17 - 29.17 Dopamine Receptor Antagonists (First Ge

29.17 Dopamine Receptor Antagonists (First-Generation Antipsychotics)

schizophrenia. Br J Psychiatry. 2013;202(2):91–93. Tejeda HA, Shippenberg TS, Henriksson R. The dynorphin/κ-opioid receptor system and its role in psychiatric disorders. Cell Mol Life Sci. 2012;69(6):857–896. Wright JM, Dobosiewicz MR, Clarke PB. The role of dopaminergic transmission through D1-like and D2-like receptors in amphetamine-induced rat ultrasonic vocalizations. Psychopharmacology. 2013;225(4):853–868. 29.17 Dopamine Receptor Antagonists (First-Generation Antipsychotics) The dopamine receptor antagonists (DRAs) represent the first group of effective agents for schizophrenia and other psychotic illnesses. The first of these drugs, the phenothiazine chlorpromazine (Thorazine), was introduced in the early 1950s. Other DRAs include all of the antipsychotics in the following groups: phenothiazines, butyrophenones, thioxanthenes, dibenzoxazepines, dihydroindoles, and diphenylbutylpiperidines. Because these agents are associated with extrapyramidal syndromes (EPSs) at clinically effective dosages, newer antipsychotic drugs—the serotonin–dopamine antagonists (SDAs)—have gradually replaced the older agents in the United States. The SDAs are differentiated from earlier drugs by their lower liability to cause extrapyramidal side effects. These newer drugs have other liabilities, most notably a propensity to cause weight gain, lipid elevations, and diabetes. Therefore, a reason to still consider use of the DRAs is their lower risk of causing significant metabolic abnormalities. Intermediate-potency DRAs, such as perphenazine (Trilafon), have been shown to be as effective and well tolerated as the SDAs. Manufacturing of molindone (Moban), the DRA with the lowest risk of weight gain and metabolic side effects, was discontinued in the United States. PHARMACOLOGICAL ACTIONS All of the DRAs are well absorbed after oral administration, with liquid preparations being absorbed more efficiently than tablets or capsules. Peak plasma

concentrations are usually reached 1 to 4 hours after oral administration and 30 to 60 minutes after parenteral administration. Smoking, coffee, antacids, and food interfere with absorption of these drugs. Steady-state levels are reached in approximately 3 to 5 days. The halflives of these drugs are approximately 24 hours. All can be given in one daily oral dose, if tolerated, after the patient is in a stable condition. Most DRAs are highly protein bound. Parenteral formulation of the DRAs results in a more rapid and more reliable onset of action. Bioavailability is also up to tenfold higher with parenteral administration. Most DRAs are metabolized by cytochrome P450 (CYP) CYP2D6 and 3A isozymes. However, there are differences among the specific agents. Long-acting depot parenteral formulations of haloperidol (Haldol, Decanoate) and fluphenazine are available in the United States. These agents are usually administered once every 1 to 4 weeks, depending on the dose and the patient. It can take up to 6 months of treatment with depot formulations to reach steady-state plasma levels,

indicating that oral therapy should be continued during the first month or so of depot antipsychotic treatment. Antipsychotic activity derives from inhibition of dopaminergic neurotransmission. The DRAs are effective when approximately 72% of dopamine D2 receptors in the brain are occupied. The DRAs also block noradrenergic, cholinergic, and histaminergic receptors, with different drugs having different effects on these receptor systems. Some generalizations can be made about the DRAs based on their potency. Potency refers to the amount of drug that is required to achieve therapeutic effects. Low-potency drugs such as chlorpromazine and thioridazine (Mellaril), given in doses of several 100 mg per day, typically produce more weight gain and sedation than high-potency agents such as haloperidol and fluphenazine, usually given in doses of less than 10 mg per day. High-potency agents are also more likely to cause EPS. Some factors influencing the pharmacological actions of DRAs are listed in Table 29.17-1. Table 29.17-1 Factors Influencing the Pharmacokinetics of Antipsychotics THERAPEUTIC INDICATIONS Many types of psychiatric and neurological disorders may benefit from treatment with DRAs. Some of these indications are shown in Table 29.17-2. Table 29.17-2 Indications for Dopamine Receptor Antagonists

