Chapter 29

Antipsychotic Agents and Lithium
1. Antipsychotic agents

- Schizophrenia
- Bipolar disorder
- Psychotic depression
- Senile psychoses
- Organic psychoses
- Drug-induced psychoses
1. Antipsychotic agents

Nature of Psychosis & Schizophrenia

- delusions (false beliefs)
- various types of hallucinations, usually auditory or visual
- disorganized thinking in a clear sensorium
- Schizophrenia is a particular kind of psychosis characterized mainly by a clear sensorium but a marked thinking disturbance. Patients with positive and negative (emotional blunting, social withdrawal, lack of motivation) symptoms, cognitive impairment, and possibly depression
1. Antipsychotic agents

Nature of Psychosis & Schizophrenia

Genes shared

- General population: 1%
- First cousins: 2%
- Uncles, aunts: 2%
- Nephews, nieces: 4%
- Grandchildren: 5%
- Half-siblings: 6%
- Parents: 6%
- Siblings: 9%
- Children: 13%
- Fraternal twins: 17%
- Identical twins: 48%
1. Antipsychotic agents

The Serotonin Hypothesis of Schizophrenia

- 5-HT2A-receptor:
  Indole hallucinogens such as LSD (lysergic acid diethylamide) and mescaline are serotonin (5-HT) agonists. The 5-HT2A-receptor stimulation was the basis for the hallucinatory effects of these agents.

- Drugs to 5-HT2A-receptor:
  5-HT2A-receptor blockade is a key factor in the mechanism of action of the main class of atypical antipsychotic drugs such as clozapine and quetiapine. These drugs block the constitutive activity of 5-HT2A receptor. These receptors modulate the release of dopamine in the cortex, limbic region, and striatum. Stimulation of 5-HT2A receptors leads to depolarization of glutamate neurons, but also stabilizes NMDA receptors on postsynaptic NMDA receptors.

- 5-HT2C-receptor:
  5-HT2C-receptor stimulation provides a further means of modulating cortical and limbic dopaminergic activity.
1. Antipsychotic agents

The Dopamine Hypothesis of Schizophrenia

- Evidence: excessive limbic dopaminergic activity plays a role in psychosis:
  - (1) many antipsychotic drugs strongly block postsynaptic D2 receptors in the central nervous system, especially in the mesolimbic and striatal-frontal system; this includes partial dopamine agonists, such as aripiprazole and bifeprunox.
  - (2) Drugs that increase dopaminergic activity, such as levodopa, amphetamines, and bromocriptine and apomorphine, either aggravate schizophrenia psychosis or produce psychosis de novo in some patients.
  - (3) Dopamine-receptor density has been found postmortem to be increased in the brains of schizophrenics who have not been treated with antipsychotic drugs.
  - (4) Some postmortem schizophrenic subjects have increased dopamine levels and D2-receptor density in the nucleus accumbens, caudate, and putamen.
  - (5) Imaging studies have shown increased amphetamine-induced striatal dopamine release, increased baseline occupancy of striatal D2 receptors by extracellular dopamine.
Rethinking:
Several of the atypical antipsychotic drugs have much less effect on D2 receptors and yet are effective in schizophrenia.
Serotonin receptors—particularly the 5-HT2A-receptor subtype—may mediate synergistic effects or protect against the extrapyramidal consequences of D2 antagonism.
The atypical antipsychotic drugs share the property of weak D2-receptor antagonist antagonism and more potent 5-HT2A-receptor blockade.
1. Antipsychotic agents

The Glutamate Hypothesis of Schizophrenia

- Phencyclidine and ketamine are noncompetitive inhibitors of the NMDA receptor that exacerbate both cognitive impairment and psychosis in patients with schizophrenia. This was the starting point for the hypothesis that hypofunction of NMDA receptors, located on GABAergic interneurons, leading to diminished inhibitory influences on neuronal function, contributed to schizophrenia.

- Ampakines are drugs that potentiate currents mediated by AMPA-type glutamate receptors. In behavioral tests, ampakines are effective in correcting behaviors in various animal models of schizophrenia and depression.
1. Antipsychotic agents

An agonist with higher affinity to D2 receptor has higher extrapyramidal toxicity
The first pathway—the one most closely related to behavior and psychosis—is the mesolimbic-mesocortical pathway, which projects from cell bodies near the substantia nigra to the limbic system and neocortex.

