Chapter 70: Schizophrenia

INTRODUCTION

- *Schizophrenia* is characterized by positive symptoms (eg, delusions, disorganized speech [association disturbance], hallucinations, behavior disturbance [disorganized or catatonic], and illusions); negative symptoms (eg, alogia [poverty of speech], avolition, flat affect, anhedonia, and social isolation); and cognitive dysfunction (eg, impaired attention, working memory, and executive function) all leading to impaired psychosocial functioning.

PATHOPHYSIOLOGY

- Schizophrenia causation theories include genetic predisposition, obstetric complications with hypoxia, increased neuronal pruning, neurodevelopmental disorders, neurodegenerative theories, dopamine receptor defect, and regional brain abnormalities including hyper- or hypoactivity of dopaminergic processes in specific brain regions. Increased ventricular size and decreased gray matter have been reported.
- Alterations in glutamatergic neurotransmission resulting in increased neuronal pruning have also been implicated in schizophrenia pathogenesis. Genes controlling *N*-methyl-D-aspartate (NMDA) receptor activity are hypothesized to be part of this process.
- Studies have also shown increased susceptibility to immune/autoimmune disorders in schizophrenia, as well as abnormalities of autoantibodies and cytokine functioning.
- Positive symptoms may be closely associated with dopamine receptor hyperactivity in the mesocaudate, whereas negative and cognitive symptoms may be most closely related to dopamine receptor hypofunction in the prefrontal cortex.

CLINICAL PRESENTATION

- Symptoms of the acute episode may include being out of touch with reality; hallucinations (especially hearing voices); delusions (fixed false beliefs); ideas of influence (actions controlled by external influences); disconnected thought processes (loose associations); illogical conversation; ambivalence (contradictory thoughts); flat, inappropriate, or labile affect; autistic thinking (withdrawn and inwardly directed thinking); uncooperativeness, hostility, and verbal or physical aggression; impaired self-care skills; and disturbed sleep and appetite.
- After the acute psychotic episode has resolved, typically there are residual features (eg, anxiety, suspiciousness, lack of motivation, poor insight, impaired judgment, social withdrawal, difficulty in learning from experience, and poor self-care skills).
- Comorbid psychiatric and medical disorders (eg depression, anxiety disorders, substance abuse, and general medical disorders such as respiratory disorders, cardiovascular disorders, and metabolic disturbances) can also occur. Medication nonadherence is also common.

DIAGNOSIS

- The *Diagnostic and Statistical Manual of Mental Disorders*, 5th ed. (*DSM-5*), specifies the following diagnostic criteria:
  - ✔ Continuous symptoms that persist for at least 6 months with at least 1 month of active phase symptoms (Criterion A) and may include prodromal or residual symptoms.
    - Criterion A: For at least 1 month, there must be at least two of the following present for a significant portion of time: delusions, hallucinations, disorganized speech, grossly disorganized or catatonic behavior, and negative symptoms. At least one symptom must be delusions, hallucinations, or disorganized speech.
    - Criterion B: Significantly impaired functioning.
- Before treatment, perform a mental status examination, physical (vitals including height and weight) and neurologic examination, complete family and social history, psychiatric diagnostic interview, and laboratory workup (complete blood count [CBC], electrolytes, hepatic function, renal function, electrocardiogram [ECG], fasting serum glucose, serum lipids, thyroid function, and urine drug screen).

TREATMENT

- Goals of Treatment: The goal is to alleviate target symptoms, avoid side effects, improve psychosocial functioning and productivity, achieve compliance with the prescribed regimen, integrate the patient back into the community, prevent relapse, and involve the patient in treatment planning.

Nonpharmacologic Therapy

- Psychosocial rehabilitation programs to improve the patients' adaptive functioning are the mainstay of nondrug treatment for schizophrenia. Programs that involve the family aimed at supportive employment and housing are effective and considered "best practices" and decrease rehospitalization while improving functioning in the community.
- It is important to frame clinical decision making in the context of a mutual process involving patient and clinician.

Pharmacologic Therapy

- Both first-generation antipsychotics (FGAs, also known as traditional) and second-generation antipsychotics (SGAs, also known as atypical) are used to treat schizophrenia. Available

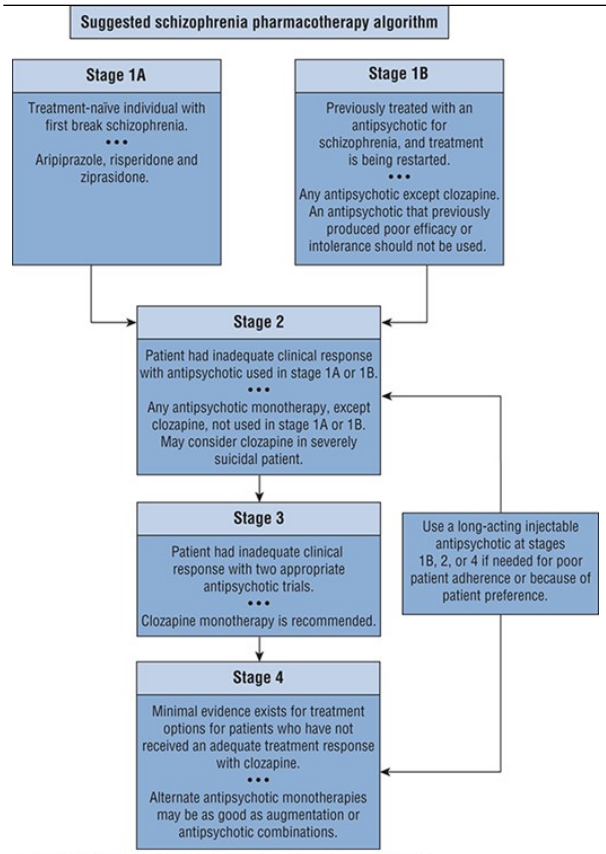
antipsychotics and dosage ranges are shown in **Table 70-1**.

