34 Antipsychotic Drugs

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DRUG LIST

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The term *psychosis* refers to a variety of mental disorders characterized by one or more of the following symptoms: diminished and distorted capacity to process information and draw logical conclusions, hallucinations, delusions, incoherence or marked loosening of associations, catatonic or disorganized behavior, and aggression or violence. Antipsychotic drugs lessen these symptoms regardless of the underlying cause or causes. These agents are prescribed for the treatment of mania, some movement disorders, and various types of nonspecific agitated behaviors but are most frequently employed in the therapy of schizophrenia. *Schizophrenia* is the term for a group of disorders marked by chronicity, impaired behavioral function, and disturbances of thinking and affect. The disorder has a prevalence of about 1% in the U. S. population, emerging most commonly during late adolescence or early adulthood.

Antipsychotic drugs have been used clinically for 50 years, and the first agents introduced, such as chlorpromazine, revolutionized the practice of psychiatry. Many newer agents have since been developed, reflecting significant degrees of success in enhancing potency and diminishing undesirable side effects. The terms *antipsychotics* and *neuroleptics* have been applied interchangeably to these drugs, but the latter term refers more appropriately to the older agents, whose extrapyramidal side effects (parkinsonism, dyskinesias, akathisia) are more prominent.

THE DISEASE OF SCHIZOPHRENIA

Schizophrenia is a group of heterogeneous, chronic psychotic disorders. Key symptoms include hallucinations, delusions, and abnormal experiences, such as the perception of loss of control of one's thoughts, perhaps to some outside entity. Patients lose empathy with others, become withdrawn, and demonstrate inappropriate or blunted mood. Discrimination of several subtypes of the disease represents only different patterns of symptoms with little value in relating behavior to neuropathology. The disorder has a strong genetic component, as demonstrated by a concordance of 40 to 50% between monozygotic twins, but no objective physiological or biochemical diagnostic tests exist.

Schizophrenic symptoms have been divided into two major categories. *Positive symptoms* are those that can be regarded as an abnormality or exaggeration of

normal function (e.g., incoherent speech, agitation). The antipsychotic drugs are generally more effective in controlling these signs. *Negative symptoms* are those that indicate a loss or decrease in function, such as poverty of speech content or blunted affect. Both types of features are observable in most patients. Negative signs are considered to be more chronic and persistent and less responsive to some antipsychotic agents. Although any of these symptoms may undergo partial remission, persistent dysfunction and exacerbations are typical.

Schizophrenic patients appear to have small brains with large ventricular volumes, indicating a relative deficit of neurons. Structural and functional brain imaging studies have strongly suggested that regions of the medial temporal lobe (e.g., hippocampus) have diminished numbers of neurons and also have demonstrated the inability of individuals with schizophrenia to activate the frontal cortex and successfully execute tasks that require frontal cortical function. However, the relationship between behavioral signs, neuropathology, and a postulated functional excess of dopamine (discussed later) is unknown, and no theory of causation is conclusive.

The Dopamine Hypothesis of Schizophrenia

The dopamine hypothesis of schizophrenia is the most fully developed theory of causation for this disorder, and until recently, it has been the foundation for the rationale underlying drug therapy for this disease. The hypothesis is based on multiple lines of evidence suggesting that excessive dopaminergic activity underlies schizophrenia: (1) drugs that increase dopaminergic activity, such as levodopa and amphetamines, either aggravate existing schizophrenia or induce a psychosis indistinguishable from the acute paranoid form of the disorder; (2) traditional antipsychotic drugs strongly block D_2-dopaminergic receptors in the central nervous system (CNS), and clinical efficacy is highly correlated with the potency of individual agents to bind to this receptor; (3) some postmortem studies have reported increases in dopamine receptor density in brains of schizophrenics who were not treated with antipsychotic drugs; and (4) clinical response to antipsychotic drug treatment is correlated with a decrease in homovanillic acid, a primary dopamine metabolite, in cerebrospinal fluid (CSF), plasma, and urine.

