Chapter 87: Schizophrenia

M. Lynn Crismon; Tawny L. Smith; Peter F. Buckley

CHAPTER SUMMARY FROM THE PHARMACOTHERAPY HANDBOOK

For the Chapter in the Schwinghammer Handbook, please go to Chapter 72, Schizophrenia.

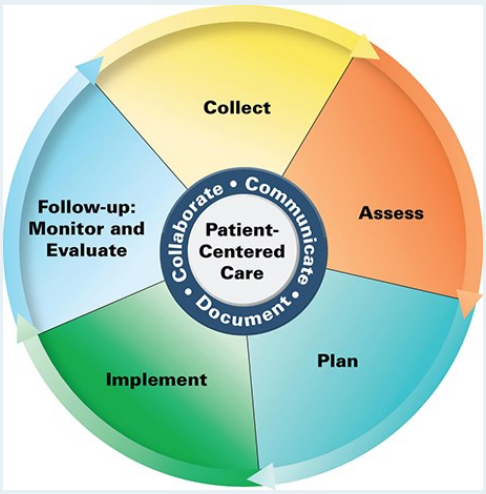
KEY CONCEPTS

KEY CONCEPTS

1. Although dysfunction in multiple neurotransmitters is involved in schizophrenia, the etiology is likely mediated by multiple subcellular processes that are influenced by different genetic polymorphisms.
2. The clinical presentation of schizophrenia is characterized by positive symptoms, negative symptoms, and impairment in cognitive functioning.
3. Comprehensive care for individuals with schizophrenia must occur in the context of a multidisciplinary mental healthcare environment that offers comprehensive psychosocial services in addition to psychotropic medication management.
4. A thorough patient evaluation (eg, history, mental status examination, physical examination, psychiatric diagnostic interview, and laboratory analysis) should occur to establish a diagnosis of schizophrenia and to identify potential co-occurring disorders, including substance use disorders and general medical disorders.
5. Given that it is challenging to differentiate among antipsychotics based on efficacy, adverse medication reaction profiles become important in choosing an antipsychotic for an individual patient.
6. Pharmacotherapy guidelines should emphasize antipsychotic monotherapies that optimize benefit-to-risk ratios before progressing to medications with greater adverse reaction risks. Combination regimens should only be used in the most treatment-resistant patients.
7. Adequate time on a given medication at a therapeutic dose is the most important variable in predicting medication response.
8. Long-term maintenance antipsychotic treatment is necessary for most patients with schizophrenia in order to prevent relapse.
9. Thorough patient and family psychoeducation should be implemented, utilizing motivational interviewing methods that focus on patient-driven outcomes in an effort to allow patients to achieve life goals.
10. Pharmacotherapy decisions should be guided by systematic monitoring of patient symptoms, preferably with the use of brief symptom rating scales and systematic assessment of potential adverse effects.

PATIENT CARE PROCESS

Patient Care Process for Schizophrenia



Collect

- Patient characteristics (eg, age, race, sex, gender identity, pregnancy status)
- Patient history (past mental and medical, medication adherence, family, social—diet, alcohol and substance use, tobacco use)

- Mental status exam
- Medications (current and past)
- Objective data
- Brief Positive and Negative Symptom Scales (see Table 87-11)
- Blood pressure (BP), heart rate (HR), height, weight, and body mass index (BMI) (see Table 87-12)
- Labs: Hemoglobin A1c (HgA1c), lipids, other tests if indicated (see Table 87-12)

Assess

- Patient's concerns and attitudes toward treatment, medication adherence (see Table 87-5)
- Symptom severity and the extent that treatment goals have been met
- Do any co-occurring disorders (mental, substance use disorder, medical) need to be addressed?
- Are patient's psychosocial needs being met? (see Table 87-2)
- Adverse medication reactions (see Tables 87-7 and 87-12)
- Potential for medication interactions (see Tables 87-9 and 87-10)
- Appropriateness and effectiveness of current psychotropic regimen

Plan*

- Actively engage patient in care plan
- Medication therapy regimen (egspecify the continuation and discontinuation of existing therapies) (see Fig. 87-1 and Tables 87-3, 87-4, and 87-6)
- Monitoring parameters including efficacy and time frame (see Tables 87-11 and 87-12)
- Patient education (eg, medication, life style management)
- Referrals to other providers as appropriate (eg, physician, psychologist, social worker)

Implement*

- Provide patient education regarding all elements of treatment plan
- Use motivational interviewing and coaching strategies to maximize adherence
- Schedule follow-up

Follow-up: Monitor and Evaluate*

- Determine symptom attainment (see Table 87-11)
- Presence of adverse effects (see Table 87-12)
- Presence of medication interactions (see Tables 87-9 and 87-10)
- Need for psychosocial interventions
- Patient adherence to treatment plan using multiple sources of information

****Collaborate with patient, caregivers, and other healthcare professionals.***

BEYOND THE BOOK

BEYOND THE BOOK

Watch the approximately 9-minute video on YouTube, "Four Patients with Schizophrenia."

For each of the patients, list the symptoms that are associated with schizophrenia. Use Table 87-11 as a reference, and for each patient list those symptoms that are present on the Brief Positive and Negative Symptom Scales. The intent of this learning activity is to help you identify symptoms associated with schizophrenia and identify symptoms that can be used to monitor response to pharmacotherapy.

INTRODUCTION

Schizophrenia is one of the most complex and challenging psychiatric disorders as it represents a heterogeneous syndrome of disorganized and bizarre thoughts, delusions, hallucinations, inappropriate affect, and impaired psychosocial functioning. From the time that Kraepelin first described dementia praecox in 1896 until publication of the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* (*DSM-5*) in 2013, the description of this illness has continuously evolved.[1] Scientific advances that increase our knowledge of central nervous system (CNS) physiology, pathophysiology, and genetics will likely improve our understanding of schizophrenia in the future.

EPIDEMIOLOGY

The lifetime prevalence of schizophrenia ranges from 0.28% to 0.6%[2] with the worldwide prevalence being similar among most cultures. Schizophrenia most commonly has its onset in late adolescence or early adulthood and rarely occurs before adolescence or after the age of 40 years. Although the prevalence of schizophrenia is equal between the sexes, the onset of illness tends to be earlier in males as they typically have their first episode during their early 20s, whereas with females it is usually during their late 20s.[1]

ETIOLOGY

Although the etiology of schizophrenia is unknown, research has demonstrated various abnormalities in brain structure and function.[3] However, these changes are not consistent among all individuals with schizophrenia. The cause of schizophrenia is likely multifactorial, that is, multiple pathophysiologic abnormalities can play a role in producing the similar but varying clinical phenotypes we refer to as schizophrenia.

A neurodevelopmental model, formed from the study of brains from individuals diagnosed with schizophrenia, has been evoked as one possible explanation for its etiology.[3,4] Although many different avenues of research have been undertaken, most find that biological and functional abnormalities in cell shape, position, symmetry, and connectivity have been associated with development of abnormal brain circuits that lead to the symptoms seen in schizophrenia.[4] The changes seen as part of this research are consistent with a cell migration abnormality during the second trimester of pregnancy, and some studies associate upper respiratory infections during the second trimester of pregnancy with a higher incidence of schizophrenia.[4] Other studies associate low birth weight (LBW; less than 2.5 kg [5.5 lb]), obstetric complications, or neonatal hypoxia with schizophrenia.[4] Theories of maternal stress have been developed which may be related to aberrations in circulating glucocorticoids in utero as a risk factor for schizophrenia.[4] Although imaging studies show decreased cortical thickness and increased ventricular size in the brains of many patients with schizophrenia, this occurs in the absence of widespread changes in the glial cells (or gliosis).[4] One hypothesis for these changes is that obstetric complications and hypoxia, in combination with a genetic predisposition, could activate a glutamatergic cascade resulting in increased neuronal pruning. Genes controlling *N*-methyl-D-aspartate (NMDA) receptor activity are hypothesized to be part of this process, as dendrite pruning, which is part of normal neurodevelopmental process, is higher in individuals with schizophrenia. As synaptic pruning predominantly involves glutamatergic dendrites, hypoxia or other prenatal insults can result in fewer basal neurons overall, and glutamatergic activation can exaggerate the pruning process.[3,4] Furthermore, a relationship has been documented between autoimmune encephalitis and psychosis, which is based upon glutamate receptor autoantibodies. This is important as studies have shown an increased susceptibility to immune/autoimmune disorders in schizophrenia, as well as abnormalities of autoantibodies and cytokine functioning.[5] Although this etiology is felt to be uncommon, it serves as a model for the heuristic immune hypothesis of schizophrenia, which also emphasizes integration of mental and physical well-being.[5] A plethora of diverse findings point to immune dysfunction in schizophrenia.

Numerous studies have shown neuropsychological abnormalities, impairment in reaching normal motor milestones and abnormal movements, in young children who later develop schizophrenia.[4] These abnormalities in brain function occur long before the onset of psychotic symptomatology and provide empirical evidence for schizophrenia being a neurodevelopmental disorder.[2] Furthermore, brain imaging studies show deteriorative brain changes in patients with frequent relapses,[4,6] with these changes being most pronounced among adolescents with early onset schizophrenia.[4,7] Therefore, continued pathophysiological changes, secondary to the original neurodevelopmental insult, may lead to the first psychotic episode, and brain morphology resembling neurodegeneration.[3,4,7]

Although the risk of developing schizophrenia is estimated as 0.28% to 0.6% worldwide, the risk is approximately 3% if a second-degree relative has the illness and 10% if there is a first-degree relative.[4] If both parents have schizophrenia, the risk of schizophrenia, to the offspring, increases to approximately 40%. Dizygotic twins report a 12% to 14% risk if one twin has the illness, with this increasing to 48% for monozygotic twins.[4] Furthermore, in siblings the onset of illness tends to occur at the same age in each, and adoption studies indicate that environmental changes during the child's developmental stages do not alter their genetic risk, both of which give less credence to the possibility of an environmental precipitant.

1 Numerous approaches have been utilized to study the genetics of neurodevelopment and schizophrenia risk, but one single genetic risk factor has not been found.[7] Genome-wide association studies (GWAS) have identified over 120 genetic small-effect loci that account for a small percent of the risk.[3,7] Of major interest is the finding that polymorphisms of the complement component 4 (*C4*) genes on chromosome 6 may be implicated in the abnormal dendritic pruning seen in individuals with schizophrenia.[8] Additionally, schizophrenia risk has been increasingly linked to about a dozen recurrent copy number variants (CNV) that have high penetrance; however, cumulatively they likely account for no more than 1% to 2% of all cases.[3,7] Genetic risk has also been attributed to the synaptic protein neurexin 1 (NRXN1) and neuregulin 1 (NRG1) which, in particular, may increase the risk of developing the first psychotic episode for those who are already at high risk.[3] MicroRNAs (mRNA), which are small noncoding RNAs critical to neurodevelopment and regulation of adult neuronal processes, have also been linked to schizophrenia risk and are being actively explored.[3]

There is an overlap—both clinically and biologically—between schizophrenia and mood disorders with single nucleotide polymorphisms (SNPs) from chromosomes 3, 10, and 12 being common across schizophrenia, bipolar disorder, and major depression. Two of these SNPs were at loci related to the pathophysiology of calcium-channels.[3,7] Some of the CMVs identified for schizophrenia risk have also been associated with autism spectrum disorder, intellectual disability, and attention-deficit hyperactivity disorder.[7] Thus, several genetic and biological studies now suggest a greater shared genetic—and neurobiological—basis across psychiatric disorders so that the idea of schizophrenia being a distinct "condition" is increasingly being challenged.

