

Schizophrenia



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LEARNING OBJECTIVES

● Upon completion of the chapter, the reader will be able to:

1. Recognize signs and symptoms of schizophrenia and be able to distinguish among positive, negative, and cognitive impairments associated with the illness.
2. Explain pathophysiologic mechanisms that are thought to underlie schizophrenia.
3. Identify treatment goals for a patient with schizophrenia.
4. Recommend appropriate antipsychotic medications based on patient-specific data.
5. Compare side-effect profiles of individual antipsychotics.
6. Educate patients and families about schizophrenia, treatments, and the importance of adherence to antipsychotic treatment.
7. Describe components of a monitoring plan to assess the effectiveness and safety of antipsychotic medications.

INTRODUCTION

- Schizophrenia is **chronic disorder** characterized by **delusions, hallucinations, disorganized thinking and speech, abnormal motor behavior**, and **negative symptoms**.
- Schizophrenia is the fourth leading cause of disability among adults and is **associated** with substantially **lower rates of employment, marriage, and independent living**.

EPIDEMIOLOGY AND ETIOLOGY

- Approximately 0.7 % of the world population suffers from schizophrenia, with symptoms typically presenting in late adolescence or early adulthood.
- **Prevalence is equal in men and women**, but symptoms appear earlier in men, typically occurring at 15 to 24 years compared to 25 to 34 years.

The etiology of schizophrenia remains unknown.

— Genetic and Enviromental play role .

PATHOPHYSIOLOGY

The dopamine hypothesis: the oldest pathophysiologic theory, **proposes that psychosis is caused by excessive dopamine in the brain.**

- **Drugs** that cause an **increase in dopamine** (eg, cocaine and amphetamines) **worsen or cause psychotic symptoms**, and **drugs** that **decrease dopamine** (eg, antipsychotics) **improve psychotic symptoms.**
- However, data reveal a more complicated picture with both **hyperdopaminergic** and **hypodopaminergic brain regions** in schizophrenia.
 - **Hypodopaminergic** activity in the prefrontal lobe is thought to relate to **the core negative symptoms.**

- “Dysregulation hypothesis,”: hyperdopaminergic and hypodopaminergic brain regions in schizophrenia.
- Other implicated neurotransmitter systems include a combined dysfunction of the dopamine and glutamate neurotransmitter systems. It is hypothesized that **glutamate impacts dopaminergic activity** in the mesolimbic and mesocortical pathways. possibly through malfunctioning N-methyl-daspartate (NMDA) receptors.
- It is notable that to date, **antipsychotics without any primary or secondary dopamine modulating properties** have been ineffective for the **treatment of positive symptoms** of schizophrenia.

CLINICAL PRESENTATION AND DIAGNOSIS

❑ *Psychotic symptoms (positive symptoms):*

- Hallucinations (distortions or exaggeration of perception).
 - Most frequently auditory, can also be visual, olfactory, gustatory, and tactile.
 - Voices may be threatening or commanding (eg, commanding the person to perform a particular action).
- Delusions (fixed false beliefs).
 - Beliefs despite invalidating evidence
 - May be bizarre in nature.
 - suspiciousness
- Thought disorder (illogical thought and speech).
 - Tangentiality (unrelated to the main topic)
 - Circumstantiality (delay in getting to the point because of unnecessary details and irrelevant remarks)
 - Perseveration (the repetition of a particular response)



❑ *Negative symptoms:*

- Impoverished speech and thinking
- Lack of social drive (avolition): lack of initiative or motivation
- Flatness of emotional expression
- Apathy: absence of interest in the environment

❑ *Cognitive impairments:*

- Attention, perception, thinking
- Processing speed
- Verbal, visual memory, and working memory
- Problem solving

- In addition to the positive, negative, and cognitive symptoms of schizophrenia, people with schizophrenia may appear: uncooperative, suspicious, hostile, anxious, or aggressive.
- Psychotic and depressive symptoms may lead to poor hygiene and impaired self-care.
- Sleep and appetite are often disturbed, and they often have difficulty living independently, forming close relation.

