

## Antipsychotics (Neuroleptics) — Classification and Side Effects

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**Antipsychotic drugs have been used to treat schizophrenia for many decades. However, they have other uses, too, including the treatment of bipolar disorder. Antipsychotic drugs principally work through their inhibition of post-synaptic dopamine receptors. These drugs are classified as first generation typical antipsychotics and second-generation atypical antipsychotics. Students should be aware of the mechanism of action, side effect profile and uses of these drugs.**



### Effects of Increasing Dopamine

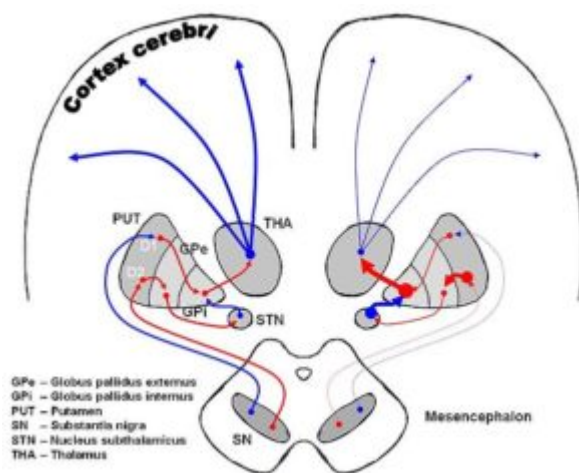
**Dopamine is a monoamine neurotransmitter** that is synthesized by the conversion of tyrosine to dopa, which undergoes decarboxylation and forms dopamine. The functions of dopamine depend on the pathway involved. They include:

- **motor control** in the **nigrostriatal pathway**;
- **behavioral effects** in the **mesolimbic and mesocortical pathways**;
- **endocrine control** in the **tuberoinfundibular pathway**.

## Dopaminergic pathways

Dopamine has been implicated in the pathogenesis of schizophrenia in what is known as the **dopamine hypothesis** or theory. Carlson, who was awarded a Nobel Prize in 2000, originally proposed this theory. **Excess levels of dopamine have been linked to psychotic behaviors**, based on pharmacological evidence and various studies involving humans and animals.

**Amphetamines cause increased levels of dopamine in the brain** and can result in acute psychotic episodes similar to what is seen in schizophrenia. Furthermore, **drugs used in Parkinson's disease, including levodopa and dopamine agonists, can cause hallucinations** as a side effect. It is also known that amphetamine, as well as other **drugs that act as dopamine agonists, worsen symptoms in patients with schizophrenia**.



**Image:** "The image shows dopaminergic pathways of the human brain in normal condition (left) and Parkinson's Disease (right). Red Arrows indicate suppression of the target, blue arrows indicate stimulation of target structure." by Chris 73. License: [CC BY 2.5](https://creativecommons.org/licenses/by/2.5/)

Studies with **brain imaging** have shown that there is **increased dopamine production and release in the striatum of the brain in schizophrenic patients**. Furthermore, amphetamine administration in schizophrenic patients has been found to result in greater dopamine release compared to control subjects.

In animal studies, **increased dopamine levels lead to stereotyped, repetitive behaviors**, like that which sometimes occurs in schizophrenia. Animals that are administered potent D2 receptor agonists like bromocriptine also develop such behaviors.

In support of such evidence, **dopamine antagonists, including antipsychotic agents, have been consistently found to be effective in treating the positive symptoms of schizophrenia**. In fact, antagonist activity at the dopamine receptors is the main mechanism of action of the antipsychotics in clinical use for schizophrenic patients.

## Schizophrenia pathogenesis

In schizophrenia, there is **overactivity of D2 receptors in the mesolimbic dopaminergic pathway**, which **causes positive symptoms**. In contrast, **negative symptoms** may be **caused by decreased activity of D1 receptors in the**

## mesocortical dopaminergic pathway.

There have been new findings regarding the pathogenesis of schizophrenia. Aside from the role of dopamine, it is believed that **glutamate underactivity** may play an important part in this condition.

## Psychotic Disorder Medication

Antipsychotic drugs work chiefly by **blocking postsynaptic dopamine D2 receptors**. Therapeutic effects are achieved when there is **a blockade of at least 80 % of the D2 receptors**.