Schizophrenia and Schizoaffective Disorder The DRAs are effective in both the short-term and long-term management of schizophrenia and schizoaffective disorder. They both reduce acute symptoms and prevent future exacerbations. These agents produce their most dramatic effects against the positive symptoms of schizophrenia (e.g., hallucinations, delusions, and agitation). Negative symptoms (e.g., emotional withdrawal and ambivalence) are less likely to improve significantly, and they may appear to worsen, because these drugs produce constriction of facial expression and akinesia, side effects that mimic negative symptoms. Schizophrenia and schizoaffective disorder are characterized by remission and relapse. DRAs decrease the risk of reemergence of psychosis in patients who have recovered while on medication. After a first episode of psychosis, patients should be maintained on medication for 1 to 2 years; after multiple episodes, for 2 to 5 years. Mania DRAs are effective for treating psychotic symptoms of acute mania. Because antimanic agents (e.g., lithium) generally have a slower onset of action than do antipsychotics in the treatment of acute symptoms, it is standard practice to initially combine either a DRA or an SDA with lithium (Eskalith), divalproex (Depakote), lamotrigine (Lamictal), or carbamazepine (Tegretol) and then to gradually withdraw the antipsychotic. Depression with Psychotic Symptoms Combination treatment with an antipsychotic and an antidepressant is one of the treatments of choice for major depressive disorder with psychotic features; the other is electroconvulsive therapy (ECT). Delusional Disorder Patients with delusional disorder often

respond favorably to treatment with these drugs. Some persons with borderline personality disorder who may develop paranoid thinking

in the course of their disorder may respond to antipsychotic drugs. Severe Agitation and Violent Behavior Severely agitated and violent patients, regardless of diagnosis, may be treated with DRAs. Symptoms such as extreme irritability, lack of impulse control, severe hostility, gross hyperactivity, and agitation respond to short-term treatment with these drugs. Children with mental disabilities, especially those with profound mental retardation and autistic disorder, often have associated episodes of violence, aggression, and agitation that respond to treatment with antipsychotic drugs; however, the repeated administration of antipsychotics to control disruptive behavior in children is controversial. Tourette's Disorder DRAs are used to treat Tourette's disorder, a neurobehavioral disorder marked by motor and vocal tics. Haloperidol and pimozide (Orap) are the drugs most frequently used, but other DRAs are also effective. Some clinicians prefer to use clonidine (Catapres) for this disorder because of its lower risk of neurological side effects. Borderline Personality Disorder Patients with borderline personality disorder who experience transient psychotic symptoms, such as perceptual disturbances, suspiciousness, ideas of reference, and aggression, may need to be treated with a DRA. This disorder is also associated with mood instability, so patients should be evaluated for possible treatment with moodstabilizing agents. Dementia and Delirium About two thirds of agitated, elderly patients with various forms of dementia improve when given a DRA. Low doses of high-potency drugs (e.g., 0.5 to 1 mg a day of haloperidol) are recommended. DRAs are also used to treat psychotic symptoms and agitation associated with delirium. The cause of the delirium needs to be determined because toxic deliriums caused by anticholinergic agents can be exacerbated by lowpotency DRAs, which often have significant antimuscarinic activity. Orthostasis, parkinsonism, and worsened cognition are the most problematic side effects in this elderly population. Substance-induced Psychotic Disorder Intoxication with cocaine, amphetamines, alcohol, phencyclidine, or other drugs can cause psychotic symptoms. Because these symptoms tend to be time limited, it is preferable to avoid use of a DRA unless the patient is severely agitated and aggressive. Usually, benzodiazepines can be used to calm the patient. Benzodiazepines should be

used instead of DRAs in cases of phencyclidine intoxication. When a patient is experiencing hallucinations or delusions as a result of alcohol withdrawal, DRAs may increase the risk of seizure. Childhood Schizophrenia Children with schizophrenia benefit from treatment with antipsychotic medication, although considerably less research has been devoted to this population. Studies are currently under way to determine if intervention with medication at the very earliest signs of disturbance in children genetically at risk for schizophrenia can prevent the emergence of more florid symptoms. Careful consideration needs to be given to side effects, especially those involving cognition and alertness. Other Psychiatric and Nonpsychiatric Indications The DRAs reduce the chorea in the early stages of Huntington's disease. Patients with this disease may develop hallucinations, delusions, mania, or hypomania. These and other psychiatric symptoms respond to DRAs. High-potency DRAs should be used. However, clinicians should be aware that patients with the rigid form of this disorder may experience acute EPS. The use of DRAs to treat impulse control disorders should be reserved for patients in whom other interventions have failed. Patients with pervasive developmental disorder may exhibit hyperactivity, screaming, and agitation with combativeness. Some of these symptoms respond to high-potency DRAs, but there is little research evidence supporting benefits in these patients. The rare neurological disorders ballismus and

