Antipsychotic Drugs

- 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.
- 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 troubling 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.

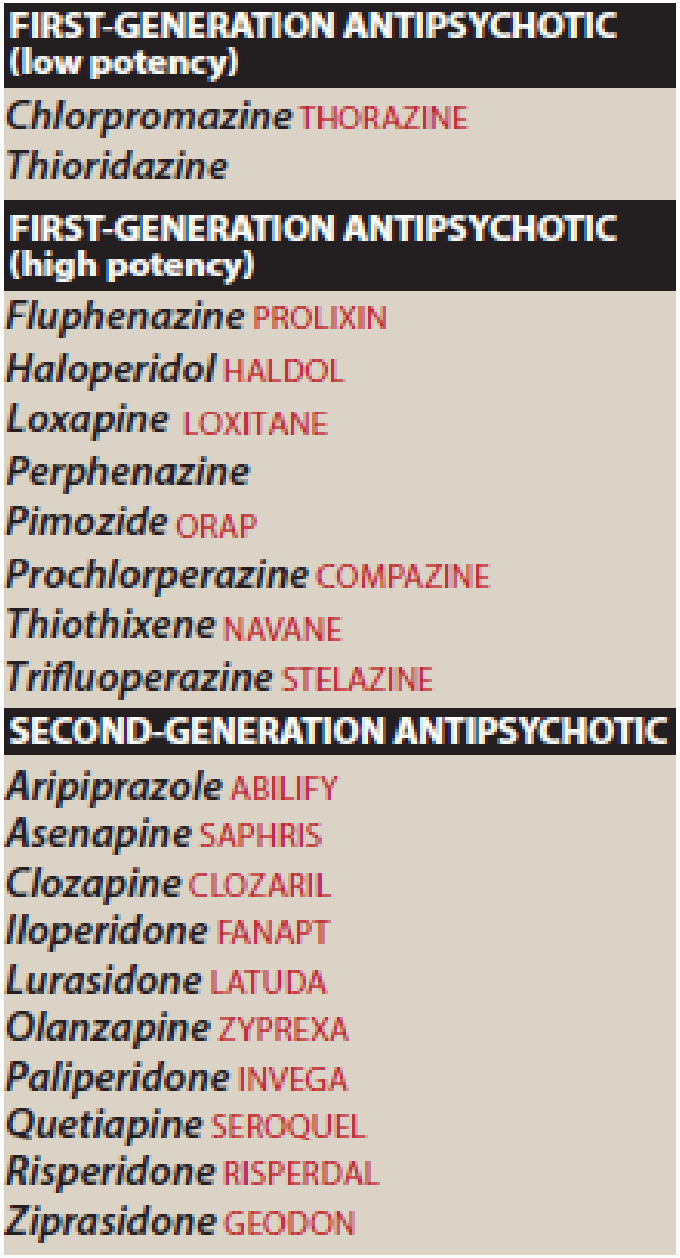

Figure 11.1
Summary of antipsychotic agents.

- 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 and probably reflects some fundamental biochemical abnormality, possibly a dysfunction of the mesolimbic or mesocortical dopaminergic neuronal pathways.

Antipsychotic Drugs

- The antipsychotic drugs are 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, typical, or traditional antipsychotics)** are competitive inhibitors at a variety of receptors, but 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), particularly drugs that bind tightly to **dopaminergic neuroreceptors**, such as **haloperidol** *[HAL-oh-PER-i-dol].*

- Movement disorders are less likely with medications that bind weakly, such as **chlorpromazine** *[klor-PROE-ma-zeen].*
- *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 side effects, such as diabetes, hypercholesterolemia, and weight gain.
- The second- generation drugs appear to owe their unique activity to blockade of both serotonin and dopamine and, perhaps, other 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.
- However, consistent 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 all first- and second generation *antipsychotics.*
- *For these patients,* **clozapine** *[KLOE-za*-peen] 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 (Figure 11.2).
2. **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), particularly 5-HT2A 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 (Figure 11.3). **Risperidone** *[ris-* PEAR-ih-dohn] blocks 5-HT2A receptors to a greater extent than it does D2 receptors, as does **olanzapine** *[oh-LANZ-ah-peen].*

- The second-generation antipsychotic **aripiprazole** *[a-rih-PIP-razole]* is a partial agonist at D2 and 5-HT1A receptors, as well as an antagonist of 5-HT2A receptors. **Quetiapine** *[qwe-TY-uh-peen]* blocks D2 receptors more potently than 5-HT2A receptors but is relatively weak at blocking either receptor.
- Its low risk for EPS may also be related to the relatively short period of time it binds to the D2 receptor.

