**PERSPECTIVE**

The first antipsychotic, chlorpromazine, was used for the treatment of psychosis in France in 1951 and in the United States in 1954. Antipsychotic use has expanded significantly since then. The historic term *neuroleptic*, used with antipsychotic medication, is no longer appropriate because newer agents cause less sedation. The term *antipsychotic* is now preferred. In 2009, U.S. poison control centers reported more than 4700 exposures to phenothiazines and 43,000 exposures to atypical antipsychotics, resulting in 0 and 8 deaths, respectively.1

**PRINCIPLES OF DISEASE**

Antipsychotic medications are used to treat agitation and psychosis caused by schizophrenia, mania, acute idiopathic psychosis, substance-induced psychosis, and dementia. The antipsychotic medications are divided into three broad categories on the basis of their receptor profiles, clinical effects, and adverse effects (Table 161-1). All antipsychotic medications effectively treat the *positive symptoms* of psychotic disorders; they reduce hallucinations, control agitation, and aid in restructuring of disordered thinking. In general, the low-potency first-generation antipsychotics (FGAs) are the most sedating. Movement disorders, including extrapyramidal symptoms (EPS) and tardive dyskinesia (TD), are significant problems with both low-potency and high-potency FGAs. In addition to producing less sedation and fewer movement disorders, the atypical or second-generation antipsychotics (SGAs) assist with the *negative symptoms* of psychotic disorders, such as flat affect, avolition, social withdrawal, and impoverished thought and speech.2 Although neuroleptic malignant syndrome (NMS) occurs with all agents, it occurs least with SGAs.

**Anatomy and Physiology**

Antipsychotic drugs block dopamine receptors in several areas of the brain, including the cerebral cortex, basal ganglia, limbic system, hypothalamus, and chemoreceptor trigger zone. All antipsychotic agents reduce the positive symptoms of schizophrenia by blocking the dopamine D2 receptor subtype in the mesolimbic region of the brain. However, blockade of D2 receptors in the nigrostriatal brain region produces undesired EPS. In addition, blockade of D2 receptors in the mesocortical brain region impairs cognition and worsens the negative symptoms of schizophrenia. SGAs block both D2 and serotonin 5-HT2A receptors. Because these agents have lower affinity for dopamine receptor antagonism and more selective binding of D2 receptors in the mesolimbic versus nigrostriatal areas of the brain, SGAs should have a lower rate of EPS and TD. The serotonin receptor antagonism is thought to reduce EPS effects and to improve the negative symptoms of schizophrenia.3,4 However, studies have found no significant difference in reported rates of EPS and TD between perphenazine (a FGA) and several SGAs.5,6 Antipsychotic medications also block other receptor types (see Table 161-1).

Some antipsychotic medications have additional clinical uses. The antiemetic effect of prochlorperazine, promethazine, and droperidol is from blockade of dopamine receptors in the chemoreceptor trigger zone of the medulla. Hydroxyzine controls itching caused by blockade histamine (H1) receptors. Prochlorperazine and droperidol abort migraine headaches by preventing dopamine-mediated meningeal artery vasodilation. Chlorpromazine can treat severe hiccups, and haloperidol is the drug of choice for certain movement disorders, including Tourette’s syndrome and Huntington’s chorea.

**Pathophysiology**

EPS can be immediate or delayed after initiation of drug therapy. The acute EPS include dystonia, akathisia, and parkinsonism, which are caused by blockade of nigrostriatal D2 receptors and reduced by blockade of muscarinic receptors. The propensity for antipsychotics to produce EPS is inversely proportional to the agents’ muscarinic receptor antagonism.7 The delayed-onset syndromes, including TD and tardive dystonia, develop after prolonged use of antipsychotic medications and are thought to occur from chronic dopamine receptor blockade in the nigrostriatal area leading to D2 receptor upregulation and hypersensitivity to dopamine.8,9 The pathophysiologic mechanism of NMS, an idiosyncratic reaction to antipsychotic medication, is unknown but thought to be neuroregulatory dysfunction secondary to D2 receptor blockade in the nigrostriatum and hypothalamus, leading to rigidity and hyperthermia, respectively.10 NMS is not associated with ryanodine receptor (RYR) gene mutations, which are associated with malignant hyperthermia.