However, the dopamine hypothesis does not account for some important observations. If an abnormality of dopamine physiology were solely responsible for the pathogenesis of schizophrenia, antipsychotic drugs would do a much better job in treating patients. As it is, they are only partially effective for most and ineffective for some patients. Moreover, there is evidence that diminished glutamatergic activity also plays a role in the disease. The primary defect could emanate from nondopaminergic systems that exert a regulatory effect on dopamine neurons, leading to disinhibition of some dopaminergic pathways.

ANTIPSYCHOTIC MECHANISMS OF ACTION

Several lines of evidence demonstrated long ago that antipsychotic drugs blocked the synaptic actions of dopamine and should be classified as dopaminergic antagonists. Three dopaminergic pathways in the brain serve as primary substrates for the pharmacological effects of these agents. The nigrostriatal system consists of neurons with cell bodies in the substantia nigra that project to the caudate and putamen, and it is primarily involved in the coordination of posture and voluntary movement. The mesolimbic–mesocortical system projects from cell bodies in the ventral mesencephalon to the limbic system and neocortex, pathways associated with higher mental and emotional functions. The tuberoinfundibular system connects arcuate and periventricular nuclei of the hypothalamus to the mammotropic cells of the anterior pituitary, thereby physiologically inhibiting prolactin secretion. *The antagonism of dopamine in the mesolimbic–mesocortical system is thought to be the basis of the therapeutic actions of the antipsychotic drugs, while antagonism of the nigrostriatal system is the major factor in the extrapyramidal side effects seen with these agents.* Moreover, antagonism of dopamine's neurohormonal action in the anterior pituitary accounts for the hyperprolactinemia associated with antipsychotic administration. Thus, the same pharmacodynamic action may have distinct psychiatric, neurological, and endocrinological outcomes.

Five subtypes of dopamine receptors have been described; they are the D_1-like and D_2-like receptor groups. All have seven transmembrane domains and are G protein–coupled. The D_1-receptor increases cyclic adenosine monophosphate (cAMP) formation by stimulation of dopamine-sensitive adenylyl cyclase; it is located mainly in the putamen, nucleus accumbens, and olfactory tubercle. The other member of this family is the D_5-receptor, which also increases cAMP but has a 10-fold greater affinity for dopamine and is found primarily in limbic regions. The therapeutic potency of antipsychotic drugs does not correlate with their affinity for binding to the D_1-receptor.

The D_2-dopaminergic receptor decreases cAMP production by inhibiting dopamine-sensitive adenylyl cyclase and opens K^+ channels but can also block Ca^{++} channels. It is located both presynaptically and postsynaptically on neurons in the caudate putamen, nucleus accumbens, and olfactory tubercle. Another member of this family is the D_3-receptor, which also decreases

cAMP formation but which has much lower expression, primarily in limbic and ventral striatal areas. The D_4-receptor also inhibits adenylyl cyclase and is found in frontal cortex and amygdala. *The binding affinity of antipsychotic agents to D_2-receptors is very strongly correlated with clinical antipsychotic and extrapyramidal potency.*

The antischizophrenic actions of these drugs may not consist simply of postsynaptic blockade of hyperactive dopamine systems. Such a blockade occurs within hours, while most symptoms improve over weeks. This discrepancy in the latency to therapeutic effect has been hypothesized to be linked to drug-induced changes in dopaminergic activity: after initiation of therapy, dopamine turnover increases, but after continued antipsychotic treatment, tolerance develops and dopamine metabolism returns to normal. This downward adjustment of dopaminergic activity is consistent with the decreased plasma concentrations of the dopamine metabolite homovanillic acid, an observation that correlates temporally with the clinical response to drug treatment.

Antipsychotic drugs also affect other transmitter systems that may contribute both to their antipsychotic actions and to their adverse reactions. Until recently the main focus in drug development was to discover agents that were more potent and selective in blocking D_2-receptors. However, newer atypical antipsychotics, such as clozapine and risperidone, have a weaker affinity for D_2-receptors and bind more strongly to 5-HT_2 (5-hydroxytryptamine) serotonergic receptors. Thus, lesser activity at the D_2-receptor relative to other transmitter receptors may diminish untoward side effects such as extrapyramidal toxicity. However, the antipsychotics also have variable antagonist actions at muscarinic, α-adrenergic, and histaminergic receptors in brain and peripheral tissue. The antimuscarinic activities cause blurred vision, dry mouth, and urinary retention and may contribute to excessive sedation. Blocking α-adrenoceptors may lead to sedation, orthostatic hypotension, and light-headedness. The antihistaminergic actions of these drugs probably contribute to drowsiness and sedation also.