Diagnosis

- diagnosis of schizophrenia is made clinically because there are no psychological assessments, brain imaging, or laboratory examinations that confirm the diagnosis.
- Patients presenting with odd behaviors, illogical thought processes, fixed false beliefs, and hallucinations should be comprehensively assessed to rule out other diagnoses or contributing factors.
- The commonly accepted diagnostic criteria for schizophrenia are from the *Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-5)*.
 - Involvement with law enforcement is fairly common for vagrancy, loitering, and disturbing the peace.
- Life expectancy is shortened due to suicide, accident

- The onset of schizophrenia can be rapid with **acute psychosis** presenting as the first symptom, or onset can be insidious with **negative symptoms** and social impairments predating psychosis by many years.
- Whether **insidious** or **acute**, the period around the diagnosis is difficult for patients, families, and clinicians because (**Patients may hide symptoms, and isolate themselves**).
- Recent data suggest that people treated early in their illness may have a better prognosis .

Diagnostic Criteria for Schizophrenia

- A. Two (or more) of the following, each present for a significant portion of time during a 1-month period (or less if successfully treated). At least one of these must be 1, 2, or 3:
1. Delusions
 2. Hallucinations
 3. Disorganized speech (eg, frequent derailment or incoherence)
 4. Grossly disorganized or catatonic behavior
 5. Negative symptoms (ie, diminished emotional expression or avolition)
- B. For a significant portion of the time since the onset of the disturbance, level of functioning in one or more major areas, such as work, interpersonal relations, or self-care, is markedly below the level achieved before onset (or when onset is in childhood or adolescence, there is a failure to achieve expected level of interpersonal, academic, or occupational functioning).
- C. Continuous signs of the disturbance persist for at least 6 months. This 6-month period must include at least 1 month of symptoms (or less if successfully treated) that meets Criterion A (ie, active-phase symptoms) and may include periods of prodromal or residual symptoms. During these prodromal or residual periods, the signs of disturbance may be manifested by only negative symptoms or by two or more symptoms listed in Criterion A present in an attenuated form (eg, odd beliefs, unusual perceptual experiences).

- D. Schizoaffective disorder and depressive or bipolar disorder with psychotic features have been ruled out because either (1) no major depressive or manic episodes have occurred concurrently with the active-phase symptoms or (2) if mood episodes have occurred during active-phase symptoms, they have been present for a minority of the total duration of the active and residual periods of the illness
- E. The disturbance is not attributable to the physiological effects of a substance (eg, drug of abuse or medication) or another medical condition
- F. If there is a history of autism spectrum disorder or communication disorder of childhood onset, the additional diagnosis of schizophrenia is made only if prominent delusions or hallucinations, in addition to the other required symptoms of schizophrenia, are also present for at least 1 month (or less if successfully treated)

SCHIZOPHRENIA

DIAGNOSIS (DSM-V)

① two of following:

at least
ONE of
these

- ☐ Delusions
- ☒ hallucinations
- ☐ Disorganized Speech
- ☒ Disorganized/catatonic behavior
- ☒ Negative symptoms

② Ongoing for
6 MONTHS { **PRODROMAL**
[ACTIVE] ~ 1 month
RESIDUAL

③ NOT another condition
{ e.g. drug abuse

TREATMENT

Desired Outcomes:

- The goals of treatment are to reduce symptomatology and psychotic relapses and to improve functional and social outcomes.
- Improvements in negative symptoms, cognitive functioning, social skills, and judgment generally require adjunctive treatments and a longer period to improve.

General Approach to Treatment

- The cornerstone of treatment is *antipsychotic medications*, and most patients with schizophrenia relapse when not medicated.
- Treatment with antipsychotic medications **should begin as soon as psychotic symptoms are recognized; why ?**
- Most patients are on lifelong antipsychotic medication because nonadherence and discontinuation are associated with high relapse rates.
- new data suggest that 1 in 7 people with schizophrenia can achieve full recovery
- If other symptoms are present, such as **depression** and **anxiety**, these symptoms should be **aggressively treated**.

Antipsychotic Treatment

- **Antipsychotic medications :**
 - First generation antipsychotic FGAs
 - second generation antipsychotic SGAs
- Compared with the First generation antipsychotic (FGAs), the SGAs are associated with **a lower risk of motor side effects** (**tremor, stiffness, restlessness, and dyskinesia**).
- With the introduction of SGAs, the use of FGAs has progressively decreased, and FGAs have less than 10% in the market.
- An **important distinction of the SGAs** is their lower propensity to cause extrapyramidal symptoms (EPSs) and *tardive dyskinesia (TD)*.

