The first-generation antipsychotics represent an older class of antipsychotics that have been the standard for treating psychotic disorders for many decades. These earlier antipsychotics are often called typical or conventional antipsychotics because, when compared with a newer class of second-generation antipsychotics, they lack a wider spectrum of therapeutic activity. Moreover, the conventional antipsychotics are associated with many side effects and lack the tolerability of the newer antipsychotics. Yet for patients in whom conventional antipsychotics are effective and tolerable, these medications continue to have a place in the treatment of mental disorders.

How Antipsychotics Work

The actions of antipsychotic medications may be explained by the dopamine receptor antagonist hypothesis. Dopamine is a neurotransmitter—a chemical produced by brain cells called neurons—that enables neurons to communicate with each other. Dopamine is released by one neuron into the space between that neuron and the next neuron and then binds to specific sites on the other neuron called receptors. The interaction of the neurotransmitter with the receptor results in very specialized activities coded in the neuron, but ultimately, an electrical impulse is generated that is released down the nerve cell. At the end of the nerve, called the nerve terminal, the electrical impulse causes further release of dopamine. This form of communication between brain cells is called neurotransmission. In select areas of the brain, excessive dopamine neurotransmission may produce psychosis. Drugs such as amphetamine and cocaine, for example, are known to increase dopamine release. In excessive amounts, these drugs induce psychotic symptoms not unlike schizophrenia.

Psychotic symptoms commonly seen in schizophrenia and other mental disorders, such as bipolar disorder, dementia, and drug-induced psychosis, include delusions, hallucinations, disorganized speech, and

First-Generation Antipsychotics

- Haldol (haloperidol)
- Loxitane (loxapine)
- Mellaril (thioridazine)
- Navane (thiothixene)
- Orap (pimozide)
- Prolixin (fluphenazine)
- Stelazine (trifluoperazine)
- Thorazine (chlorpromazine)
- Trilafon (perphenazine)
bizarre, agitated, or catatonic behavior. These symptoms are also called the positive symptoms of psychosis because of the excessive and overt nature of their clinical presentation.

Antipsychotics work principally by blocking, or antagonizing, the action of dopamine at its receptors, decreasing the chemical signal that drives psychotic behavior. That is, antipsychotics decrease neurotransmission by blocking dopamine from binding to the receptors. Both conventional and second-generation antipsychotics are dopamine antagonists and are therefore effective in treating the positive symptoms of psychosis. In areas of the brain where antipsychotics have no therapeutic benefits, they may produce side effects.

Common Side Effects

The side effects commonly seen with conventional antipsychotics include sedation, anticholinergic effects, extrapyramidal symptoms (EPS), orthostatic hypotension, weight gain, photosensitivity, and elevated prolactin levels.

Sedation and the feeling of tiredness are common with all antipsychotics, but the low-potency conventional antipsychotics, such as Thorazine (chlorpromazine) and Mellaril (thioridazine), are generally more sedating than the higher-potency agents, such as Haldol (haloperidol) and Prolixin (fluphenazine). Sometimes sedation may be useful to decrease agitation and help the patient sleep, but too often patients experience daytime sedation and fatigue that is not well tolerated.

Extrapyramidal symptoms are neurological disturbances caused by antipsychotics (or a neurological disorder) in the area of the brain that controls motor coordination. High-potency first-generation antipsychotics, such as Haldol (haloperidol) and Prolixin (fluphenazine), are more likely to induce EPS than the lower-potency agents. The antipsychotics can produce symptoms that mimic Parkinson's disease. They cause Parkinson-like symptoms (parkinsonism) that include muscle stiffness, rigidity, tremor, drooling, and a "mask-like" face. However, unlike Parkinson's disease, which is a progressive neurological disease, parkinsonism from antipsychotic medications is reversible. It may be treated, and prevented, by using antiparkinson agents (also called anticholinergic agents), such as Cogentin (benztropine), Benadryl (diphenhydramine), Artane (trihexyphenidyl), and Kemadrin (procyclidine).

Akathisia is another form of EPS characterized as a subjective sense of restlessness accompanied by fidgeting, inability to sit still, nervousness, muscle discomfort, and agitation. Generally, antiparkinson agents are not effective in managing akathisia. Use of Inderal (propranolol), a beta-blocker, may be helpful.

Dystonia is a type of EPS with acute onset. It is manifested by a sudden spasm of muscles involving the tongue, jaw, and neck. This is not an allergic reaction to the antipsychotic medication. Although a dystonic reaction may be painful and frightening, it can be rapidly reversed with an intramuscular injection of an anticholinergic medication, such as Cogentin or Benadryl. With a dystonic reaction, the patient should seek immediate medical attention and receive treatment.

Elevation of prolactin levels is common with conventional antipsychotics. Prolactin is a hormone produced in the area of the brain called the pituitary gland. It is normally elevated in women following childbirth, stimulating lactation, or milk production. The elevation of prolactin caused by antipsychotic medications may cause breast enlargement and milk production (galactorrhea) in both women and men. Elevated prolactin is also associated with impotence in men and irregular or absence of menstruation in women. When side effects from elevated prolactin levels affect the patient, the alternative is to switch to one of the second-generation antipsychotic agents, which do not elevate prolactin.

