbody>
</table>

### Imidazopyridine:
- Such as zolpidem (stilnox®) and alpidem, which are non-benzodiazepine hypnotic agents. Acting on the high-affinity benzodiazepine receptor subtype in the brain. They have no major effect on sleep stages, have no rebound effect after withdrawal, and used mainly as hypnotic.
- Zolpidem was the first non-benzodiazepine ω1 “BDZ 1” agonist marketed. It is a hypnotic agent with minimal anticonvulsant and anxiolytic effects.

### Cyclopyrolone:

zopiclone (Imovane) a non benzodiazepine hypnotic agent, Acting on the high-affinity benzodiazepine receptor subtype in the brain, at 7.5mg dose. It decreases sleep latency, increase total sleep duration, reduce the number of awakenings and increase sleep efficiency, REM sleep is substantially unaffected by zopiclone. Rebound effect and withdrawal symptoms do not accompany discontinuation of Zopiclone, it is also devoid of abuse and dependence potential.
Buspirone “BuSpar®”

has anxiolytic and antidepressant activities and is a partial 5HT₁A agonist. Its anxiolytic activity is reportedly due to its ability to diminish 5-HT release (via 5HT₁A agonism). High short-term synaptic levels of 5-HT are characteristic of anxiety. Also, since it is a partial agonist, it can stimulate postsynaptic receptors when 5-HT levels are low in the synapse, as is the case in depression. A number of other spirones are in development as anxiolytics and antidepressants.³⁴
Anticonvulsant

Epilepsy

- A classification of the types of epilepsy has been widely accepted because its accuracy facilitates diagnosis, drug selection and precise discussion of seizure. The major classification types are:
  - a) generalized seizures, which essentially involve the entire brain and do not have an apparent local onset
  - (b) unilateral seizures, which involve one entire side of the body
  - (c) partial (or focal) seizures that have a focus (i.e., begin locally)
  - d) erratic seizures of the newborn: and
  - (e) unclassified seizures (severe seizures associated with high mortality such that time does not permit a precise categorization).

- Two major types of generalized seizures are the generalized tonic—clonic seizure (grand mal) and the non-convulsive seizures or absence (petit mal) seizures. The typical generalized tonic—clonic seizure is often preceded by a series of bilateral muscular jerks: followed by loss of consciousness. which in turn is followed by a series of tonic and then clonic spasms. The typical absence seizure (classic petit mal) consists of a sudden brief loss of consciousness. sometimes with no motor activity, although often some minor clonic motor activity exists.

- Major types of focal (partial) epilepsy are simple focal and complex focal seizures. A prototypic simple partial seizure is jacksonian motor epilepsy in which the Jacksonian march may be seen. As the abnormal discharge proceeds over the cortical site involved, the visible seizure progresses over the area of the body controlled by the cortical site. The complex partial seizure is represented by the psychomotor or temporal lobe seizure. There is an aura, then a confused or bizarre but seemingly purposeful behavior lasting 2 to 3 minutes often with no memory of the event. The seizure may be misdiagnosed as a psychotic episode. This is extremely difficult epilepsy to treat. Much effort has been made in recent years to develop drugs to control it.

- Each of the epilepsy types is characterized by a typical abnormal pattern in the EEG. The EEG indicates sudden, excessive electrical activity in the brain, Antiepileptic drugs act to prevent, Stop or lessen this activity.
  - The precise causes of the sudden, excessive electrical discharges may be many, and not all are understood.
  - A working hypothesis is that there is a site or focus of damaged or abnormal and, consequently hyper excitable neurons in the brain.
  - These can fire excessively and sometimes recruit adjacent neurons that in turn induce other neurons to fire.

The location and the extent of the abnormal firing determine the epilepsy.

- Experimentally a brief and much localized electrical stimulus is applied to a site in the brain, with long intervals between applications. As the process is repeated neuronal after discharges grow both longer and more intense at the original site and at new sites far from the original site.
- Progressively more severe seizures can be induced, and these can arise from secondary foci that have been kindled far from the site of stimulation.
**General Mode of Action of Antiepileptics**

- A major mode of action of anticonvulsants can be positive allosteric modulation of GABAA receptors. This is probably the mode of action of benzodiazepines and a major mode of action of barbiturates.
- On the basis of the structure of barbiturates, some inorganic cation blocking action would be expected as well—voltage-gated sodium channel for phenobarbital and calcium T channel block for 5,5-dialkyl members Oxazolidine-2,4-diones (only trimethadione remains) and succinimides appear to act via calcium T-type channel block.
- Some sodium channel block could be expected among phenyl-substituted succinimides. The major mode of action for phenytoin (and probably monophenyl substituted hydantoins) carbamazepine, oxcarbazepine, Valproic acid, Felbamate, Topiramate. Lamotrigine and zonisamide is reported to be voltage-gated sodium channel block and is in accord with their structures.

**General Mode of Action of Antiepileptics**

- Side effects of direct ionotropic glutamic acid receptor blocking has been a serious problem, Because of this, present approaches are to use the modulatory route. That is lessen ionotropic glutamate activity by (a) using drugs that act at the glyeine modulatory site on NMDA and developing antagonists of members group II and group III metabotropic receptors and agonists of metapotropic group I glutamic acid receptors. These drugs would lower ionotropic glutaminergic activity.
- Adenosine which may be an endogenous anticonvulsant continues to serve as a model but, for reasons such as poor brain distribution and an array of cardiovascular effects of agonists has not yet yielded useful drugs. Elaboration of roles of receptor subtypes may give leads to drug design.

**Antiepileptic Agents mechanism of action**

![Antiepileptic Agents mechanism of action diagram](image)
An overall pattern in the anticonvulsant agents is that $R, R'$ should be both hydrocarbon radicals.