While the blockade of dopamine receptors is an immediate effect of drug administration, the **therapeutic effect may be delayed for up to several weeks**, and the reason for this is unknown. The therapeutic effects of antipsychotic drugs include **decreased dopaminergic neuronal activity and an upregulation of dopamine receptors**. However, an immediate effect of antipsychotics is their sedating quality, making them useful in acute behavioral emergencies.

Antipsychotics are broadly divided into two categories: **first-generation antipsychotics, also known as typical antipsychotics, and second-generation antipsychotics, called atypical antipsychotics**. The first-generation antipsychotic agents were introduced in the 1950s, while atypical second-generation agents were developed in more recent times.

Typical and atypical antipsychotics differ in relation to their mechanism of action, side effect profile, and clinical effect. **Typical antipsychotics primarily bind and inhibit dopaminergic D2 receptors and treat positive symptoms. Atypical antipsychotics bind to D2 receptors as well as serotonergic 5-HT2a receptors**. Atypical agents treat positive symptoms, but **may also have an effect in improving negative symptoms and cognitive impairment** because of 5-HT2a receptor antagonism.

One of the key differences between typical and atypical antipsychotic drugs is that **the newer atypical agents have a lower incidence of extrapyramidal motor side effects**. This is because the newer agents have **activity at other receptors**. Other reasons for reduced extrapyramidal effects may include the fact that some of these drugs **dissociate rapidly from the dopamine receptor, while others act as partial agonists**.

## Examples of typical and atypical antipsychotics

Typical (first generation)	Atypical (second generation)
Chlorpromazine Clopenthixol Flupenthixol Fluphenazine Haloperidol	Amisulpride Aripiprazole Clozapine Quetiapine Risperidone Sertindole Ziprasidone Zotepine

# Side Effects of Antipsychotics

## Extrapyramidal motor side effects

Motor disturbances are the result of direct or indirect **blockade of D2 receptors in the nigrostriatal dopaminergic pathway**. The first-generation antipsychotic drugs are traditionally associated with a greater incidence of motor disturbances, compared to atypical antipsychotics. However, even the atypical antipsychotics can cause extrapyramidal effects, including olanzapine, quetiapine, and risperidone.

## Cardiac effects

Antipsychotics use may cause a **prolonged QT interval**, which can lead to **ventricular arrhythmias** and **sudden cardiac death**.

## Endocrine effects

Blockade of dopamine receptors in the tuberoinfundibular pathway results in **increased prolactin secretion**, as one of the functions of dopamine is to suppress prolactin. [Hyperprolactinemia](#) can lead to menstrual irregularities, breast enlargement, and galactorrhea.

## Anti-muscarinic effects

Blockade of muscarinic cholinergic receptors may cause effects such as **dry mouth and eyes, blurred vision, increased intraocular pressure, urinary retention, constipation, and confusion**.

## Anti-adrenergic effects

The blockade of adrenergic receptors can result in **orthostatic hypotension** and reflex tachycardia.

## Anti-histamine effects

The blockade of histamine receptors can result in **sedation**. This is an effect of certain phenothiazine antipsychotics such as chlorpromazine.

## Metabolic and cardiovascular side effects

This group of side effects is very important to consider. Antipsychotics can cause **weight gain, diabetes mellitus, and cardiovascular disease**. These side effects are more common with the second-generation atypical antipsychotics, such as olanzapine, clozapine, and quetiapine. As a result, the cardiovascular health of patients on antipsychotics needs to be monitored closely.

## Sexual dysfunction

Decreased libido and erectile dysfunction may occur in men. Those conditions are a result of a combination of dopamine, adrenergic and muscarinic receptor blockade.

Other side effects include **allergic reactions** (e.g., urticaria), idiosyncratic reactions such as **obstructive jaundice** (with phenothiazines), **leukopenia and agranulocytosis** (higher incidence with clozapine).

## Neuroleptic malignant syndrome

A **rare syndrome occurring in 1–2 % of patients**. It is characterized by

**hyperthermia, muscle rigidity, mental confusion, and autonomic nervous system dysfunction.** This syndrome is **fatal in 10–20 %** of the cases as it can cause renal or cardiovascular failure. Treatment is by the immediate cessation of the antipsychotic drug and administration of bromocriptine, a dopamine receptor agonist, and dantrolene, a skeletal muscle relaxant.

## Bipolar Disorder Medication

Drugs used in the treatment of bipolar disorder include:

- Lithium
- Anti-epileptic drugs
- Atypical antipsychotic drugs
- Antidepressants (for bipolar depression)
- Other drugs, including benzodiazepine, memantine, amantadine, and ketamine.