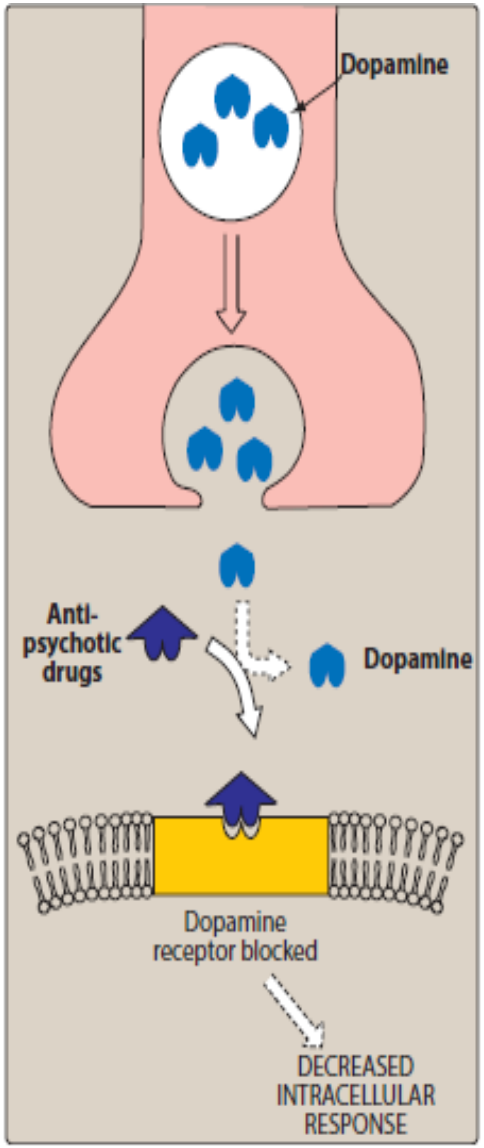

Figure 11.2
Dopamine-blocking actions of antipsychotic drugs.

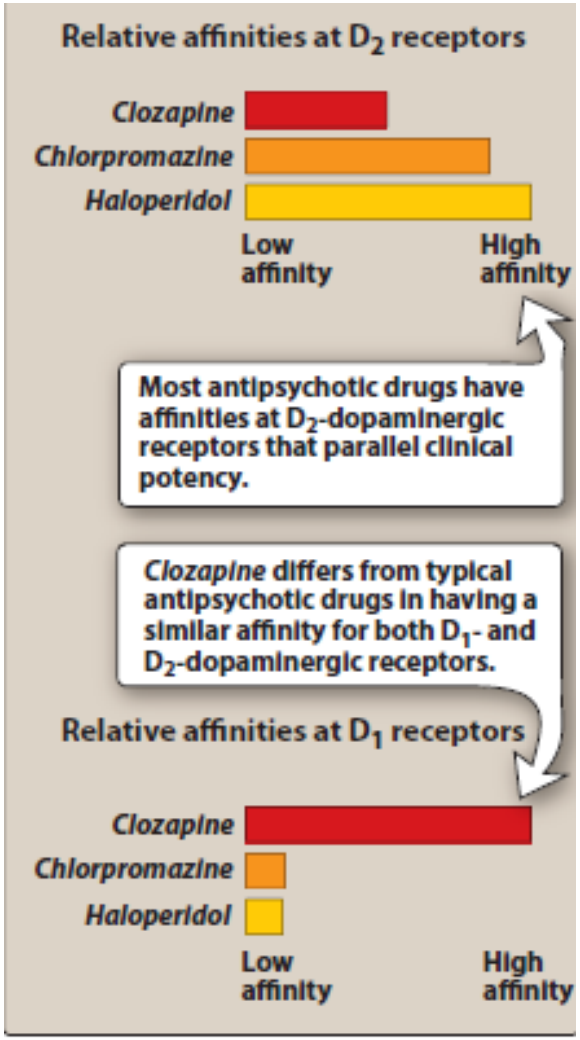

Figure 11.3
Relative affinity of *clozapine*, *chlorpromazine*, and *haloperidol* at D_1 and D_2 dopaminergic receptors.