- **Table 70-2** summarizes the long-acting injectable antipsychotics (LAIAs), including dosage range, conversion from oral to LAIA, and injection method/technique.
- The exact mechanism of action of antipsychotics is unknown. FGAs have been found to have high D_2 antagonism and low serotonin-2 receptor [$5\text{-}HT_{2A}$] antagonism. SGAs exhibit moderate-to-high D_2 antagonism and high $5\text{-}HT_{2A}$ antagonism, and clozapine shows low D_2 antagonism and high $5\text{-}HT_{2A}$ antagonism.
- Base antipsychotic selection on: (1) the need to avoid certain side effects, (2) concurrent medical or psychiatric disorders, and (3) patient or family history of response. **Figure 70-1** is an algorithm for management of schizophrenia. Clozapine has superior efficacy for suicidal behavior.
- In first-episode schizophrenia, initiate antipsychotic dosing at the lower end of the dosing range. Use of SGAs during the first acute episode results in greater treatment retention and relapse prevention compared to FGAs. **Aripiprazole, risperidone**, or **ziprasidone** may be preferred first line.
- Risperidone injection is more effective than oral risperidone in preventing relapse over a 1-year period for first episode schizophrenia. A long-acting antipsychotic should be considered during stages 1A, 1B, and 2.
- In Stage 3, **clozapine** monotherapy is recommended.
- For Stage 4, minimal evidence exists for any treatment option for patients who do not have adequate symptom improvement with clozapine. Use of antipsychotic combinations is controversial, as limited evidence supports increased efficacy, despite this practice being somewhat common.
- Predictors of antipsychotic response include prior response to the drug selected, absence of alcohol or drug abuse, acute onset and short duration of illness, later age of onset, affective symptoms, family history of affective illness, medication adherence employment, and good premorbid adjustment. Negative symptoms are generally less responsive to antipsychotic therapy.
- An initial dysphoric response, (eg, dislike of the medication or feeling worse, combined with anxiety or akathisia) portends a poor drug response, adverse effects, and nonadherence.
- The importance of developing a therapeutic alliance between the patient and the clinician cannot be overemphasized.
- **Table 70-3** outlines the relative adverse effect incidence of commonly used antipsychotics, which often follows their binding affinities.
- Anticholinergic side effects, most likely to occur with low-potency FGA, clozapine, and olanzapine, include impaired memory, dry mouth, constipation, tachycardia, blurred vision, inhibition of ejaculation, and urinary retention. Elderly patients are especially sensitive to these side effects.
- Sedation can be reduced if most or the entire antipsychotic daily dose is taken at bedtime.
- Antipsychotics are highly lipophilic, bind highly to membranes and plasma proteins, have large volumes of distribution, and are largely metabolized by cytochrome P450 (CYP) pathways (except ziprasidone). Pharmacogenetics may impact the pharmacokinetics of the antipsychotics.
- Most antipsychotics have elimination half-lives of 24 hours or more, except quetiapine and ziprasidone. Therefore, most can be dosed once daily.
- Antipsychotic pharmacokinetics can be significantly affected by concomitant enzyme inducers or inhibitors. Smoking is a potent inducer of hepatic enzymes and may increase antipsychotic clearance by as much as 50%. Asenapine, an inhibitor of CPY2D6, is the only antipsychotic that significantly affects the pharmacokinetics of other medications. Fluvoxamine, an inhibitor of CYP1A2, increases clozapine serum concentrations by two- to three-fold. Ketoconazole profoundly decreases lurasidone metabolism, and it is recommended that they not be used concomitantly. Carbamazepine reportedly decreases aripiprazole serum concentrations. Reduce the iloperidone dose by 50% when used with CYP2D6 inhibitors such as fluoxetine or paroxetine.

FIGURE 70-1

Pharmacotherapy algorithm for treatment of schizophrenia.

Schizophrenia should be treated in the context of an interprofessional model that addresses the psychosocial needs of the patient, necessary psychiatric pharmacotherapy, psychiatric co-occurring mental disorders, treatment adherence, and any medical problems the patient may have.