Antipsychotic medications produce cardiovascular side effects, most commonly orthostatic hypotension with reflexive tachycardia due to alpha-adrenergic blockade. Many agents cause conduction delays, predominantly QT prolongation, resulting in prolonged repolarization and potentially torsades de pointes (TdP).11 The degree of prolongation varies between antipsychotic agents, increasing with dose and with concomitant use of other drugs that prolong the QT interval.12,13 The phenothiazines, particularly thioridazine and mesoridazine, have the greatest risk of cardiac toxicity. QT prolongation has also been reported with the butyrophenones haloperidol and droperidol.12,14 The atypical antipsychotics produce less cardiotoxicity than the traditional agents do, although most can cause repolarization abnormalities in therapeutic doses and overdose.12,15,16 Ultimately, a correlation
between QT prolongation and dysrhythmias or TdP has not been established, but antipsychotics are associated with an increased risk of sudden death, particularly with heart disease and in elderly patients. However, psychotic disorders themselves are associated with an increased risk of sudden death.

Clozapine produces agranulocytosis in 1 or 2% of treated patients; however, this has been reduced to 0.4% after strict adherence to labeling requirements. Although the mechanism of agranulocytosis is unknown, research supports an immunogenic cause and direct cytotoxic effect on human bone marrow mesenchymal stromal cells. Seizure rarely occurs with antipsychotic drugs, but clozapine has the highest seizure incidence. Drug dosing and the patient’s seizure risk profile influence seizure susceptibility. FGAs and SGAs have been associated with weight gain, glycermic dysregulation, and dyslipidemia. The cause is not fully understood but partly blamed on the pharmacodynamic profile of these agents.

**CLINICAL FEATURES**

**Acute Overdose**

In overdose, antipsychotic medications produce signs and symptoms that are exaggerations of the clinical effects. Most patients will have symptoms within a few hours. Central nervous system (CNS) depression is universally present, ranging from mild sedation and confusion to coma and loss of brainstem reflexes. Airway reflexes can be impaired. Respiratory depression can occur after a massive overdose with profound CNS depression. Pupils can be of any size. Mild orthostatic hypotension is a common finding from alpha-adrenergic blockade. Overdose with low-potency FGAs can cause an anticholinergic delirium. EPS have been reported with the FGAs and SGAs.

Atypical antipsychotic overdose is similar to that of traditional antipsychotics. Overdoses are characterized by CNS depression and tachycardia. Miosis may be present, potentially mimicking opioid toxicity. Extremity twitching is common. With the exception of clozapine, seizures rarely occur in overdose. Acute EPS have been reported, especially for risperidone overdose.

**Acute Extrapyramidal Syndromes**

_Acute dystonia_ is manifested as intermittent, involuntary motor tics or spasms of antagonistic muscle groups that most often involve the facial, neck, back, or limb muscles. This results in trismus, facial grimacing, dysarthria, tongue and lip distortion, torticollis, or oculogyric crisis. Dystonic reactions usually develop within the first several doses of treatment or after a large increase in dosage. _Laryngeal dystonia_ is a rare but life-threatening form of dystonia that is manifested as stridor, difficulty in breathing, or choking sensation. Increased risk of death due to choking has been documented in schizophrenic patients.

_Akathisia_ is a subjective feeling of restlessness associated with objective motor restlessness, including repetitive foot shuffling, truncal rocking, or pacing. The subjective distress may precipitate aggressive behavior. Akathisia usually develops within the first few days of treatment, but 40% of patients given 10 mg of intravenous prochlorperazine developed akathisia within 1 hour.