PHARMACOLOGY

Phenothiazines are classified on the basis of their chemistry, pharmacological actions, and potency. Chemical classifications include the aliphatic (e.g., chlorpromazine; *Thorazine*), piperidine (e.g., thioridazine; *Mellaril*), and piperazine subfamilies. The piperazine derivatives are generally more potent and pharmacologically selective than the others. The thioxanthenes (e.g., thiothixene; *Navane*) are chemically related to the phenothiazines and have nearly equivalent potency. The butyrophenone haloperidol (*Haldol*) is structurally distinct from the two preceding groups, offering greater potency and fewer autonomic side effects. The dibenzodiazepine clozapine (*Clozaril*) bears some structural resemblance to the phenothiazine group but causes little extrapyramidal toxicity. The benzisoxazole risperidone (*Risperdal*) is representative of many of the newer agents in having a unique structure relative to the older groups while retaining antipsychotic potency and a better side effect profile.

Pharmacokinetics

Most of the antipsychotics are readily but incompletely absorbed, and many undergo significant first-pass metabolism. The oral bioavailability of chlorpromazine and thioridazine is in the range of 25 to 35%, while that of haloperidol, which is less likely to be metabolized, has an oral bioavailability of about 65%. The antipsychotics are highly lipid soluble and are about 95% bound to proteins. Generally they have a much longer clinical duration of action than could be estimated from their plasma half-lives; this is likely due to their sequestration in fat tissue. Depot preparations are more slowly absorbed and longer acting, and thus can be administered parenterally at intervals up to 3 weeks. The main routes of metabolism are mediated by hepatic oxidative microsomal enzymes and by glucuronidation. Some metabolites, such as 7-hydroxychlorpromazine, retain measurable activity, but this effect is not considered to be clinically important; an exception to this observation is the major metabolite of thioridazine, which is more potent than the parent drug. Since drug blood concentrations of the less potent antipsychotics are lower after several weeks of treatment at the same dose, it is believed that these compounds may weakly induce their own metabolism. Also, the ability to metabolize and eliminate these drugs has been shown to diminish with age. Typical elimination half-lives vary from 12 to 24 hours.

Pharmacological Distinctions

Despite differences in potency, all commonly used antipsychotic drugs have approximately equal efficacy in equivalent doses. However, individual patients may be more responsive to one drug class than another. Prototype or representative members of the antipsychotics are arranged in decreasing order of potency in Table 34.1. While the sedative and autonomic effects of the high-potency drugs are less prominent, these agents are more likely to cause acute extrapyramidal symptoms. Generally, these trends are reversed as potency decreases.

All antipsychotics block D_2-receptors, but the degree of blockade in relation to actions on other receptors varies greatly. For example, chlorpromazine and

TABLE 34.1 Pharmacological Distinctions Among Representative Antipsychotic Drugs

Drug	Chemical Classification	Equivalent Oral Dose (mg)	Side Effects		
			Sedation	Autonomic[a]	Extrapyramidal Reactions[b]
Haloperidol	Butyrophenone	2	+	+	+++
Pimozide[c]	Diphenylbutylpiperidine	2	+	+	+++
Risperidone	Benzisoxazole	4	++	++	++
Thiothixene	Thioxanthene	5	++	++	++
Olanzapine	Thienobenzodiazepine	5	+	++	+
Clozapine	Dibenzodiazepine	75	+++	+++	+/-
Chlorpromazine	Phenothiazine (Aliphatic)	100	+++	+++	++
Thioridazine	Phenothiazine (Piperidine)	100	+++	+++	+

[a]α_1-Antiadrenergic and anticholinergic effects.
[b]Excluding tardive dyskinesia, which appears to be produced to the same degree and frequency by all agents except clozapine.
[c]Pimozide is used principally in the treatment of Tourette's syndrome.

