

Antipsychotics 1

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BCPS

FIRST-GENERATION ANTIPSYCHOTIC (low potency)

Chlorpromazine

Thioridazine

FIRST-GENERATION ANTIPSYCHOTIC (high potency)

Fluphenazine

Haloperidol

Loxapine

Molindone

Perphenazine

Pimozide

Prochlorperazine

Thiothixene

Trifluoperazine

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, which, in turn, may influence the adverse effect profile of the drug.

SECOND-GENERATION ANTIPSYCHOTIC (atypical antipsychotic)

Risperidone

Ziprasidone

Paliperidone

Iloperidone

Lurasidone

Olanzapine

Quetiapine

Clozapine

Asenapine

THIRD-GENERATION ANTIPSYCHOTICS

Aripiprazole

Brexipiprazole

Cariprazine

First-generation antipsychotics

The first-generation antipsychotic drugs (also called conventional) are competitive inhibitors at a variety of receptors, but their antipsychotic effects reflect competitive blockade of dopamine D2 receptors. First generation antipsychotics are more likely to be associated with movement disorders known as extrapyramidal symptoms (EPS), particularly drugs that bind tightly to dopaminergic neuroreceptors, such as *haloperidol*. Movement disorders are somewhat less likely with medications that bind less potently, such as *chlorpromazine*. No one drug is clinically more effective than another

Second-generation antipsychotic drugs

The second-generation antipsychotic drugs (also called “atypical” antipsychotics) have a lower incidence of EPS than the first-generation agents, but are associated with a higher risk of metabolic adverse effects, such as diabetes, hypercholesterolemia, and weight gain. The second-generation drugs owe their unique activity to blockade of both serotonin and dopamine receptors.

1. 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. Differences in therapeutic efficacy among the second-generation drugs have not been established, and individual patient response and comorbid conditions must often be used to guide drug selection.
2. Refractory patients: Approximately 10% to 20% of patients with schizophrenia have an insufficient response to first- and second-generation antipsychotics. For these patients, *clozapine* has shown to be an effective antipsychotic with a minimal risk of EPS. However, its clinical use is limited to refractory patients because of serious adverse effects. *Clozapine* can produce bone marrow suppression, seizures, and cardiovascular side effects, such as orthostasis. The risk of severe agranulocytosis necessitates frequent monitoring of white blood cell counts.

Mechanism of action

1. 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.

2. Serotonin receptor–blocking activity: Most of the second-generation agents exert part of their action through inhibition of serotonin receptors (5-HT), particularly 5-HT_{2A} receptors. *Clozapine* has high affinity for D₁, D₄, 5-HT₂, muscarinic, and α -adrenergic receptors, but it is also a weak dopamine D₂ receptor antagonist. *Risperidone* blocks 5-HT_{2A} receptors to a greater extent than it does D₂ receptors, as does *olanzapine*. The second-generation antipsychotics *aripiprazole*, *brexpiprazole*, and *cariprazine* are partial agonists at D₂ and 5-HT_{1A} receptors, as well as antagonists of 5-HT_{2A} receptors. *Quetiapine* is relatively weak at blockade of D₂ and 5-HT_{2A} receptors. Its low risk for EPS may also be related to the relatively short period of time it binds to the D₂ receptor. *Pimavanserin* appears to act as an inverse agonist and antagonist at the 5-HT_{2A} receptor and the 5-HT_{2C} receptor, with no appreciable affinity for dopamine receptors. *Pimavanserin* is indicated for psychosis associated with Parkinson disease

Actions

The clinical effects of antipsychotic drugs reflect a blockade at dopamine and/or serotonin receptors. However, many antipsychotic agents also block cholinergic, adrenergic, and histaminergic receptors. It is unknown what role, if any, these actions have in alleviating the symptoms of psychosis. However, the undesirable adverse effects of antipsychotic drugs often result from pharmacological actions at these other receptors.

1. Antipsychotic effects: All antipsychotic drugs can reduce hallucinations and delusions associated with schizophrenia (known as “positive” symptoms) by blocking D2 receptors in the mesolimbic system of the brain. 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 with both acute and chronic treatment. Blockade of dopamine receptors in the nigrostriatal pathway is believed to cause these unwanted movement symptoms. The second-generation antipsychotics exhibit a lower incidence of EPS.

3. Antiemetic effects: 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, particularly *thioridazine*, *chlorpromazine*, *clozapine*, and *olanzapine*, 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. The anticholinergic effects may actually assist in reducing the risk of EPS with these agents.

5. Other effects: Blockade of α -adrenergic receptors causes orthostatic hypotension and light-headedness. The antipsychotics also alter temperature-regulating mechanisms and can produce poikilothermia (condition in which body temperature varies with the environment). In the pituitary, antipsychotics that block D2 receptors may cause an increase in prolactin release. Sedation occurs with those drugs that are potent antagonists of the H1-histamine receptor, including *chlorpromazine*, *olanzapine*, *quetiapine*, and *clozapine*. Sexual dysfunction may also occur with the antipsychotics due to various receptor-binding characteristics. Weight gain is also a common adverse effect of antipsychotics and is more significant with the second-generation agents.

ANTIPSYCHOTIC DRUGS

