A. INTRODUCTION

Antipsychotic (neuroleptic) agents are primarily used in the therapy of schizophrenia, organic psychoses, the manic phase of manic-depressive illness and other acute or chronic idiopathic psychotic illnesses.

B. MECHANISM OF ACTION

Evidence supports the hypothesis that the etiology of psychotic disorders lies in neurochemical defects of dopaminergic and serotonergic pathways in the brain. This hypothesis is supported by the fact that the primary pharmacological action of antipschotic agents is antagonism of dopamine and/or serotonin receptor in the CNS.

A development-based classification of antipsychotic drugs:

<table>
<thead>
<tr>
<th>Order of binding affinity for CNS NT receptors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Classical Antipsychotics (phenothiazines)</td>
</tr>
<tr>
<td>Atypical (SDA) Antipsychotics</td>
</tr>
<tr>
<td>• First-generation (butyrophenones)</td>
</tr>
<tr>
<td>• Second-generation (risperidone, clozapine)</td>
</tr>
<tr>
<td>[ D_2 = D_1 &gt; \alpha_1 \approx 5HT_2 ]</td>
</tr>
<tr>
<td>[ D_2 &gt; D_1 = 5HT_2 &gt; \alpha_1 ]</td>
</tr>
<tr>
<td>[ D_2 \approx 5HT_2 &gt;&gt; D_1 &gt; \alpha_1 ]</td>
</tr>
</tbody>
</table>
Dopamine Biosynthesis and Catabolism

L-Tyrosine $\xrightarrow{\text{Tyrosine hydroxylase}}$ L-Dihydroxyphenylalanine (L-DOPA)

L-DOPA $\xrightarrow{\text{Pyridoxal phosphate}}$ L-Aromatic amino acid decarboxylase (L-AAAD)

L-Aromatic amino acid decarboxylase (L-AAAD)

Dopamine $\xrightarrow{\text{Dopamine } \beta\text{-hydroxylase}}$ R-Norepinephrine

Dopamine $\xrightarrow{\text{MAO}}$ 3,4-Dihydromandelic acid

3,4-Dihydromandelic acid $\xrightarrow{\text{Aldehyde oxidase}}$ Dopamine

3,4-Dihydromandelic acid $\xrightarrow{\text{Catechol O-methyl transferase}}$ 3-Methoxytyramine

3-Methoxytyramine $\xrightarrow{\text{MAO}}$ 3-Methoxydopamine

3-Methoxydopamine $\xrightarrow{\text{Aldehyde oxidase}}$ 3-Methoxytyramine
Serotonin Biosynthesis and Catabolism

L-Tryptophan

\[ \text{L-Tryptophan} \xrightarrow{\text{Tryptophan hydroxylase}} \text{L-5-Hydroxytryptophan} \]

\((\text{rate limiting})\)

\[ \text{L-5-Hydroxytryptophan} \xrightarrow{\text{Aromatic Amino Acid Decarboxylase}} \text{5-Hydroxytryptamine (5-HT, serotonin)} \]

5-Hydroxyindoleacetaldehyde (5-HIAA)

\[ \text{5-Hydroxyindoleacetaldehyde} \xrightarrow{\text{MAO}} \text{5-Hydroxytryptamine (5-HT, serotonin)} \]

5-Hydroxyindoleacetic Acid (5-HIAA)

\[ \text{5-Hydroxyindoleacetaldehyde} \xrightarrow{\text{Aldehyde oxidase}} \text{5-Hydroxyindoleacetic Acid (5-HIAA)} \]
C. ANTIPSYCHOTIC DRUG CLASSES

PHENOTHIAZINE DERIVATIVES

- The first-used class of efficacious antipsychotic agents – Chlorpromazine, the prototypical member of this class, was first used to treat mental disease in 1951.
- Nonselective DA-receptor antagonists; also act at other neurotransmitter receptors giving rise to significant AR profiles

1. Structural Properties
- phenothiazine or bioisosteric heterocycle
- a *connector* alkyl (side) chain terminated by
- an aliphatic 3⁺-amine function

2. Physicochemical Properties
- the phenothiazine heterocycle confers a high degree of lipophilicity on these antipsychotics which is balanced (solubility) by the cationized (at physiologic pH) amine function
- the phenothiazines possess two potentially basic functional groups:
  - the N¹⁰-amine which is very weakly basic (pKₐ >10) because of the electron-withdrawing effects of the 2 benzene rings attached to it and is not appreciably cationized at phys. pH,
  - the side chain tertiary amine function which confers strong organic basicity on the antipsychotic phenothiazines.