D. 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 (Figure 11.4).
- It is unknown what role, if any, these actions have in alleviating the symptoms of psychosis.
- However, the undesirable side 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**.**

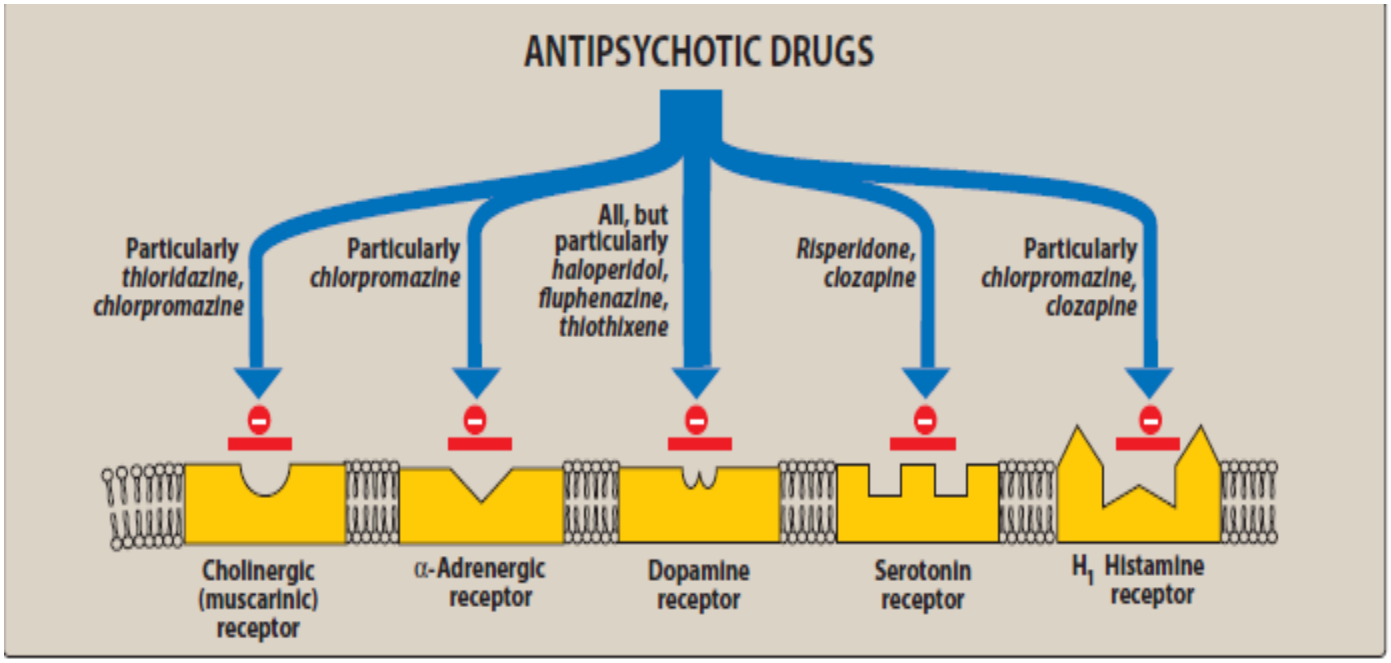

Figure 11.4

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

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 probably causes these unwanted movement symptoms.
- 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,** 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 **block D2 receptors**, leading to 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.

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.