PATHOPHYSIOLOGY

Studies have found consistent decreases in gray matter in multiple brain areas, including the frontal lobes, cingulate gyri, and medial temporal regions among others. A longitudinal study of high-risk youth showed a substantially greater decrease in gray matter in high-risk youth who progressed to psychosis than in high-risk youth who did not progress to psychosis or in normal controls.[9] Additionally, increases in ventricular size, as well as decreased white matter in the corpus callosum, have been observed.[9] Changes in hippocampal volume may correspond with impairment in neuropsychological testing.[4,6] It is felt then, that rather than a decrease in the number of neurons in affected brain areas, a decrease in axonal and dendritic communications between cells can result in a loss of connectivity impacting neuronal adaptivity and CNS homeostasis,[4,6] which are likely consistent with the evidence for abnormal neuronal pruning.[2] Intense research efforts have been made to explore and link brain imaging and other biomarkers to disease expression and progression, in an effort to arrive at clinically relevant biomarkers that could aid treatment of schizophrenia—just as has occurred in cancer and other medical conditions.

1 Historically, schizophrenia has been attributed to dopamine (DA) receptor defects, but increasingly subcortical dopaminergic dysregulation, including increased DA synthesis and release have been observed.[10] While presynaptic changes in dopaminergic neurons occur and are consistent with the neurodevelopmental model that has been proposed,[3,6] numerous positron emission tomography (PET) studies have shown brain abnormalities including increased glucose metabolism in the caudate nucleus and decreased blood flow and glucose metabolism in the frontal lobe and left temporal lobe.[4] These findings may indicate dopaminergic hyperactivity in the head of the caudate nucleus and dopaminergic hypofunction in the frontotemporal regions, which may be confirmed by alterations in dopamine-2 (D_2) receptor densities.[4,6] However, increases in presynaptic DA synthesis and release into the striatum may only translate into a small increase in $D_{2/3}$ receptor availability.[11]

Additionally, PET studies assessing dopamine-1 (D_1) receptor function suggest that subpopulations of patients with schizophrenia may have decreased densities of D_1 receptors in the caudate nucleus and the prefrontal cortex, in addition to the D_2 receptors. Clinically this may lead to hypofrontality within the prefrontal cortex, which can be associated with a lack of volition and cognitive dysfunction, core features of schizophrenia. It is unknown whether these changes represent a primary event or secondary processes related to other pathophysiologic abnormalities in schizophrenia. Because of the heterogeneity in the clinical presentation of schizophrenia, the DA hypothesis may be more applicable to individuals who respond to antipsychotic treatment, with multiple different etiologies possibly being responsible for causing

schizophrenia.[4,6] While attempts have been made to develop relationships between these abnormal findings and behavioral symptoms present in patients with schizophrenia, the positive symptoms of schizophrenia are possibly more closely associated with DA-receptor hyperactivity in the mesocaudate, whereas negative symptoms and cognitive impairment are most closely related to DA-receptor hypofunction in the prefrontal cortex. As the presynaptic D_1 receptors in the prefrontal cortex are thought to be involved in modulating glutamatergic activity, this hypofunctionality can impact working memory in individuals with schizophrenia.[4,6]

One can examine different neurotransmitter alterations in the context of different proposed phases of schizophrenia.[12] The Predrome Phase typically occurs before an individual is diagnosed with schizophrenia. This phase can last weeks to years where clinically high-risk individuals are thought to exhibit glutamategic synaptic dysfunction that results in a glutamate signaling defect, leading to some affective and/or psychotic symptoms. Partial compensation by gamma-aminobutyric acid (GABA) downregulation and synaptic proliferation are associated with the Prodromal Phase. This deficit in GABA is felt to result in less inhibition of excitatory circuits, producing dopaminergic dysfunction, the onset of psychosis, and the Syndrome Phase, with the degree of dopamine dysfunction associated with more severe disease.[6] During the Syndrome Phase, most individuals are officially diagnosed with schizophrenia. In the last phase, the Chronic Phase, years of chronic schizophrenia symptoms and treatments are thought to be associated with the loss of gray matter compounding the synaptic deficits.[12]

As the glutamatergic system is one of the most widespread excitatory neurotransmitter systems in the brain, hypo- or hyperactive alterations in function can result in toxic neuronal reactions.[12] Dopaminergic innervation from glutamate in the ventral striatum decreases the limbic system's inhibitory activity (perhaps through GABA interneurons) and thus increases arousal. The corticostriatal glutamate pathways have the opposite effect, whereas inhibiting dopaminergic function from the ventral striatum allows increased inhibitory activity in the limbic system. Due to the interaction between glutamatergic and dopaminergic tracts, as well as through GABA interneurons, glutamatergic deficiency produces symptoms similar to those of dopaminergic hyperactivity and possibly those seen in schizophrenia. Therefore, alterations in the interactions between dopamine and glutamate due to NMDA hypofunction have been associated with the latent clinical expression of psychotic symptoms in late adolescence or early adulthood.

Schizophrenia is a complex disorder, and multiple etiologies likely exist. Based on current knowledge, it is naïve to think that any one proposed etiology or one dysfunction in neurotransmission can adequately explain the genesis of this complex disease. Moreover, ongoing research into distinct biomarkers for schizophrenia, as well as the promise of stem cell research to disentangle the pathobiology of this enigmatic disorder, will also help identify phenotypes and help to determine the boundaries between psychosis and mood disorders.[3,7,11,13]

CLINICAL PRESENTATION

The clinical presentation of functional psychosis seen with schizophrenia is highly variable. Despite numerous attempts to portray a stereotype in movies and on television, the stereotypic person with schizophrenia essentially does not exist, and schizophrenia is not a "split personality." It is a chronic disorder of thought and affect with the individual having a significant disturbance in interpersonal relationships and ability to function in society.

The first psychotic episode can be sudden in onset with few premorbid symptoms, or more commonly is preceded by withdrawn, suspicious, peculiar behavior, termed schizoid. During acute psychotic episodes, the patient loses touch with reality, and in a sense, the brain creates a false reality to replace it. Acute psychotic symptoms can include hallucinations (especially hearing voices), delusions (fixed false beliefs), and ideas of influence (beliefs that one's actions are controlled by external influences). Thought processes are disconnected (loose associations), the patient may not be able to carry on logical conversation (alogia), and can have simultaneous contradictory thoughts (ambivalence). The patient's affect can be flat (no emotional expression), or it can be inappropriate and labile. The patient is often withdrawn and inwardly directed (autism). Uncooperativeness, hostility, and verbal or physical aggression can be seen because of the patient's misperception of reality. Self-care skills are impaired, and patients may be dirty and unkempt with generally poor hygiene during acute episodes. Sleep and appetite are often disturbed. When the acute psychotic episode remits, the patient typically has residual features, which is an important point in differentiating schizophrenia from other psychotic disorders. Although residual symptoms and their severity vary, patients can have difficulty with anxiety management, suspiciousness, and lack of volition, motivation, insight, and judgment. They often have difficulty living independently, and because of poor anxiety management and suspiciousness, they are frequently withdrawn socially, and have difficulty forming close relationships with others. Impaired volition and motivation contribute to poor self-care skills and make it difficult for the patient with schizophrenia to maintain employment.

Patients with schizophrenia frequently experience a lack of historicity, or difficulty in learning from their experiences, resulting in them repeatedly making the same mistakes in social conduct and situations requiring judgment. They have difficulty understanding the importance of treatment, including medications, in maintaining their ability to function. Therefore, they tend to discontinue treatments, increasing the risk of relapse and rehospitalization.

The co-occurrence of substance use disorder (SUD) (predominantly alcohol or polysubstance—alcohol, cannabis, and cocaine) in patients with schizophrenia is very common and is another frequent reason for relapse and hospitalization.[1] This effect can be caused by direct toxic effects of these substances on the brain,[14] but is also caused by the medication nonadherence that is associated with substance use. Some substances—most notably heavy cannabis use during adolescence—have been associated with a higher prevalence of schizophrenia, as cannabis use raises the risk of schizophrenia four- to sixfold.[15]

Although the course of schizophrenia is variable, the long-term prognosis for many patients is poor. It is marked by intermittent acute psychotic episodes and impaired psychosocial functioning between acute episodes, with most of the deterioration in psychosocial functioning occurring within 5 years after the first psychotic episode.[16] By late life, the patient can appear "burned out," that is, they cease to have acute psychotic episodes, but residual symptoms persist (the chronic phase). In a subpopulation of patients, probably 5% to 15%, psychotic symptoms are nearly continuous, and response to antipsychotics is poor.[16]

Schizophrenia is a chronic disorder, and the patient's history must be carefully assessed for dysfunction that has persisted for longer than 6 months. After their first episode, patients with schizophrenia rarely have a level of adaptive functioning as high as before the onset of the disorder. *The Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* (*DSM-5*) should be consulted for the complete criteria for a diagnosis of schizophrenia.[1] The *DSM-5* also asks the clinician to specify the episode severity for schizophrenia after having the diagnosis for at least 1 year and whether the patient is presenting with catatonia.[1]

The *DSM-5* classifies the symptoms of schizophrenia into two categories: positive and negative; however, greater emphasis is now being placed on a third symptom category, cognitive dysfunction.[1,16] The areas of cognition found to be abnormal in schizophrenia include attention, working memory, and executive function. Positive symptoms have traditionally attracted the most attention and are the ones most improved by antipsychotics. However, negative symptoms and impairment in cognition are more closely associated with poor psychosocial function.

CLINICAL PRESENTATION: Schizophrenia and Symptoms Clusters

Positive Symptoms

- Suspiciousness
- Unusual thought content (delusions)
- Hallucinations
- Conceptual disorganization

Negative Symptoms

- Affective flattening
- Alogia
- Anhedonia
- Avolition

Cognitive Symptoms

- Impaired attention
- Impaired working memory
- Impaired executive function

Along with these characteristic features of schizophrenia, many patients also have comorbid psychiatric and general medical disorders.[2,16] These include depression, anxiety disorders, SUD, and general medical disorders such as respiratory disorders, cardiovascular disorders, and metabolic disturbances. These comorbidities substantially complicate the clinical presentation and course of schizophrenia.

Symptom complexes are correlated with prognosis, cognitive functioning, structural abnormalities in the brain, and response to antipsychotic medications. Negative symptoms and cognitive impairment are more closely associated with prefrontal lobe dysfunction and positive symptoms with temporolimbic abnormalities. As many patients demonstrate both positive and negative symptoms, those with negative symptoms frequently have more antecedent cognitive dysfunction, poor premorbid adjustment, low level of educational achievement, and a poorer overall prognosis.[1,16]

TREATMENT

Desired Outcome

3 Pharmacotherapy is a mainstay of treatment in schizophrenia, as it is impossible to effectively implement psychosocial rehabilitation programs without antipsychotic treatment in most patients.[14] The most current treatment guidelines for schizophrenia espouse 24 recommendations, three of which relate to overall assessment and treatment planning, 11 of which cover medication treatments, and the remaining 10 focus on psychosocial approaches to care (Table 87-1). A pharmacotherapeutic treatment plan should be developed that delineates medication-related aspects of therapy. Most deterioration in psychosocial functioning occurs during the first 5 years after the initial psychotic episode, and treatment should be particularly assertive during this period.[16] The individualized treatment plan created for each patient should have explicit end points defined, including realistic goals for the target symptoms most likely to respond, and the relative time course for response.[17] Other desired outcomes include avoiding unwanted adverse medication reactions, integrating the patient back into the community, increasing adaptive functioning to the extent possible, and preventing relapse.