## Mood Stabilizers

**Lithium or an antiepileptic drug is typically used as a mood stabilizer for the long-term treatment of bipolar disorder.** They act prophylactically to prevent mood swings and therefore reduce manic and depressive episodes.

### Lithium

Lithium is used for the **prophylactic treatment of bipolar disorder as a mood stabilizer** and in the **treatment of acute mania**. The mechanism of action of lithium is poorly understood. It **may act by interfering with the formation of inositol triphosphate and inhibiting kinases.**

Lithium has a **narrow therapeutic range, between 0.5–1 mmol/L**. At levels **above 1.5 mmol/L, it becomes toxic**. Toxic effects of lithium include

- gastrointestinal disturbances such as nausea and vomiting
- tremor
- nephrogenic diabetes insipidus
- **renal failure**
- thyroid enlargement
- hypothyroidism
- weight gain
- hair loss
- mild cognitive impairment

**Acute toxicity** can cause significant **neurological effects, including confusion, motor impairment, seizures, coma, and death.**

## Antiepileptic Drugs

Certain antiepileptic drugs may also be used as a mood stabilizer in the treatment of bipolar disorder. These include **carbamazepine, lamotrigine, and sodium valproate**. They are clinically effective and have a better side effect profile than lithium. The action of antiepileptic drugs in controlling bipolar disorder may be related to their **anticonvulsant activity and blockade of sodium channels.**

There are some differences between the antiepileptic drugs used for bipolar disorder. Carbamazepine and valproate can be used for the treatment of acute mania. Both valproate and lamotrigine are effective for the long-term treatment of bipolar disorder, whereas carbamazepine is less effective in treating bipolar depression.

## Atypical Antipsychotics

**Atypical antipsychotic drugs such as olanzapine and risperidone have a role to play in treating bipolar disorder.** Their main mechanism of action is a blockade of D2 receptors as well as 5HT-2 receptors. All atypical antipsychotics can treat mania. Some may also be effective in treating bipolar depression.

## Antidepressants

**Antidepressants are to be used with caution in patients with bipolar disorder as they may induce or exacerbate mania.** They may be administered in conjunction with a mood stabilizer.

## Clinical Uses of Antipsychotics

Antipsychotics are used in the treatment of:

- [Schizophrenia](#)
- [Bipolar disorder](#)
- Schizoaffective disorder
- Gilles de la Tourette's syndrome
- Severe anxiety (short term)
- Pain and restlessness for palliative care

Antipsychotics are conventionally used for the management of schizophrenia. Schizophrenia is a **psychotic disorder that affects 1 % of the population, making it the most common psychotic disorder.** It causes **positive symptoms**, such as delusions, hallucinations and thought disorder, and **negative symptoms**, including social withdrawal and a flattened affect.

**Longer-acting depot formulations** of antipsychotic drugs are also available and may be used in cases of patient preference or if compliance is a problem.

It should be noted that not all patients with schizophrenia respond to therapy with antipsychotic agents. In patients who are **resistant to two or more different antipsychotic agents, clozapine is recommended**, given its potency. However, because of its potentially dangerous side effects, including leukopenia, agranulocytosis, and myocarditis, it is usually reserved for resistant cases.

It requires close monitoring when used, with weekly blood tests in the first 6 months of use. About **30 % of patients have treatment-resistant schizophrenia**, which means that they are resistant to all available antipsychotics.

## Drug-Induced Dyskinesia

Motor side effect	Description	Management
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Acute dystonia	Spasms of the facial or neck muscles. Occurs within the first few weeks of commencing an antipsychotic drug. Generally decreases over time.	Improves when the drug is ceased. May be treated with an anticholinergic.
Akathisia	Psychomotor restlessness.	Improves when the drug is ceased. May be treated with an anticholinergic.
Parkinsonianism	Bradykinesia, tremor, rigidity and shuffling gait.	Improves when the drug is ceased. May be treated with an anticholinergic.
Tardive dyskinesia	A serious and potentially disabling condition. Involuntary movements of the face, tongue, trunk, and limbs. This occurs after months or years of starting a first-generation antipsychotic drug, affecting 20–40 % of patients. More common in patients over the age of 50.	It does not improve when the drug is ceased. Usually irreversible.

## References

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