- If $R, R'$ are lower alkyl groups, the anticonvulsant agent would be active against absence seizures (petit mal), and inactive against generalized tonic-clonic (grand mal) or partial seizures.
- If one of the substituents is an aryl group, activity will be directed against generalized tonic-clonic (grand mal) or partial seizures. And inactive against absence seizures.

**Barbiturates**

- Although sedative-hypnotic barbiturates commonly display anticonvulsant properties, only phenobarbital and mephobarbital (and marginally methabarbital) display adequate anticonvulsant selectivity for use as antiepileptics.

**Metabolism:**

- Phenobarbital is metabolized primarily by hydroxylation to 5-$p$- hydroxyphenil derivative (inactive). This metabolite is conjugated with glucuronic acid and excreted in the urine. Phenobarbital is (metabolism inducer) agent.
- Mephobarbital is extensively demethylated to phenobarbital. Mephobarbital is used in the partial and generalized seizures.
- Methabarbital (1-methyl,5,5-diethyl barbituric acid) is metabolized through 1-demethylation forming barbital (5,5 diethyl barbituric acid), has less sedation than phenobarbital.

**Hydantoins**

- Are close structural relatives of the barbiturates. Differing in lacking the 6-oxo moiety. Therefore, they are cyclic monoacylureas rather than diacylureas (barbiturate).
- The compounds have anti generalized tonic-clonic seizures (grand mal). Phenytoin (diphenyl hydantoin) is also used in partial seizures. All the clinically useful compounds posses an aryl substituent on the 5-position. Phenytoin is not used in absence seizures because it may increase their frequency.

**Pharmacokinetic:**

- Phenytoin is absorbed in a limited way because of extremely low solubility of the unionized form in the gastrointestinal fluids and in the plasma. The ionized phenytoin is highly soluble in intestinal fluid. In the plasma it is highly bonded to plasma proteins. Fat tissues and other tissues also absorb it.

**Toxicity**

- It doesn’t present sedation and in therapeutic doses it is relatively safe. It does however present several undesirable side effects which limits its use in favor of carbamazepine and valproic acid.
Oxazolidinediones

- Are isosters of hydantoins by replacing the NH group at position 1 with an oxygen atom to yield the oxazolidine 2,4 dione system. These agents are used in the management of absence seizure.
- Dermatological and hematological toxicities limit their clinical use only in case of patients that don’t tolerate succinimides or valproic acid.

Succinimides

- Isosters of oxazolidinediones by replacing the O atom by a CH2 group. They were introduced to replace oxazolidinediones because these were too toxic in the treatment of absence seizures.
- Ethosuximide is the most effective and least toxic in the treatment of absence seizure (different kinds). It can also be used in combination with other drugs to treat patients with other generalized seizures.

Pharmacokinetic

- Are readily absorbed from the gastrointestinal tract and reaches maximal blood concentration in 3-7h.

Metabolism

- Through aromatic or aliphatic oxidative hydroxylation and ring cleavage.

Ureas: carbamazepine (tegretol®)

- Used in the partial and generalized seizures in adults. Truly, the two phenyls on the nitrogen fit the pattern antigeneraized tonic-clonic activity.
- Like phynitoin, carbamazepine prevents the spread of seizure produced by the brain. It depresses sodium and potassium conductance, and depresses synaptic transmission in the reticular activating system, thalamus, and limbic structures. It alters the concentration (reduction) of cyclic nucleotides (cAMP) which may contribute to its mechanism of action.

Metabolism of Carbamazepine: through oxidative hydroxylation in position 10,11 to form the trans diol (through the epoxide intermediate). The epoxide in some patients could give an idiosyncratic reaction as aplastic anemia.
Oxacarbazepine
- is chemically related to carbamazepine with less undesirable side effects, due to the lack of the double bond in position 10 - it is however less potent than carbamazepine, but has the same indications.

Valproic acid (Depakin®): "sodium valproate": is the dipropylacetic acid or 2-propylpentanoic acid.
- Many carboxylic acids have anticonvulsant activity, although often of a low order of potency, possibly in part because extensive dissociation at physiologic pH produces poor partitioning across blood brain barrier (BBB).
  - **Mechanism of action**
    - first theory: through elevating brain levels of the inhibitory neurotransmitter (GABA), second theory: by directly inhibiting membrane conductance and permeability.
  - **Uses**
    - Has good potency and is used against several seizure types. It is the drug of choice for typical and atypical absence seizures, and in absence seizure with generalized tonic-clonic seizures.
  - **Metabolism**
    - Conjugation of the carboxylic acid group.
    - Oxidation of one of the hydrocarbon chain (ω, ω-1).

Benzodiazepines
- Diazepam, clonazepam, clorazepate: are used in status epilepticus, and in other types of seizure. They produce, however, tolerance rapidly, to be rendered inactive as anticonvulsants. Clonazepam, produces tolerance less rapidly than the others.
  - **Mechanism of action**: the same seen for their sedative activity.
  - Clorazepate is decarboxylated in the acidic medium of the stomach to the desmethyl diazepam, which represents the active compound.

Aminoacid derivatives
- Gabapentin: is the 1-aminomethyl cyclohexane acetic acid. It hasn’t any direct GABAnergic activity. It is active in case of patients with refractory epilepsy of various seizure types (in partial and generalized tonic-clonic type).
- Vigabatrin: is the γ-vinylGABA, it acts by inhibiting GABA transaminase, the principle responsible of the catabolism of GABA, producing enhancement in GABA concentration. Only the S (+) isomer possesses pharmacological activity. The drug is most useful in partial seizure and primarily generalized.