Second-Generation (Atypical) Antipsychotics

- Risperidone (Initial: 1–2 mg, Target: 4–6mg)
 - Olanzapine (Initial: 5–10 mg, Target: 10 –20 mg)
 - Quetiapine (Initial: 25 mg twice daily, Target: 300–750 mg)
 - Ziprasidone (Initial: 20 twice daily, Target: 120–160 daily dose)
 - Aripiprazole (Initial: 10–15 mg, Target: 15–30)
 - Paliperidone (Initial: 6 mg, Target: 3–12 mg)
 - Iloperidone (Initial: 1 mg twice daily, Target: 12–24 mg total daily dose)
 - Asenapine (Initial: 5 mg twice daily, Target: 10–20 mg total daily dose)
 - Lurasidone (Initial: 40 mg , Target: 40–160 mg)
- Many SGAs carry an increased risk for weight gain and for the development of glucose and lipid abnormalities.



Flupentixol + Melitracen



First-Generation (Typical) Antipsychotics^a

Class	Agent (Brand Name)	Dosage Range (mg/day)	Chlorpromazine Equivalents (mg)	Available Formulations
Butyrophenone	Haloperidol (Haldol)	5–30	2	T, LC, I
Dibenzoxazepine	Loxapine (Loxitane, Adasuve)	25–100	10	C, IP
Diphenylbutylpiperidine	Pimozide (Orap)	1–10	1–2	T
Phenothiazines SE	Chlorpromazine (Thorazine)	300–800	100	T, LC, I, R
	Fluphenazine (Prolixin)	2–40	2	T, L, I
	Perphenazine (Trilafon)	8–64	10	T, LC
	Thioridazine (Mellaril)	300–800	100	T, LC
	Trifluoperazine (Stelazine)	15–30	5	T
Thioxanthenes	Thiothixene (Navane)	5–40	4	C

^aLow-potency antipsychotics include thioridazine, mesoridazine, and chlorpromazine. High-potency antipsychotics include haloperidol, fluphenazine, thiothixene, and pimozide.

C, capsule; C-SR, controlled or sustained release; I, injection; L, liquid solution, elixir, or suspension; LC, liquid concentrate; R, rectal suppository; T, tablet; IP, inhalation powder.

Table 37–3

Comparative Side Effects Among the SGAs and Haloperidol

Side Effect	Cloz	Risp ^a	Olan	Quet	Zip	Ari	Ilo	Asen	Lur	Hal
Anticholinergic side effects	+++	±	++ (Higher doses)	+	±	±	±	+	±	±
EPS at clinical doses	+	+	±	±	±	±	+	+	+	++
Dose-dependent EPS	0	++	+	0	+	±	+	+	+	+++
Orthostatic hypotension	+++	++	+	++	+	+	++	+	+	++
Prolactin elevation	0	+++	+	±	+	0	+	±	±	+
QTc prolongation	+	±	±	+	+	±	+	+	+	±
Sedation	+++	+	+	++	+	+	++	+	+	+
Seizures	++	±	±	±	±	±	±	±	±	±
Weight gain	+++	++	+++	++	+	+	+	+	+	±
Glucose dysregulation	++	+	++	+	±	±	±	±	±	±
Lipid abnormalities	+++	+	+++	++	±	±	±	±	±	±

Cloz, clozapine; Risp, risperidone; Olan, olanzapine; Quet, quetiapine; Zip, ziprasidone; Ari, aripiprazole; Ilo, iloperidone; Asen, asenapine; Lur, lurasidone; Hal, haloperidol.

^aSide effects similar for paliperidone.

0, absent; ±, minimal; +, mild or low risk; ++, moderate; +++, severe; EPS, extrapyramidal side effects; SGA, second-generation antipsychotic.

Side Effects of the First-Generation Antipsychotics

- The FGAs are commonly associated with **EPS**:
 - (including akathisia (20% to 40%)[motor or subjective restlessness],
 - dystonia [muscle spasm], and
 - pseudoparkinsonism (30% to 60%) [akinesia, tremor, and rigidity])
- **TD** is a movement disorder (13% to 36%).
- **Neuroleptic malignant syndrome (NMS)**, a life-threatening emergency characterized by **hyperthermia**, **severe muscular rigidity**, **autonomic instability**, and **altered consciousness**.. FGAs and SGA may induce NMS.