Source: Terry L. Schwinghammer, Joseph T. DiPiro, Vicki L. Ellingrod, Cecily V. DiPiro: *Pharmacotherapy Handbook, 11e*

TABLE 70-1

Available Antipsychotics and Dosage Ranges

Generic Name	Trade Name	Starting Dose (mg/day)	Usual Dosage Range (mg/day)	Comments
First-generation antipsychotics				
Chlorpromazine	Thorazine	50–150	300–1000	Most weight gain among FGAs
Fluphenazine	Prolixin	5	5–20	
Haloperidol	Haldol	2–5	2–20	Higher dropout rate in first episode
Loxapine	Loxitane	20	50–150	
Loxapine inhaled	Adasuve	10	10; max 10 mg per 24 hrs	Approved REMS program only
Perphenazine	Trilafon	4–24	16–64	
Thioridazine	Mellaril	50–150	100–800	Significant QTc prolongation
Thiothixene	Navane	4–10	4–50	
Trifluoperazine	Stelazine	2–5	5–40	
Second-generation antipsychotics				
Aripiprazole	Abilify	5–15	15–30	
Asenapine	Saphris	5	10–20	Sublingual only, no food or drink for 10 minutes after administration
Brexpiprazole	Rexulti	1	2–4	
Cariprazine	Vraylar	1.5	1.5–6	Due to long half-life, steady state is not reached for several weeks
Clozapine	Clozaril	25	100–800	Check plasma level before exceeding 600 mg
Iloperidone	Fanapt	1–2	6–24	Care with dosing in CYP2D6 slow metabolizers
Lurasidone	Latuda	20–40	40–120	Take with food, ≥350 calories (1460 J)
Olanzapine	Zyprexa	5–10	10–20	Avoid in first episode because of weight gain
Paliperidone	Invega	3–6	3–12	Bioavailability increased when administered with food
Quetiapine	Seroquel	50	300–800	
Quetiapine XR	Seroquel XR	300	400–800	
Risperidone	Risperdal	1–2	2–8	
Ziprasidone	Geodon	40	80–160	Take with food, ≥500 calories (2100 J)

Note: In first-episode patients, starting dose and target dose should generally be 50% of the usual dose range. See Long-Acting Injectable Antipsychotics in text for dosing of these agents.

REMS, Risk Evaluation and Mitigation Strategy; XR: extended release.

TABLE 70-2

Summary of Available Long-Acting Injectable (LAI) Antipsychotics

Medication Name Parameter	Fluphenazine Decanoate	Haloperidol Decanoate	Risperidone (Risperdal Consta)	Risperidone (PERSERIS)	Paliperidone Palmitate (Invega Sustenna®)	Paliperidone Palmitate (Invega Trinza®) (1MPP)	Olanzapine Pamoate (Zyprexa Relprevv®) (3MPP)	Aripiprazole Monohydrate (Abilify Maintena®)	Aripiprazole (Lauroxil Aristada®)
Dose range (mg)	12.5–100	20–450	12.5–50	90–120	39–234	273–819	150–405	160–400	441–882

PO Overlap		None	4 weeks (none if loading); use PO dose patient was taking prior to injection	3 weeks after first injection: use PO dose patient was taking prior to injection	None	None	None	None	2 weeks PO dose ranges from 10 to 20 mg/day	21 days PO overlap after first injection
Recommended maximum dose		100 mg every 2–3 weeks	450 mg every 4 weeks	50 mg every 2 weeks	120 mg	234 mg every 4 weeks	819 mg every 3 months	300 mg every 2 weeks or 405 mg every 4 weeks	400 mg monthly	882 mg monthly
Initiation or loading dose		Can load	Can load	None	None	Initiation required	None required, dose used depends on last Invega Sustenna dose as follows: if 78 mg give 273 mg; if 117 mg give 410 mg; if 156 mg give 546 mg	Initiation required	None	None required, dose depends on PO dose as follows: If 10 mg/day PO give 441 mg/month IM If 15 mg/day PO give 662 mg/month IM If 20 mg PO give 882 mg/month IM
Time to peak		8–24 hours	4–11 days	4–5 weeks	4–6 hours	13 days	30–33 days	<1 week	5–7 days	5–6 days
T_{ss}		2–3 months	2–3 months	6–8 weeks	60 days	7–11 months	Continues steady-state	3 months	3–4 months	4 months
Half-life		14.2 ± 2.2[a] days	21 days	3–6 days	9–11 days	25–49 days	84–89 days (deltoid) 118–139 days (gluteal)	30 days	29.9–46.5 days	29.2–34.9 days
Injection site	Gluteal	Yes	Yes	Yes	Abdominal only	Yes after 2nd dose	Yes	Yes	Yes	Yes for all dose strengths
	Deltoid	Yes	Yes	Yes		Yes	Yes	No	No	Yes, but only 441 mg dose
Notes			Z-track	Subcutaneous injection		Avoid use in patients	Requires at least a 4-	Monitor for PDSS	Maintenance dose reduced	May require up to 2

						with moderate-to-severe renal impairment (CrCl <50 mL/min [0.83 mL/sec])	month trial with Invega Sustenna. Not recommended in patients with moderate or severe renal impairment (CrCl <50 mL/min[0.83 mL/sec])	subject to REMS	to 300 mg if patient experiences adverse events. Dose adjustment needed in CYP2D6 slow metabolizers. Avoid use in patients taking CYP 3A4 inhibitors >14 days	weeks of PO trial to establish tolerability to aripiprazole before initiating LAIA Avoid use of strong CYP2D6 and 3A4 inhibitors on 662 and 882 mg dose, no adjustment needed for 441 mg dose
				A starting dose of 12.5 mg is recommended in patients with hepatic or renal impairment	90 mg = 3 mg PO risperidone 120 mg = 4 mg PO risperidone						

[a]Based on multiple-dose data. Single-dose data indicate a β-half-life of 6–10 days.

CrCl, creatine clearance; IM, intramuscular; LAIA, long-acting injectable; PO, oral; T_{ss}, time to steady state.