TABLE 87-1

Guidelines for the Care of Patients with Schizophrenia

Patients have a comprehensive initial assessment
Initial assessment includes a quantitative measure of symptoms—functioning
Treatment planning includes evidence based pharmacologic and nonpharmacologic treatments
Patients receive antipsychotic medications for treatment, evaluating both efficacy and safety
Patients whose illness has improved with medication receive continued antipsychotic treatment
Patients with treatment resistant schizophrenia receive clozapine
Patients with persistent suicidality/risk of suicidality despite other treatments receive clozapine
*Patients with aggression that persists despite other treatments receive clozapine
*Patients with preference and/or history of inadequate medication noncompliance receive long-acting injectable antipsychotic medication
Patients with antipsychotic-induced dystonia receive an anticholinergic medicine
*Patients with antipsychotic-induced parkinson symptoms have their medication dosage reduced or switched to another antipsychotic or receive an anticholinergic medication
*Patients with antipsychotic induced akathisia have their medication dosage reduced, switch to another antipsychotic, or receive either a benzodiazepine or beta blocker
Patients with at least moderate tardive dyskinesia that is antipsychotic induced receive a vesicular monoamine transporter 2 (VMAT2) reversible inhibitor
Patients with first episode psychosis are treated in a comprehensive program
Patients receive cognitive behavioral therapy
Patients receive psychoeducation
Patients receive supported employment opportunities
Patients with social complications contributing to recurrent relapses receive assertive community treatment
*Patients with family contact receive family supportive activities
*Patients receive recovery-based activities
*Patients receive cognitive remediation
*Patients with focus on social performances receive social skills training
*Patients receive supportive psychotherapy

** Recommended or suggested by the American Psychiatric Association (APA). Data from References 18 and 20-22.*

Nonpharmacologic Therapy

Psychosocial rehabilitation programs focused on improving patients' adaptive functioning are the mainstay of non-medication treatment for schizophrenia. These programs include case management, psychoeducation, targeted cognitive therapy, basic living skills, social skills training, basic education, work programs, supported housing, and financial support. In particular, programs aimed at supportive employment and housing are effective and considered "best practices." Those that involve families in the care and life of the patient have been shown to decrease rehospitalization and improve functioning in the community. For particularly low-functioning patients, assertive intervention programs, referred to as *active community treatment* (ACT), are effective in improving patients' functional outcomes. These ACT teams are available on a 24-hour basis and work in the patient's home and/or place of employment to provide comprehensive treatment, including medication, crisis intervention, daily living skills, and supported employment and housing.[18] Pharmacotherapy cannot be successful without proper attention to these other aspects of care, as people with schizophrenia need comprehensive care, with coordination of services across psychiatric, SUD, medical, social, and rehabilitative services. In the United States, care coordination is often insufficient, putting patients at risk to "fall through the cracks." Some countries have implemented more robust primary and secondary preventative approaches, highlighting early identification, ease of access to care, and staging of disease management.[19] The National Institute of Mental Health (NIMH) Recovery After Initial Schizophrenia Episode (RAISE) study found that four core interventions ("personalized medication management, family psychoeducation, resilience-focused individual therapy, and supported employment and education") significantly improved the quality of life over a 24-month period for individuals with early schizophrenia as compared to usual community care.[20]

The patient-centered approach to the recovery-based system of care is growing, where the person's lifetime aspirations and goals become the center of care, rather than symptom reduction being the primary focus. This recovery-based approach recognizes the strengths and resilience of people with schizophrenia, and acknowledges how people with schizophrenia can be a support to others who are living with the illness.[20] It is important to frame clinical decision making in the context of a mutual process involving patient and clinician. Psychosocial/cognitive behavioral strategies can help some patients, and emerging computer-based therapies and social media–related approaches may be helpful. Cognitive remediation—which uses computer-based cognitive retraining techniques—has been shown to be of benefit.[21] Social media and mobile technology strategies may be harnessed to improve communications, medication adherence, and potentially detect early warning signs of impending relapse in patients with schizophrenia.

Pharmacologic Therapy

4 The importance of an initial accurate diagnostic assessment cannot be overemphasized. A thorough mental status examination (MSE), psychiatric diagnostic interview, physical and neurologic examination, complete family and social history, and laboratory workup must be performed to confirm the diagnosis and exclude general medical or substance-induced causes of psychosis. Laboratory tests, biologic markers, and commonly available brain imaging techniques do not assist in the diagnosis of schizophrenia or selection of medication. A pretreatment patient workup not only is important in excluding other pathology but also serves as a baseline for monitoring potential adverse medication reactions, and should include vital signs, complete blood count, electrolytes, hepatic function, renal function, electrocardiogram (ECG), fasting serum glucose, hemoglobin A1c, serum lipids, thyroid function, and urine drug screen.

5 Both first-generation antipsychotics (FGAs, also known as traditional) and second-generation antipsychotics (SGAs, also known as atypical) are used in the treatment of schizophrenia,[14,23] with no absolute criterion distinguishing between the two. As compared with FGAs, SGAs appear to have the ability to produce antipsychotic response with fewer occurring extrapyramidal symptoms (EPS). Other attributes that have been ascribed to some SGAs include enhanced efficacy (particularly for negative symptoms and cognition), near absence of propensity to cause tardive dyskinesia, and lack of effect on serum prolactin.[24] To date, only clozapine truly fulfills all of these criteria, with other SGAs having some of these attributes.[24] Therefore, the major factor used in practice when distinguishing among antipsychotics is adverse effects.[22-24] While the SGAs have a lower risk of neurologic adverse reactions, particularly effects on movement, this is offset by increased risk of metabolic syndrome with some SGAs, including weight gain, hyperlipidemias, and diabetes mellitus. Adverse medication reaction profiles differ among antipsychotics, and this information should be used in combination with individual patient characteristics when choosing a medication for an individual patient.

Results from the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) study, primarily in patients with chronic schizophrenia, indicate that olanzapine, compared with quetiapine, risperidone, ziprasidone, and the FGA perphenazine, had modest but not statistically significant superiority in maintenance therapy with treatment persistence as the primary clinical outcome.[17] However, increased metabolic effects occurred with olanzapine, and additional studies of patients early on in their illness highlight the high rate of cardiometabolic disturbances with olanzapine and the need to tailor treatment.[25]

Previous patient or family history of response to an antipsychotic is helpful in the selection of an agent. Acquisition cost varies significantly among different antipsychotics and dosage forms, and should be considered in context of any potential advantages of an agent. Table 87-2 lists antipsychotics and their usual dosage ranges.

TABLE 87-2

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	300-1,000	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	Maximum 10 mg per 24 hours. 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	REMS program. Check plasma level before exceeding 600 mg
Iloperidone	Fanapt	1-2	6-24	Care with dosing in CYP2D6 slow metabolizers
Lumateperone	Caplyta	42	42	Bioavailability increased by 9% when administered with high fat meal
Lurasidone	Latuda	20-40	40-120	Take with food; ≥350 calories (1,460 Joules)
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 mg	400-800	
Risperidone	Risperdal	1-2	2-8	
Ziprasidone	Geodon	40	80-160	Take with food, ≥500 calories (2,100 Joules)

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

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.

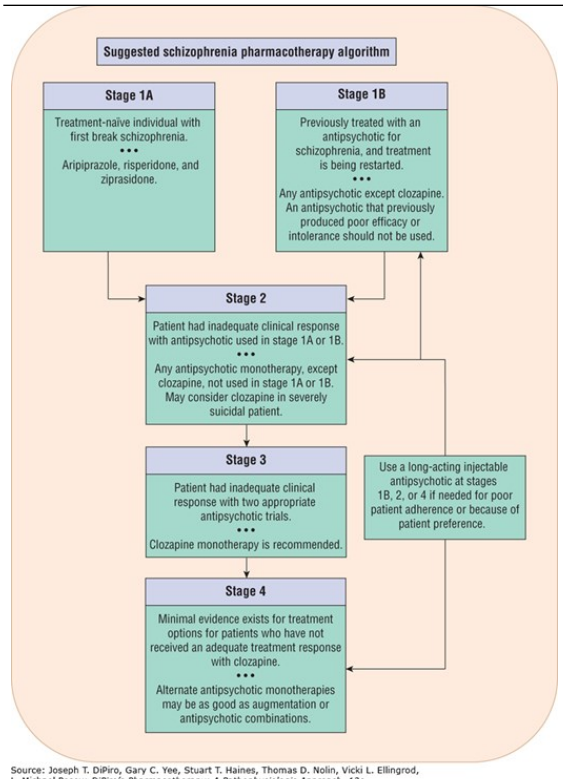
Data from References 24 and 26-33.

Published Guidelines and an Algorithm Example

Figure 87-1 outlines a suggested pharmacotherapeutic algorithm for schizophrenia, based on information from four published guidelines, the Psychopharmacology Algorithm Project at the Harvard Medical School Department of Psychiatry South Shore Program,[23] the Canadian Schizophrenia Guidelines,[22] the guidelines from the World Federation of Biological Psychiatry, and the APA Guidelines.[14,22,24]

FIGURE 87-1

Suggested 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. (See the text for a description of the algorithm stages.)



Stage 1A of the treatment algorithm applies to those patients experiencing their first acute episode of schizophrenia. Use of SGAs during the first acute episode may result in greater treatment retention and effectiveness in preventing a second psychotic episode compared to FGAs. In addition, SGAs carry a reduced risk of EPS.[24] Among the SGAs, aripiprazole, olanzapine, quetiapine, risperidone, and ziprasidone have evidence of efficacy in first-episode patients, with lurasidone showing efficacy in adolescents with schizophrenia, but most were not treatment naive.[23,34] Despite its efficacy, olanzapine is not recommended in first episode because of weight gain and adverse metabolic effects.[23,24]

Since quetiapine is associated with less time to rehospitalization compared to other SGAs and causes greater weight gain, some guidelines do not recommend it in stage 1A.[23] This leaves aripiprazole, risperidone, and ziprasidone as the evidence-based options in first-episode patients (stage 1A).[23] Of these, aripiprazole and ziprasidone produce the least weight gain. However, few head-to-head clinical trials have been conducted, and the level of evidence is not sufficiently high to recommend these as the only preferred agents in first episode.[14,22] The 2021 APA Guidelines do not provide any preference among initial antipsychotic selection. Because first-episode patients demonstrate greater sensitivity to adverse medication reactions, antipsychotic dosing should be initiated at the lower end of the dose range.[20,22,23]

In first-episode patients, long-acting risperidone injectable was more effective than oral risperidone in preventing relapse over a 1-year period.[35] The relapse rate was six times higher in the oral risperidone group than with the long-acting injectable (LAI); therefore, risperidone LAI can be considered as a treatment option for first-episode patients. If this medication is used, patients should first be stabilized on oral risperidone. It is critical that enriched psychosocial programs be implemented along with appropriate pharmacotherapy.

