- Treatment of Mania and Bipolar Disorder
- Antipsychotic (neuroleptic) drugs

Lecture 5

College of Pharmacy

By:

Assist. Prof. Dr. Rafat Abdulhassan Mohammed Jawad

Treatment of Mania and Bipolar Disorder

A. Lithium

- Lithium salts are **used acutely and prophylactically for managing bipolar patients**.
- It is effective in treating 60% to 80% of patients exhibiting mania and hypomania.
- Although many cellular processes are altered by treatment with lithium, the mode of action is unknown.
- The **therapeutic index of lithium is extremely low**, and lithium can be **toxic.**
- Common adverse effects may include headache, dry mouth, polydipsia, polyuria, polyphagia, GI distress, fine hand tremor, dizziness, fatigue, dermatologic reactions, and sedation.
- Adverse effects due to higher plasma levels may indicate toxicity and include ataxia, slurred speech, coarse tremors, confusion, and convulsions.
- Thyroid function may be decreased and should be monitored.
- Lithium is renally eliminated, and though caution should be used when dosing this drug in renally impaired patients, it may be the best choice in patients with hepatic impairment.

B. Other drugs

Several antiepileptic drugs, including carbamazepine, valproic acid, and lamotrigine are approved as **mood stabilizers** for **bipolar disorder**. Other agents that **may improve manic symptoms** include the older (chlorpromazine and haloperidol) and newer antipsychotics. The atypical antipsychotics risperidone, olanzapine, ziprasidone, aripiprazole, asenapine, cariprazine, and quetiapine are also used for the management of **mania**. Quetiapine, lurasidone, and the combination of olanzapine and fluoxetine have been approved for **bipolar depression**.

Antipsychotic drugs

- The antipsychotic drugs are used primarily to treat **schizophrenia**, but they are **also effective in other psychotic and manic states**.
- The use of antipsychotic medications involves a difficult trade-off between the benefit of alleviating psychotic symptoms and the risk of a wide variety of adverse effects.
- 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.**

FIRST-GENERATION ANTIPSYCHOTIC (low potency)
Chlorpromazine GENERIC ONLY
Thioridazine GENERIC ONLY
FIRST-GENERATION ANTIPSYCHOTIC (high potency)
Fluphenazine GENERIC ONLY
Haloperidol HALDOL
Loxapine GENERIC ONLY
Molindone GENERIC ONLY
Perphenazine GENERIC ONLY
Pimozide ORAP
Prochlorperazine COMPRO, PROCOMP
Thiothixene GENERIC ONLY
Trifluoperazine GENERIC ONLY
SECOND-GENERATION ANTIPSYCHOTIC
Aripiprazole ABILIFY, ARISTADA
Asenapine SAPHRIS
Brexpiprazole REXULTI
Cariprazine VRAYLAR
Clozapine CLOZARIL, FAZACLO
Iloperidone FANAPT
Lurasidone LATUDA
Olanzapine ZYPREXA
Paliperidone INVEGA
Pimavanserin NUPLAZID
Quetiapine SEROQUEL
Risperidone RISPERDAL
Ziprasidone GEODON

- The antipsychotic drugs are usually divided into first- and second-generation agents.
- **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.

A. 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.**
- They 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.

B. 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.**
- 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.
- 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.**

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 (Figure 1).