hemiballismus (which affect only one side of the body), characterized by propulsive movements of the limbs away from the body, also respond to treatment with antipsychotic agents. Other miscellaneous indications for the use of DRAs include the treatment of nausea, emesis, intractable hiccups, and pruritus. Endocrine disorders and temporal lobe epilepsy may be associated with psychosis that responds to antipsychotic treatment. The most common side effects of DRAs are neurological. As a rule, low-potency drugs cause most nonneurological adverse effects, and the high-potency drugs cause most neurological adverse effects. PRECAUTIONS AND ADVERSE REACTIONS Table 29.17-3 summarizes the most common adverse events associated with the use of DRAs. Table 29.17-3 Dopamine Receptor Antagonists: Potency and Adverse Effects

Neuroleptic Malignant Syndrome A potentially fatal side effect of DRA treatment, neuroleptic malignant syndrome, can occur at any time during the course of DRA treatment. Symptoms include extreme hyperthermia, severe muscular rigidity and dystonia, akinesia, mutism, confusion, agitation, and increased pulse rate and blood pressure. Laboratory findings include increased white blood cell (WBC) count, and levels of creatinine phosphokinase, liver enzymes, plasma myoglobin, and myoglobinuria, occasionally associated with renal failure. The symptoms usually evolve over 24 to 72 hours, and the untreated syndrome lasts 10 to 14 days. The diagnosis is often missed in the early stages, and the withdrawal or agitation may mistakenly be considered to reflect increased psychosis. Men are affected more frequently than are women, and young persons are affected more commonly than are elderly persons. The mortality rate can reach 20 to 30 percent, or even higher when depot medications are involved. Rates are also increased when high doses of high-potency agents are used. If neuroleptic malignant syndrome is suspected, the DRA should be stopped immediately and the following done: medical support to cool the person; monitoring of vital signs, electrolytes, fluid balance, and renal output; and symptomatic treatment of fever. Antiparkinsonian medications may reduce some of the muscle rigidity. Dantrolene (Dantrium), a skeletal muscle relaxant (0.8 to 2.5 mg/kg every 6 hours, up to a total dosage of 10 mg a day) may be useful in the treatment of this disorder. When the person can take oral medications, dantrolene can be given in doses of 100 to 200 mg a day. Bromocriptine (20 to 30 mg a day in four divided doses) or amantadine can be added to the regimen. Treatment should usually be continued for 5 to 10 days. When drug treatment is restarted, the clinician should consider switching to a low-potency drug or an SDA, although these agents—including clozapine—may also cause neuroleptic malignant syndrome.

Seizure Threshold DRAs may lower the seizure threshold. Chlorpromazine, thioridazine, and other lowpotency drugs are thought to be more epileptogenic than are high-potency drugs. The risk of inducing a seizure by drug administration warrants consideration when the person already has a seizure disorder or brain lesion. Sedation Blockade of histamine H1 receptors is the usual cause of sedation associated with DRAs. Chlorpromazine is the most sedating typical antipsychotic. The relative sedative properties of the drugs are summarized in Table 29.17-3. Giving the entire daily dose at bedtime usually eliminates any problems from sedation, and tolerance for this adverse effect often develops. Central Anticholinergic Effects The symptoms of central anticholinergic activity include severe agitation; disorientation to time, person, and place; hallucinations; seizures; high fever; and dilated pupils. Stupor and coma may ensue. The treatment of anticholinergic toxicity consists of discontinuing the causal agent or agents, close medical supervision, and physostigmine (Antilirium, Eserine), 2 mg by slow intravenous (IV) infusion, repeated within 1 hour as necessary. Too much physostigmine is dangerous, and symptoms of physostigmine toxicity

