

Antipsychotic Drugs

Overview:

The antipsychotic drugs (also called neuroleptics or major tranquilizers) are used primarily to treat schizophrenia, but they are also effective in other psychotic and manic states.

Antipsychotic drugs are not curative and do not eliminate chronic thought disorders, but they often decrease the intensity of hallucinations and delusions and permit the person with schizophrenia to function in a supportive environment.

Schizophrenia:

Schizophrenia is a type of chronic psychosis characterized by delusions, hallucinations (often in the form of voices), and thinking or speech disturbances. The onset of illness is often during late adolescence or early adulthood. It occurs in about 1% of the population and is a chronic and disabling disorder. Schizophrenia has a strong genetic component.

Genetic Etiology:

It occurs due to activation of Dopamine receptors and over-release of dopamine binding to these receptors causing Schizophrenia.

Competitive Inhibition can block the dopamine receptors.

Antipsychotic Drugs:

The antipsychotic drugs are divided into first (Typical)- and second-generation agents (Atypical)

The first-generation drugs are further classified as “low potency” or “high potency.”

This classification does not indicate clinical effectiveness of the drugs, but rather specifies affinity for the dopamine D2 receptor.

Classification of Antipsychotic Drugs:

1. FIRST-GENERATION ANTIPSYCHOTIC (low potency):

- Chlorpromazine
- Thioridazine

Key: CT

2. FIRST-GENERATION ANTIPSYCHOTIC (high potency):

- Fluphenazine
- Haloperido

- Thiothixene
- Prochlorperazine

KEY: FHTP

3. SECOND-GENERATION ANTIPSYCHOTIC:

- Aripiprazole
- Clozapine
- Olanzapine
- Risperidone
- Quetiapine

KEY: AC ORQ

A. First-generation antipsychotics:

Their antipsychotic effects reflect competitive blocking of dopamine D2 receptors. First-generation antipsychotics are more likely to be associated with movement disorders known as extrapyramidal symptoms (EPS) e.g. haloperidol.

B. Second-generation antipsychotic drugs:

The second-generation antipsychotic drugs (also called “atypical” anti- psychotics) have a lower incidence of EPS than the first- generation agents. The second-generation drugs appear to owe their unique activity to blockade of both serotonin and dopamine and, perhaps, other receptors.

Drug selection: Second-generation agents are generally used as first-line therapy for schizophrenia to minimize the risk of debilitating EPS associated with the first-generation drugs that act primarily at the dopamine D2 receptor. **The second-generation antipsychotics exhibit an efficacy that is equivalent to, and occasionally exceeds, that of the first-generation antipsychotic agents.**

Refractory patients: Approximately 10% to 20% of patients with schizophrenia have an insufficient response to all first- and second- generation antipsychotics. For these patients, **clozapine** has shown to be an effective antipsychotic with a minimal risk of EPS.

Mechanism of action:

- **Dopamine antagonism:** All of the first-generation and most of the second-generation antipsychotic drugs block D2 dopamine receptors in the brain and the periphery.

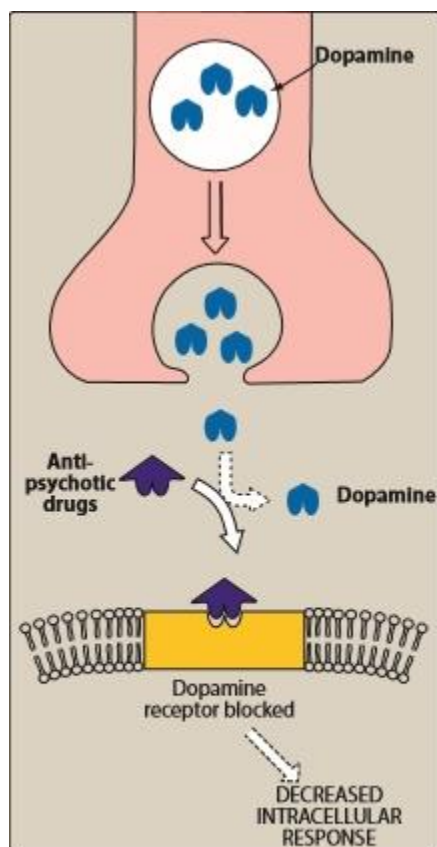


Figure 11.2
Dopamine-blocking actions of antipsychotic drugs.

- **Serotonin receptor-blocking activity:** Most of the second-generation agents appear to exert part of their unique action through inhibition of serotonin receptors (5-HT).