Risk factor NMS :

- **Rapid** dose **escalation**,
- use of **high-potency FGAs** at higher doses, and
- **younger patients** have a higher risk of NMS

(ttt of NMS are: DC the agent and O2, IV fluid and antipyretic).

- **Dermatologic side effects:**
- **Sedation and anticholinergic side effects**
- **orthostatic hypotension and tachycardia**
- **QTc prolongation**

Table 37-6

Side Effects of First-Generation Antipsychotics

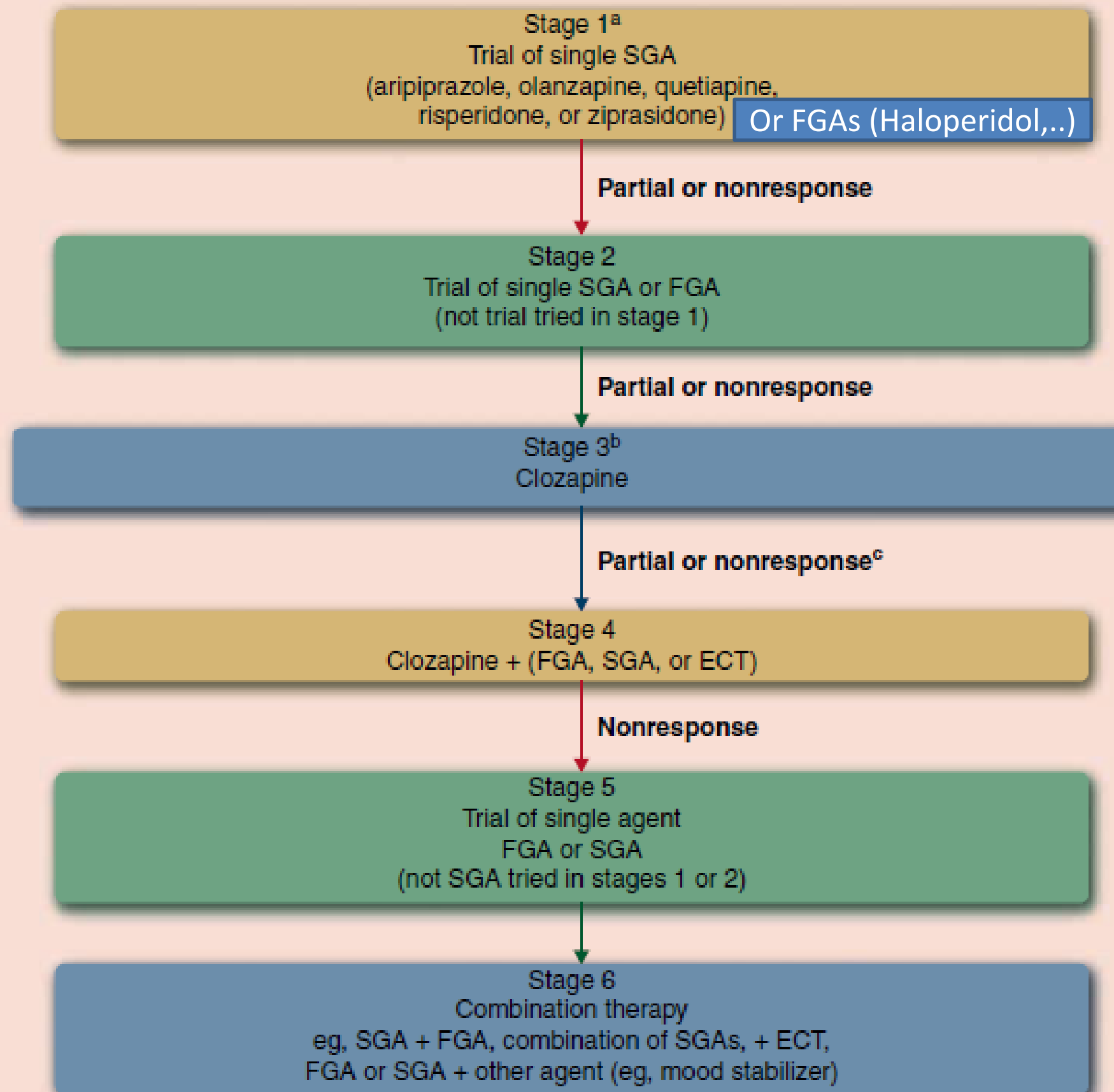
	EPS	Sedation	Anticholinergic Side Effects	Cardiovascular Side Effects	Seizure Effects/QTc Prolongation
■ Chlorpromazine	++	++++	+++	++++	++
■ Thioridazine	++	++++	++++	++++	+++
Loxapine	+++	+++	++	+++	+
Trifluoperazine	+++	++	++	++	+
Perphenazine	+++	++	++	++	+
Thiothixene	+++	++	++	++	+
Fluphenazine	++++	++	++	++	+
Haloperidol	++++	+	+	+	+