The antipsychotic action is now thought to be produced (at least in part) by their ability to block dopamine in the mesolimbic and mesocortical systems.
Antipsychotic Agents and Lithium

1. Antipsychotic agents

B. Dopamine receptor and their effects
A summary of the relative receptor-binding affinities of several key agents:

- Chlorpromazine: $\alpha_1 = 5$-HT2A > D2 > D1
- Haloperidol: D2 > $\alpha_1$ > D4 > 5-HT2A > D1 > H1
- Clozapine: D4 = $\alpha_1$ > 5-HT2A > D2 = D1
- Olanzapine: 5-HT2A > H1 > D4 > D2 > $\alpha_1$ > D1
- Aripiprazole: D2 = 5-HT2A > D4 > $\alpha_1$ = H1 >> D1
- Quetiapine: H1 > $\alpha_1$ > M1,3 > D2 > 5-HT2A

Thus, most of the atypical and some typical antipsychotic agents are at least as potent in inhibiting 5-HT2 receptors as they are in inhibiting D2 receptors.
## 2. Pharmacological effects

### C. Differences among antipsychotic drugs

<table>
<thead>
<tr>
<th>Type</th>
<th>Manifestations</th>
<th>Mechanism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Autonomic nervous system</td>
<td>Loss of accommodation, dry mouth, difficulty urinating, constipation</td>
<td>Muscarinic cholinocceptor blockade</td>
</tr>
<tr>
<td></td>
<td>Orthostatic hypotension, impotence, failure to ejaculate</td>
<td>-Adrenoceptor blockade</td>
</tr>
<tr>
<td>Central nervous system</td>
<td>Parkinson's syndrome, akathisia, dystonias</td>
<td>Dopamine-receptor blockade</td>
</tr>
<tr>
<td></td>
<td>Tardivedyskinesia</td>
<td>Supersensitivity of dopamine receptors</td>
</tr>
<tr>
<td></td>
<td>Toxic-confusional state</td>
<td>Muscarinic blockade</td>
</tr>
<tr>
<td>Endocrine system</td>
<td>Amenorrhea-galactorrhea, infertility, impotence</td>
<td>Dopamine-receptor blockade resulting in hyperprolactinemia</td>
</tr>
<tr>
<td>Other</td>
<td>Weight gain</td>
<td>Possibly combined H₁ and 5-HT₂ blockade</td>
</tr>
</tbody>
</table>
Nonpsychotic persons also experience impaired performance as judged by a number of psychomotor and psychometric tests. Psychotic individuals, however, may actually show improvement in their performance as the psychosis is alleviated.
Antipsychotic drugs produce shifts in the pattern of electroencephalographic (EEG) frequencies, usually slowing them and increasing their synchronization. To induce seizures...
Antipsychotic Agents and Lithium

3. Clinical Pharmacology

Indications - Psychiatric indications

- Schizophrenia
- Psychotic bipolar disorder
- Psychotic depression, and treatment resistant depression.
- Schizoaffective disorders, which share characteristics of both schizophrenia and affective disorders. The manic phase in bipolar affective disorder often requires treatment with antipsychotic agents
- Others: Tourette's syndrome, Alzheimer's disease, psychotic depression.
3. Clinical Pharmacology

Indications - nonpsychiatric indications

- **Antiemetic**: due to dopamine-receptor blockade, such as prochlorperazine and benzquinamide.
- **Pruritus**: H1-receptor-blocking action, such as Phenothiazines.
- **Preoperative sedatives**: such as promethazine.
### Table 29-3 Some Representative Antipsychotic Drugs.