include hypersalivation and sweating. Atropine sulfate (0.5 mg) can reverse the effects of physostigmine toxicity. Cardiac Effects The DRAs decrease cardiac contractility, disrupt enzyme contractility in cardiac cells, increase circulating levels of catecholamines, and prolong atrial and ventricular conduction time and refractory periods. Low-potency DRAs, particularly the phenothiazines, are usually more cardiotoxic than are high-potency drugs. One exception is haloperidol, which has been linked to abnormal heart rhythm, ventricular arrhythmias, torsades de pointes, and sudden death when injected IV. Pimozide, sulpiride, and droperidol (a butyrophenone) also prolong the QTc interval and have clearly been associated with torsades de pointes and sudden death. In one study, thioridazine was responsible for 28 (61 percent) of the 46 sudden antipsychotic deaths. In 15 of these cases, it was the only drug ingested. Chlorpromazine also causes prolongation of the QT and PR intervals, blunting of the T waves, and depression of the ST segment. These drugs are thus indicated only when other agents have been ineffective. Sudden Death Occasional reports of sudden cardiac death during treatment with DRAs may be the

result of cardiac arrhythmias. Other causes may include seizure, asphyxiation, malignant hyperthermia, heat stroke, and neuroleptic malignant syndrome. However, there does not appear to be an overall increase in the incidence of sudden death linked to the use of antipsychotics. Orthostatic (Postural) Hypotension Orthostatic (postural) hypotension is most common with low-potency drugs, particularly chlorpromazine, thioridazine, and chlorprothixene. When using intramuscular (IM) lowpotency DRAs, the clinician should measure the patient’s blood pressure (lying and standing) before and after the first dose and during the first few days of treatment. Orthostatic hypotension is mediated by adrenergic blockade and occurs most frequently during the first few days of treatment. Tolerance often develops for this side effect, which is why initial dosing of these drugs is lower than the usual therapeutic dose. Fainting or falls, although uncommon, may lead to injury. Patients should be warned of this side effect and instructed to rise slowly after sitting and reclining. Patients should avoid all caffeine and alcohol; should drink at least 2 L of fluid a day; and if not under treatment for hypertension, should add liberal amounts of salt to their diet. Support hose may help some persons. Hypotension can usually be managed by having patients lie down with their feet higher than their heads and pump their legs as if bicycling. Volume expansion or vasopressor agents, such as norepinephrine (Levophed), may be indicated in severe cases. Because hypotension is produced by α-adrenergic blockade, the drugs also block the α-adrenergic stimulating properties of epinephrine, leaving the β-adrenergic stimulating effects untouched. Therefore, the administration of epinephrine results in a paradoxical worsening of hypotension and is contraindicated in cases of antipsychoticinduced hypotension. Pure α-adrenergic pressor agents, such as metaraminol (Aramine) and norepinephrine, are the drugs of choice in the treatment of the disorder. Hematologic Effects Temporary leukopenia with a WBC count of about 3,500 is a common but not serious problem. Agranulocytosis, a life-threatening hematologic problem, occurs in about 1 in 10,000 persons treated with DRAs. Thrombocytopenic or nonthrombocytopenic purpura, hemolytic anemias, and pancytopenia may occur rarely in persons treated with DRAs. Although routine complete blood counts (CBCs) are not indicated, if a person reports a sore throat and fever, a CBC should be done immediately to check for the possibility of a serious blood dyscrasia. If blood index values are low, administration of DRAs should be stopped, and the patient should be transferred to a medical facility. The mortality rate for the complication may be as high as 30 percent. Peripheral Anticholinergic Effects Peripheral anticholinergic effects, consisting of dry mouth and nose, blurred vision,