thioridazine block α-adrenoceptors (autonomic side effects) more potently than D_2-receptors and also block 5-HT_2 serotonergic and H_1 histamine receptors (sedative side effects) to a significant extent. However, their affinity for D_1-receptors is weak. Haloperidol and pimozide (*Orap*) act mainly on D_2-receptors (extrapyramidal toxicity) with negligible activity at D_1-receptors. Clozapine, risperidone, and olanzapine (*Zyprex*) show marked clinical differences from the other drugs. Clozapine binds more to D_4, 5-HT_2, α_1-, and H_1-receptors (autonomic and sedative side effects) than to either D_2 (low extrapyramidal activity) or D_1 sites. Risperidone binds primarily to D_2-, 5-HT_2-, and α_1-receptors, retaining high potency with lesser potential for side effects. Current drug development is directed toward a search for atypical antipsychotics like clozapine that have a broad spectrum of effects on other neurotransmitter receptors.

Other Pharmacological Actions

Antipsychotic drugs produce shifts in the pattern of electrographic (EEG) frequencies, usually slowing them and causing hypersynchrony. This slowing is sometimes focal or unilateral, which may pose diagnostic problems, but the frequency and amplitude changes are readily apparent. The hypersynchrony produced by these drugs probably accounts for their activating effect on the EEG in epileptic patients and for the low incidence of seizures in patients with no history of seizure disorders.

Antipsychotics produce striking effects on the reproductive system. Amenorrhea and increased libido have been reported in women, whereas decreased libido and gynecomastia have been observed in men. Some of these actions are undoubtedly the result of a drug-associated blockade of dopamine's tonic normal inhibition of prolactin secretion, but they may also be partially due to an enhanced peripheral conversion of androgens to estrogens.

Orthostatic hypotension and high resting pulse rates can result from the use of the low-potency phenothiazines. Mean arterial pressure, peripheral resistance, and stroke volume are decreased, while pulse rate is increased. Abnormal electrocardiograms (ECGs) have been observed, especially following thioridazine administration. These findings include prolongation of the QT interval and abnormal configurations of the ST segment and T waves, the latter being rounded, flattened, or notched. These effects are readily reversed upon drug withdrawal.

CLINICAL USES

The treatment of schizophrenia is the primary indication for the use of these drugs. The principal goals for the management of a chronic schizophrenic disorder are the minimizing of symptoms and the prevention of exacerbations. Antipsychotic effectiveness is demonstrated by their ability to reduce the rate of relapse in the chronic condition by about two-thirds to three-quarters compared to no treatment. Drug choice is determined mainly by the patient's past responses and the drug's potential for producing adverse effects. The clinical trend is to prescribe the higher-potency atypical agents.

All antipsychotics except clozapine have a similar potential for producing tardive dyskinesia, the most serious adverse effect. Clozapine is reserved for patients who have failed to respond to therapy with at least two other antipsychotics and for those who have disabling tardive dyskinesia. Therapy with clozapine has been reported to salvage up to half of otherwise treatment-refractory pa-

tients. Its second-line status follows from its ability to cause seizures and a fatal agranulocytosis in large doses.

Substantial therapeutic margins exist for doses of antipsychotic drugs. Once the disorder is controlled, single daily doses are preferred. Bedtime dosing facilitates compliance and takes advantage of the sedation produced by some agents, and patients have fewer adverse reactions. Use of large doses, or rapidly increasing doses to treat severe conditions, has not proved beneficial because of the incidence of acute dystonic reactions. A parenteral form of haloperidol offers the advantage of greater bioavailability and so can be used for rapid initiation or for long-term maintenance in noncompliant individuals. During maintenance therapy, continual dosing with the smallest possible antipsychotic dose is preferred, as opposed to "as needed" treatment for recurrent episodes. Therapy is typically continued for at least a year after remissions are apparent.

Schizoaffective disorders have depression or mania as a major component in addition to psychosis. Thus, lithium or an antidepressant may have to be added to the regimen. Antipsychotic agents are also used in the initial therapy of mania because the patient's response is more rapid than with lithium. As the condition subsides, the antipsychotic can be withdrawn.