Actions:

The clinical effects of antipsychotic drugs appear to reflect a blockade at dopamine and/or serotonin receptors. However, many of these agents also block cholinergic, adrenergic, and histaminergic receptors.

1. **Antipsychotic effects:** reduce hallucinations and delusions associated with schizophrenia by blocking D₂ receptors. The “negative” symptoms, such as blunted affect, apathy, and impaired attention, as well as cognitive impairment, are not as responsive to therapy, particularly with the first-generation antipsychotics. Many second-generation agents, such as clozapine, can ameliorate the negative symptoms to some extent.
2. **Extrapyramidal effects:** Dystonias (sustained contraction of muscles leading to twisting, distorted postures), Parkinson-like symptoms, akathisia (motor restlessness), and tardive dyskinesia (involuntary movements, usually of the tongue, lips, neck, trunk, and limbs) can occur

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with both acute and chronic treatment. The second- generation antipsychotics exhibit a lower incidence of EPS.

3. **Antiemetic effects:** With the exception of aripiprazole, most of the antipsychotic drugs have antiemetic effects that are mediated by blocking D2 receptors of the chemoreceptor trigger zone of the medulla
4. **Anticholinergic effects:** Some of the antipsychotics produce anticholinergic effects. These effects include blurred vision, dry mouth (the exception is clozapine, which increases salivation), confusion, and inhibition of gastrointestinal and urinary tract smooth muscle, leading to constipation and urinary retention.
5. **Other effects:** Blockade of α -adrenergic receptors causes orthostatic hypotension and lightheadedness. The antipsychotics also alter temperature-regulating mechanisms, increase in prolactin release, Sexual dysfunction may also occur with the antipsychotics.

Therapeutic uses:

- Treatment of schizophrenia
- Prevention of nausea and vomiting
- Used as tranquilizers
- Management of the manic and mixed symptoms associated with bipolar disorder.

Absorption and Metabolism:

After oral administration, the antipsychotics show variable absorption that is unaffected by food. They are metabolized to many different metabolites, usually by the cytochrome P450 system in the liver.

These agents readily pass into the brain and have a large volume of distribution.

Some metabolites are active and have been developed as pharmacological agents themselves.

Adverse effects:

- **Extrapyramidal effects:** Parkinson- like symptoms of bradykinesia, rigidity, and tremor.
- **Tardive dyskinesia :** Patients display involuntary movements, including bilateral and facial jaw movements and “fly-catching” motions of the tongue.
- **Neuroleptic malignant syndrome:** characterized by muscle rigidity, fever, altered mental status and stupor, unstable blood pressure, and myoglobinemia.
- **Other effects:** confusion, drowsiness, dry mouth, urinary retention, constipation, and loss of visual accommodation etc.

Cautions and Contraindications:

All antipsychotics may lower the seizure threshold and should be used cautiously in patients with seizure disorders or those with an increased risk for seizures, such as withdrawal from alcohol. These agents also carry the warning of increased risk for mortality when used in elderly patients with dementia-

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related behavioral disturbances and psychosis. Antipsychotics used in patients with mood disorders should also be monitored for worsening of mood and suicidal ideation or behaviors.

Maintenance treatment:

Patients who have had two or more psychotic episodes secondary to schizophrenia should receive maintenance therapy for at least 5 years

A. Clozapine:

It reduces negative symptoms in psychosis. It can be used alone or used in combination with Barbiturates and Benzodiazepines. Antipsychotic effect takes several days to weeks.

Clozapine has high affinity for D1, D4, 5-HT2, muscarinic, and α -adrenergic receptors, but it is also a weak dopamine D2 receptor antagonist.

It is used in combination with narcotic analgesics.

Also show anti-muscarinic effects (blockade of muscarinic receptors)

Actions, Therapeutic Uses and Adverse effects are same as above mentioned.

B. Promethazine:

It is used in Pruritus (itching, redness etc.)

It has anti-histaminic property

Adverse Effects: Extra pyramidal effects, anti-cholinergic effects like discussed above.