<table>
<thead>
<tr>
<th>Drug Class</th>
<th>Drug</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phenothiazines</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aliphatic</td>
<td>Chlorpromazine&lt;sup&gt;1&lt;/sup&gt;</td>
<td>Generic, inexpensive</td>
<td>Many adverse effects, especially autonomic</td>
</tr>
<tr>
<td>Piperidine</td>
<td>Thioridazine&lt;sup&gt;2&lt;/sup&gt;</td>
<td>Slight extrapyramidal syndrome; generic</td>
<td>800 mg/d limit; no parenteral form; cardiotoxicity</td>
</tr>
<tr>
<td>Piperazine</td>
<td>Fluphenazine&lt;sup&gt;3&lt;/sup&gt;</td>
<td>Depot form also available (enanthate, decanoate)</td>
<td>(?) Increased tardive dyskinesia</td>
</tr>
<tr>
<td>Thioxanthene</td>
<td>Thiothixene</td>
<td>Parenteral form also available; (?) decreased tardive dyskinesia</td>
<td>Uncertain</td>
</tr>
<tr>
<td>Butyrophenone</td>
<td>Haloperidol</td>
<td>Parenteral form also available; generic</td>
<td>Severe extrapyramidal syndrome</td>
</tr>
<tr>
<td>Dibenzoxazepine</td>
<td>Loxapine</td>
<td>(?) No weight gain</td>
<td>Uncertain</td>
</tr>
<tr>
<td>Dibenzodiazepine</td>
<td>Clozapine</td>
<td>May benefit treatment-resistant patients; little extrapyramidal toxicity</td>
<td>May cause agranulocytosis in up to 2% of patients; dose-related lowering of seizure threshold</td>
</tr>
<tr>
<td>Benzisoxazole</td>
<td>Risperidone</td>
<td>Broad efficacy; little or no extrapyramidal system dysfunction at low doses</td>
<td>Extrapyramidal system dysfunction and hypotension with higher doses</td>
</tr>
<tr>
<td>Thienobenzodiazepine</td>
<td>Olanzapine</td>
<td>Effective against negative as well as positive symptoms; little or no extrapyramidal system dysfunction</td>
<td>Weight gain; dose-related lowering of seizure threshold</td>
</tr>
<tr>
<td>Dibenzothiazepine</td>
<td>Quetiapine</td>
<td>Similar to olanzapine; perhaps less weight gain</td>
<td>May require high doses if there is associated hypotension; short $t_{1/2}$ and twice-daily dosing</td>
</tr>
<tr>
<td>Dihydroindolone</td>
<td>Ziprasidone</td>
<td>Perhaps less weight gain than dozapine, parenteral form available</td>
<td>QT&lt;sub&gt;e&lt;/sub&gt; prolongation</td>
</tr>
<tr>
<td>Dihydrocarbostyril</td>
<td>Aripiprazole</td>
<td>Lower weight gain liability, long half-life, novel mechanism potential</td>
<td>Uncertain, novel toxicities possible</td>
</tr>
</tbody>
</table>
Bipolar disorder, once known as manic-depressive illness, is a psychotic disorder distinct from schizophrenia.

Lithium was the first agent shown to be useful in the treatment of the manic phase of bipolar disorder. Lithium continues to be used for acute-phase illness as well as for prevention of recurrent manic and depressive episodes.

Others:
- Carbamazepine and valproic acid for the treatment of acute mania and for prevention of its recurrence.
- Lamotrigine is approved for prevention of recurrence.
- Gabapentin, oxcarbazepine, and topiramate
- Aripiprazole, chlorpromazine, olanzapine, quetiapine, risperidone, and ziprasidone
- Olanzapine plus fluoxetine in combination and quetiapine
4. Lithium an others

Nature of bipolar disorder

- Manic phase: excitement, hyperactivity, impulsivity, disinhibition, aggression, diminished need for sleep, psychotic symptoms in some (but not all) patients, and cognitive impairment.

- Depressive phase: depressed mood, diurnal variation, sleep disturbance, anxiety, and sometimes, psychotic symptoms. Mixed manic and depressive symptoms are also seen. Patients with bipolar disorder are at high risk for suicide.
Antipsychotic Agents and Lithium

4. Lithium and others
Antipsychotic Agents and Lithium

5. Clinical Pharmacology of Lithium

Applications

- Bipolar Affective Disorder
- Other Applications
  - Recurrent endogenous depression with a cyclic pattern
  - Schizoaffective disorder
6. Other drugs for bipolar disorder

- **VALPROIC ACID**
  Valproic acid (valproate), an antiepileptic, shows efficacy equivalent to that of lithium during the early weeks of treatment. It is significant that valproic acid has been effective in some patients who have failed to respond to lithium.

- **CARBAMAZEPINE**
  Carbamazepine may be used to treat acute mania and also for prophylactic therapy. Carbamazepine may be used alone or, in refractory patients, in combination with lithium or, rarely, valproate.

- **OTHER DRUGS**
  Lamotrigine has been reported to be useful in preventing the depression that often follows the manic phase of bipolar disorder.

  Riluzole, a neuroprotective agent that is approved for use in amyotrophic lateral sclerosis.

  Ketamine, a noncompetitive NMDA antagonist previously discussed as a drug believed to model schizophrenia but thought to act by producing relative enhancement of AMPA receptor activity; and AMPA receptor potentiatators.