constipation, urinary retention, and mydriasis, are common, especially with lowpotency DRAs, for example, chlorpromazine, thioridazine, mesoridazine (Serentil). Some persons may also have nausea and vomiting. Constipation should be treated with the usual laxative preparations, but severe constipation can progress to paralytic ileus. A decrease in the DRA dosage is warranted in such cases. Pilocarpine (Salagen) may be used to treat paralytic ileus, although the relief is only transitory. Bethanechol (Urecholine) (20 to 40 mg a day) may be useful in some persons with urinary retention. Weight gain is associated with increased mortality and morbidity and with medication noncompliance. Low-potency DRAs may cause significant weight gain but not as much as is seen with the SDAs olanzapine (Zyprexa) and clozapine (Clozaril). Molindone and perhaps loxapine (Loxitane) appear to be least likely to cause weight gain. Endocrine Effects Blockade of the dopamine receptors in the tuberoinfundibular tract results in the increased secretion of prolactin, which can result in breast enlargement, galactorrhea, amenorrhea, and inhibited orgasm in women and impotence in men. The SDAs, with the exception of risperidone (Risperdal), are not particularly associated with an increase in prolactin levels and may be the drugs of choice for persons experiencing disturbing side effects from increased prolactin release. Sexual Adverse Effects Both men and women taking DRAs can experience anorgasmia and decreased libido. Up to 50 percent of men who take antipsychotics report ejaculatory and erectile disturbances. Sildenafil (Viagra), vardenafil (Levitra), and tadalafil (Cialis) are often used to treat psychotropic-induced orgasmic dysfunction, but they have not been studied in combination with the DRAs. Thioridazine is particularly associated with decreased libido and retrograde ejaculation in men. Priapism and reports of painful orgasms have also been described, both possibly resulting from α1-adrenergic antagonist activity. Skin and Eye Effects Allergic dermatitis and photosensitivity may occur, especially with low-potency agents. Urticarial, maculopapular, petechial, and edematous eruptions may occur early in treatment, generally in the first few weeks, and remit spontaneously. A photosensitivity reaction that resembles a severe sunburn also occurs in some persons taking chlorpromazine. Persons should be warned of this adverse effect, should spend no more than 30 to 60 minutes in the sun, and should use sunscreens. Long-term chlorpromazine use is associated with blue-gray discoloration of skin areas exposed to sunlight. The skin changes often begin with a tan or golden brown color and progress to such colors as slate gray, metallic blue, and purple. These discolorations resolve when the patient is switched to another medication.

Irreversible retinal pigmentation is associated with the use of thioridazine at dosages above 1,000 mg a day. An early symptom of the side effect can sometimes be nocturnal confusion related to difficulty with night vision. The pigmentation can progress even after thioridazine administration is stopped, finally resulting in blindness. It is for this reason that the maximum recommended dosage of thioridazine is 800 mg per day. Patients taking chlorpromazine may develop a relatively benign pigmentation of the eyes, characterized by whitish brown granular deposits concentrated in the anterior lens and posterior cornea and visible only by slit-lens examination. The deposits can progress to opaque white and yellow-brown granules, often stellate. Occasionally, the conjunctiva is discolored by a brown pigment. No retinal damage is seen, and vision is almost never impaired. This condition gradually resolves when chlorpromazine is discontinued. Jaundice Elevations of liver enzymes during treatment with a DRA tend to be transient and not clinically significant. When chlorpromazine first came into use, cases of obstructive or cholestatic jaundice were reported, usually in the first month of treatment and heralded by symptoms of upper abdominal pain, nausea, and vomiting. This was followed by fever; rash; eosinophilia; bilirubin in the urine; and increases in levels of serum bilirubin, alkaline phosphatase, and hepatic transaminases. Reported

cases are now extremely rare, but if jaundice occurs, the medication should be discontinued. Overdoses Overdoses typically consist of exaggerated DRA side effects. Symptoms and signs include central nervous system (CNS) depression, EPS, mydriasis, rigidity, restlessness, decreased deep tendon reflexes, tachycardia, and hypotension. The severe symptoms of overdose include delirium, coma, respiratory depression, and seizures. Haloperidol may be among the safest typical antipsychotics in overdose. After an overdose, electroencephalography (EEG) shows diffuse slowing and low voltage. Extreme overdose may lead to delirium and coma, with respiratory depression and hypotension. Lifethreatening overdose usually involves ingestion of other CNS depressants, such as alcohol or benzodiazepines. Activated charcoal, if possible, and gastric lavage should be administered if the overdose is recent. Emetics are not indicated because the antiemetic actions of the DRAs inhibit their efficacy. Seizures can be treated with IV diazepam (Valium) or phenytoin (Dilantin). Hypotension can be treated with either norepinephrine or dopamine but not epinephrine. Pregnancy and Lactation There is a low correlation between the use of antipsychotics during pregnancy and congenital malformations. Nevertheless, antipsychotics should be avoided during

pregnancy, particularly in the first trimester unless the benefit outweighs the risk. Highpotency drugs are preferable to low-potency drugs because the low-potency drugs are associated with hypotension. DRAs are secreted in the breast milk, although concentrations are low. Women taking these agents should be advised against breastfeeding. DRUG INTERACTIONS Many pharmacokinetic and pharmacodynamic drug interactions are associated with these drugs (Table 29.17-4). CYP2D6 is the most common hepatic isozyme involved in DRA pharmacokinetic interactions. Other common drug interactions affect the absorption of the DRAs. Table 29.17-4 Antipsychotic Drug Interactions