Weight gain is a frequent side effect of all antipsychotic medications. Certain antipsychotics are associated with greater weight gain than others. It is unclear whether this is due to an underlying metabolic change caused by the antipsychotic or to increased appetite. Weight should be monitored closely during therapy, and if weight gain occurs, an intervention program of diet and exercise should be started.

When antipsychotics interfere with the action of cholinergic neurons in the nervous system, they produce bothersome anticholinergic side effects. When an organ system is affected by cholinergic inhibition, it causes side effects particular to that organ. For example, when the gastrointestinal tract is affected, dry mouth,
cramping, and constipation result. Other anticholinergic side effects include blurred vision (when muscles of the eyes are affected) and difficulty urinating (when the bladder is affected). The low-potency first-generation antipsychotics have more anticholinergic activity than the high-potency agents. When antipsychotics are combined with other medications with significant anticholinergic activity, such as tricyclic antidepressants and antiparkinson agents, the anticholinergic action of the medications are additive. Seniors and individuals with a medical condition may be especially sensitive to anticholinergic side effects. Excessive anticholinergic activity may induce delirium, a toxic reaction that impairs consciousness, causes confusion, and makes it difficult for the person to sustain their attention.

Antipsychotic medications may block a compensatory response—the narrowing of blood vessels—that counterbalances postural change, resulting in a momentary drop in blood pressure when the person rises too rapidly, which may cause dizziness and lightheadedness. This reaction is known as **orthostatic hypotension**. Patients, especially seniors and those taking antihypertensive medications, need to be cautious and rise slowly to allow their body to adjust to the change in position, avoiding a sudden drop in their blood pressure.

### Adverse Reactions and Precautions

Adverse reactions may be defined as those reactions from the medication that are usually rare but may have serious consequences. Some medications may enhance ultraviolet light absorption—a reaction known as **photosensitivity**—in the skin. The conventional antipsychotics, such as Thorazine, Prolixin, Stelazine, Trilafon, Serentil, and Mellaril, are notorious for inducing photosensitivity. Patients taking these medications should use sunscreen and protective clothing to prevent sunburn. In addition, all antipsychotics are associated with neuroleptic malignant syndrome (NMS), heatstroke, tardive dyskinesia (TD), seizures, and arrhythmias.

#### Neuroleptic Malignant Syndrome

**Neuroleptic malignant syndrome** is a rare, toxic reaction to all antipsychotics. The symptoms are severe muscle stiffness, rigidity, elevated body temperature, increased heart rate and blood pressure, irregular pulse, and sweating. NMS may lead to delirium and coma. It can be fatal if medical intervention is not immediately provided. There is no test to predict whether an individual may develop NMS when exposed to an antipsychotic. Thus NMS must be recognized early because it is a medical emergency that requires immediate discontinuation of the antipsychotic, hospitalization, and intensive medical treatment.

#### Heatstroke

Antipsychotics may disrupt the area of the brain that regulates temperature, and individuals taking antipsychotics may be especially sensitive to heat. Their body temperature may rise to dangerous levels when they are exposed to hot weather, resulting in a condition commonly known as **heatstroke**. Conventional antipsychotics appear to have a higher occurrence of causing heat-regulating disturbances. Individuals taking antipsychotics must take precautions to protect themselves from prolonged exposure to hot, humid weather.

#### Tardive Dyskinesia

**Tardive dyskinesia** is a potential adverse reaction from antipsychotic medications. It is a late-onset abnormal involuntary movement disorder. It is a potentially irreversible condition with symptoms that commonly include “pill-rolling” movements of the fingers, darting and writhing movements of the tongue, lip puckering, facial grimacing, and other irregular movements. The risk of TD is increased the longer the person has been taking the antipsychotic, and this risk also increases with age.
With several decades of experience, scientists now have a better understanding of the relative risk of TD with conventional antipsychotics than with the second-generation antipsychotics. However, because the second-generation antipsychotics have a very low incidence of EPS, these newer antipsychotics may also have very low risk of inducing TD. For example, the oldest second-generation antipsychotic, Clozaril, rarely causes TD according to more than 30 years of clinical experience. When early signs of TD are detected in the patient taking a conventional antipsychotic, an option is to switch to a second-generation antipsychotic, which may reverse the symptoms or decrease any further progression of TD.

Seizures

Antipsychotics can lower the seizure threshold and induce seizures in susceptible individuals, especially in those with a history of seizure disorder. Of the conventional antipsychotics, Loxitane (loxapine) and Thorazine (chlorpromazine) have a higher incidence of seizures than other conventional agents. Patients with a seizure disorder who are receiving anticonvulsants often receive antipsychotics without any increase in seizures.

Arrhythmia

Antipsychotics may slow electrical conduction in heart tissues (myocardium). Some patients taking antipsychotics show on their electrocardiogram (ECG) a prolongation of the electrical impulse as it travels in the myocardium. This abnormal ECG finding, called QTc prolongation, may signal a potential for developing an irregular heartbeat (arrhythmia). Mellaril (thioridazine) and Orap (pimozide) are associated with a greater tendency to alter the electrical impulse, and therefore these antipsychotics have a higher risk of causing arrhythmias, especially in individuals with cardiac disease. Patients who have a history of arrhythmia should have an ECG before starting an antipsychotic and periodically during treatment.