- H₂O solubility of the AP phenothiazines is increased for oral dosage formulation by treatment with an acid:
• conversely, the H₂O soly of these drugs can be reduced through the formation of bioreversible hydrocarbon esters (prodrugs) thereby lowering dissolution rates and facilitating formulation of long-acting (1-3 weeks) depot injections:

**Fluphenazine**
(tid and qid)

Fluphenazine enanthate: n = 5 (1-2 wks.)
Fluphenazine decanoate: n = 8 (2-3 wks)

3. Structure-activity Relationships

• structural/steric complementarity has been demonstrated between the phenothiazines and the CNS neurotransmitter dopamine providing an explanation for the ability of the antipsychotic molecules to interact in an antagonistic fashion with DA–receptors:

A = phenothiazine antipsychotic
B = dopamine
C = superposition of phenothiazine and dopamine structures (note complementarity of Ar rings and basic amine functions)
D = superposition of phenothiazine (with alkylamine side chain oriented in opposite direction) – not lack of complementarity of basic amine functions
• structural modification of the phenothiazines:

(1) *thioxanthene* bioisosteres - derived by replacing the N-CH$_2$ structural feature of the phenothiazines with a bioisosteric double bond:

![Thioxanthene Bioisosteres](image)

(2) addition of an electronegative atoms/group at C2 of the phenothiazine ring enhances antipsychotic potency, e.g.:

\[
X = SO_2NR_2 > CF_3 > COCH_3 > Cl
\]

(3) a 3-carbon alkyl connector between phenothiazine heterocycle and terminal 3°-amine function is optimal for dopamine-receptor blockade and antipsychotic activity. Shortening of the chain to 2-carbons results in a change in receptor affinity from DA to CNS histamine receptors.

![Antidopaminergic & Antihistaminic](image)
(4) Structural modification of the side chain amine function yields three AP phenothiazine subclasses:

- Aliphatic phenothiazine derivatives
- Piperidine phenothiazine derivatives
- Piperazine phenothiazine derivatives

(5) Pharmacologic/therapeutic profiles of these 3 classes of antipsychotics differ as follows:

- Antipsychotic potency: piperazines > piperidines > aliphatics
- EPS frequency: piperazines > piperidines > aliphatics
- Sedation: aliphatics ≈ piperidines > piperazines
- Hypotension: aliphatics > piperidines > piperazines

4. Biotransformation of the Antipsychotic Phenothiazines

- As depicted, several different biotransformation reactions occur for the same phenothiazine molecule, numerous metabolites are formed and excreted,
- The 7-OH metabolite is an active antidopaminergic while the sulfoxide (S=O) metabolite is inactive
- Note that the thioxanthene derivatives do not form aromatic hydroxylated metabolites
- Metabolic pathways are significantly altered by a variety of factors (age, sex, interaction with other drugs, route of administration, etc.)
4. Therapeutic Phenothiazines

**Aliphatic and Piperidine Phenothiazines**

<table>
<thead>
<tr>
<th>Name</th>
<th>R =</th>
<th>X =</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chlorpromazine</td>
<td>(CH₂)₂N(CH₃)₂</td>
<td>Cl</td>
</tr>
<tr>
<td>Triflupromazine</td>
<td>(CH₂)₂N(CH₃)₂</td>
<td>CF₃</td>
</tr>
<tr>
<td>Promazine (antiemetic)</td>
<td>(CH₂)₃N(CH₃)₂</td>
<td>H</td>
</tr>
<tr>
<td>Thioridazine Mesoridazine</td>
<td>(CH₂)₂N(CH₃)₂</td>
<td>SCH₃, SOCH₃</td>
</tr>
<tr>
<td>Piperactazine Perphenazine</td>
<td>(CH₂)₂−N(CH₃)₂−OH</td>
<td>COCH₃, Cl</td>
</tr>
</tbody>
</table>

**Piperazine Phenothiazines**

<table>
<thead>
<tr>
<th>Name</th>
<th>R =</th>
<th>X =</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prochlorperazine</td>
<td>CH₃</td>
<td>Cl</td>
</tr>
<tr>
<td>Fluphenazine</td>
<td>(CH₂)₂OH</td>
<td>CF₃</td>
</tr>
<tr>
<td>Trifluoperazine</td>
<td>CH₃</td>
<td>CF₃</td>
</tr>
<tr>
<td>Acetophenazine</td>
<td>(CH₂)₂OH</td>
<td>COCH₃</td>
</tr>
<tr>
<td>Thiethylperazine</td>
<td>(CH₂)₂OH</td>
<td>SCH₂CH₃</td>
</tr>
</tbody>
</table>
### HETEROCYCLIC ANALOGUES OF THE PHENOTHIAZINES