+, very low; ++, low; +++, moderate; +++, high; EPS, extrapyramidal side effects.

Treatment Guidelines and Algorithms

- A **widely accepted treatment algorithm** in the United States is the Texas Implementation of Medication Algorithms ([TIMA](#)).
- **Choice of antipsychotic** should be guided by considering the **clinical characteristics of the patient** and the **efficacy** and **side-effect profiles** of the medication.
- **Stages may be skipped** depending on the **clinical picture** or history of **antipsychotic failures**.
- **According new guidelines for** schizophrenia, the **FGAs or SGAs (except clozapine)** should be used as **first-line treatment**.
- Treatment with a given drug should be **continued for 4 to 6 weeks to assess response**.
- If only **partial response** or **nonresponse is noted**, a **trial of a second SGA** should be initiated.

First episode or never before treated with an SGA



^aIf patient is nonadherent to medication, the clinician may use risperidone microspheres, haloperidol, or fluphenazine decanoate at any stage, but should carefully assess side effects.

Treatment Adherence

- Neurocognitive deficits and paranoid symptoms may hamper adherence.
- Antipsychotic side effects such as EPS, weight gain, and sexual dysfunction are also major contributing factors to treatment nonadherence.
- treatment with long-acting formulations should be encouraged, Risperidone, paliperidone, olanzapine, and aripiprazole are available as long-acting injectable formulations.
- Oral tolerability of these agents should be ensured prior to initiating long-acting injection; Why ?

Special Populations

Children and Adolescents:

- The diagnosis of schizophrenia in children and adolescents is often **challenging**.
- differential diagnosis :
 - **autistic spectrum disorders,**
 - **attention-deficit/hyperactivity disorder (ADHD), and**
 - **language or communication disorders.**
- The existence of prominent hallucinations or delusions **helps make the diagnosis because they are not prominent in other disorders.**

- Because of concerns about EPS and TD in children and adolescents, it is recommended that antipsychotic therapy be initiated with SGAs.
- Aripiprazole, risperidone, quetiapine, olanzapine, and paliperidone are approved by (FDA) for the treatment of schizophrenia in pediatric and adolescent populations.
- Agents with significant sedative and anticholinergic side effects are not preferred because they can interfere with thinking, thus impairing school performance.

Elderly:

- Psychotic symptoms in late life (after 65 years of age) generally **result** from an ongoing chronic illness (PD, AD); however, a **small percentage** of patients develop psychotic symptoms known as late-life schizophrenia.
- Older adults are particularly vulnerable to the side effects of the FGAs(Pseudoparkinsonism,TD, Orthostasis, anticholinergic effects).
- SGAs dosing in the elderly is **initiated lower**, and **titration is slower** than in younger adults. Maximum doses are often **half of adult doses**.

Dually Diagnosed Patients:

Dually Diagnosed Patients: **Estimates** of the **proportion of schizophrenia patients** abusing alcohol and/or illicit drugs range from 40% to 60%.

Dually diagnosed patients are more likely to be:

- **nonadherent** with treatment
 - **poorer response rate** to the FGAs,
 - **more severe psychosis**, and
 - **higher rates of relapse** and rehospitalization
- **SGAs are effective** in this population, and they **may cause a reduction in the use of drugs and alcohol**.

Treatment-Resistant Patients:

- For 20% to 30% of people with schizophrenia, **drug treatment is ineffective**.