2. **Prevention of nausea and vomiting: The older antipsychotics** (most commonly, **prochlorperazine** *[PROE-clor-PEAR-a-zeen])* 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** *[PIM-oh-zide] is primarily indicated for treatment of the* motor and phonic tics of Tourette disorder.
- **Risperidone** *and* **haloperidol** *are also commonly prescribed for this tic disorder.*

➢ *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** [loo-RAS-i-done] and **quetiapine** *are indicated for the treatment of* bipolar depression.
- **Paliperidone** *[pal-ee-PEAR-i-dohn] 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.

Absorption and metabolism

- After oral administration, the antipsychotics show variable absorption that is unaffected by **food** (except for **ziprasidone** *[zi-PRAS-i-done]* 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.
- 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 ofloxapine).*
- Fluphenazine decanoate, haloperidol decanoate, risperidone microspheres, paliperidone palmitate, aripiprazole monohydrate, and olanzapine pamoate are long-acting injectable (LAI) formulations of antipsychotics.
- These **formulations** have a therapeutic duration of action of up to **2 to 4 weeks** and, therefore, 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% (Figure 11.6).

1. **Extrapyramidal effects:**

- **The inhibitory effects of dopaminergic** neurons are normally balanced by the excitatory actions of cholinergic neurons in the striatum.
- Blocking dopamine receptors alters this balance, causing a relative excess of cholinergic influence, which results in extrapyramidal motor 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.