<table>
<thead>
<tr>
<th>Structural Class</th>
<th>Structure</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Thioxanthenes</strong></td>
<td><img src="image1.png" alt="Thioxanthenes Structure" /></td>
</tr>
<tr>
<td>- olefin bioisosteres of the phenothiazines</td>
<td></td>
</tr>
<tr>
<td>- e.g. Thiothixene</td>
<td></td>
</tr>
</tbody>
</table>

| **Arylbutylpiperidines**     | ![Arylbutylpiperidines Structure](image2.png) |
| - potent D2 receptor antagonists |
| - two structural variants:   | Haloperidol and Decanoate Prodrug |
| 1) Fluorobutyropheneone      | ![Haloperidol and Decanoate Prodrug](image3.png) |
| (Haloperidol)                |           |
| 2) Diarylbutylpiperidine     | ![Pimozide](image4.png) |
| (Pimozide)                   |           |

| **Dihydroindolones**         | ![Dihydroindolones](image5.png) |
| - Molindone Hydrochloride    |           |
### Structural Class

<table>
<thead>
<tr>
<th>Structural Class</th>
<th>Structure</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dibenzazepines</strong></td>
<td></td>
</tr>
<tr>
<td>- four structural variants</td>
<td></td>
</tr>
<tr>
<td>1) Dibenzoxazepine (X=O)</td>
<td><img src="#" alt="Loxapine succinate" /></td>
</tr>
<tr>
<td>(Loxapine)</td>
<td></td>
</tr>
<tr>
<td>2) Dibenzodiazepine (X=NH)</td>
<td><img src="#" alt="Clozapine" /></td>
</tr>
<tr>
<td>(Clozapine)</td>
<td></td>
</tr>
<tr>
<td>3) Dibenzothiazepine (X=S)</td>
<td><img src="#" alt="Quetiapine fumarate" /></td>
</tr>
<tr>
<td>(Quetiapine)</td>
<td></td>
</tr>
<tr>
<td>4) Thienobenzodiazepine</td>
<td><img src="#" alt="Olanzapine" /></td>
</tr>
<tr>
<td>(X=NH)</td>
<td></td>
</tr>
</tbody>
</table>

| **Benzisoxazoles**            |                                          |
| - Risperidone                 | ![Risperidone](#)                       |

**Benzisoxazoles**

- Risperidone
ARYLBUTYLPIPERIDINES

- **Structural Variants:**

  ![Chemical Structures]

  - *Flurobutyrophenone*
  - *Diarylbutylpiperidine*

- **Physicochemical Properties**
  - lipophilic
  - basic (3°-amine) - forms H₂O-soluble salts

- **Structure-activity Relationships**
  - para-F or similar electronegative substituent (e.g. CF₃) provides maximal potency,
  - lengthening, shortening or branching of the butyro (4 carbon) chain decreases neuroleptic potency,
  - terminal basic amine function may vary in structure but is usually incorporated in a 6-membered heterocyclic ring
  - replacement of the C=O function with a CH-Ar structural feature yields therapeutically-useful antipsychotics (e.g. pimozide)

- **Metabolism**
DIBENZAZEPINES

- A class of neuroleptics that utilizes the tricyclic dibenzazepine heterocycle as a basic structural feature,
- The dibenzazepine heterocycle is a lipophilic structure with very weakly basic properties,
- Structural variants of dibenzazepines:
  - Dibenzoxazepine ($X = O$)
  - Dibenzodiazepine ($X = NH$)
  - Dibenzothiazepine ($X = S$)
  - Piperazine substitution at C-11 providing a center ($N^4$) of basicity for $H_2O$-solubilizing salt formation to facilitate oral dosage formulation

\[
\begin{align*}
\text{Aromatic (imine) } & \ N \\
\text{Dibenzazepine heterocycle} & \\
& \bigg\{ \text{Piperazine} \bigg\} \\
\text{S} & \text{thiophene bioisostere} \\
& \text{may be NH, O, S} \\
\end{align*}
\]

- atypical antipsychotics:
  - clozapine
  - quetiapine
  - olanzapine
RISPERIDONE

- a benzisoxazole derivative with high affinity for central serotonergic 5-HT₂, dopaminergic D₂ (SDA ratio = 5) and adrenergic α₁-receptors in vivo
- has improved efficacy vs. both positive (delusions and hallucinations) and negative (diminished emotions, low motivation) symptoms of schizophrenia and reduced EPS
- HCl salt used for oral formulation

![Chemical structure of Risperidone]

• Metabolism

(1) Alicyclic hydroxyation ([O]) – the 9-OH metabolite is a potent atypical antipsychotic
(2) Oxidative N-dealkylation (OD)
(3) Benzisoxazole ring cleavage

![Metabolism pathways of Risperidone]