Tourette's syndrome, a heterogeneous behavioral disorder associated with motor and vocal tics of variable form and severity, can be effectively treated with haloperidol. Antipsychotics can also be employed to control disturbed behavior in senile dementia or Alzheimer's disease, since they decrease confusion, agitation, and hyperactivity. Most of these drugs also exhibit a strong antiemetic effect and can sometimes be used clinically for this purpose.

ADVERSE EFFECTS

Antipsychotic drugs are characterized by high therapeutic indices with respect to mortality, but side effects occur routinely at therapeutic doses, mostly as extensions of pharmacological actions (Table 34.2). The characteristic neurological symptoms (discussed next) caused by these agents are particularly troublesome, often limit the tolerated dose, and may interfere with the desired benefits and patient compliance.

Sedation

Sedation is common after use of all antipsychotic drugs and is especially notable with the low-potency phenothiazines; this is a result of their activity at α_1-adrenergic and H_1-histaminergic receptors. However, sedation decreases during long-term treatment, and many patients become tolerant to this effect. Single daily doses given at bedtime minimize this problem.

Extrapyramidal Reactions

Two extrapyramidal conditions, acute dystonia and akathisia, occur early during treatment, while parkinsonism tends to evolve gradually over days to weeks. All three reactions occur most commonly with the high-potency antipsychotics (Table 34.1) and are related to high D_2-receptor occupancy. Acute dystonia, which occurs in about 5% of patients on antipsychotic therapy, consists of uncontrollable movements and distortions of the face, head, and neck. It can be treated with centrally acting antimuscarinic agents, such as benztropine, while antipsychotic therapy is temporarily discontinued. When this reaction subsides, the anticholinergic can be withdrawn.

The incidence of akathisia is about 20%; the syndrome consists of intense motor restlessness and agitation that contribute to a behavioral deterioration. It is frequently unresponsive to anticholinergics and is more effectively treated with benzodiazepines and β-adrenergic antagonists, such as propranolol.

Signs of parkinsonism—akinesia, tremor, rigidity—can develop gradually, but this reaction usually responds favorably to central antimuscarinic agents. As with dystonia, parkinsonism may subside, permitting withdrawal of the antimuscarinic drug.

TABLE 34.2 Significant Adverse Effects of Antipsychotic Drugs

Type	Manifestations	Mechanism
Sedation	Drowsiness, lethargy	α_1-adrenoceptor block, H_1 histamine receptor block
Extrapyramidal reactions	Dystonias, akathisia, parkinsonism	D_2-receptor block
	Tardive dyskinesia	D_2-receptor up-regulation (?)
	Neuroleptic malignant syndrome	Extrapyramidal sensitivity
Autonomic signs	Dry mouth, blurred vision, urinary retention, constipation	Muscarinic cholinoreceptor block
	Orthostatic hypotension, impotence	α_1-Adrenoceptor block
Endocrine signs	Amenorrhea, galactorrhea, infertility, impotence	D_2-receptor block resulting in hyperprolactinemia

Tardive dyskinesia is a late-occurring syndrome of abnormal movements of the face and tongue with widespread choreoathetosis. It is the most serious adverse effect of the antipsychotic drugs. It can be expected to occur in 20 to 40% of chronically treated patients; there is no established treatment, and reversibility may be limited. These reactions are more frequent and severe in the elderly.

Tardive dyskinesia is generally accepted to be a D_2 supersensitivity phenomenon, though research has not unequivocally established this postulate. An appropriate clinical response to these symptoms would be to reduce the dose or discontinue the antipsychotic agent and then eliminate all drugs with central anticholinergic action, such as antidepressants. The rationale is to balance the risks of continuing treatment in a patient with tardive dyskinesia with the benefits of antipsychotic administration. If these steps are not helpful, clozapine therapy can be considered, or diazepam can be employed to enhance GABAergic activity. Prevention of this reaction is important. Generally, antipsychotics should be prescribed in minimally effective doses and their use reserved for time-limited treatment except in the treatment of chronic schizophrenic disorders.