TABLE 70-3

Relative Side-Effect Incidence of Commonly Used Antipsychotics[a,b]

	Sedation	EPS	Anticholinergic	Orthostasis	Weight Gain	Prolactin
Aripiprazole	+	+/++[c]	+	+	+	+
Asenapine	+	+/++	±	+	++	+
Brexpiprazole	+	+/++[c]	+	+	+	+
Cariprazine	±	+/++[c]	+	+	+	+
Chlorpromazine	++++	+++	+++	++++	++	+++
Clozapine	++++	+	++++	++++	++++	+
Fluphenazine	+	++++	+	+	+	++++
Haloperidol	+	++++	+	+	+	++++
Iloperidone	+	±	+	+++	++	+
Lurasidone	++	+	+	+	+	+
Olanzapine	++	++	++	++	++++	+
Paliperidone	+	++	+	+	++	++++
Perphenazine	++	++++	++	+	+	++++
Quetiapine	++	+	++	++	++	+
Risperidone	+	++	+	++	++	++++
Thioridazine	++++	+++	++++	++++	+	+++
Thiothixene	+	++++	+	+	+	++++
Ziprasidone	++	++	+	+	+	+

[a]Side effects shown are relative risk based on doses within the recommended therapeutic range.

[b]Individual patient risk varies depending on patient-specific factors.

[c]Primarily akathisia.

EPS, extrapyramidal side effects—include dystonias, pseudoparkinsonism, akathisia, and tardive dyskinesia.

Relative side effect risk: ±, negligible; +, low; ++, moderate; +++, moderately high; ++++, high.

Initial Therapy

- The goals during the first 7 days of treatment are decreased agitation, hostility, anxiety, and aggression and normalization of sleep and eating.
- Titrate the antipsychotic dose over the first few days to an average effective dose in (the middle of the ranges shown in **Table 70-1**), with the dose for first episode psychosis being half of that used for chronically ill patients. Rapid titration of dose is not recommended. If there is no improvement within 2 weeks at a therapeutic dose, then move to the next treatment stage in **Figure 70-1**.
- In partial responders who are tolerating the antipsychotic well, it may be reasonable to titrate above the usual dose range for 2–4 weeks with close monitoring.
- Intramuscular (IM) antipsychotic administration (eg, aripiprazole 5.25–9.75 mg, ziprasidone 10–20 mg, olanzapine 2.5–10 mg, or haloperidol 2–5 mg) can be used to calm agitated patients. However, this approach does not improve the extent of response, time to remission, or length of hospitalization. IM **lorazepam**, 2 mg, as needed for agitation added to the maintenance antipsychotic is a rational alternative to an injectable antipsychotic. Combining IM lorazepam with olanzapine or clozapine is not recommended because of the risk of hypotension, central nervous system (CNS) depression, and respiratory depression.
- Inhaled **loxapine** powder, FDA-approved for acute agitation associated with schizophrenia or in adults, can be administered only in a healthcare facility and through the FDA-approved Risk Evaluation and Mitigation Strategy (REMS). Use is limited to one 10-mg inhaled dose per 24 hours. Patients with any lung disease associated with bronchospasm (eg, asthma, chronic obstructive

pulmonary disease) are excluded. It may offer no advantage over IM and oral products.

Stabilization Therapy

- During weeks 2 and 3, the goal is to improve socialization, self-care, and mood. Dose titration may continue every 1–2 weeks as long as the patient has no side effects.
- If the patient begins to show an adequate response at a particular dose, then continue that dosage as long as symptoms continue to improve. Improvement in formal thought disorder may require an additional 6–8 weeks.

Maintenance Therapy

- The goal of maintenance therapy is relapse prevention; therefore, continue medication for at least 12 months after remission of the first psychotic episode. Many experts recommend treatment for at least 5 years, and lifetime pharmacotherapy at the lowest effective dose is necessary in most patients with schizophrenia.
- In general, when switching from one antipsychotic to another, the first should be tapered and discontinued over at least 1–2 weeks while the second antipsychotic is initiated and tapered upward. Slow titration of antipsychotics (especially FGAs and clozapine) can be done to avoid cholinergic rebound.

Management of Treatment-Resistant Schizophrenia

- Only clozapine has shown superiority over other antipsychotics; however, improvement occurs slowly, with 60% of patients improving if used for up to 6 months.
- Because of the risk of orthostatic hypotension, clozapine is usually titrated more slowly than other antipsychotics. If a 12.5-mg test dose does not produce hypotension, then 25 mg at bedtime is recommended, increased to 25 mg twice daily after 3 days, then increased in 25–50 mg/day increments every 3 days until a dose of at least 300 mg/day is reached.
- A 12-hour postdose clozapine serum concentration of at least 350 ng/mL (1.07 µmol/L) is associated with efficacy. Monitor serum concentrations of clozapine before exceeding 600 mg daily, in patients with unusual or severe adverse effects, in those concomitantly taking potentially interacting medications, in those with age or pathophysiologic changes suggesting altered kinetics, and in those suspected of medication nonadherence.
- Mood stabilizers (eg, **lithium**, **valproic acid**, and **carbamazepine**) may improve labile affect and agitation in patients with refectory schizophrenia. Selective serotonin reuptake inhibitors (SSRIs) may improve obsessive-compulsive symptoms that worsen or arise during clozapine treatment.
- Combining a FGA and SGA and combining different SGAs have been suggested, but no data support or refute these strategies. If tried, one of the drugs should be discontinued if there is no improvement within 6–12 weeks.