_A parkinsonian syndrome_ of bradykinesia, masked facies, shuffling gait, muscle rigidity, and resting tremor frequently develops during the first month of treatment; 90% of cases occur within 3 months of treatment. _Perioral tremor_ (rabbit syndrome), in which
Tardive Dyskinesia

TD is a chronic movement disorder induced by prolonged use of antipsychotic medication. Typical signs of TD include quick, involuntary movements of the face (blinking, grimaces, tongue movements, and chewing), extremities, or trunk. Twenty percent of patients treated with long-term traditional antipsychotics are affected. TD is difficult to treat and is frequently permanent. Anticholinergic agents may worsen TD; reduction of the antipsychotic dose or a change to an alternative agent should be considered. TD improves in some patients switched to clozapine; amantadine improved symptoms compared with placebo in a small study. Respiratory dyskinesia, a variant of TD, is characterized by oro-facial dyskinesia, dyspnea, dysphonia, and respiratory alkalosis. This chronic disorder often goes undiagnosed and can cause repeated bouts of aspiration pneumonia.

Neuroleptic Malignant Syndrome

NMS is a serious idiosyncratic drug reaction that typically develops during the first month of therapy but has occurred during stable drug regimens. Risk factors include rapid drug loading, high dosage, high-potency antipsychotics, parenteral formulations, dehydration, preceding psychomotor agitation, and previous episodes of NMS. Other medications may contribute to NMS, including lithium, which inhibits dopamine secretion, as can withdrawal from dopaminergic agents used to treat Parkinson’s disease. The incidence of NMS in patients treated with antipsychotics is approximately 0.02%. Atypical antipsychotic agents, including clozapine, risperidone, olanzapine, quetiapine, ziprasidone, amisulpride, and aripiprazole, have been associated with NMS.

Table 161-2 lists the diagnostic criteria for NMS. Other features of NMS may include salorrhea, dysartria, dysphagia, metabolic acidosis, liver function elevations, sodium imbalance, dehydration, elevations in serum catecholamines, coagulopathy, generalized slowing on the electroencephalogram, pulmonary embolism, and renal failure. Atypical presentations may lack full diagnostic criteria for NMS.

Most patients have the cardinal features of altered mental status, muscle rigidity, hyperthermia, and autonomic nervous system instability during several hours to days. However, the signs of NMS may develop gradually and in any order. Agitation, often mistaken for worsening psychosis, may occur first. Physicians should consider discontinuation of antipsychotic drugs in a patient who has one or more of the major manifestations of NMS. Most episodes resolve within 2 weeks after cessation of the offending medication, but some cases last several months.

Cardiovascular Toxicity and Dysrhythmias

The most common cardiac effect is sinus tachycardia with a normal QRS duration. If QRS prolongation is present, another drug effect should be suspected. QT prolongation occurs during therapeutic dosing of many antipsychotic agents. Therapeutic doses of thioridazine, followed by ziprasidone, prolong the QT interval more than risperidone, olanzapine, quetiapine, or haloperidol does. QT prolongation associated with TdP is a well-described adverse effect of thioridazine, mesoridazine, droperidol, sertindole, and haloperidol. Among FGAs, thioridazine carries the greatest risk of cardiotoxicity. Among SGA overdoses, whereas ziprasidone carries the greatest risk of QTc prolongation, TdP has been reported with amisulpride overdose. QT prolongation should be considered a “class effect” of all antipsychotic medications.

Agranulocytosis

Clozapine produces agranulocytosis; 75% of occurrences develop within the first 18 weeks after initiation of therapy, peaking at 3 months. The concomitant use of other bone marrow-suppressing agents (e.g., carbamazepine) should be avoided. Clozapine administration must be halted if the total white blood cell count falls below 3000 cells/mL or if the absolute neutrophil count is less than 1500 cells/mL. Agranulocytosis has not been reported after an acute overdose. Olanzapine, whose chemical structure is similar to that of clozapine, has also been associated with neutropenia and agranulocytosis, but all patients recovered after discontinuation of olanzapine.

Seizures

Antipsychotic medications can lower the seizure threshold and induce epileptiform electroencephalographic abnormalities in many asymptomatic patients. However, antipsychotic-induced seizures are rare except for clozapine, which causes a dose-related increase in risk of seizures (approximately 5% at high doses). Antipsychotics can be prescribed for patients with known seizure disorder.