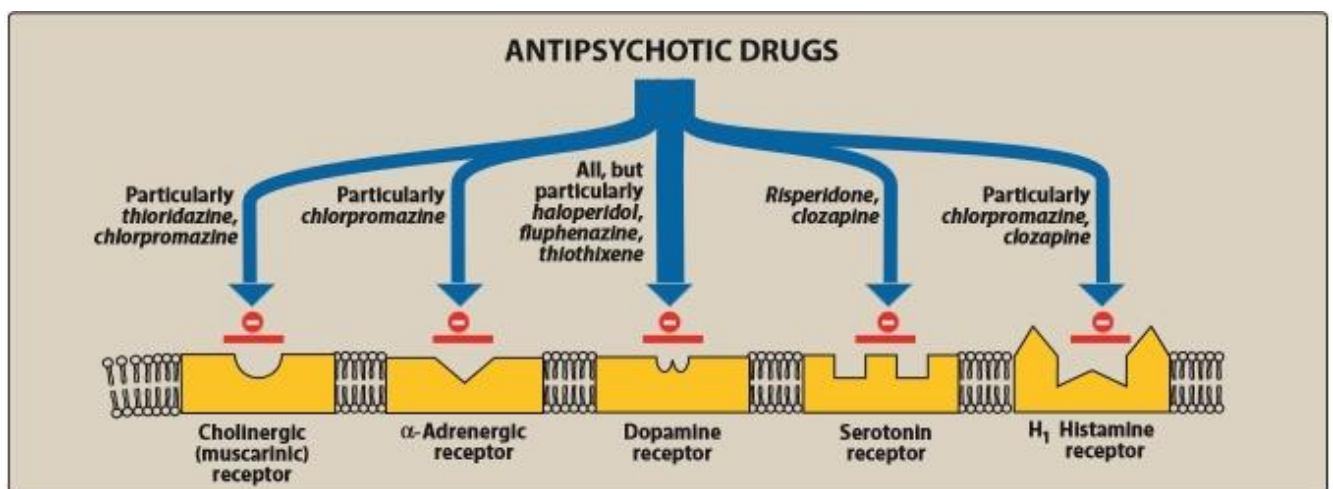


Figure 11.4

Antipsychotic drugs block at dopaminergic and serotonergic receptors as well as at adrenergic, cholinergic, and histamine-binding receptors.

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DRUG	THERAPEUTIC NOTES
First generation	
<i>Chlorpromazine</i>	Moderate to high potential for EPS; moderate to high potential for weight gain, orthostasis, sedation, anti-muscarinic effects.
<i>Fluphenazine</i>	Oral formulation has a high potential for EPS; low potential for weight gain, sedation, and orthostasis; low to moderate potential for antimuscarinic effects; common use is in the LAI formulation administered every 2–3 weeks in patients with schizophrenia and a history of noncompliance with oral antipsychotic regimens.
<i>Haloperidol</i>	High potential for EPS; low potential for anti-adrenergic (orthostasis) or antimuscarinic adverse events; low potential for weight gain or sedation; available in a LAI formulation administered every 4 weeks.
Second generation	
<i>Aripiprazole</i>	Low potential for EPS; low potential for weight gain; low potential for sedation and antimuscarinic effects; also approved for the treatment of bipolar disorder; also approved for autistic disorder in children, and as an adjunctive treatment for major depression.
<i>Asenapine</i>	Low potential for EPS; low potential for weight gain; low to moderate potential for sedation; low potential for orthostasis; also approved for the treatment of bipolar disorder; available as a sublingual formulation.
<i>Clozapine</i>	Very low potential for EPS; risk for blood dyscrasias (for example, agranulocytosis = ~1%); risk for seizures; risk for myocarditis; high potential for the following: sialorrhea, weight gain, antimuscarinic effects, orthostasis, and sedation.
<i>Olanzapine</i>	Low potential for EPS; moderate to high potential for weight gain and sedation; low potential for orthostasis; also approved for the treatment of bipolar disorder; available as a LAI formulation administered every 2–4 weeks.
<i>Paliperidone</i>	Low to moderate potential for EPS; low potential for weight gain; low potential for sedation; available as a LAI formulation administered every 4 weeks; also approved for use in schizoaffective disorder.
<i>Quetiapine</i>	Low potential for EPS; moderate potential for weight gain; moderate potential for orthostasis; moderate to high potential for sedation; also approved for the treatment of bipolar disorder and as an adjunctive treatment for major depression.
<i>Risperidone</i>	Low to moderate potential for EPS; low to moderate potential for weight gain; low to moderate potential for orthostasis; low to moderate potential for sedation; also approved for the treatment of bipolar disorder; also approved for autistic disorder in children; available as a LAI formulation administered every 2 weeks.
<i>Ziprasidone</i>	Low potential for extrapyramidal effects; contraindicated in patients with history of cardiac arrhythmias; minimal weight gain. Used in treatment of bipolar depression.

Figure 11.8

Summary of antipsychotic agents commonly used to treat schizophrenia. EPS = extrapyramidal effects; LAI = long-acting injectable.