Stage 1B addresses pharmacotherapy for a patient who was previously treated with an antipsychotic, and treatment is being restarted because the patient stopped taking the medication. If during the initial antipsychotic trial, the patient experienced a robust improvement in symptoms, good tolerability, and is positive about taking this antipsychotic again, then that medication can be restarted. If a different medication is needed, one from stage 2 should be used. Stage 2 addresses pharmacotherapy in a patient who had inadequate clinical improvement with the antipsychotic used in stage 1A or 1B, or the patient responded but subsequently had a relapse while taking the medication. Stage 2 recommends antipsychotic monotherapy with an FGA or SGA not used in stage 1 or stage 1B.[14,22-24] Because of safety concerns and the need for white blood cell (WBC) monitoring, clozapine is not generally recommended at stage 2.[14,22,23] However, clozapine has superior efficacy in decreasing suicidal behavior, and it should be considered at stage 2 for the patient with suicidal thoughts.[22,23] Clozapine can also be considered at stage 2 in patients with a history of violence or comorbid substance use disorder.[22,23,36] If a patient has an unacceptable adverse medication reaction with the antipsychotic used during stage 1A, stage 1B, or stage 2, then an alternate antipsychotic for that stage should be chosen.

Long-acting injectable antipsychotics (LAIAs) should be considered as an option at stage 2. The use of LAIAs should be discussed with the patient as a life style choice, and their use should not be reserved for patients with poor medication adherence. In fact, if a patient prefers receiving a LAIA, it should be considered as an option at Stages 1A, 1B, and 2.[22-24] If there is good documentation of poor symptom improvement with two different antipsychotic trials at appropriate dose and duration, then pharmacotherapy should be initiated with the stage 3 recommended treatment clozapine.[22-24] In stage 4, minimal evidence exists for any treatment option for patients who do not have adequate symptom improvement with clozapine. The Harvard Department of Psychiatry South Shore algorithms present various treatment options for such patients; however, none of these options have conclusive evidence.[23] It is important to note that the use of antipsychotic combinations is controversial, as limited evidence supports increased efficacy for antipsychotic polypharmacy, despite this practice being somewhat common.[22,23] The APA Guidelines state that electroconvulsive therapy (ECT) combined with an antipsychotic may be useful in some patients with treatment resistance.[22]

Predictors of Response

Obtaining a thorough medication history is important, and previous treatment response should help guide antipsychotic selection, in that either a good prior response favors the use of the same agent or a negative prior response suggests the selection of a dissimilar medication. Substance use can influence psychiatric presentation and needs to be considered when making decisions regarding a patient's diagnosis or antipsychotic response. Amphetamines and other CNS stimulants, cocaine, corticosteroids, digitalis glycosides, indomethacin, cannabis, pentazocine, phencyclidine, other medications, and substances can induce psychosis in susceptible individuals or exacerbate psychosis in patients with preexisting psychiatric illness.[1,16,22,23] Patients with schizophrenia who use alcohol or other substances usually have a poor response to medications and a poor overall prognosis. Furthermore, alcohol, cannabis, caffeine, and nicotine use may potentially interact with antipsychotics.

Individual predictors of patient response have been either proposed or identified. Acute onset of symptoms and short duration of illness, presence of acute stressors or precipitating factors, later age of onset, family

history of affective illness, and good premorbid adjustment as reflected in stable interpersonal relationships or employment are all predictors of good response.[14]

Although controversial, affective symptoms can correlate with an overall good response, while negative symptoms and neuropsychological deficits related to cognition and neurologic soft signs can correlate with poor antipsychotic response.[14,16,22,23] Subjective positive patient response within the first 48 hours after FGA administration can be associated with medication responsiveness,[37] whereas an initial dysphoric response, demonstrated by stating a dislike of the medication, feeling worse or "zombie-like," anxiety or akathisia-like symptoms, is associated with poor medication response, adverse effects, and nonadherence.

The importance of developing a therapeutic alliance between the patient and the clinician cannot be underestimated (see Chapter e81, "Evaluation of Psychiatric Illness"). Patients who form positive therapeutic alliances are more likely to be adherent with all aspects of therapy, experience a better outcome at 2 years, and require lower antipsychotic doses.[20] However, a certain minority of patients fail to benefit from antipsychotic therapy, and their psychosocial functioning can worsen with antipsychotic continuation.

Initial Treatment in an Acute Psychotic Episode

The goals during the first 7 days of treatment should be decreased agitation, hostility, combativeness, anxiety, tension, and aggression, and normalization of sleep and eating patterns. The usual recommendation is to initiate therapy and to titrate the dose over the first few days to an average effective dose, unless the patient's physiologic status or history indicates that this dose can result in unacceptable adverse medication reactions. Because of strong alpha-1 (α_1) receptor antagonism and resulting risk of hypotension, iloperidone and clozapine should be titrated more slowly than other SGAs. Rapid titration to high doses is not recommended. Table 87-2 lists the usual dosage range, with an average dose typically being midrange.[14,22-24] Because patients with first-episode psychosis have an increased sensitivity to adverse medication reactions, particularly EPS, typical dosing ranges are approximately 50% of the doses used in chronically ill individuals.[22,23] If "cheeking" of medication is suspected (where the patient places the medication in their cheek and then spits it out later), liquid formulations and orally disintegrating tablets are available for some antipsychotics. If a patient has no improvement after 2 weeks at a therapeutic dose, then later clinical response is unlikely, and moving to the next treatment stage of the algorithm is recommended.[38]

Although some clinicians believe that larger daily doses are necessary in patients with more severe symptoms, data do not support this practice. Some symptoms, such as agitation, tension, aggression, and increased motor activity, may respond more quickly, but adverse medication reactions can be more common with higher doses. However, interindividual differences in dosage and response do occur. In patients with partial response who are tolerating the chosen antipsychotic, it may be reasonable to titrate above the usual dose range. However, this tactic should be time-limited (ie, 2-4 weeks), and if the patient does not achieve further improvement, either the dose should be decreased or an alternative treatment strategy should be tried. As previously stated, rapid titration of antipsychotic dosage is not indicated[14,22-24]; however, intramuscular (IM) antipsychotic administration (eg, haloperidol 2-5 mg IM, olanzapine 2.5-10 mg IM, or ziprasidone 10-20 mg IM) can be used to assist in calming a patient with severe agitation. Clinically, agitation can manifest as loud, physically or verbally threatening behavior, motor hyperactivity, or physical aggression. Although use of IM antipsychotics can assist in calming a patient with acute agitation due to psychosis, it does not improve the rate of remission, time to remission, or the length of hospitalization. Haloperidol (an FGA) given IM for treatment of acute aggression is associated with a higher incidence of EPS than IM SGAs. If the patient is receiving an antipsychotic within the usual therapeutic range, the use of lorazepam 2 mg IM as needed in combination with the maintenance antipsychotic is a rational alternative for treatment of aggression. Hypotension, respiratory depression, CNS depression, and death have been reported with injectable lorazepam in combination with either olanzapine or clozapine; thus, injectable lorazepam is not recommended in combination with either of these medications.[24]

Inhaled loxapine powder is Food and Drug Administration (FDA)-approved for treatment of acute agitation associated with schizophrenia or bipolar disorder. Because of the risk of bronchospasm, pulmonary distress, and pulmonary arrest, the medication can only be administered in a healthcare facility through the FDA-approved Risk Evaluation and Mitigation Strategy (REMS). Before administration, patients must be screened for a history of asthma, chronic obstructive pulmonary disease, or other lung disease associated with bronchospasm, and use is limited to one 10 mg inhaled dose per 24-hour period.[26] Whether inhaled loxapine offers any therapeutic advantages in acute agitation compared with other antipsychotics is unknown, and patients must be sufficiently cooperative to inhale it appropriately.

Stabilization Therapy

7 Symptom improvement may occur over 6 to 12 weeks with appropriate medication therapy and comprehensive treatment. During the first 2 to 3 weeks, goals should include increased socialization and improvement in self-care habits and mood. Improvement in any formal thought disorder should follow and may take an additional 6 to 8 weeks. Patients who are early in the course of their illness tend to experience a more rapid resolution of symptoms than individuals who are more chronically ill. In general, if a patient has shown no improvement after 2 weeks of treatment at therapeutic doses, or has achieved only a partial decrease in positive symptoms within 8 to 12 weeks at adequate doses, then the next algorithm stage should be considered. In more chronically ill patients, symptoms may continue to improve over 3 to 4 months. Quantifying symptom change using a brief symptom rating scale can be helpful in monitoring treatment and making decisions. An optimum target medication dose should be estimated in the initial treatment plan. If the patient begins to show adequate response at a dose, then the patient should remain at this dosage if symptoms continue to improve. In general, adequate time on a therapeutic antipsychotic dose is the most important factor in predicting medication response. However, if necessary, dose titration can continue within the therapeutic range every 1 or 2 weeks if the patient has no adverse medication reactions.

Before changing medications in a patient with poor response, the following should be considered: Were the initial target symptoms indicative of schizophrenia or did they represent manifestations of a different diagnosis, a long-standing behavioral problem, a substance use disorder, or a general medical condition? Is the patient adherent with pharmacotherapy? Are the persistent symptoms poorly responsive to antipsychotics (eg, impaired insight or judgment, or fixed delusions)? How does the patient's current status compare with response during previous exacerbations? Would this patient potentially benefit from advancing to a different treatment stage (Fig. 87-1)? Does this patient have treatment-resistant schizophrenia?

The conclusion that the patient with a partial response has achieved as much symptomatic improvement as possible is one that must be made with great care as treatment goals must be realistic. Medications are effective in decreasing many of the symptoms of schizophrenia (and are thus referred to as palliative), but they are not curative, and not all symptoms may abate. Although one should aim to achieve full remission to minimal residual positive symptoms, it is still unclear what a realistic goal is regarding maximum improvement in negative symptoms.

It is important to screen patients for co-occurring psychiatric disorders, and their presence can become more apparent during the stabilization or maintenance phases of treatment. Examples include substance use disorders, depression, obsessive-compulsive disorder, and panic disorder. As co-occurring disorders will limit symptom and functional improvement and increase the risk of relapse. It is critical that treatment for the co-occurring disorder be implemented in combination with evidence-based treatment for schizophrenia.