The *neuroleptic malignant syndrome* is a rare medical emergency involving extrapyramidal symptoms that occurs in about 1% of patients receiving antipsychotics. The concern is not the incidence but that about 10% of these cases are fatal. The condition is marked by hyperthermia or fever, diffuse muscular rigidity with severe extrapyramidal effects, autonomic dysfunction such as increased blood pressure and heart rate, and fluctuating levels of consciousness. Neuroleptic malignant syndrome is most common in males, with about 80% of cases occurring in patients under 40 years of age. Treatment should include general supportive measures, such as rehydration and body cooling; antipsychotic therapy should be discontinued. Short-term therapy with dantrolene in combination with antiparkinson agents such as bromocriptine has been employed to control the muscular rigidity and hyperthermia.

Autonomic and Endocrine Effects

Most antipsychotics have both α-adrenergic and cholinergic antagonist activities, and blocking actions at histamine and serotonin receptors also contribute to the autonomic effects of some agents. Postural hypotension and depression of medullary cardiovascular centers resulting from α_1-adrenoceptor blockade is particularly troublesome in elderly or debilitated patients. β_2-Agonists, such as epinephrine, are contraindicated, as they may worsen the hypotension. The anticholinergic effects can be very bothersome but usually subside as tolerance to these effects occurs. Typically, autonomic signs can be controlled by adjustment of dose.

All antipsychotics except clozapine and perhaps olanzapine produce hyperprolactinemia by removing the inhibitory actions of dopamine on prolactin secretion. This results in amenorrhea, galactorrhea, and infertility in women and in loss of libido and impotence in men. Inhibition of the release of follicle-stimulating and luteinizing hormones may also play a role. In addition, weight gain is common, and food intake must be monitored.

Other Adverse Effects

Cholestatic jaundice is observed infrequently, usually during the first few weeks of treatment. This is thought to be a hypersensitivity reaction and is usually mild and self-limited. Cutaneous allergic reactions are occasionally reported. Both types of problems normally disappear upon changing to an antipsychotic from a different chemical class. Photosensitivity usually manifests as an acute hypersensitivity reaction to sun with sunburn or rash, but the condition is generally mild and does not require dosage adjustment.

Opacities of the cornea and lens due to deposition of fine particulate matter are a common complication of chlorpromazine therapy but regress after drug withdrawal. The most serious ocular complication is pigmentary retinopathy associated with high-dose thioridazine administration; it is an irreversible condition leading to decreased visual acuity and possibly blindness.

Agranulocytosis is a potentially catastrophic idiosyncratic reaction that usually appears within the first 3 months of therapy. Although the incidence is extremely low (except for clozapine), mortality is high. Thus, any fever, sore throat, or cellulitis is an indication for discontinuing the antipsychotic and immediately conducting white blood cell and differential counts.

Contraindications for antipsychotic therapy are few; they may include Parkinson's disease, hepatic failure, hypotension, bone marrow depression, or use of CNS depressants. Overdoses of antipsychotics are rarely fatal, except for thioridazine, which is associated with major ventricular arrhythmias, cardiac conduction block, and sudden death. For other agents gastric lavage should be attempted even if several hours have elapsed since the drug was taken, because gastrointestinal motility is decreased and the tablets may still be in the stomach. Moreover, activated charcoal effectively binds most of these drugs and can be followed by a saline cathartic. The hypotension often responds to fluid replacement or pressor agents such as norepinephrine.

DRUG INTERACTIONS

Because of their multiple effects, antipsychotic drugs produce more important pharmacodynamic than phar-

macokinetic interactions. The action of other CNS depressants may be enhanced, and concurrent use of tricyclic antidepressants or other agents with anticholinergic activity may cause additive CNS dysfunction and peripheral anticholinergic effects. The hypotensive effects of an antipsychotic may be increased by diuretics, captopril, and other antihypertensive medications. Antipsychotic agents are also susceptible to enhanced metabolism by inducers of microsomal mixed-function oxidases.

