DRUGS THAT ACT IN THE CNS

Antipsychotics 2

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Antipsychotic drugs/ Therapeutic uses

1. Treatment of schizophrenia:

The antipsychotics are considered the only efficacious pharmacological treatment for **schizophrenia**.

The **first-generation** antipsychotics are most effective in treating **positive symptoms** of schizophrenia.

The atypical **antipsychotics** with **5-HT2A receptor–blocking** activity may be effective in many patients who are **resistant to the traditional** agents, especially in treating the **negative symptoms** of schizophrenia.

Antipsychotic drugs/ Therapeutic uses

2. Prevention of nausea and vomiting:

The older antipsychotics (most commonly, **prochlorperazine**) are useful in the treatment of drug-induced nausea.

Antipsychotic drugs/ Therapeutic uses

3. Other uses:

The antipsychotic drugs can be used as **tranquilizers** to manage agitated and disruptive behavior secondary to other disorders.

Chlorpromazine is used to treat **intractable hiccups**.

Pimozide is primarily indicated for treatment of the motor and phonic tics of **Tourette disorder**.

However, risperidone and haloperidol are also commonly prescribed for **this tic disorder**.

Antipsychotic drugs/ Therapeutic uses

3. Other uses:

Also, risperidone and aripiprazole are approved for the management of disruptive behavior and irritability secondary to **autism**.

Many antipsychotic agents are approved for the management of the manic and mixed symptoms associated with **bipolar disorder**.

Lurasidone and quetiapine are indicated for the treatment of **bipolar depression.**

Paliperidone is approved for the treatment of **schizoaffective disorder**.

Some antipsychotics (aripiprazole and quetiapine) are used as adjunctive agents with antidepressants for treatment of **refractory depression**.

DRUG	THERAPEUTIC NOTES
First generation	
Chlorpromazine	Moderate to high potential for EPS; moderate to high potential for weight gain, orthostasis, sedation, anti-muscarinic effects.
Fluphenazine	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.
Haloperidol	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	
Aripiprazole	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.
Asenapine	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.
Clozapine	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.
Olanzapine	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.
Paliperidone	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.
Quetiapine	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.
Risperidone	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.
Ziprasidone	Low potential for extrapyramidal effects; contraindicated in patients with history of cardiac arrhythmias; minimal weight gain. Used in treatment of bipolar depression.

Antipsychotic drugs/ Absorption and metabolism

After **oral** administration, the antipsychotics show variable absorption that is unaffected by food (except for **ziprasidone and paliperidone,** the absorption of which is increased with food).

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

They are metabolized to many different metabolites, usually by the cytochrome P450 system in the liver, particularly the CYP2D6, CYP1A2, and CYP3A4 isoenzymes.

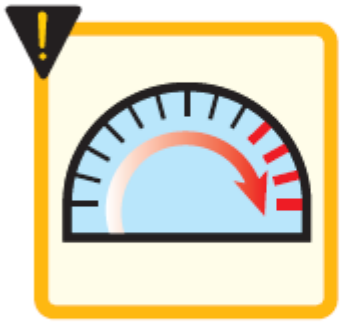
Antipsychotic drugs/ Absorption and metabolism

Some metabolites are active and have been developed as pharmacological agents themselves (for example, paliperidone is the active metabolite of risperidone).

Fluphenazine decanoate, haloperidol decanoate, risperidone microspheres, paliperidone palmitate, aripiprazole monohydrate, and olanzapine pamoate **are long-acting injectable** (LAI) formulations of antipsychotics.