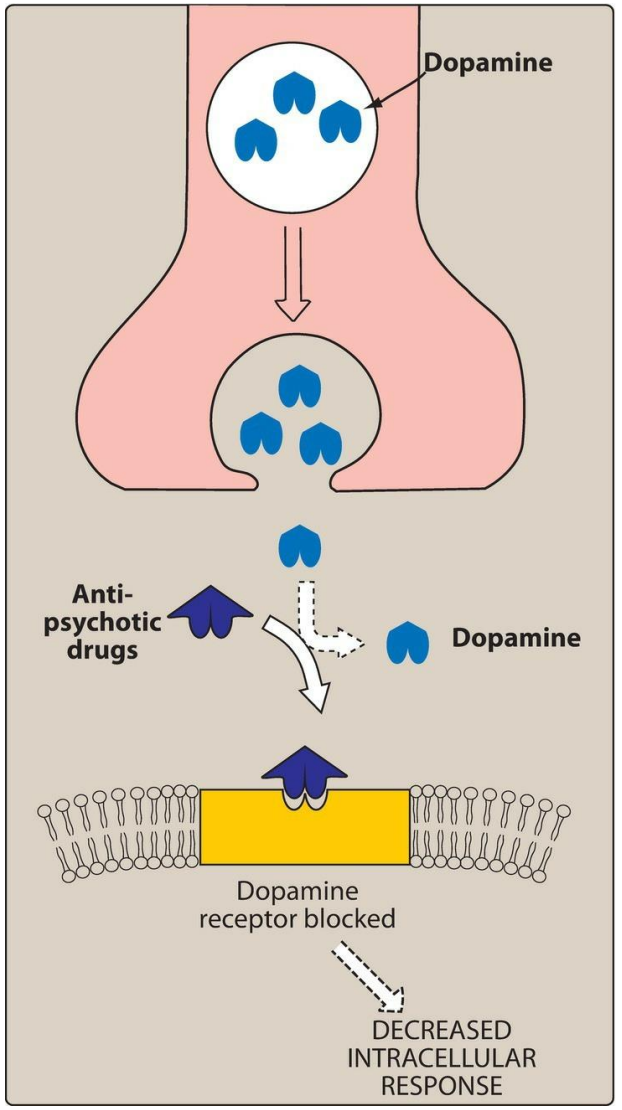


Figure 1: Dopamine-blocking actions of antipsychotic drugs

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-HT2A receptors.

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 (Figure 2). The undesirable adverse effects of antipsychotic drugs often result from pharmacological actions at these other receptors.

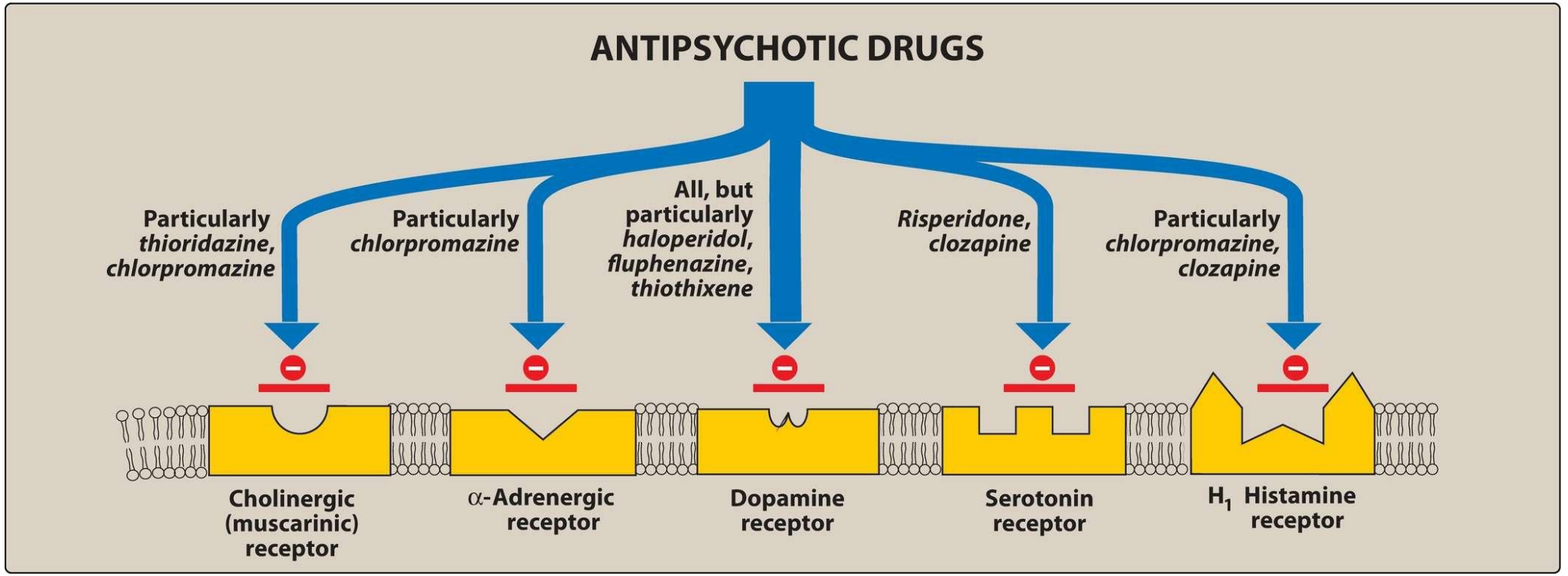


Figure 2: Antipsychotic drugs block dopaminergic and serotonergic receptors as well as adrenergic, cholinergic, and histamine-binding receptors.

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.

Therapeutic uses

1. Treatment of schizophrenia

The antipsychotics are the only efficacious pharmacological treatment for schizophrenia. The first-generation antipsychotics are generally most effective in treating the 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.