Extrapyramidal Side Effects

Dystonias

- Dystonias are prolonged tonic muscle contractions (occurring usually within 24–96 hours of dosage initiation or dosage increase); they may be life-threatening (eg, pharyngeal–laryngeal dystonias). Other dystonias are trismus, glossospasm, tongue protrusion, blepharospasm, oculogyric crisis, torticollis, and retrocollis. Risk factors include younger (male) patients and use of FGA, high-potency agents, and high dose.
- Treatment includes IM or IV anticholinergics (**Table 70-4**) or benzodiazepines. **Benztropine** 2 mg, or **diphenhydramine** 50 mg, may be given IM or IV, or **diazepam**, 5–10 mg by slow IV push, or **lorazepam**, 1–2 mg IM, may be given. Relief usually occurs within 15–20 minutes of IM injection or 5 minutes of IV administration.
- Prophylactic anticholinergic medications are reasonable when using high-potency FGAs (eg, haloperidol and fluphenazine) in young men or in patients with a prior dystonia. Risk can be minimized by using lower initial doses or by using an SGA.

TABLE 70-4

Agents Used to Treat Extrapyramidal Side Effects

Generic Name	Equivalent Dose (mg)	Daily Dosage Range (mg)
Antimuscarinics		
Benztropine[a]	1	1–8[b]
Biperiden[a]	2	2–8
Trihexyphenidyl	2	2–15
Antihistaminic		
Diphenhydramine[a]	50	50–400
Dopamine agonist		
Amantadine	NA	100–400
Benzodiazepines		
Lorazepam[a]	NA	1–8
Diazepam	NA	2–20
Clonazepam	NA	2–8
β-Blockers		
Propranolol	NA	20–160

[a]Injectable dosage form can be given intramuscularly for relief of acute dystonia.

[b]In treatment-refractory cases, dosage can be titrated to 12 mg/day with careful monitoring; nonlinear pharmacokinetics has been reported.

NA, not applicable.

Akathisia

- Akathisia occurs in 20%–40% of patients treated with high-potency FGA and consists of subjective complaints (feelings of inner restlessness) and/or objective symptoms (pacing, shifting, shuffling, or tapping feet).
- Reduction in antipsychotic dose is the best intervention but is not always feasible. Switching to an SGA is an option, although akathisia may occur with some SGAs. Aripiprazole, risperidone, quetiapine, and clozapine appear to have the lowest risk. Benzodiazepines should be avoided in patients with a history of substance abuse. **Propranolol** (up to 160 mg/day) is reported to be effective. Emerging literature suggests that agents with antagonist activity at the 5-HT_2 receptor (**cyproheptadine**, **mirtazapine**, and **trazodone**) may be protective against akathisia.

Pseudoparkinsonism

- *There are four cardinal symptoms*
  - ✔ Akinesia, bradykinesia, or decreased motor activity, including mask-like facial expression, micrographia
  - ✔ Tremor, predominantly at rest; decreasing with movement
  - ✔ Cogwheel rigidity; the patient's limbs yield in jerky, ratchet-like fashion when moved passively by the examiner
  - ✔ Stooped, unstable posture and slow, shuffling, or festinating gait
- Possible accessory symptoms include seborrhea, sialorrhea, hyperhidrosis, fatigue, weakness, dysphagia, and dysarthria.
- Risk factors include FGA use (especially in high dose), increasing age, and possibly female gender.
- Symptoms start 1–2 weeks after initiation of antipsychotic therapy or dose increase. Risk with SGAs is low except with risperidone in doses greater than 6 mg/day.
- **Benztropine** has a half-life that allows once- to twice-daily dosing. Typical dosing is 1–2 mg twice daily up to a maximum of 8 mg daily. **Diphenhydramine** produces more sedation (see **Table 70-4**). All of the anticholinergics have been abused for euphoriant effects. **Amantadine** is as effective as anticholinergics with less effect on memory.

- Attempt to taper and discontinue these agents 6 weeks to 3 months after symptoms resolve.

Tardive Dyskinesia

- Tardive dyskinesia (TD) is characterized by abnormal involuntary movements.
- The classic presentation is buccolingual-masticatory or orofacial movements that may interfere with chewing, wearing dentures, speech, respiration, or swallowing. Facial movements include frequent blinking, brow arching, grimacing, upward deviation of the eyes, and lip smacking. Restless choreiform and athetotic movements of the limbs occur in later stages. Movements may worsen with stress, decrease with sedation, and disappear with sleep.
- Screen at baseline and at least quarterly using the Abnormal Involuntary Movement Scale (AIMS) and the Dyskinesia Identification System Condensed User Scale (DISCUS) to detect TD.
- TD prevention includes: (1) use SGAs first-line; (2) biyearly TD screening; and (3) discontinue antipsychotics or switch to SGAs at the earliest symptoms of TD, if possible.
- Risk factors for TD include duration of antipsychotic therapy, higher dose, possibly cumulative dose, possibly female gender, increasing age, occurrence of acute extrapyramidal symptoms, poor antipsychotic response, diagnosis of organic mental disorder, diabetes mellitus, and mood disorders. With FGAs the prevalence of TD ranges from 20%–50%. With SGAs, the risk of TD is ~3.0% per year in nonelderly adults compared to 7.7% per year for FGAs.
- The American Academy of Neurology guideline recommends short-term treatment of TD with **clonazepam** or **ginkgo biloba**.
- **Deutetrabenazine** and **valbenazine** are vesicular monoamine transporter-2 (VMAT2) inhibitors approved for TD treatment in adults. Warnings associated with their use include suicidality, depression, and QT interval prolongation.