Antacids, activated charcoal, cholestyramine (Questran), kaolin, pectin, and cimetidine (Tagamet) taken within 2 hours of antipsychotic administration can reduce the absorption of these drugs. Anticholinergics may decrease the absorption of the DRAs. The additive anticholinergic activity of the DRAs, anticholinergics, and tricyclic drugs may result in anticholinergic toxicity. Digoxin (Lanoxin) and steroids, both of which decrease gastric motility, can increase DRA absorption. Phenothiazines, especially thioridazine, may decrease the metabolism of and cause toxic concentrations of phenytoin. Barbiturates may increase the metabolism of DRAs. Tricyclic drugs and selective serotonin reuptake inhibitors (SSRIs) that inhibit CYP2D6 —paroxetine (Paxil), fluoxetine (Prozac), and fluvoxamine (Luvox)—interact with

DRAs, resulting in increased plasma concentrations of both drugs. The anticholinergic, sedative, and hypotensive effects of the drugs may also be additive. Typical antipsychotics may inhibit the hypotensive effects of α-methyldopa (Aldomet). Conversely, typical antipsychotics may have an additive effect on some hypotensive drugs. Antipsychotic drugs have a variable effect on the hypotensive effects of clonidine. Propranolol (Inderal) coadministration increases the blood concentrations of both drugs. The DRAs potentiate the CNS-depressant effects of the sedatives, antihistamines, opiates, opioids, and alcohol, particularly in persons with impaired respiratory status. When these agents are taken with alcohol, the risk for heat stroke may be increased. Cigarette smoking may decrease the plasma levels of the typical antipsychotic drugs. Epinephrine has a paradoxical hypotensive effect in persons taking typical antipsychotics. These drugs may decrease the blood concentration of warfarin (Coumadin), resulting in decreased bleeding time. The phenothiazines, thioridazine, and pimozide should not be coadministered with other agents

that prolong the QT interval. Thioridazine is contraindicated in patients taking drugs that inhibit the CYP2D6 isoenzyme or in patients with reduced levels of CYP2D6. LABORATORY INTERFERENCES Chlorpromazine and perphenazine (Trilafon) may cause both false-positive and falsenegative results in immunological pregnancy tests and falsely elevated bilirubin (with reagent test strips) and urobilinogen (with Ehrlich's reagent test) values. These drugs have also been associated with an abnormal shift in results of the glucose tolerance test, although that shift may reflect the effects of the drugs on the glucose-regulating system. Phenothiazines have been reported to interfere with the measurement of 17-ketosteroids and 17-hydroxycorticosteroids and to produce false-positive results in tests for phenylketonuria. DOSAGE AND CLINICAL GUIDELINES Contraindications to the use of DRAs include the following: (1) a history of a serious allergic response; (2) the possible ingestion of a substance that will interact with the antipsychotic to induce CNS depression (e.g., alcohol, opioids, barbiturates, and benzodiazepines) or anticholinergic delirium (e.g., scopolamine and possibly phencyclidine [PCP]); (3) the presence of a severe cardiac abnormality; (4) a high risk for seizures; (5) the presence of narrow-angle glaucoma or prostatic hypertrophy if a drug with high anticholinergic activity is to be used; and (6) the presence or a history of tardive dyskinesia. Antipsychotics should be administered with caution in persons with hepatic disease, because impaired hepatic metabolism may result in high plasma concentrations. The usual assessment should include a CBC with WBC indexes, liver function tests, and electrocardiography (ECG), especially in women older than 40 years of age and men older than 30 years of age. Elderly persons and children are more sensitive to side effects than are young adults, so the dosage of the drug should be adjusted accordingly.