2. Prevention of nausea and vomiting

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

3. Other uses

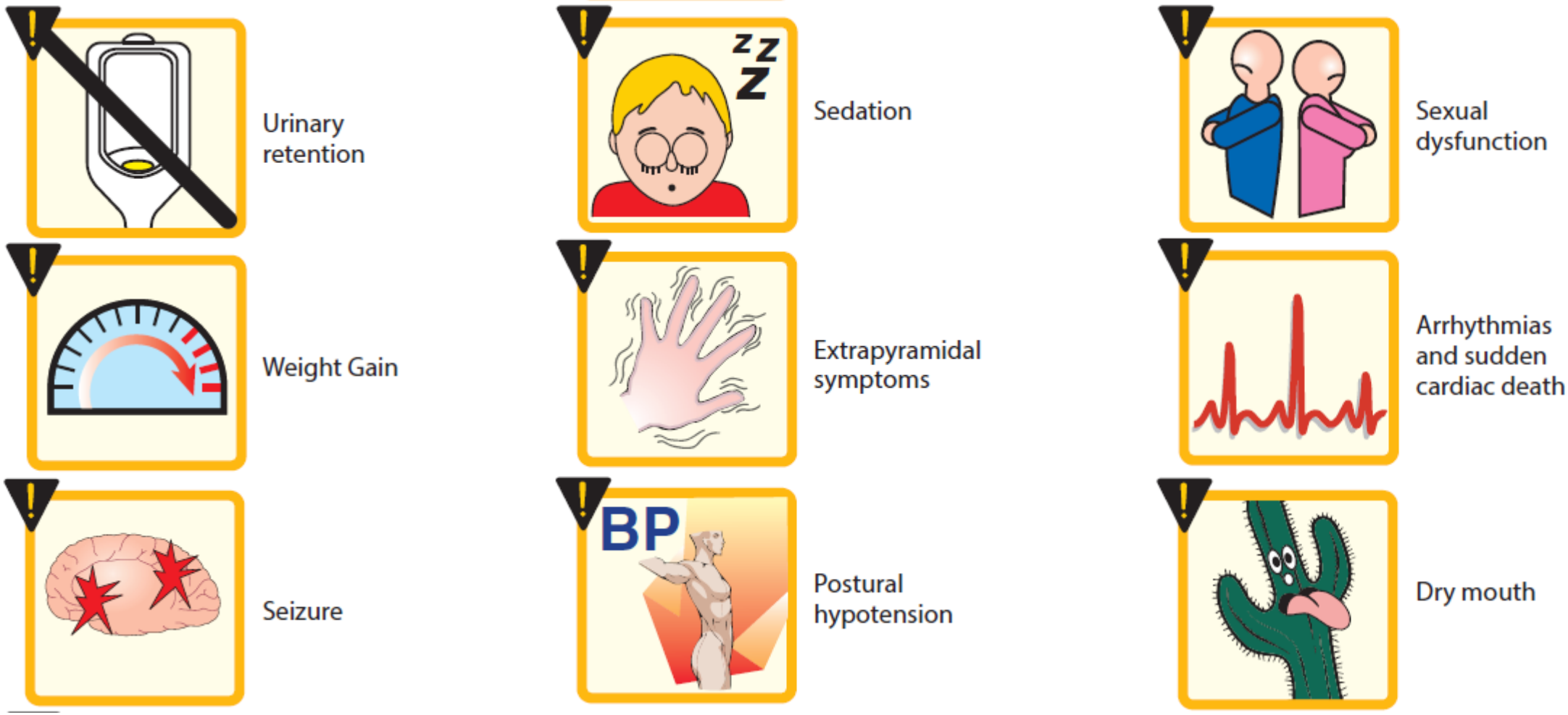
- The antipsychotic drugs can be used as tranquilizers to manage agitated and disruptive behavior secondary to other disorders.
- **Chlorpromazine** is used to treat intractable hiccups.
- **Pimozide** is primarily indicated for treatment of the motor and phonic tics of Tourette disorder.
- However, risperidone and haloperidol are also commonly prescribed for this tic disorder. Also, **risperidone and aripiprazole** are approved for the management of disruptive behavior and irritability secondary to autism.
- **Lurasidone and quetiapine** are indicated for the treatment of bipolar depression.
- **Paliperidone** is approved for the treatment of schizoaffective disorder.
- Some antipsychotics (**aripiprazole, brexpiprazole, and quetiapine**) are used as adjunctive agents with antidepressants for treatment-refractory depression.