Maintenance Treatment

Maintenance medication therapy prevents relapse, as shown in numerous double-blind studies, which is a major goal of treatment.[14,22-24] The average relapse rate after 1 year is 18% to 32% with active medication (including some patients with nonadherence) versus 60% to 80% for placebo.[14,22-24]

8 After treatment of the first psychotic episode in a patient with schizophrenia, medication should be continued for at least 18 months after remission.[14,22-24] Many experts recommend that patients with robust medication response be treated for at least 5 years; however, in chronically ill individuals, continuous or lifetime pharmacotherapy is necessary in most patients to prevent relapse. This practice should be approached with the lowest effective antipsychotic dose that is tolerated by the patient.[14,22-24]

Antipsychotics should be tapered slowly before discontinuation as abrupt discontinuation, especially with clozapine, can result in withdrawal symptoms, felt to be a manifestation of rebound cholinergic outflow. Insomnia, nightmares, headaches, gastrointestinal symptoms (eg, abdominal cramps, stomach pain, nausea, vomiting, and diarrhea), restlessness, increased salivation, and sweating are reported. Although available evidence does not indicate a best way to switch from one antipsychotic to another, it is often recommended to taper and discontinue the first antipsychotic over at least 1 to 2 weeks while the second antipsychotic is

initiated and the dose titrated.[24] Tapering needs to occur more slowly with clozapine.[38]

Long-Acting Injectable Antipsychotics

Early studies did not consistently demonstrate an advantage of LAIAs over oral agents. However, studies, designed to reflect real-world practices, have more consistently demonstrated an advantage in reduced hospitalizations and relapse prevention in patients with schizophrenia, findings that were confirmed in a meta-analysis.[39,40] Despite the potential advantages, the use of LAIAs is relatively low compared with oral antipsychotics, and in most Western countries use falls below 20%.[41] Barriers to LAIA use may be clinician or patient driven and include: biases and attitudes, limited insurance coverage, or lack of experience with LAIAs.[42] Traditionally, LAIAs have been primarily used later in the course of treatment and in patients who are unreliable in taking oral medication. It has been suggested to offer LAIAs to patients as a treatment option earlier in their disease before they develop a pattern of nonadherence.[41,42] For example, they can be presented to a patient as a life style option, in which the patient does not need to take a medication daily.[22] Normalizing the use of LAIAs, providing appropriate education to families and patients on LAIAs, utilizing motivational interview techniques, and offering it as an early treatment option may aid in improving LAIA acceptability with patients.[39]

Treatment nonadherence rates as high as 60% in patients with schizophrenia can lead to negative clinical outcomes.[41] Nonadherence can be due to several factors including cognitive impairment, persistent symptoms, substance use, or lack of insight. However, before declaring a patient as nonadherent, it should be determined whether the patient is experiencing adverse medication reactions. If so, an alternative medication with better tolerability should be considered before initiating a LAIA. The patient's motivation for treatment is a major factor influencing outcome.

There are 10 LAIAs available for use in the United States: risperidone (two different formulations), paliperidone palmitate (three formulations), aripiprazole (monohydrate and lauroxil), olanzapine pamoate, haloperidol decanoate, and fluphenazine decanoate. Conversion from an oral antipsychotic to a LAIA should start with stabilization on an oral dosage form of the same agent for a short trial (4-14 days) to determine whether the patient tolerates the medication without significant adverse medication reactions, especially if the patient has no previous exposure to the oral agent.[39]

With risperidone microspheres (Consta), measurable serum concentrations are not seen until approximately 3 weeks after single-dose administration. Thus, it is important that the oral antipsychotic be administered for at least 3 weeks after the first injection. The recommended starting dose with risperidone microspheres is 25 mg. Clinical experience suggests that titration to doses greater than or equal to 37.5 mg per injection may be necessary for maintenance treatment; however, efficacy was demonstrated with doses of 25 to 50 mg IM every 2 weeks. Dose adjustments are recommended to be made no more often than once every 4 weeks.[43] Doses above 50 mg every 2 weeks are not recommended, as research indicates no greater clinical efficacy but more EPS.[25] With risperidone extended-release injectable suspension (PERSERIS), dosing is 90 or 120 mg once monthly, no oral overlap or loading dose is necessary, and it is the only LAIA that is administered subcutaneously in the abdomen.[44]

Paliperidone palmitate (Invega Sustenna) has the advantage of easy conversion from oral paliperidone to IM treatment, as there is no need for oral overlap, and this formulation offers once-monthly injections with the option to convert to 3-month or 6-month formulations.[43] It is initiated with 234 mg on day 1 and 156 mg a week later (+/− 4 days) with deltoid administration for the first two doses as gluteal absorption results in 28% lower C_{max}. The 1-month paliperidone palmitate (1MPP) IM doses are then titrated according to response within a range of 39 to 234 mg and can be injected into either the deltoid or gluteal muscle.[43] If a patient's oral paliperidone is established prior to converting to the 1MPP, the maintenance dose required for similar paliperidone exposure is outlined in Table 87-5.[45]

A 3-month paliperidone palmitate (3MPP, Invega Trinza) and 6-month paliperidone palmitate (6MPP, Invega Hafyera) LAIA are approved for the management of schizophrenia, with both formulations being found to significantly delay time to relapse compared with placebo. The 3MPP and 6MPP provide the longest dosing interval available, but require patients to be treated for at least 4 months with 1MPP prior to 3MPP initiation. Those who have received at least one dose of the 3MPP may be converted to the 6MPP. The first 3MPP dose is based on the previous 1 month injection dose, and the first 6MPP dose is based on either the 1- or 3-month injection dose, as shown in Table 87-3.[46]

TABLE 87-3

Summary of Available Long-Acting Injectable Antipsychotics (LAIAs)

Medication Name	Fluphenazine Decanoate	Haloperidol Decanoate	Risperidone (Risperdal Consta)	Risperidone (PERSERIS)	Paliperidone Palmitate (Invega Sustenna) (1MPP)	Paliperidone Palmitate (Invega Trinza) (3MPP)	Paliperidone Palmitate (Invega Hafyera) (6MPP)	Olanzapine Pamoate (Zyprexa Relprevv)	Aripiprazole Monohydrate (Abilify Maintena)	Aripiprazole (Lauroxil Aristada)
Dose Range (mg)	12.5-100	20-450	12.5-50	90-120	39-234	273-819	1,092-1,560	150-405	300-400	441-882[b]
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	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 monthly	234 mg every 4 weeks	819 mg every 3 months	1,560 mg every 6 months	300 mg every 2 weeks or 405 mg every 4 weeks	400 mg monthly	882 mg monthly
Initiation or Loading	Can Load	Can Load	None	None	Initiation required	None required, dose based on last Invega Sustenna dose: If 78 mg give 273 mg If 117 mg give 410 mg If 156 mg give 546 mg If 234 mg give 819 mg	None required, dose used depends on last Invega Sustenna or Trinza dose For Invega Sustenna: If 156 mg give 1,092 mg If 234 mg give 1,560 mg For Invega Trinza: If 546 mg give 1,092 mg If 819 mg give 1,560 mg	Initiation required	None	None required, dose based on PO dose: If 10 mg/day give 441 mg If 15 mg/day give 662 mg If 20 mg give 882 mg
Time to peak	8-24 hours	4-11 days	4-5 weeks	4-6 hr	13 days	30-33 days	29-32 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	Continues steady state	3 months	3-4 months	4 months
Half-life	14 ± 2[a] days	21 days	3-6 days	9-11 days	25-49 days	84-89 days (deltoid) 118-139 days (gluteal)	148-159 days	30 days	30-47 days	29-35 days
Injection Site: Gluteal	Yes	Yes	Yes	Abdominal only	Yes after 2nd dose	Yes	Yes	Yes	Yes	Yes
Injection Site: Deltoid	Yes	Yes	Yes		Yes	Yes	No	No	No	Yes, but only 441 mg dose
Injection Method/Technique	Z-Track	Z-Track			Subcutaneous Injection					
Notes			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	Avoid use in patients with moderate-to-severe renal impairment (CrCl <50 mL/min [0.83 mL/s])	Requires at least a 4-month trial with 1MPP. Not recommended in patients with moderate or severe renal impairment (CrCl <50 mL/min [0.83 mL/s])	Requires at least a 4 month trial with 1MPP or at least 1 cycle of 3MPP. Not recommended in patients with moderate or severe renal impairment (CrCl <50 mL/min [0.83 mL/s])	Monitor for PDSS Subject to REMS	Maintenance dose reduced 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	May require 2 week PO trial to establish efficacy before initiating LAIA Avoid use of strong CYP2D6 and 3A4 inhibitors for 662 and 882 mg dose, no adjustment needed for 441 mg dose

CrCl, creatine clearance; IM, intramuscular; LAIA, long-acting injectable; PO, oral; Tss, time to steady state.

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

[b]Additional dosing regimens include extended intervals up to 1,064 mg every 8 weeks; loading protocol with Aristada Initio 675 mg + maintenance Aristada dose + PO 30 mg ×1 dose does not require PO overlap.

Data from References 38, 43, and 45-52.

Olanzapine pamoate monohydrate is a LAIA administered every 2 or 4 weeks that does not require oral overlap. It is recommended for deep gluteal injection, and the initial injectable dose varies from 210 to 405 mg depending on the oral olanzapine daily maintenance dose and the frequency of injectable administration.[43,50] A disadvantage to olanzapine pamoate is its association with post-injection delirium/sedation syndrome (PDSS) occurring in <2% of patients.[50] The symptoms of PDSS are similar to those of an oral olanzapine overdose and include delirium, ataxia, confusion, heavy sedation, or altered levels of consciousness. Although PDSS can occur with any dose and at any time during treatment, most cases have occurred within the first three injections.[51] The most likely explanation for the occurrence of PDSS is an accidental intravascular injection resulting in the medication dissolving more rapidly and sharp increases in plasma levels.[51,52] The product labeling contains an FDA-boxed warning regarding PDSS, and olanzapine pamoate is subject to a REMS with the FDA labeling limiting the availability of olanzapine LAIA to a restricted distribution program. The injection must be administered in a registered healthcare facility, and the patient must be observed by a health professional for at least 3 hours after administration and must not drive or operate machinery that day.[50]

Aripiprazole monohydrate LAIA (Abilify Maintena) is administered as a single intramuscular injection in the gluteal or deltoid muscle once a month at a starting and maintenance dose of 400 mg. If the patient does not tolerate the 400 mg dose, the next injection can be reduced to 300 mg. After the first injection of aripiprazole monohydrate LAIA, a 14-day overlap with oral aripiprazole (10-20 mg/day) or any other antipsychotic is recommended.[43] Aripiprazole lauroxil LAIA (Aristada) is administered as a single intramuscular injection in the deltoid (441 mg only) or gluteal (441, 662, or 882 mg, once a month). The 882 mg dose can be administered every 6 weeks and the 1,084 mg every 2 months. Aripiprazole lauroxil has the advantage of having initiation dosing available (Aristada Initio)[47]; however, if Aristada Initio is not utilized, oral overlap is required for 3 weeks with this LAIA formulation.[52]

For the FGA fluphenazine decanoate, the simplest dosing conversion method recommends 1.25 times the oral fluphenazine daily dose for stabilized patients, rounding to the nearest 12.5 mg interval, which is administered in weekly doses for the first 4 to 6 weeks; or 1.6 times the oral daily dose given weekly for the first 4 weeks for more acutely ill patients.[48] Subsequently, fluphenazine decanoate can be administered once every 2 to 3 weeks. Although oral fluphenazine can be overlapped for 1 week, the dose should be reduced by half with the first injection to reduce the risk of EPS.[48] For haloperidol decanoate, the first dose should be 10 to 20 times the oral haloperidol daily dose. In patients who are at high risk of relapse, and are tolerant to oral haloperidol, a loading dose of 20 times the oral dose can be considered.[48] In patients naïve to haloperidol decanoate, the initial injection is limited to 100 mg followed by the remaining balance of the first monthly dose given 3 to 7 days later.[43] Overlap with oral haloperidol overlap is not necessary if the patient receives a loading dose, but is recommended for the first month if a loading dose strategy is not utilized. The maintenance dose is typically 10 to 15 times the oral dose once monthly. Table 87-3 provides a summary of the LAIAs.