Various patients may respond to widely different dosages of antipsychotics; therefore, there is no set dosage for any given antipsychotic drug. Because of side effects, it is reasonable clinical practice to begin at a low dosage and increase as necessary. It is important to remember that the maximal effects of a particular dosage may not be evident for 4 to 6 weeks. Available preparations and dosages of the DRAs are given in Table 29.17-5. Table 29.17-5 Dopamine Receptor Antagonists Short-term Treatment The equivalent of 5 to 20 mg of haloperidol is a reasonable dose for an adult in an acute state. An elderly person may benefit from as little as 1 mg of haloperidol. The administration of more than 25 mg of chlorpromazine in one injection may result in serious hypotension. IM administration results in peak plasma levels in about 30 minutes versus 90 minutes using the oral route. Doses of drugs for IM administration are about half those given by the oral route. In a short-term treatment setting, the person should be observed for 1 hour after the first dose of medication. After that time, most clinicians administer a second dose or a sedative agent (e.g., a benzodiazepine) to achieve effective behavioral control. Possible sedatives include lorazepam (Ativan) (2 mg IM) and amobarbital (50 to 250 mg IM).

Rapid Neuroleptization Rapid neuroleptization (also called psychotolysis) is the practice of administering hourly IM doses of antipsychotic medications until marked sedation is achieved. However, several research studies have shown that merely waiting several more hours after one dose yields the same clinical improvement as is seen with repeated doses. Nevertheless, clinicians must be careful to keep patients from becoming violent while they are psychotic. Clinicians can help prevent violent episodes by using adjuvant sedatives or by temporarily using physical restraints until the persons can control their behavior. Early Treatment A full 6 weeks may be necessary to evaluate the extent of the improvement in psychotic symptoms. However, agitation and excitement usually improve quickly with antipsychotic treatment. About 75 percent of persons

with a short history of illness show significant improvement in their psychosis. Psychotic symptoms, both positive and negative, usually continue to improve 3 to 12 months after the initiation of treatment. About 5 mg of haloperidol or 300 mg of chlorpromazine is a usual effective daily dose. In the past, much higher doses were used, but evidence suggests that it resulted in more side effects without additional benefits. A single daily dose is usually given at bedtime to help induce sleep and to reduce the incidence of adverse effects. However, bedtime dosing for elderly persons may increase their risk of falling if they get out of bed during the night. The sedative effects of typical antipsychotics last only a few hours, in contrast to the antipsychotic effects, which last for 1 to 3 days. Intermittent Medications It is common clinical practice to order medications to be given intermittently as needed (PRN). Although this practice may be reasonable during the first few days that a person is hospitalized, the amount of time the person takes antipsychotic drugs, rather than an increase in dosage, is what produces therapeutic improvement. Clinicians on inpatient services may feel pressured by staff members to write PRN antipsychotic orders; such orders should include specific symptoms, how often the drugs should be given, and how many doses can be given each day. Clinicians may choose to use small doses for the PRN doses (e.g., 2 mg of haloperidol) or use a benzodiazepine instead (e.g., 2 mg of lorazepam IM). If PRN doses of an antipsychotic are necessary after the first week of treatment, the clinician may want to consider increasing the standing daily dose of the drug. Maintenance Treatment The first 3 to 6 months after a psychotic episode are usually considered a period of stabilization. After that time, the dosage of the antipsychotic can be decreased about 20 percent every 6 months until the minimum effective dosage is found. A person is usually