Other Antipsychotic Adverse Effects

Seizures

- The highest risk for antipsychotic-induced seizures is with chlorpromazine or clozapine. Seizures are more likely with initiation of treatment, higher doses, and rapid dose increases.
- Dosage reduction should occur for an isolated seizure, and anticonvulsant therapy is usually not recommended.
- If a change in antipsychotic therapy is required, risperidone, thioridazine, haloperidol, pimozide, trifluoperazine, and fluphenazine may be considered.

Thermoregulation

- Poikilothermia, the body temperature adjusting to the ambient temperature, can be a serious side effect of antipsychotic therapy in temperature extremes. Hyperpyrexia, leading to heat stroke, may be dangerous in hot weather or during exercise. Hypothermia is also a risk, especially in older individuals. These problems are more common with the use of low-potency FGAs and can occur with the more anticholinergic SGAs.

Neuroleptic Malignant Syndrome

- Neuroleptic malignant syndrome (NMS) occurs in 0.5%–1% of patients taking FGAs, and can occur with SGAs, including clozapine, but is less frequent.
- Symptoms develop rapidly over 24–72 hours (eg, body temperature exceeding 38°C [100.4°F]), altered level of consciousness, autonomic dysfunction (tachycardia, labile blood pressure, diaphoresis, and tachypnea), and rigidity.
- Myoglobinuria, leukocytosis, increases in creatine kinase (CK), aspartate aminotransferase (AST), alanine aminotransferase (ALT), and lactate dehydrogenase (LDH) are common.
- Discontinue antipsychotics and provide supportive care. Bromocriptine reduces rigidity, fever, and CK levels in up to 94% of patients. Amantadine has been used successfully in up to 63% of patients. **Dantrolene** has been used with favorable effects on temperature, heart rate, respiratory rate, and CK in up to 81% of patients.
- Antipsychotic rechallenge with the lowest effective dose of an SGA or low-potency FGA may be considered only after at least 2 weeks without antipsychotics. Monitor carefully and titrate the dose slowly.

Endocrine Effects

- Antipsychotic-induced prolactin elevations associated with galactorrhea, gynecomastia, decreased libido, and menstrual irregularities are common and are likely with FGAs, risperidone, and paliperidone. Possible management strategies include switching to an agent with lower risk (eg, aripiprazole, asenapine, iloperidone, lurasidone, brexpiprazole, and cariprazine). Dopamine agonists are not recommended due to potential psychosis exacerbation.
- Weight gain with antipsychotic therapy may be most likely with olanzapine, clozapine, risperidone, quetiapine, and iloperidone. Ziprasidone, aripiprazole, asenapine, lurasidone, brexpiprizole, and cariprazine appear to cause minimal weight gain.
- Patients with schizophrenia have a high prevalence of type 2 diabetes, which may be adversely affected by antipsychotics. Olanzapine and clozapine have the highest risk of causing new-onset diabetes, followed by risperidone and quetiapine. The risk with aripiprazole and ziprasidone is likely less than with other SGAs.

Cardiovascular Adverse Effects

- Orthostatic hypotension (defined as >20 mm Hg drop in systolic blood pressure upon standing) is greatest with low-potency FGAs, clozapine, iloperidone, quetiapine, and combination antipsychotics. Patients with diabetes and cardiovascular disease and older patients are predisposed. Dose reduction or changing to an antipsychotic with less α-adrenergic blockade may help, and tolerance may develop within 2–3 months.
- The low-potency piperidine phenothiazines (thioridazine), clozapine, iloperidone, and ziprasidone are the most likely to cause ECG changes, including increased heart rate, flattened T waves, ST-

segment depression, and prolongation of QT and PR intervals. Thioridazine prolongs the QTc on average about 20 milliseconds longer than haloperidol, risperidone, olanzapine, or quetiapine. For thioridazine, the effect is dose related, and the drug's labeling carries a boxed warning for torsades de pointes and sudden death.