Differential Considerations

Differential considerations include a broad list of agents and clinical conditions that produce altered mental status, orthostatic hypotension, anticholinergic syndrome, seizure, QT prolongation, or TdP. Although the signs of NMS are similar, serotonin syndrome is more likely to have clonus, heatstroke is evident from the circumstances, and the causes of these conditions are quite different. Malignant hyperthermia should be considered in patients receiving inhalational anesthetics or succinylcholine.
Table 161-3 Differential Diagnosis of Neuroleptic Malignant Syndrome

<table>
<thead>
<tr>
<th>DISEASE*</th>
<th>PATHOLOGIC MECHANISM</th>
<th>DIFFERENTIATING FACTOR</th>
<th>TIME COURSE</th>
<th>TREATMENT</th>
</tr>
</thead>
</table>
| Neuroleptic malignant syndrome | Impaired thermoregulation in hypothalamus and basal ganglia due to relative lack of dopamine activity | Antipsychotic medication use, muscle rigidity (diagnostic criteria in Table 161-2) | Gradual, progresses during several days | Stop offending medication  
Hydration  
Active cooling  
Intravenous benzodiazepines to relax muscles and control agitation  
Neuromuscular blockade (nondepolarizing agents)  
Controversial: Bromocriptine or amantadine  
Dantrolene |
| Serotonin syndrome | Excess serotonin and dopamine levels in central nervous system | Medications (usually a combination) that increase serotonin levels (e.g., SSRIs, MAOIs, dextromethorphan, lithium, meperidine, tramadol, tryptophan); muscle rigidity | Usually rapid after introduction of new medication or increase in dose; can be gradual | Stop offending medication  
Hydration  
Active cooling  
Cyproheptadine |
| Heatstroke | Environmental heat stress | Environmental exposure history; muscle rigidity rare | Rapid or gradual | Hydration |
| Malignant hyperthermia | Genetic instability of sarcoplasmic reticulum, causing massive calcium release after administration of triggering medication | Occurs after administration of inhalational anesthetic or succinylcholine; muscle rigidity | Sudden, provoked by administration of anesthetic | Stop anesthetic  
Hydration  
Active cooling  
Dantrolene |

MAOIs, monoamine oxidase inhibitors; SSRIs, selective serotonin reuptake inhibitors.
*Other clinical entities to consider in the diagnosis of these conditions include Addison’s syndrome, central nervous system infection, delirium tremens, hypocalcemia, hypoglycemia, hyponatremia, intracranial hemorrhage, lethal catatonia, poisoning (e.g., amphetamines, anticholinergics, cocaine, nicotine, salicylates, sympathomimetics, strychnine, theophylline), sedative-hypnotic drug withdrawal, sepsis, status epilepticus (including nonconvulsive status), tetanus, thalamic infarct, thyroid storm, and psychotic agitation.

**DIAGNOSTIC STRATEGIES**

Blood levels are neither readily available nor helpful. As with any patient who presents with altered mental status, vital signs, blood glucose concentration, and pulse oximetry are indicated.

An electrocardiogram should be obtained in patients with significant antipsychotic overdose and in symptomatic patients taking thioridazine, mesoridazine, droperidol, or sertindole. Patients receiving high-dose intravenous haloperidol or droperidol for sedation may need rhythm monitoring, and if QT prolongation is present, serum potassium, calcium, and magnesium levels should be measured.

Patients who have NMS, parkinsonism with marked muscle rigidity, or prolonged seizures are at risk for rhabdomyolysis and should have serum creatine kinase, renal function, and urine myoglobin measured. Patients taking clozapine or olanzapine who present with infection or fever should be checked for leukopenia. Olanzapine and clozapine have been associated with new-onset diabetes with ketoacidosis.1

Other testing, such as brain computed tomography, lumbar puncture, serum acetylcholinesterase level, and electrolyte measurements, may be helpful in some cases but are not indicated when the context and presentation support antipsychotic toxicity as the cause.

**MANAGEMENT**

**Acute Overdose**

Treatment is supportive; there is no specific antidote. Endotracheal intubation may be required to prevent aspiration or, less often, to support respiration. Hypotension is generally mild and responds to intravenous crystalloids. An alpha-adrenergic pressor such as norepinephrine may be used if needed. If sedation and miosis suggest opioid intoxication, a trial of naloxone is warranted. Phystostigmine and flumazenil are not indicated and may precipitate seizures.