A standard definition of treatment resistance is: persistent positive symptoms despite treatment with at least two different antipsychotics given at adequate doses for an adequate duration (4–6 weeks).

- Clozapine remains the only drug in treatment-resistant patients, and it is the **only drug approved for treatment-resistant schizophrenia**, with response rates of 30% to 50% in treatment-resistant patients.
- Clozapine is FDA approved for treatment of **suicidal behavior in people with psychosis**.
- The optimal plasma level of clozapine is a minimum trough level of 300 to 350 ng/mL (equ. 200-400 mg)
- S/E: **agranulocytosis (Neutropenia)** (potentially life-threatening side effect.), required long-term hematologic monitoring.
- Orthostatic hypo, dyslipidemia, sedation, weight gain, anticholinergic are also common.

Acutely Psychotic Patients:

- **IM SGAs** are now recommended as first-line therapy in agitated schizophrenia patients.
- IM benzodiazepines most often **lorazepam** almost without concomitant oral antipsychotics are also used.

Adjunct Treatments:

- **Anticholinergic medications** (eg, **benztropine**, 1 to 2 mg two times daily; **trihexyphenidyl** 1 to 3 mg three times daily; and **diphenhydramine**, 25 to 50 mg two times daily) are used to treat EPS or as prophylactic at high risk patient.
- **β-Blockers** (eg, **propranolol 30–120 mg/day**) are sometimes effective for patients who develop akathisia.
- In some situations, the concomitant use of **benzodiazepines** (eg, **lorazepam 1–3 mg/day**) with the **SGAs** may be necessary for **agitation or insomnia**.
- In **schizoaffective disorder**: **Mood stabilizers**, such as **lithium** and the **anticonvulsants**, have long been used adjunctively with the **antipsychotics**.
- **Schizophrenia who have depressive symptoms**: **SSRI with SGA** (need dose adjustment).

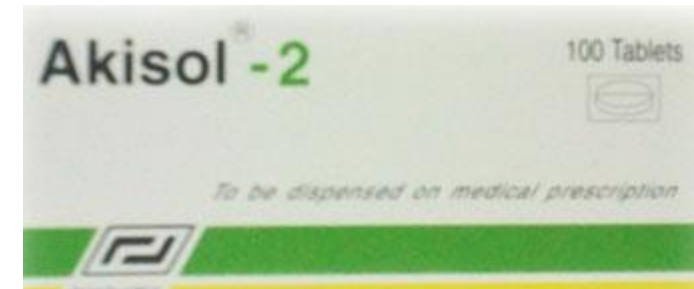


Table 37–2

Second-Generation (Atypical) Antipsychotics

Second-Generation Antipsychotic	Usual Starting and Target Dose (mg/day) (Schizophrenia)	Maximum Dose Likely to Be Beneficial (mg/day)	Available Dosage Forms
Aripiprazole (Abilify)	Initial: 10–15 Target: 15–30	30	<ul style="list-style-type: none"> • 2-, 5-, 10-, 15-, 20-, and 30-mg tablets • 1-mg/mL oral solution • 10- and 15-mg Abilify Discmelt orally disintegrating tablets • IM 9.75 mg/1.3 mL • Abilify Maintena extended-release 300- and 400-mg vial powder for suspension long acting injection • 5- and 10-mg sublingual tablets
Asenapine (Saphris)	Initial: 5 twice daily Target: 10–20 total daily dose	10–20	
Clozapine (Clozaril, Fazaclo, Versacloz, also available generically)	Initial: 12.5–25/day Target: 300–450	500–800	<ul style="list-style-type: none"> • 25-, 50-, 100-, and 200-mg tablets • FazaClo (orally disintegrating tablets) 12.5-, 25-, 100-, 150-, 200-mg • Versacloz (oral suspension) 50 mg/mL • 1-, 2-, 4-, 6-, 8-, 10-, 12-mg tablets
Iloperidone (Fanapt)	Initial: 1 twice daily Target: 12–24 total daily dose	24	
Lurasidone (Latuda)	Initial: 40 Target: 40–160	160	<ul style="list-style-type: none"> • 20-, 40-, 60-, 80-, 120 mg tablets
Olanzapine (Zyprexa, also available generically)	Initial: 2.5–10 Target: up to –20	30–40 ^a	<ul style="list-style-type: none"> • 2.5-, 5-, 7.5-, 10-, 15-, and 20-mg tablets