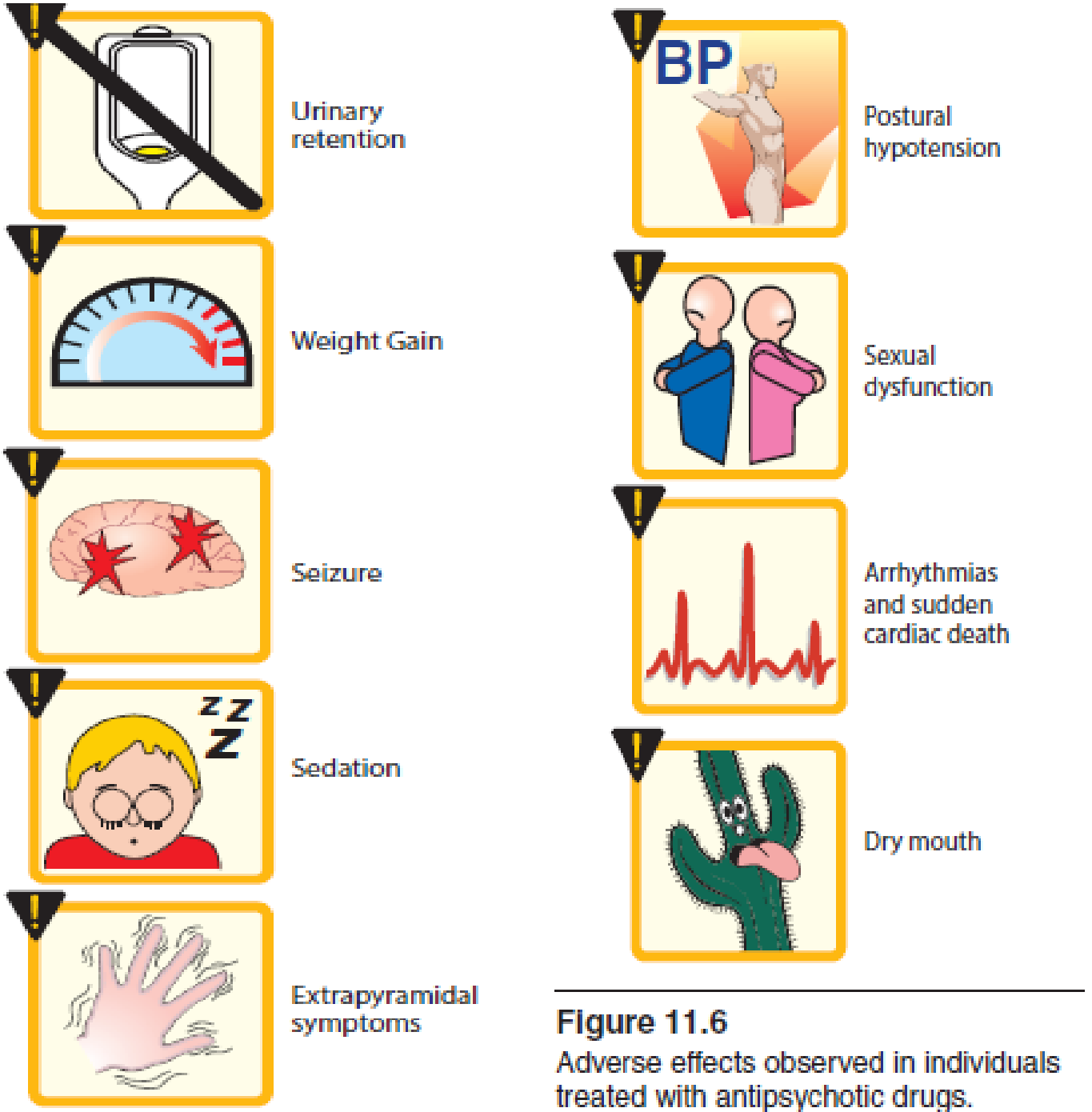

Figure 11.6
Adverse effects observed in individuals treated with antipsychotic drugs.

- If cholinergic activity is also blocked, a new, more nearly normal balance is restored, and extrapyramidal effects are minimized.
- This can be achieved by administration of an **anticholinergic** drug, such as *benztropine.*
- *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 [THYE-oh-RID-azeen],* show fewer extrapyramidal disturbances, because the cholinergic activity is already strongly dampened.
- This contrasts with *haloperidol and fluphenazine [floo-FEN-a-zeen], 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.

✓ **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.
- A prolonged holiday from antipsychotics may cause the symptoms to diminish or disappear within a few months.
- 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.
- 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.
- Traditional anti-EPS medications may actually worsen this condition.

✓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.*

❑ Other effects:

- **Drowsiness occurs due to CNS depression and** antihistaminic effects, usually during the first few weeks of treatment.
- Confusion sometimes results.
- 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.
- 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** *[eye-low-PEAR-ee-dohn] also have* cautions with their use due to this effect.
- Other antipsychotics have a general precaution regarding QT prolongation, even if the risk is relatively low.

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.
- 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.

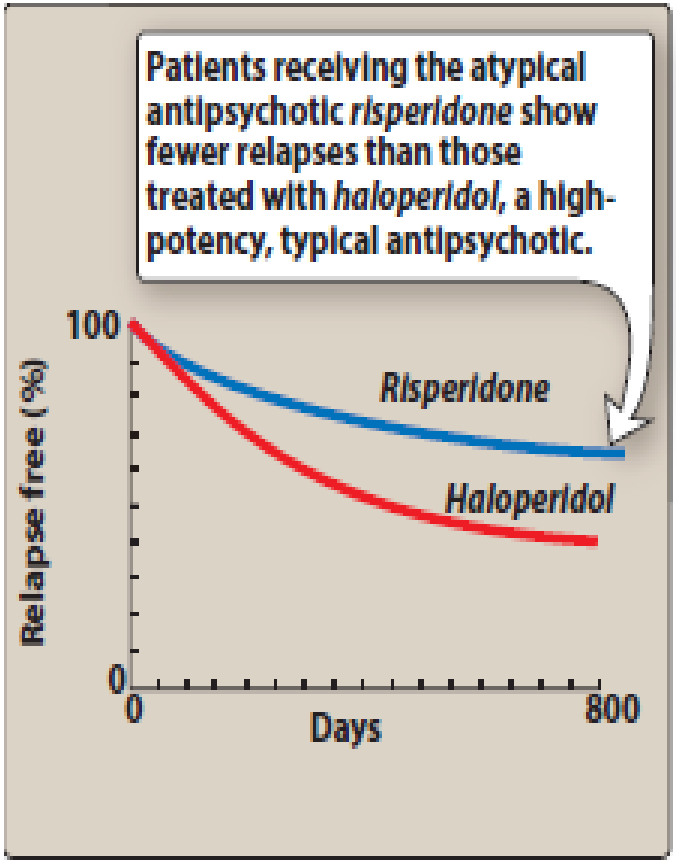

Figure 11.7

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.
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.

Figure 11.8

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