Activated charcoal has no proven benefit and may increase the morbidity of the overdose if it is administered to a patient with altered mental status at risk for aspiration.

**Acute Extrapyramidal Syndromes**

Dystonia will usually respond within 30 minutes to diphenhydramine 25 to 50 mg intravenously, intramuscularly, or orally or benzotropine 1 to 2 mg intramuscularly or orally. Benzodiazepines may also be effective. If relief is not achieved, an alternative diagnosis should be sought. Akathisia is treated similarly or with a lipophilic beta-adrenergic blocker (e.g., propranolol). Treatment of parkinsonism syndrome may include anticholinergic agents. Patients with EPS who respond to diphenhydramine or benzotropine should continue therapy for at least 48 hours to prevent recurrence.2,50 In addition, patients should be referred to their treating physician, who may reduce the antipsychotic dose or change to an alternative agent as necessary. Benztropine, diphenhydramine, and the older antipsychotic medications cause anticholinergic effects, so combination therapy may worsen dry mouth, blurred vision, and urinary retention.

**QT Prolongation and Torsades de Pointes**

Correction of hypokalemia, hypomagnesemia, and hypocalcemia shortens the QT interval. Treatment of TdP includes intravenous magnesium sulfate, overdrive pacing, and possibly isoproterenol.
Antiarrhythmic drugs that prolong the QT interval should be avoided.

**Neuroleptic Malignant Syndrome**

Treatment of NMS consists of supportive care and discontinuation of the offending medication. Agitation, psychomotor hyperactivity, and muscle rigidity should be treated with liberal doses of intravenous benzodiazepines. Lorazepam can be administered intravenously, 1 or 2 mg every 3 minutes, until muscle rigidity improves. Refractory cases or cases at risk for aspiration can be managed with rapid sequence intubation and neuromuscular blockade with a nondepolarizing agent (e.g., rocuronium and vecuronium). Hyperthermia should be managed with intravenous fluids and active external cooling with mist and fans. If rhabdomyolysis is present, intravenous hydration and urinary alkalinization are used to prevent renal damage.

Bromocriptine and amantadine have been suggested for treatment of NMS but do not consistently show a benefit. Bromocriptine is administered orally or by nasogastric tube, beginning with 5 mg every 8 hours and titrated to a maximum of 20 mg per dose. The dose of amantadine for NMS is 200 mg orally every 12 hours. Response to therapy requires at least 24 hours. Dantrolene, which inhibits the release of calcium from the sarcoplasmic reticulum, has no proven benefit. Because the muscle rigidity of NMS is thought to be from dopamine blockade in the CNS rather than a muscle abnormality, dantrolene offers no advantage over benzodiazepines and neuromuscular blockade.

**DISPOSITION**

Patients with NMS and overdose patients with hypotension, coma, TdP, or airway compromise should be admitted, usually to a critical care unit. Patients with a prolonged QT interval (QTc > 460 milliseconds) or symptomatic ingestions of thioridazine or mesoridazine should have at least 12 hours of cardiac monitoring. Patients with minimal signs of toxicity should be observed in the emergency department for a minimum of 4 hours from the time of ingestion, with hospitalization for persistent or worsening signs and symptoms. Criteria for hospital discharge include return to normal mental status and resolution of any vital sign, metabolic, and electrocardiographic abnormalities. Psychiatric consultation may be necessary to assess the risk of suicide.

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**KEY CONCEPTS**

- Extrapyramidal movement disorders are a common complication of antipsychotic medications and are treated with benztrtopine, diphenhydramine, and benzodiazepines.
- The most common finding in antipsychotic overdose is central nervous system depression. Treatment centers on supportive care, airway control, and cardiac monitoring.
- QT prolongation and torsades de pointes are potential complications of many antipsychotic medications in overdose and can occur with therapeutic doses of some agents.
- The neuroleptic malignant syndrome is characterized by altered mental status, hyperthermia, muscle rigidity, and autonomic instability. Supportive care includes airway management, benzodiazepines, neuromuscular blockade, and active cooling.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.
References