<u>Paliperidone</u> (Invega)	<u>Initial: 6</u> Target: 6–12	<u>6–12</u>	<ul style="list-style-type: none"> • <u>suspension long acting injection</u> • 1.5-, 3-, 6-, and 9-mg tablets • Invega Sustenna 39-, 78-, 117-, 156-, 234-mg prefilled syringes • 25-, 50-, 100-, 200-, 300-, and 400-mg tablets • Seroquel XR (extended-release tablets) 50-, 150-, 200-, 300-, and 400-mg tablets
<u>Quetiapine</u> (Seroquel, also available generically)	Regular release <u>Initial: 25 twice daily</u> Target: 300–750 Extended release Initial: 300 Target 400–800	800	<ul style="list-style-type: none"> • 0.25-, 0.5-, 1-, 2-, 3-, and 4-mg tablets • 1 mg/mL (30 mL) solution • Risperdal M-tab (orally disintegrating tablets) 0.5-, 1-, 2-, 3-, and 4-mg tablets • Risperdal Consta long-acting injectable 12.5-, 25-, 37.5-, and 50-mg vial/kit • 20-, 40-, 60-, and 80-mg capsules • IM 20 mg/mL
<u>Risperidone</u> (Risperdal, also available generically)	<u>Initial: 1–2</u> Target: 4–6	6–8	
<u>Ziprasidone</u> (Geodon, also available generically)	Initial: <u>20 twice daily</u> Target: 120–160 total daily dose	<u>160–240^a</u>	

Table 37–8

Monitoring of White Blood Cell Count and Absolute Neutrophil Count During Clozapine Treatment

	Hematologic Values	Frequency of WBC and ANC Monitoring
<u>Before clozapine initiation</u>	Recommended levels: <u>$WBC \geq 3.5 \times 10^3/mm^3$</u> ($3.5 \times 10^9/L$) and <u>$ANC \geq 2 \times 10^3/mm^3$</u> ($2 \times 10^9/L$) No history of a <u>myeloproliferative disorder</u> or clozapine-induced agranulocytosis	
<u>Initiation to 6 months</u>	<u>$WBC \geq 3.5 \times 10^3/mm^3$</u> ($3.5 \times 10^9/L$) and <u>$ANC \geq 2 \times 10^3/mm^3$</u> ($2 \times 10^9/L$)	<u>Weekly for 6 months</u>
<u>6–12 months</u>	<u>$WBC \geq 3.5 \times 10^3/mm^3$</u> ($3.5 \times 10^9/L$) and <u>$ANC \geq 2 \times 10^3/mm^3$</u> ($2 \times 10^9/L$)	<u>Every 2 weeks for 6 months</u>
<u>After 12 months of therapy</u>	<u>$WBC \geq 3.5 \times 10^3/mm^3$</u> ($3.5 \times 10^9/L$) and <u>$ANC \geq 2 \times 10^3/mm^3$</u> ($2 \times 10^9/L$)	<u>Every 4 weeks</u>
<u>Whenever clozapine is discontinued</u>		Weekly for at least 4 weeks from day of discontinuation
<u>Mild leukopenia or granulocytopenia</u>	WBC value lies between <u>$3 \times 10^3/mm^3$</u> ($3 \times 10^9/L$) and <u>$3.5 \times 10^3/mm^3$</u> ($3.5 \times 10^9/L$) or ANC lies between <u>$1.5 \times 10^3/mm^3$</u> ($1.5 \times 10^9/L$) and <u>$2 \times 10^3/mm^3$</u> ($2 \times 10^9/L$)	<u>Twice weekly until returned to recommended levels</u>
<u>Moderate leukopenia or granulocytopenia</u>	WBC value lies between <u>$2 \times 10^3/mm^3$</u> ($2 \times 10^9/L$) and <u>$3 \times 10^3/mm^3$</u> ($3 \times 10^9/L$) or ANC value lies between <u>$1 \times 10^3/mm^3$</u> ($1 \times 10^9/L$) and <u>$1.5 \times 10^3/mm^3$</u> ($1.5 \times 10^9/L$)	<u>Interrupt therapy; monitor daily until $WBC > 3 \times 10^3/mm^3$</u> ($3 \times 10^9/L$) and <u>$ANC > 1.5 \times 10^3/mm^3$</u> ($1.5 \times 10^9/L$); then twice weekly until back to recommended levels
<u>Severe leukopenia or granulocytopenia or agranulocytosis</u>	<u>$WBC < 2 \times 10^3/mm^3$</u> ($2 \times 10^9/L$) or <u>$ANC < 1 \times 10^3/mm^3$</u> ($1 \times 10^9/L$) <u>$ANC \leq 0.5 \times 10^3/mm^3$</u> ($0.5 \times 10^9/L$) (agranulocytosis)	<u>Discontinue treatment and do not rechallenge; monitor daily until $WBC > 3 \times 10^3/mm^3$</u> ($3 \times 10^9/L$) and <u>$ANC > 1.5 \times 10^3/mm^3$</u> ($1.5 \times 10^9/L$); then twice weekly until back to recommended levels