Absorption and metabolism

- After oral administration, the antipsychotics show variable absorption that is unaffected by food (except for ziprasidone, lurasidone, 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 P-450 system in the liver, particularly the CYP2D6, CYP1A2, and CYP3A4 isoenzymes. Some metabolites are active and have been developed as pharmacological agents themselves (for example, paliperidone is the active metabolite of risperidone, and the antidepressant amoxapine is the active metabolite of loxapine).
- Fluphenazine decanoate, haloperidol decanoate, risperidone microspheres, paliperidone palmitate, aripiprazole monohydrate, aripiprazole lauroxil, and olanzapine pamoate are **long-acting injectable (LAI) formulations of antipsychotics**.
- These formulations usually have a therapeutic duration of action of 2 to 4 weeks, with some having a duration of 6 to 12 weeks. Therefore, these LAI formulations are often used to treat outpatients and individuals who are nonadherent with oral medications.

Adverse effects

Adverse effects of the antipsychotic drugs can occur in practically all patients and are significant in about 80%.



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**.

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. The rate of relapse may be lower with second-generation drugs (Figure 3).

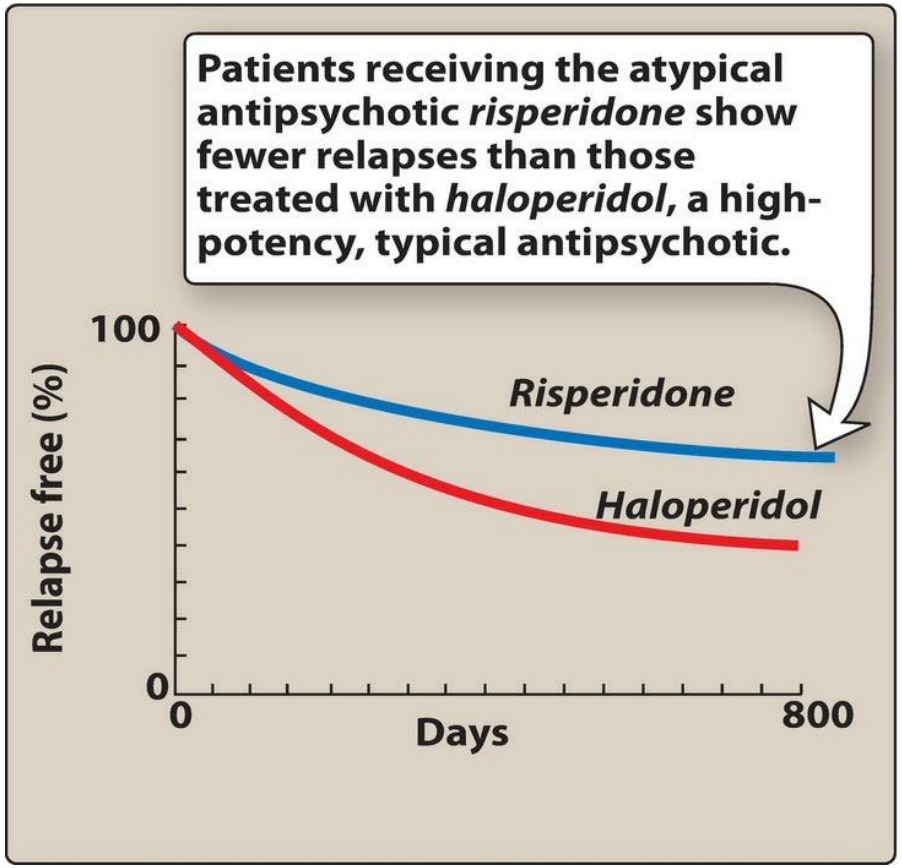


Figure 3: Rates of relapse among patients with schizophrenia after maintenance therapy with either risperidone or haloperidol.

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; two LAI formulations are available.
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.
Brexpiprazole	Low potential for EPS; low potential for weight gain; low potential for sedation; also approved as an adjunctive treatment for partial response or refractory major depression with an antidepressant.
Cariprazine	Low potential for EPS; low potential for weight gain; possible nausea and gastrointestinal distress; also approved for manic/mixed episodes associated with bipolar disorder.
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.
Lurasidone	Low potential for EPS; minimal weight gain; also approved for use in treating depression associated with bipolar disorder; food increases absorption.
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 and as an alternate LAI formulation administered every 12 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.

Figure 4: Summary of antipsychotic agents commonly used to treat schizophrenia. EPS = extrapyramidal effects; LAI = long-acting injectable.


Thank You!