Study Questions

1. Which of the following agents possesses pharmacological actions characterized by high antipsychotic potency, high potential for extrapyramidal toxicity, and a low likelihood of causing sedation?
(A) Thioridazine
(B) Haloperidol
(C) Flumazenil
(D) Clozapine
(E) Carbamazepine

2. Tardive dyskinesia after long-term antipsychotic administration is thought to be due to
(A) A decrease in dopamine synthesis
(B) Enhanced stimulation of D_2 dopamine autoreceptors
(C) Loss of cholinergic neurons in striatum
(D) Up-regulation of striatal dopamine receptors
(E) Increased tolerance to antipsychotic agents

3. Which neuroleptic agent has the lowest likelihood of producing tardive dyskinesia?
(A) Imipramine
(B) Chlorpromazine
(C) Clozapine
(D) Fluoxetine
(E) Thiothixene

4. Which clinical condition poses the greatest concern to a patient on antipsychotic therapy?
(A) Epilepsy
(B) Nausea associated with motion sickness
(C) Manic phase of bipolar disorder
(D) Hallucinogen-induced psychosis
(E) Tourette's syndrome

5. Mr. James began haloperidol therapy for schizophrenia and within several weeks developed bradykinesia, rigidity, and tremor. Though his psychoses were well controlled, he was switched to another agent, thioridazine, which proved to be as effective as haloperidol in managing his primary condition and did not result in the undesirable symptoms. The most likely explanation for these observations is that
(A) Haloperidol acts presynaptically to block dopamine release.
(B) Haloperidol activates GABAergic neurons in the striatum.
(C) Haloperidol has a low affinity for D_2-receptors.
(D) Thioridazine has greater α_1-adrenergic blocking activity than haloperidol.
(E) Thioridazine has greater muscarinic blocking activity in brain than haloperidol.

6. Which drug may be useful in the management of the neuroleptic malignant syndrome, although it can worsen the symptoms of schizophrenia?
(A) Risperidone
(B) Thiothixene
(C) Haloperidol
(D) Bromocriptine
(E) Valproic acid

ANSWERS

1. B. The question describes the pharmacological profile of a high-potency classical antipsychotic agent, most likely of the butyrophenone or phenothiazine class. Thioridazine is a low-potency piperidine phenothiazine agent with significant affinity for α_1-adrenergic and muscarinic receptors, having a high potential for sedation as a side effect. Haloperidol is a high-potency butyrophenone with its primary action at the D_2 dopaminergic receptor, so it produces a significant incidence of extrapyramidal toxicity and little sedation. Clozapine is a low-potency atypical antipsychotic that binds primarily to D_4, 5-HT_2, and α_1 receptors and possesses very little extrapyramidal toxicity but significant sedative and autonomic side effects. Flumazenil is a benzodiazepine antagonist, and carbamazepine is an anticonvulsant; neither possesses significant antipsychotic properties.

2. D. This question concerns the most important extrapyramidal reaction to long-term antipsychotic administration—tardive dyskinesia—and its generally accepted basis. Although some tolerance to the sedative effects of antipsychotics can occur, there is no evidence linking this to tardive dyskinesia. Antipsychotic agents enhance dopamine synthesis acutely by blocking D_2-autoreceptors by which the transmitter normally inhibits dopamine cell firing and synthesis. Long-term treatment with a D_2-receptor antagonist causes depolarization inactivation

of dopamine neurons with diminished transmitter production and release. However, a decrease in dopamine synthesis has not been linked with tardive dyskinesia. On the contrary, lower dopamine tone would more resemble a parkinsonian state, whereas in tardive dyskinesia, antidopaminergic drugs tend to suppress the dyskinetic symptoms, and dopaminergic agonists worsen the condition. Therefore, it is generally accepted that up-regulated dopamine receptors underlie tardive dyskinesia. There is no evidence that the antipsychotics lead to loss of striatal cholinergic neurons.