maintained on antipsychotic medications for 1 to 2 years after the first psychotic episode. Antipsychotic treatment is often continued for 5 years after a second psychotic episode, and lifetime maintenance is considered after the third psychotic episode, although attempts to reduce the daily dosage can be made every 6 to 12 months. Antipsychotic drugs are effective in controlling psychotic symptoms, but persons may report that they prefer being off the drugs because they feel better without them. The clinician must discuss maintenance medication with patients and take into account their wishes, the severity of their illnesses, and the quality of their support systems. It is essential for the clinician to know enough about the patient’s life to try to predict upcoming stressors that might require increasing the dosage or closely monitoring compliance. Long-acting Depot Medications Long-acting depot preparations may be needed to overcome problems with compliance. IM preparations are typically given once every 1 to 4 weeks. Two depot preparations, a decanoate and an enanthate, of fluphenazine and a decanoate preparation of haloperidol are available in the United States. The preparations are injected IM into an area of large muscle tissue, from which they are absorbed slowly into the blood. Decanoate preparations can be given less frequently than enanthate preparations because they are absorbed more slowly. Although stabilizing a person on the oral preparation of the specific drugs is not necessary before initiating the depot form, it is good practice to give at least one oral dose of the drug to assess the possibility of an adverse effect, such as severe EPS or an allergic reaction. It is reasonable to begin with either 12.5 mg (0.5 mL) of fluphenazine preparation or 25 mg (0.5 mL) of haloperidol decanoate. If symptoms emerge in the next 2 to 4 weeks, the person can be treated temporarily with additional oral medications or with additional small depot injections. After 3 to 4 weeks, the depot injection can be increased to a single dose equal to the total of the doses given during the initial period. A good reason to initiate depot treatment with low doses is that the absorption of the preparations may be faster than usual at the onset of treatment, resulting in

frightening episodes of dystonia that eventually discourage compliance with the medication. Some clinicians keep persons drug free for 3 to 7 days before initiating depot treatment and give small doses of the depot preparations (3.125 mg of fluphenazine or 6.25 mg of haloperidol) every few days to avoid those initial problems. PLASMA CONCENTRATIONS Genetic differences among persons and pharmacokinetic interactions with other drugs influence the metabolism of the antipsychotics. If a person has not improved after 4 to 6 weeks of treatment, the plasma concentration of the drug should be determined if feasible. After a patient has been on a particular dosage for at least five times the halflife of the drug and thus approaches steady-state concentrations, blood levels may be helpful. It is standard practice to obtain plasma samples at trough levels—just before

the daily dose is given, usually at least 12 hours after the previous dose and most commonly 20 to 24 hours after the previous dose. In fact, most antipsychotics have no well-defined dose–response curve. The best-studied drug is haloperidol, which may have a therapeutic window ranging from 2 to 15 ng/mL. Other therapeutic ranges that have been reasonably well documented are 30 to 100 ng/mL for chlorpromazine and 0.8 to 2.4 ng/mL for perphenazine. Treatment-resistant Persons Unfortunately, 10 to 35 percent of persons with schizophrenia do not obtain significant benefit from the antipsychotic drugs. Treatment resistance is a failure on at least two adequate trials of antipsychotics from two pharmacological classes. It is useful to determine plasma concentrations for such persons because it is possible that they are slow or rapid metabolizers or are not taking their medication. Clozapine has been conclusively shown to be effective when given to patients who have failed multiple trials of DRAs. Adjunctive Medications It is common practice to use DRAs in conjunction with other psychotropic agents, either to treat side effects or to further improve symptoms. Most commonly, this involves the use of lithium or other mood-stabilizing agents, SSRIs, or benzodiazepines. It was once held that antidepressant drugs exacerbated psychosis in patients with schizophrenia. In all likelihood, this observation involved patients with bipolar disorder who were misdiagnosed as having schizophrenia. Abundant evidence suggests that antidepressants in fact improve symptoms of depression in patients with schizophrenia. In some cases, amphetamines can be added to DRAs if patients remain withdrawn and apathetic. CHOICE OF DRUG Given their proven efficacy in managing acute psychotic symptoms and the fact that prophylactic administration of antiparkinsonian medication prevents or minimizes acute motor abnormalities, DRAs are still valuable, especially for short-term therapy. There is a considerable cost advantage to a DRA antiparkinsonian regimen compared with monotherapy with a newer antipsychotic agent. Concern about the development of DRA-induced tardive dyskinesia is the major deterrent to long-term use of these drugs, yet it is not clear that SDAs are completely free of this complication. Thus, DRAs still occupy an important role in psychiatric treatment. DRAs are not predictably interchangeable. For reasons that cannot be explained, some patients do better on one drug than another. Choice of a particular DRA should be based on the known adverse effect profile of the drugs. Other than a significant advantage in terms of medication cost, the choice currently would be an SDA. If a DRA is thought to be preferable, a highpotency antipsychotic is favored, even though it may be associated with more neurological adverse effects, mainly because there is a higher incidence of other adverse

---

Revision #1
Created 2026-01-04 19:51:46 UTC by Omar Ayman
Updated 2026-01-04 19:51:46 UTC by Omar Ayman