Methods to Enhance Patient Adherence

Treatment nonadherence rates are as high as 60% in patients with schizophrenia, which can lead to negative clinical outcomes.[41] If nonadherence is suspected, the clinician should ask in a nonjudgmental manner if the patient is having any difficulty taking their medication and then the reason for nonadherence should be determined. If nonadherence is occurring because of adverse effects, then a medication with a more favorable tolerability profile should be considered. Suspected nonadherence can also be assessed by obtaining an antipsychotic serum concentration.[53]

Maintaining appropriate medication adherence is often challenging for individuals with chronic illnesses and partial adherence is a reality and should be expected to be the norm.[24] Individuals with serious psychiatric disorders have higher nonadherence rates than those with general medical disorders, with the following explanations provided: denial of illness, lack of insight, grandiosity or paranoia, no perceived need for medication, perceived lack of input into choice of medication or dosage, adverse medication reactions, misperceived "allergies," too many medications prescribed, or too many doses prescribed daily (see Table 87-4). It is estimated that half of patients with schizophrenia or schizoaffective disorder take their medication less than 70% of the time.[24] Discussions regarding this topic should be approached in a positive, nonjudgmental manner, with the clinician actively engaging the patient in care and using motivational interviewing techniques as mechanisms to enhance therapeutic alliance and patient adherence.

TABLE 87-4

Nonadherence with Antipsychotic Medications Is a Multidimensional Dilemma

Patient Factors	Medication Factors	Other Factors
Lack of insight	Efficacy	Family perspectives
Paranoia	Adverse medication reactions	Cultural influences
Attitude to ward medications	Mode of delivery/ingestion	Clinician perspectives and influences
Prior experiences	Cost	Insurance coverage
Perception of efficacy of medication	Availability	Cost of care
Comorbid substance use disorder		Medication access and support
		Mental illness stigma

Data from References 54 and 55.

Numerous different methods have been used to improve treatment adherence of patients with schizophrenia. Interventions that provide continuous focus on adherence and that are of long duration have shown benefit. These should incorporate problem-solving techniques and be accompanied by technical learning aids. As previously noted, programs need to include a focus on patient-driven outcomes, and not just medication adherence, and interventions should include efforts to allow patients to achieve life goals and function. This requires that programs be tailored to the needs of individual patients.[54] Psychoeducation strategies should include motivational interviewing techniques in individual counseling as well as group activities.

Compliance therapy, targeted cognitive behavioral therapy focusing on medication adherence, can improve patient adherence, but the success seen in early studies has not been consistently replicated.[54]

Groups facilitated by trained individuals who have the illness are thought to be more effective in enhancing awareness and acceptance of schizophrenia and necessary treatment, than groups led only by professionals. Active involvement of family members further increases the likelihood of patient adherence with treatment. In addition to programs provided by community mental health centers, support groups operated by consumer groups such as the National Alliance on Mental Illness (NAMI) are available for patients and their families in most urban areas. In the hospital, self-medication administration can reinforce the patient's perception of his or her active role in treatment. When patients miss outpatient appointments, active outreach interventions must be implemented to enhance patient engagement in treatment.[54]

The LAIAs have been a mainstay of treatment for people who are nonadherent with taking oral medications. However, for various reasons, they are used in only a relatively small subset of patients, and many patients simply do not like getting injections. Abilify MyCite, an FDA-approved technology, includes a biosensor inside the aripiprazole tablet; after the medication is ingested, the coating is degraded and a specific patch worn

by the patient picks up a biosensor signal from the formulation.[49] Data are then transferred to a smart phone application and can be shared by the patient with the treating clinician via the Internet. It is not clear whether this technology improves patient adherence in a population that is often suspicious and paranoid. Regardless, a great deal of education is necessary to make sure that the patient knows how to use the technology and to assure that the patient wears the patch and uses the smart phone application correctly.

Management of Treatment-Resistant Schizophrenia

In general, "treatment resistant" describes a patient who has had inadequate symptom response from multiple antipsychotic trials.[22-24,53] The clinical definition of treatment resistance requires persistent symptoms of at least moderate severity, despite treatment with two different antipsychotics at adequate dosage for at least 6 weeks, each with good treatment adherence.[53] Between 10% and 30% of patients receive minimal symptomatic improvement after multiple antipsychotic monotherapy trials.[22-24] An additional 30% to 60% of patients have partial but inadequate improvement in symptoms or unacceptable adverse medication reactions associated with antipsychotic use. In patients not responding to two or more pharmacotherapy trials, a treatment-refractory evaluation should be performed to reexamine diagnosis, substance use, medication adherence, and psychosocial stressors. Targeted cognitive behavioral therapy or other psychosocial augmentation strategies should be considered.[22,23] While clozapine remains the treatment of choice for treatment-resistant schizophrenia, its use has declined over time in favor of sequential treatment trials of SGAs. This is problematic and trainees need exposure to initiating clozapine therapy, given the low likelihood of later use in clinical practice without this experience.

Clozapine

Only clozapine has shown superiority over other antipsychotics in randomized clinical trials for the management of treatment-resistant schizophrenia as most other SGAs have either not been studied in this patient population, or have been evaluated in small open trials. In a seminal study, clozapine was effective in approximately 30% of patients with treatment-resistant schizophrenia, compared with only 4% treated with a combination of chlorpromazine and the anticholinergic benztropine.[56] Other candidates for clozapine include those patients with severe suicidality, aggressive behavior, or those who cannot tolerate neurologic adverse medication reactions from conservative doses of other antipsychotics.

Symptomatic improvement with clozapine in the treatment-refractory patient often occurs slowly, and as many as 60% of patients continue to improve if clozapine is used for up to 6 months. This, in combination with clozapine's tolerability profile, provides sufficient information to conclude that clozapine is not a panacea for schizophrenia. Polydipsia and hyponatremia (psychogenic water drinking) are a frequent problems among treatment-refractory patients, and clozapine reportedly decreases water drinking and increases serum sodium in such patients.[23,24]

Because of the risk of orthostatic hypotension, clozapine is usually titrated more slowly than other antipsychotics, particularly on an outpatient basis. If a 12.5-mg test dose does not produce hypotension, then clozapine 25 mg at bedtime is recommended, increased to 25 mg twice a day after 3 days, and then increased in 25 to 50 mg/day increments every 3 days until a dose of at least 300 mg/day is reached. If tolerated, a minimum trial should be 3 months with a clozapine serum concentration of at least 350 ng/mL (mcg/L; 1.07 µmol/L). Because high doses are associated with significantly increased adverse medication reactions, including seizures, a clozapine serum concentration is recommended before exceeding 600 mg/day.[24] If the clozapine serum concentration is greater than 350 ng/mL (mcg/L; 1.07 µmol/L), then further dosage increases are not indicated.[53]

Augmentation and Combination Strategies

Limited empirical evidence exists to guide treatment decisions for patients who do not respond to clozapine.[22-24] Current strategies include augmentation with a non-antipsychotic medication in patients with poor or partial response, or combination treatment using two antipsychotics simultaneously.

In a small, single blind, randomized trial, 50% of patients demonstrated clinically significant improvement in symptoms with electroconvulsive therapy (ECT) augmentation of clozapine, compared with no responders in the clozapine monotherapy group. When the patients in the clozapine monotherapy group received ECT, 47% demonstrated clinically significant improvement.[23]

Mood stabilizers are frequently used as an augmentation strategy, and while lithium does not enhance the antipsychotic effect, it may improve labile affect and agitated behavior in select patients.[23] Enzyme induction with carbamazepine can cause a decrease in antipsychotic serum concentrations and potentially worsen psychotic symptoms in some patients.[23,57]

Only limited data are available to support antidepressant augmentation of antipsychotics.[22-24] However, consistently positive results have been reported when using selective serotonin reuptake inhibitors (SSRIs) to treat obsessive-compulsive symptoms that worsen or arise during clozapine treatment.

Combining an FGA with an SGA and combining different SGAs have been suggested as intervention strategies for treatment-resistant patients. Pharmacodynamically, there is limited rationale to explain how combinations of antipsychotics would produce enhanced efficacy, but increased adverse medication reactions, particularly increased EPS, metabolic effects, and hyperprolactinemia, are possible results.[22] The evidence to support antipsychotic combinations is scant. However, a large Finnish database study, using patients as their own controls, found that clozapine plus aripiprazole had a lower rehospitalization rate than any other monotherapy or combination antipsychotic treatment.[58] This observational study was not in patients identified as treatment resistant. Regardless, this topic remains highly contentious, and clinicians' practice is often not aligned with available evidence. Moreover, the availability of new treatment options can result in combination therapies being tried with antipsychotics with insufficient scientific evidence. This approach further complicates the application of systematic, evidence-based treatments for schizophrenia. In general, a series of antipsychotic monotherapy courses, including clozapine, are preferred over antipsychotic combinations.[22] However, when clozapine fails to produce desired outcomes, a time-limited combination trial is sometimes considered (eg, maximum 12 weeks) with the patient carefully evaluated using standardized rating scales to assess symptomatology.[23] If no apparent improvement is observed, then one of the medications should be tapered and discontinued. However, if the patient has a partial response (greater than or equal to 20% improvement in positive symptoms) after 12 weeks with combination treatment, medications should be titrated to doses at the upper end of the therapeutic range, and treatment should continue for an additional 12 weeks before a change in treatment is considered.

Violence in Schizophrenia

Most people with schizophrenia do not exhibit violent behavior; however, they are more likely to be violent than the general population. The rate of violence in people with schizophrenia is 9.9% compared with 1.6% in the general population.[36] Risk factors for violence include those associated with violence in the general population (eg, childhood trauma and exposure to violence, alcohol and substance use disorders, psychopathy, and access to firearms) and (to lesser extent) psychotic symptoms.[36] Most of the risk of violence is associated with co-occurring substance use disorders.[36] Patients are at risk to become violent when they relapse and so keeping patients clinically stable is a major consideration. Clozapine has been found to be superior to other antipsychotics in decreasing aggressive and violent behavior.[36] Some states have outpatient commitment laws where patients at risk of violence are "forced" to get ongoing care, and if they default, they are sent back to the hospital. Patients who are dangerous are invariably managed either in the legal system itself or legally as "forensic" patients where they are held by court order in a psychiatric facility.