3. **C.** Tardive dyskinesia is an extrapyramidal reaction that occurs most commonly after long-term administration of high-potency butyrophenone, thioxanthene, or phenothiazine. Thus, thiothixene is not a good choice. Chlorpromazine is a low-potency phenothiazine agent with moderate potential to cause extrapyramidal signs. Clozapine is well known to have the lowest potential for producing tardive dyskinesia during chronic therapy. It has other undesirable side effects, but clinical experience with other newer atypical antipsychotics is not sufficient to establish their potential for causing this disorder. Imipramine and fluoxetine are antidepressants.
4. **A.** The question concerns actions of antipsychotic agents that may have untoward consequences when combined with other coincident or preexisting medical conditions. These drugs have an activating effect on the EEG in epileptic patients and thus may worsen that condition. Generally, the antipsychotics have antiemetic properties but generally are more potent than is necessary to treat motion sickness. The other three conditions listed—C, D, and E—are indications for the use of antipsychotic agents.
5. **E.** The question concerns the emergence of parkinsonian signs relatively early in a patient's therapy for schizophrenia and their elimination by switching treatment to a second agent, thioridazine. Haloperidol has high affinity for D_2-dopaminergic receptors and is well known to have a high potential for causing these kinds of extrapyramidal signs. The drug has no direct action on GABAergic neurons and does not act presynaptically to affect dopamine release. While thioridazine binds to D_2-dopaminergic receptors with an affinity similar to that of haloperidol, it also has much greater antimuscarinic activity. This latter action can compensate for dopamine receptor blockade in the nigrostriatal tract, so that extrapyramidal function is more appropriately maintained. Thioridazine has greater α_1-adrenergic blocking activity than haloperidol, but this is not thought to play a role in elimination of the parkinsonian signs.
6. **D.** The neuroleptic malignant syndrome is an infrequent extrapyramidal reaction with a relatively high rate of lethality. It is marked by muscle rigidity, high fever, and autonomic instability. It may result from too-rapid block of dopaminergic receptors in individuals who are highly sensitive to the extrapyramidal effects of antipsychotic drugs. Management consists of control of fever, use of muscle relaxants, and administration of the dopamine agonist bromocriptine, which is likely to worsen the psychotic symptoms. Choices A to C are antipsychotics and would likely worsen neuroleptic malignant syndrome. Valproic acid has antimanic, antimigraine, and anticonvulsant properties, but it is not used to treat the syndrome in question.

SUPPLEMENTAL READING

Ananth J, Burgoyne KS, Gadasalli R, and Aquino S. How do the atypical antipsychotics work? J Psychiatry Neurosci 2001;26:385–394.

Kane JM. Schizophrenia. N Engl J Med 1996;334:34–41.

Konradi C and Heckers S. Antipsychotic drugs and neuroplasticity: Insights into the treatment and neurobiology of schizophrenia. Biol Psychiatry 2001;50:729–742.

Marder SR. Antipsychotic medications. In Schatzberg, AF and Nemeroff CB (eds.). Textbook of Psychopharmacology. Washington: American Psychiatric, 1998.

Rector NA and Beck AT. A clinical review of cognitive therapy for schizophrenia. Curr Psychiatry Rep 2002;4:83–96.

Tuunainen A, Wahlbeck K, and Gilbody S. Newer atypical antipsychotic medication in comparison to clozapine: A systematic review of randomized trials. Schizophr Res 2002;56:1–10.

CASE Study Refractory Schizophrenia

Ms. Anderson is a 29-year-old single woman who was diagnosed with schizophrenia more than 5 years ago. She started with haloperidol and then after several months switched to thiothixene. While her extrapyramidal signs with these agents were not unacceptable, the frequency of her acute psychotic episodes marked by paranoid delusions was not substantially diminished. Subsequently she was also given a trial of thioridazine with a similar clinical response to those of the earlier agents. What antipsychotic agent would be the most appropriate next choice for this patient? What are the primary concerns with the use of this drug, and what precautions should be taken during therapy with this agent?

ANSWER: Clozapine would be the next best choice in the treatment of this patient. Therapy with this drug has been reported to salvage as many as 50% of otherwise treatment-refractory individuals. Clozapine does not have the status of a first-line agent because of its undesirable side effects. De novo seizures occur in 2 to 5% of treated patients, and agranulocytosis is a problem. The significance of agranulocytosis is not the incidence (1–2%) but the severity: about 10% of these cases are fatal. *As a result, weekly blood counts are mandatory for patients receiving clozapine.* Patients should also be alert for sudden onset of any fever or chills. Other atypical antipsychotics, such as risperidone and olanzapine, are available, but clinical experience with these agents is insufficient to establish their value in treating refractory patients.