Antipsychotic drugs/ Adverse effects

Urinary retention



Weight Gain

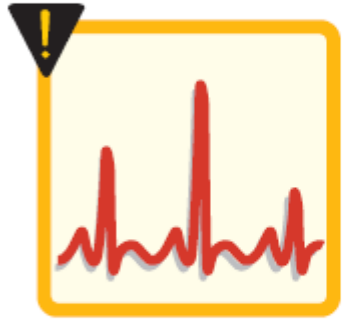
Seizure

Sedation

Extrapyramidal symptoms

Postural hypotension

Sexual dysfunction



Arrhythmias and sudden cardiac death

Dry mouth

Antipsychotic drugs/ Adverse effects

1. Extrapyramidal effects:

The appearance of the movement disorders is generally time and dose dependent, with dystonias occurring within a few **hours to days** of treatment, followed by akathisias occurring within **days to weeks**.

Parkinson-like symptoms of bradykinesia, rigidity, and tremor usually occur within **weeks to months** of initiating treatment.

Tardive dyskinesia, which can be **irreversible**, may occur after **months or years** of treatment.

Antipsychotic drugs/ Adverse effects

1. Extrapyramidal effects:

The therapeutic trade-off is a lower incidence of EPS in exchange for the side effect of muscarinic receptor blockade.

Those antipsychotic drugs that exhibit strong **anticholinergic** activity, such as **thioridazine**, show **fewer extrapyramidal** disturbances, because the cholinergic activity is already strongly dampened.

This contrasts with **haloperidol and fluphenazine**, which have low anticholinergic activity and **produce extrapyramidal** effects more frequently because of the preferential blocking of dopaminergic transmission.

Akathisia may respond better to β blockers (for example, propranolol) or benzodiazepines, rather than anticholinergic medications.

Antipsychotic drugs/ Adverse effects

2. Tardive dyskinesia:

Long-term treatment with antipsychotics can cause this motor disorder.

Patients display involuntary movements, including bilateral and facial jaw movements and “fly-catching” motions of the tongue.

However, in many individuals, tardive dyskinesia is **irreversible** and persists after discontinuation of therapy.

Tardive dyskinesia is postulated to result from **an increased number of dopamine** receptors that are synthesized as a compensatory response to long-term dopamine receptor blockade.

Antipsychotic drugs/ Adverse effects

2. dyskinesia:

This makes the **neuron supersensitive** to the actions of dopamine, and it allows the dopaminergic input to this structure to overpower the cholinergic input, causing excess movement in the patient.

3. Neuroleptic malignant syndrome:

This potentially **fatal reaction** to antipsychotic drugs is characterized by muscle rigidity, fever, altered mental status and stupor, unstable blood pressure, and myoglobinemia.

Treatment necessitates discontinuation of the antipsychotic agent and supportive therapy.

Administration of **dantrolene or bromocriptine** may be helpful.

Antipsychotic drugs/ Adverse effects

4. Other effects:

Drowsiness occurs due to CNS depression and **antihistaminic** effects, usually during the first few weeks of treatment.

Those antipsychotic agents with potent **antimuscarinic** activity often produce dry mouth, urinary retention, constipation, and loss of visual accommodation.

Others may block **α-adrenergic** receptors, resulting in lowered blood pressure and orthostatic hypotension.

The antipsychotics depress the hypothalamus, affecting **thermoregulation** and causing amenorrhea, galactorrhea, gynecomastia, infertility, and erectile dysfunction.

Antipsychotic drugs/ Adverse effects

4. Other effects:

Significant **weight gain** is often a reason for nonadherence.

Glucose and lipid profiles should be monitored in patients taking antipsychotics due to the potential for the **second generation** agents to increase these laboratory parameters and the possible exacerbation of preexisting diabetes or hyperlipidemia.

Some antipsychotics have been associated with mild to significant **QT prolongation**.

Thioridazine has the highest risk, and ziprasidone and iloperidone also have cautions with their use due to this effect.

Antipsychotic drugs/ 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-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.

Antipsychotic drugs/ Maintenance treatment:

Patients who have had **two or more psychotic episodes** secondary to schizophrenia should receive maintenance therapy for at least 5 years, and some experts prefer indefinite therapy.

Low doses of antipsychotic drugs are not as effective as higher-dose maintenance therapy in preventing relapse.

The rate of relapse may be lower with second-generation drugs