Antipsychotic Mechanism of Action

The exact mechanism of actions of antipsychotics are unknown. Antipsychotics are classified into three different categories: (a) typical (traditional or FGAs) (high D_2 antagonism and low serotonin-2 receptor [$5\text{-}HT_{2A}$] antagonism); (b) atypical (SGAs) (moderate-to-high D_2 antagonism and high $5\text{-}HT_{2A}$ antagonism); and (c) atypical clozapine-like (low D_2 antagonism and high $5\text{-}HT_{2A}$ antagonism).[59] With the exception of aripiprazole

and brexpiprazole, all current SGAs have a greater affinity for 5-HT_{2A} receptors than D_2 receptors, and brexpiprazole shows stronger antagonism of the 5-HT_{2A} receptor than aripiprazole.[59,60] Brexpiprazole also demonstrates higher affinity for the serotonin-1A (5-HT_{1A}) receptor compared to aripiprazole but with less intrinsic D_2 activity than aripiprazole.[60]

Prospective studies of antipsychotic receptor binding in humans have used PET scans to examine neurotransmitter receptor binding 12 hours post-dose in small numbers of individuals at steady-state concentrations. It has been proposed that at least 60% to 65% D_2 receptor occupation is necessary to decrease positive psychotic symptoms, whereas blockade of approximately 77% or more of D_2 receptors is associated with EPS.[59] Table 87-5 outlines the relative differences in receptor binding for various agents. In general, all FGAs are DA receptor antagonists with high affinity for D_2 receptors, and during chronic treatment, between 70% and 90% of D_2 receptors in the striatum are usually occupied. In contrast, during clozapine treatment only 38% to 47% of D_2 receptors are occupied, even with high doses. Newer SGAs have variable D_2 binding. Low D_2 binding seen with the SGAs, can be directly associated with how rapidly the antipsychotic disassociates from the D_2 receptor.[59] This transient blockade of DA receptors may be adequate to produce antipsychotic effect, but longer term D_2 blockade is required for production of EPS and sustained hyperprolactinemia. Aripiprazole and brexpiprazole are partial agonists at D_2 receptors, and represent a further elaboration of the DA hypothesis of antipsychotic action.[59,60]

TABLE 87-5

Relative Neuroreceptor Binding Affinities of Select Antipsychotics

	Aripiprazole	Asenapine	Chlorpromazine	Clozapine	Haloperidol	Iloperidone	Lumateperone	Lurasidone	Olanzapine	Paliperidone	Quetiapine	Risperidone	Ziprasidone
D_1	-	++	+	+	+				++	+	-	+	+
D_2	++++	+++	+++	+	++++	+++	++	+++	++	+++	+	+++	+++
D_3	++	+++	+++	+	+++	+++	++		+	++	-	++	++
D_4	+	+++	+++	++	+++	++			++	-	-	-	++
5-HT_{1A}	++	++	-	-	-	++		+	-	-	-	-	+++
5-HT_{1D}	+			-	-				-	+	-	+	+++
5-HT_{2A}	+++	+++	++	+++	+	++++	++++	+++	+++	+++	++	++++	++++
5-HT_{2C}	+	++++	++	++	-	++	+		++	+	-	++	++++
5-HT_6	+	+++	++	++	-	++			++	-	-	-	+
5-HT_7	++	+++	++	++	-			++++	-	++	-	+++	++
α	+	+++	++++	+++	+++	++++	++	+	++	+++	+++	+++	++
α	+	++	+	+	-	++		+	+	++	-	++	-
H_1	+	++	++++	+++	-	++	-	-	+++	-	++	-	-
m_1	++	-		++++	-	-	+/-	-	+++	-	++	-	-

Relative neuroreceptor binding affinities of select antipsychotics.

(-) = minimal or none; (+) = low; (++) = moderate; (+++) = high; (++++) = very high

Data from References 61 and 62.

Iloperidone's pharmacology is different in that it has high affinity for D_2, dopamine-3 (D_3), and 5-HT_{2A} receptors, and moderate affinity for dopamine-4 (D_4), serotonin-6 (5-HT_6), serotonin-7 (5-HT_7), and α_1-receptors.[27] Asenapine has high affinity for 5-HT_{2A} and D_2 receptors as well as for α_1- and histamine-1 receptors with D_2 occupancy approximating 80% with a sublingual dose of 5 to 10 mg twice daily.[28] Cariprazine has high affinity for D_2 and D_3 receptors as a partial agonist, with the D_3 potency being significantly greater than D_2. It is also a partial agonist at 5-HT_{1A} receptors and an antagonist at serotonin-1B (5-HT_{1B}) receptors.[29] Therefore, given all of these different mechanisms of action, our understanding of the manner in which they produce a clinical profile is still in its infancy.

With low-dose risperidone (2-5 mg/day), D_2 binding ranges from 60% to 79%, but with doses greater than 6 mg daily, binding commonly exceeds the 77% threshold associated with the development of EPS. Risperidone 2 mg/day produces 5-HT_{2A} binding greater than 70%, and with 4 mg/day it is nearly 100%.[59] Olanzapine 10 to 20 mg/day produces D_2 binding ranging from 71% to 80%, whereas at 30 to 40 mg/day, it ranges from 83% to 88%. Ziprasidone has the highest 5-HT_{2A}-to-D_2 affinity ratio of any of the currently available antipsychotics. It is also a potent serotonin-1A (5-HT_{1A}) agonist.[59]

Quetiapine has the lowest D_2 binding. At doses of 300 to 600 mg/day, 12-hour post-dose D_2 binding ranges from 0% to 27%. Even at quetiapine 800 mg/day, only 30% of D_2 receptors are occupied. At these same daily doses, 45% to 90% of 5-HT_{2A} receptors are occupied. However, when quetiapine D_2 binding is examined 2 to 3 hours post-dose, 58% and 64% of receptors were occupied with 400 and 450 mg, respectively.

Lumateperone is a moderate antagonist at both D_1 and D_2 receptors and a potent antagonist at 5-HT_{2A} receptors. In individuals with schizophrenia, lumateperone occupied approximately 42% of D^2 receptors. It is also a presynaptic DA agonist and a 5-HT reuptake inhibitor. It indirectly modulates glutamatergic activity resulting in increased NMDA and AMPA activity.[33,62]

The primary therapeutic effects of antipsychotics are thought to occur in the limbic system, including the ventral striatum, whereas EPS are thought to be related to DA blockade in the dorsal striatum. For SGAs, 5-HT_{2A} antagonism in combination with modest D_2 blockade leads to release of DA in the prefrontal cortex, and this is one explanation for the decrease in negative symptoms and improvement in cognition reported with these antipsychotics.[48] Medications that are not D_2 antagonists are currently in clinical trials for the treatment of schizophrenia. If these medications are approved by the FDA, they may have a significant effect on how we look at antipsychotic mechanisms of action and efficacy.

As discussed, antipsychotics vary in their effects on other neurotransmitter receptor systems.[59] Although the significance of these different mechanisms on efficacy is unclear, they do potentially explain differences in adverse medication reaction profiles. These differences in pharmacodynamics profiles point out that the SGAs are not alike, and patients obtaining an inadequate clinical response (either efficacy or adverse medication reactions) with one antipsychotic may have a superior response/tolerability on an alternate medication. Thus, serial SGA monotherapy trials should be tried in patients receiving a suboptimal clinical response (see Fig. 87-1).

Pharmacokinetics

As a class, antipsychotics are highly lipophilic and highly bound to membranes and plasma proteins. They distribute readily into most tissues with a high blood supply and can accumulate in tissues; therefore, they have large volumes of distribution.[63] Most antipsychotics are largely metabolized, primarily through the cytochrome P450 (CYP) pathways in the liver, except for ziprasidone, which is largely metabolized by aldehyde oxidase. Fluphenazine and perphenazine are metabolized through CYP2D6, and thus are susceptible to pharmacogenetically regulated metabolism.[64] This is also one of the major pathways for the metabolism of aripiprazole, brexpiprazole, haloperidol, iloperidone, and risperidone.[64] Thirty percent to 35% of people of African and Asian descent are slow to intermediate CYP2D6 metabolizers, and approximately 0% to 5% of African American, 1% of Asian, and 5% to 10% of White populations are poor metabolizers.[65] In addition, some people of Swedish descent and up to 30% of those from Northern Africa may be ultra-rapid CYP2D6 metabolizers.[66] Genetic variation within CYP1A2 can potentially result in a decrease in the metabolic rate of clozapine, whereas smoking may increase clozapine and olanzapine metabolism due to the effect of cigarette smoke inducing CYP1A2 linked to a specific genotype.[64,65] Pharmacogenomics should be considered when dosing and monitoring the clinical effects of antipsychotics.[64-66] Additional resources related to specific gene and drug pairs for pharmacogenomics information can be obtained at the Clinical Pharmacogenomics Implementation Consortium (CPIC) Website (www.cipicpgx.org). Table 87-6 outlines the prominent metabolic pathways of selected antipsychotics.

TABLE 87-6

Pharmacokinetic Parameters of Selected Antipsychotics

Medication	Bioavailability (%)	Half-Life	Major Metabolic Pathways	Active Metabolites
Selected First-Generation Antipsychotics (FGAs)				
Chlorpromazine	10-30	8-35 hr	FMO3, CYP3A4	7-Hydroxy, others
Haloperidol	40-70	12-36 hr	**CYP2D6**, CYP1A2, CYP3A4	Reduced haloperidol
Perphenazine	20-25	8.1-12.3 hr	**CYP2D6**	7-OH-perphenazine
Second-Generation Antipsychotics (SGAs)				
Aripiprazole	87	48-68 hr	**CYP2D6, CYP3A4**	Dehydroaripiprazole
Asenapine	<2 orally	13-39 hr	**CYP1A2, UGT1A4**, CYP2D6, CYP3A4	None known
	35 SL			
	Nonlinear			
Brexpiprazole	95	91 hr	**CYP2D6, CYP3A4**	DM-3411
Cariprazine		2-4 days, DDCAR 1-3 weeks	**CYP3A4,** CYP2D6	Desmethyl cariprazine (DCAR),
				Didesmethyl cariprazine (DDCAR)
Clozapine	12-81	11-105 hr	**CYP1A2, CYPD6, CYP3A4**	Desmethylclozapine
Iloperidone	96	18-33 hr	**CYP2D6, CYP3A4**	P88
Lumateperone	4.4	13-21 hr	**CYP3A4,** CYP1A2, CYP2C8, Aldoketoreductase 1C1, UGT1A1, UGT1A4, UGT 2B15	IC200131, IC200161, IC200565
Lurasidone	10-20	18 hr	**CYP3A4,** CYP1A2	ID-14233 and ID-14326
Olanzapine	80	20-70 hr	CYP1A2, CYP3A4, FMO3	*N*-Glucuronide; 2-OH-methyl; 4-*N*-oxide
Paliperidone ER	28	23 hr	Renal unchanged (59%)	None known
			CYP3A4 and multiple pathways	
Quetiapine	9 ± 4	6.88 hr	**CYP3A4**, CYP3A5	N-desalkylquetiapine
Quetiapine XR		7 hr	**CYP3A4**, CYP3A5	N-desalkylquetiapine
Risperidone	68	3-24 hr	**CYP2D6**, CYP3A4	9-OH-risperidone
Ziprasidone	59	4-10 hr	Aldehyde oxidase, CYP3A4, CYP1A2	None

UGT, UDP glucuronosyltransferases genes; FMO3, flavin containing monooxygenase 3 gene; SL, sublingual.

[a]**Bold** print indicates major pathway.

Data from References 27-29, 33, 60, and 63-67.

Asenapine is unique in that it has less than 2% bioavailability after oral administration, but has a bioavailability of approximately 35% sublingually—the FDA-approved route of administration. Eating and drinking within 10 minutes after sublingual administration will reduce bioavailability, and bioavailability decreases with single doses above 10 mg.[28,66]

Most antipsychotics have long elimination half-lives, generally 24 hours or more, with the exception of quetiapine and ziprasidone, which have short half-lives.[63,66] Among the SGAs, only clozapine has an established therapeutic serum concentration, with efficacy being associated with a clozapine plasma concentration greater than 350 ng/mL (mcg/L; 1.07 µmol/L).[63] Whether a potential maximum therapeutic clozapine serum concentration exists is unknown. Clozapine serum concentration should be obtained before exceeding 600 mg daily, in patients who develop unusual or severe adverse medication reactions, in patients who are taking concomitant medications that can cause medication interactions, in patients who have age or pathophysiologic changes suggesting a change in pharmacokinetics, or for assessment of patient adherence.[63,66]

Adverse Medication Reactions

Table 87-7 presents the relative risk of common categories of antipsychotic adverse medication reactions, which are discussed below with respect to organ system affected. A general approach to monitoring and assessing adverse medication reactions requires prospective monitoring by clinicians, preferably using a thorough review of systems approach. Patient-oriented self-rated scales can be helpful, as many patients with schizophrenia do not readily endorse adverse medication reactions.