- Iloperidone pharmacogenomic metabolism may increase the risk of QTc prolongation in CYP2D6 poor metabolizers. High IV doses of haloperidol also can prolong the QTc, and it also carries a boxed warning.
- Medication discontinuation should occur with QTc prolongation consistently exceeding 500 milliseconds. Torsades rarely happens in the absence of additional risk factors (eg, age greater than 60, female gender, preexisting cardiac or cerebrovascular disease, hepatic impairment, hypokalemia, hypomagnesemia, additional meds that prolong the QTc interval, metabolic inhibition by another medication, or preexisting QTc prolongation).
- In patients older than 50 years, pretreatment ECG and serum potassium and magnesium levels are recommended.
- Myocarditis is an infrequent and dose-independent adverse effect that is most likely to occur with clozapine but has been reported with quetiapine, and possibly with olanzapine. Recommended laboratory monitoring has been proposed with baseline and weekly monitoring of C-reactive protein (CRP) for the first 4 weeks, while troponin (I or T) and B-type natriuretic peptide monitoring has also been suggested. Cardiomyopathy, a potentially life-threatening adverse effect, can also be seen with clozapine, which typically presents later in the course of treatment than myocarditis, with an average time of onset of 14 months. Clozapine rechallenge after myocarditis is debated, and not recommended after cardiomyopathy.
- Those taking FGAs or SGAs have twice the risk of sudden cardiac death than nonusers. Use of antipsychotics was associated with a 1.53-fold increase in ventricular arrhythmia or sudden cardiac death.
- Compared to the general population, the risk of venous thromboembolism (VTE) is twofold higher in individuals with schizophrenia with both FGAs and SGAs associated with this risk. Although the mechanism of this risk is unknown, increased sedative side effects, metabolic side effects, antipsychotic effect on platelet aggregation, and hyperprolactinemia indirectly increasing venous stasis have been proposed.

Lipid Effects

- Some SGAs and phenothiazines cause elevations in serum triglycerides and cholesterol. Olanzapine, clozapine, and quetiapine have the highest risk for dyslipidemia.
- Weight gain, diabetes, and lipid abnormalities during antipsychotic therapy are consistent with development of metabolic syndrome (consisting of raised triglycerides, ≥150 mg/dL [1.70 mmol/L]), low high-density lipoprotein cholesterol (≤40 mg/dL [1.03 mmol/L] for males, ≤50 mg/dL [1.29 mmol/L] for females), elevated fasting glucose (≥100 mg/dL [5.6 mmol/L]), blood pressure elevation (≥130/85 mm Hg), and weight gain (abdominal circumference >102 cm [40 in.] for males, >89 cm [35 in.] for females).

Psychiatric Side Effects

- Aripiprazole has been associated with impulse control disorders such as pathological gambling, uncontrolled sexual urges, uncontrolled spending, binge or compulsive eating, and other intense urges.

Ophthalmologic Effects

- Exacerbation of narrow-angle glaucoma can occur with antipsychotics and/or anticholinergic use.
- Opaque deposits in the cornea and lens may occur with chronic phenothiazine treatment, especially chlorpromazine. Although visual acuity is not usually affected, periodic slit-lamp examinations are recommended with long-term phenothiazine use. Baseline and periodic slit-lamp examinations are also recommended for quetiapine-treated patients because of cataract development in animal studies.
- Thioridazine doses greater than 800 mg daily (the recommended maximum dose) can cause retinitis pigmentosa with permanent visual impairment or blindness.

Genitourinary System

- Urinary hesitancy and retention are common, especially with low-potency FGAs and clozapine, and in men with benign prostatic hyperplasia.
- Urinary incontinence may result from α-blockade, and among the SGAs, it is especially problematic with clozapine.
- Risperidone and paliperidone produce at least as much sexual dysfunction as FGAs, but other SGAs (which have a weaker effect of prolactin) pose less risk. Priapism, a sustained and painful erection that is unprovoked and persists for longer than an hour, is increasingly reported with antipsychotic medication use.

Hematologic System

- Antipsychotics can cause transient leukopenia, but it usually does not progress to clinical significance. Clozapine, chlorpromazine, and olanzapine have the highest risk for neutropenia.
- Agranulocytosis reportedly occurs in 0.01% of patients receiving FGAs, and it may occur more frequently with chlorpromazine and thioridazine. The onset is usually within the first 8 weeks of therapy.
- Agranulocytosis can manifest as sore throat, leukoplakia, erythema, and ulcerated pharynx. Patients with these symptoms taking antipsychotics should have an absolute neutrophil count (ANC). If the ANC is less than 500/μL (0.5×10^9/L), discontinue the antipsychotic with close monitoring for secondary infection.
- The risk of developing neutropenia or agranulocytosis with clozapine is approximately 3% and 0.8%, respectively. Increasing age and female gender increase risk. The greatest risk is between 1 and 6 months of initiating treatment. The baseline ANC must be at least 1500/μL (1.5×10^9/L) in order to start clozapine. Weekly ANC monitoring for the first 6 months is FDA mandated. After this time, if the ANC remains greater than 1500/μL (1.5×10^9/L), ANC monitoring can be decreased to every 2 weeks for the next 6 months. Subsequently, if all ANCs remain greater than 1500/μL (1.5×10^9/L) ANC monitoring can be decreased to monthly. If at any time the ANC drops to less than 500/μL (0.5×10^9/L), clozapine must be discontinued and the ANC monitored daily until it is greater than 1500/μL (1.5×10^9/L). Refer to the product labeling for more detailed information regarding ANC monitoring, including monitoring for mild and moderate leukopenia.

Dermatologic System

- Allergic reactions are rare and usually occur within 8 weeks of initiating therapy. They manifest as maculopapular, erythematous, or pruritic rashes.
- Contact dermatitis, on the skin or oral mucosa, may occur. Swallowing of the FGA oral concentrates quickly may decrease rashes on the oral mucosa.
- Ziprasidone can cause a rare but fatal skin reaction called Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS).
- Both FGAs and SGAs can cause photosensitivity with severe sunburns. Patients should use maximal blocking sunscreens, hats, protective clothing, and sunglasses when in the sun.
- Blue-gray or purplish discoloration of skin exposed to sunlight may occur with higher doses of low-potency phenothiazines (especially chlorpromazine) given long term. This may occur with concurrent corneal or lens pigmentation.