Antipsychotic Dosing of Long-Acting Preparations

Drug	Starting Dose	Maintenance Dose	Comments
Aripiprazole long-acting injection (Abilify Maintena)	400 mg monthly and 14 consecutive days of concurrent oral aripiprazole (10–20 mg) or current oral antipsychotic after first injection	400 mg monthly	Establish tolerability with oral agent first. Dosage adjustments for CYP2D6 poor metabolizers, and in persons who take strong CYP2D6 or 3A4 inhibitors; recommend to avoid use if strong 3A4 inducer
Haloperidol decanoate	20 × oral haloperidol daily dose; in the elderly use 10–15 × oral haloperidol daily dose; Generally 100–450 mg/mo Initial dose should not exceed 100 mg regardless of previous dose requirements (if > 100 mg, give 3–7 days apart)	10–15 × oral haloperidol daily dose, generally 50–300 mg/mo	With initial dosing, oral supplementation may temporarily be necessary; deep IM injection generally with 21-gauge needle; maximum volume per injection site should not exceed 3 mL Available in 50 and 100 mg/mL (5-mL vials and 1-mL ampules)
Fluphenazine decanoate	1.2 × oral fluphenazine daily dose; generally 12.5-mg/2–3 weeks	Based on starting dose and clinical response Generally 12.5–25 mg dosed at 2–4-week intervals (may be up to 6 weeks in some cases)	Can be administered IM or SC; 21-gauge needle, must be dry Should not exceed 100 mg; when dosing above 50 mg, should increase in increments of 12.5 mg Available in 25 mg/mL (5-mL vials)
Olanzapine (Zyprexa Relprevv)	To target oral 10 mg/day dose: Either 210 mg/2 week or 405 mg/4 week during first 8 weeks To target oral 15 mg/day dose: 300 mg/2 week for first 8 weeks To target 20 mg/day oral dose: 300 mg/2 week	To target oral 10 mg/day dose: after 8 weeks, give 150 mg/2 week or 300 mg/4 week To target oral 15 mg/day dose: after 8 weeks, 210 mg/2 week or 405 mg/4 week To target 20 mg/day oral dose: continue with 300 mg/2 week	Gluteal injection, 19-gauge needle Do not confuse with rapid-acting IM injection Must reconstitute with included diluent Measure amount to inject from vial (there will be remaining suspension in vial) Zyprexa Relprevv Patient Care Program: 3-hour observation period; patient must

Paliperidone (Invega Sustenna)	Initiate with 234 mg on day 1 and 156 mg 1 week later, both in deltoid muscle	Recommended monthly maintenance dose is 117 mg (range, 39–234 mg)	First two doses must be given in the deltoid muscle; after that, monthly doses given in either the deltoid or gluteal muscle; available as 39-, 78-, 117-, 156-, and 234-mg prefilled syringes
Risperidone long-acting injection (Risperdal Consta)	25 mg every 2 weeks	25–50 mg every 2 weeks	Previous antipsychotics should be continued for 3 weeks after initial dose of risperidone long-acting injection Recommended to establish tolerability with oral risperidone prior to initiation of long-acting injection Available in 12.5-, 25-, 37.5-, and 50-mg vial/kit; must use needle supplied with kit, administer IM