Use in Pregnancy and Lactation

- Haloperidol is the best-studied FGA with approximately 400 reported exposures. A small study found a twofold elevated risk of preterm birth in women with schizophrenia taking FGAs as compared with mothers not taking antipsychotics. Risk of neonatal EPS is increased with in utero exposure to FGAs, with effects in the infant lasting for 3–12 months after birth.
- All SGAs cross the blood–placental barrier to varying degrees. A meta-analysis found a greater risk of birth defects and preterm births with first trimester exposure to SGA, but no specific abnormality was identified. Other larger studies also suggest that aripiprazole, olanzapine, quetiapine, risperidone, and ziprasidone collectively do not increase the risk of congenital malformations or cardiac malformation. Large, well-controlled studies are needed to clarify the safety of SGAs during pregnancy.
- For all of the FGAs, the overall relative infant doses (RID) obtained through breastfeeding is thought to be less than 10%, which is a common threshold indicating that these medications are safe for use. Olanzapine and quetiapine have reported RIDs of less than 4%. Risperidone and aripiprazole have higher RIDs up to approximately 9%. Breastfeeding while on clozapine is not recommended due to the risk of severe neutropenia and seizures in the infant.

EVALUATION OF THERAPEUTIC OUTCOMES

- **Table 70-5** summarizes antipsychotic adverse effects, patient monitoring parameters, and frequency of monitoring parameters.
- The four-item Positive Symptom Rating Scale and the Brief Negative Symptom Assessment are brief enough to be useful in the outpatient setting to measure changes in symptomatology. Patient-rated self-assessments can also be useful, as they engage the patient in treatment and can open the door for patient education and addressing misconceptions. Clinicians should be assertive in attempting to achieve symptom remission.

TABLE 70-5

Antipsychotic Adverse Effects and Monitoring Parameters

Adverse Reaction	Monitoring Parameter	Frequency	Comments
Adverse effect monitoring parameters for all antipsychotic medications			
Akathisia	Ask about restlessness or anxiety. Observe patient for restlessness. Barnes Akathisia Scale can also be used	Every visit	
Anticholinergic side effects	Ask patient about constipation, blurry vision, urinary retention, or unusual dry mouth	Every visit	
Glucose intolerance	FBS or HbA1c	At baseline, after 3 months, and if normal, then annually	
Hyperlipidemia	Lipid profile	At baseline, after 3 months, and if normal, then annually	
Orthostatic hypotension	Ask patient about dizziness on standing. If present, check BP and HR in sitting and standing positions	Every visit	The degree of orthostatic change in BP to produce symptoms varies. In general, a BP change of 20 mm Hg or more is significant
Hyperprolactinemia	In women, ask about expression of milk from the breast and menstrual irregularities. In men, ask about breast enlargement or expression of milk from nipples. If symptoms present, check serum prolactin level	Every visit	In the absence of symptoms, there is no need to monitor serum prolactin
Sedation	Ask patient about unusual sedation or sleepiness	Every visit	
Sexual dysfunction	Ask patient about decreased sexual desire, difficulty being aroused, or problems with orgasm	Every visit	Patients with schizophrenia have more sexual dysfunction than the normal population. Compare symptoms with medication-free state
Tardive dyskinesia	Standardized rating scale such as the AIMS or the DISCUS	At baseline, and then every 3 months for FGAs and every 6 months for SGAs	
Weight gain	Measure body weight, BMI, and waist circumference	At baseline, monthly for the first 3 months, and then quarterly	Waist circumference is the single best predictor of cardiac morbidity
Adverse effect monitoring parameters for specific antipsychotics			
Agranulocytosis	White blood cell (WBC) and absolute neutrophil counts (ANC)	At baseline, weekly for 6 months, then every 2 weeks for 6 months, and then monthly	Clozapine only
Sialorrhea or excess drooling	Ask patient about problems with excess drooling, waking in the morning with a wet ring on his or her pillow. Visual observation of the patient for drooling	Every visit	Clozapine only
Bronchospasm, respiratory distress, respiratory depression, respiratory arrest	Before administration, screen patients for a history of asthma, chronic obstructive pulmonary disease, or other lung disease associated with bronchospasm. Monitor patient every 15 minutes for a minimum of 1 hour after drug administration for signs and symptoms of bronchospasm (ie, vital signs and chest auscultation). Only one 10 mg dose can be given every 24 hours	Every dose administration	Inhaled loxapine only. Can only be administered in approved healthcare facilities registered in REMS program
Postinjection sedation/delirium syndrome	Observe the patient for at least 3 hours after drug administration. Monitor for possible sedation, altered level of consciousness, coma, delirium, confusion, disorientation, agitation, anxiety, or other cognitive impairment	Every dose administration	Long-acting olanzapine pamoate monohydrate only. Can only be administered in approved healthcare facilities registered in REMS program

AIMS, abnormal involuntary movement scale; DISCUS, dyskinesia identification system condensed user scale, FBS, fasting blood sugar; FGA, first-generation antipsychotic; SGA, second-generation antipsychotic.

See Chapter 84, Schizophrenia, authored by M. Lynn Crismon, Tawny Smith, and Peter F. Buckley, for a more detailed discussion of this topic.