TABLE 87-7

Relative Incidence of Adverse Medication Reactions from Commonly Used Antipsychotics[a,b]

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

EPS, extrapyramidal side effects—includes dystonias, parkinsonism, akathisia, and tardive dyskinesia.

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

[a]Adverse medication reactions 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.

As mentioned previously, adverse medication reactions are one of the primary predictors of patient nonadherence. With the variety of antipsychotics available, using an alternative should be considered to improve patient outcomes in those who endorse poorly tolerated adverse medication reactions. As we learn more about relative risks (eg, metabolic, QTc prolongation, and EPS), it will be necessary to regularly reconsider which antipsychotics should be considered first-line treatment alternatives.

Endocrine System

Within the hypothalamic tuberoinfundibular tract, DA blockade results in increased prolactin levels with hyperprolactinemia occurring in up to 71% of patients diagnosed with schizophrenia and treated with antipsychotics.[68] While US-based studies show no sex difference in the incidence of antipsychotic-induced hyperprolactinemia, UK-based studies suggest females are twice as likely to experience antipsychotic-induced hyperprolactinemia than males (52% vs 26%, respectively).[68,69] The major symptoms associated with hyperprolactinemia are gynecomastia, galactorrhea, menstrual irregularities, infertility, and sexual dysfunction. Although the clinical significance is unclear, chronic hyperprolactinemia has been associated with decreased bone mineral density, which may put patients at higher risk of osteoporosis.[70] Tolerance does not appear to develop to antipsychotic-induced hyperprolactinemia.[71] In general, FGAs are associated with higher rates of hyperprolactinemia than SGAs, the exceptions being risperidone and paliperidone which have reported rates exceeding 70%.[68,69,71] As they have poor penetration of the blood-brain barrier, their greater presence at D_2 receptors in the pituitary gland may be contributing to this adverse effect.[68,69,71] On the other hand, a D_2 partial agonist, aripiprazole is more prolactin sparing and other newer antipsychotics including asenapine, iloperidone, lurasidone, brexpiprazole, cariprazine, and lumateprone have not been shown to induce clinically meaningful changes in prolactin levels.[27,28,30,68,72,73]

If a patient experiences symptomatic hyperprolactinemia, switching to an agent that has minimal sustained effect on prolactin is a reasonable treatment option, as is attempting to lower the antipsychotic dose. However, both interventions run the risk of relapse. Augmentation with aripiprazole 5 to 30 mg daily may help reduce risperidone-induced hyperprolactinemia.[74] However, there have also been case series reporting symptom exacerbation with the addition of aripiprazole and, in general, antipsychotic polypharmacy is discouraged.[68] Dopamine agonists, bromocriptine, cabergoline, and pramipexole have been shown to decrease

prolactin, but this approach is not recommended due to the lack of controlled trials, as well as reports of psychosis exacerbation.[68] For females with schizophrenia who suffer from amenorrhea due to antipsychotic-induced hyperprolactinemia, metformin 750 to 1,500 mg/day has been shown to restore menstrual function, with associated reduction in prolactin level.[75] While this is a potentially appealing intervention, especially in patients who are gaining weight and at risk for Type 2 diabetes mellitus (T2DM), additional evidence is needed before recommending metformin as a first-line intervention for females with antipsychotic-induced hyperprolactinemia.[75]

Weight gain is frequently reported in both adults and children receiving antipsychotics,[76,77] and is often seen within the first 12 weeks of antipsychotic initiation, with the rate of weight gain decreasing over time.[76,77] The risk of cardiovascular-related mortality is higher in individuals with schizophrenia,[78] and this is further aggravated by medication-related weight gain and the high prevalence of smoking. Additionally, obesity is a risk factor for diabetes mellitus.[78,79] Weight gain during treatment is concerning for patients and a reason for poor medication adherence.[55] Clozapine and olanzapine have the highest rates of antipsychotic-induced weight gain (AIWG), with olanzapine being the most studied and likely producing the highest risk. Mid-risk antipsychotics include asenapine, iloperidone, paliperidone, quetiapine, and risperidone. Aripiprazole, lurasidone, and ziprasidone are associated with the lowest risk of AIWG.[28,30,72,76] Newer agents, brexpiprazole, cariprazine and lumateperone, also appear to have low risk of AIWG, similar to aripiprazole.[31,33,73]

Although the exact mechanism for AWIG uncertain, it has been associated with antihistaminic effects, antimuscarinic effects, adrenaline alpha-1, and blockade of 5-HT_{2C} receptors.[77] However, dietary factors and activity levels can play a significant role in this population, as well as nourishment after a period of poor self-care. The risk of weight gain may be greater in patients with their first psychotic episode and those who are underweight at baseline.

Several different genetic variations have been associated with predisposition for AIWG. The 5-HT_{2c} gene and its relationship to AIWG is the most extensively studied polymorphism.[64,80] A meta-analysis of all genetic studies looking at the C–759T promoter region polymorphism of the *5-HT_{2C}* receptor gene confirmed the relationship with AIWG. While the C allele is the major allele in the population, the meta-analysis found that T allele is protective against AIWG.[80] In this same meta-analysis, polymorphisms of dopamine receptor D_2 (*D2*), alpha-2 adrenergic receptor (α_2), and melanocortin-4 receptor (*MC4R*) genes were also found to be associated with AIWG. Insulin-induced gene 2 (*INSIG2*) and Guanine Nucleotide Binding Protein (*GNB3*) had smaller effect sizes, but were also found to be associated with AIWG. Polymorphisms in leptin and leptin receptor genes, methylenetetrahydrofolate reductase (*MTHFR*), and brain-derived neurotrophic factor (*BDNF*) gene have been genetic targets; however, results are inconsistent regarding a potential relationship between these polymorphisms and AIWG.[64,80,81] In general, AIWG is most likely polygenic and impacted by environmental factors.

The combination of olanzapine and samidorphan was FDA-approved for use in schizophrenia and bipolar disorder in May 2021. The addition of samidorphan, a functional opioid antagonist, to olanzapine is a novel approach to attenuate olanzapine-induced weight gain. In a 24-week Phase 3 trial, the olanzapine/samidorphan combination resulted in significantly less weight gain compared to olanzapine monotherapy, with the mean increase in weight of 3.18 kg (7.01 lb) and 5.08 kg (11.2 lb), respectively.[82] Additionally, significantly fewer subjects in the combination group had >7% weight gain as compared to olanzapine monotherapy (27.5% vs 42.7%, respectively). Unfortunately, the olanzapine/samidorphan combination did not result in any metabolic benefit when compared to olanzapine monotherapy.[82]

Several other approaches have been recommended to address weight gain. Switching the antipsychotic to another agent with less weight gain liability is one choice, and an American Diabetes Association consensus task force recommends consideration of a change in antipsychotic if a patient gains more than 5% of baseline body weight after starting the medication.[83] Metformin is effective in treating AIWG with a meta-analysis indicating an average of a 3.17 kg (6.99 lb) weight loss compared with placebo.[84] Dietary restriction, exercise, and behavior modification programs are reported to be successful. Both the Reducing Weight and Diabetes Risk in an Underserved Population (STRIDE) and the Randomized Trial of Achieving Healthy Lifestyles in Psychiatric Rehabilitation (ACHIEVE) clinical trials showed behavioral weight loss interventions resulted in significant weight loss in patients with mental illness receiving antipsychotics. The STRIDE study also showed reductions in fasting glucose over 6- and 12-month periods using such interventions.[80,85,86]

The Improving Metabolic Parameters in Antipsychotic Child Treatment (IMPACT) trial is the only randomized trial to compare different strategies to address overweight/obese youth who had experienced significant weight gain on antipsychotics.[87] All groups received health lifestyle education and were randomized to either the addition of metformin, a switch to aripiprazole, or continuing their baseline antipsychotic. In this 24-week trial, the additional of metformin or a switch to aripiprazole resulted in a decrease in BMI z-score where continued antipsychotic resulted in an increase.[87]

Patients with schizophrenia have a twofold higher prevalence of T2DM compared with the general population.[78] While the illness itself contributes to elevated risk, antipsychotics are a major contributing factor, with individuals exposed to antipsychotics having higher rates of T2DM than those unexposed.[78,79] The exact mechanism by which antipsychotics elevate the risk of T2DM is unknown. While weight gain seen with antipsychotics can lead to insulin resistance and elevated risk of T2DM, a systematic review of antipsychotic-associated diabetic ketoacidosis (DKA) found that weight gain was only associated with roughly half of the included cases, and DKA was often the first indicator of a diabetes diagnosis. The SGAs can rapidly and directly influence glucose metabolism independent of AIWG and adiposity.[88] Antipsychotics also may directly cause T2DM through increased insulin resistance or impaired β-cell function or a combination of the two.[79] The greatest increase in glucose impairment typically occurs during the first 14 weeks of treatment,[85] and for clozapine, olanzapine, quetiapine, and risperidone nearly 60% of new-onset diabetes occurred within the first 6 months of treatment initiation.[83,85]

The FDA-approved product labeling for all SGAs reflects the increased risk of diabetes mellitus in patients taking these medications, but risk varies based on the antipsychotic. Clozapine and olanzapine have the highest risk of new-onset diabetes followed by quetiapine and risperidone, while the risk appears lowest with ziprasidone and aripiprazole.[83,85] Although inadequate data are available for asenapine, iloperidone, lurasidone, brexpiprazole, cariprazine, and lumateperone, their risk also appears low.[33,89] Olanzapine is not recommended as a first-line antipsychotic option due to its metabolic risks[14,22,23]; therefore, designing care models and standards for managing diabetes in patients with schizophrenia is important in addressing this major health problem.

Cardiovascular System

Orthostatic Hypotension

Orthostatic hypotension, thought to be caused by α-adrenergic blockade, is a common adverse reaction of antipsychotics.[90] Clozapine and quetiapine had the highest incidence of orthostatic hypotension in the CATIE study, and iloperidone appears to have the highest risk among newer SGAs.[90] Orthostatic hypotension can occur in any patient, but patients with diabetes and preexisting cardiovascular disease and older adults are particularly predisposed. Other risk factors may include dehydration, presence of alcohol associated neuropathy and antipsychotic combination treatment.[90,91] Patients should be advised to avoid sudden positional changes to allow for adaptation. Tolerance to orthostatic hypotension may occur within 2 to 3 months. If not, lower doses or a change to an antipsychotic with less α-blockade can be attempted. Fluid resuscitation or increasing salt intake may also help minimize orthostatic blood pressure changes.[90,91]

Electrocardiographic Changes

The electrocardiographic (ECG) changes seen with antipsychotics include increased heart rate (through sinus tachycardia from anticholinergic effects, or reflex tachycardia from α-adrenergic blockade), flattened T waves, ST segment depression, and prolongation of QT and PR intervals. The most clinically important of these potential changes is prolongation of the QTc interval, which has been associated with ventricular arrhythmias, including torsade de pointes syndrome. This is thought to occur as a result of blockade of the cardiac delayed potassium rectifier channel as well as impairment in autonomic function.[89,91] Among the antipsychotics, thioridazine is most likely to cause these changes and has been shown to prolong the QTc an average of about 30 msec, which is over 20 msec longer than haloperidol, risperidone, olanzapine, or quetiapine, and 15 msec longer than ziprasidone.[92] Thioridazine's effect on QTc prolongation is dose related, and has led to a boxed warning in the FDA-approved product labeling. A comprehensive review was not able to stratify the degree of QTc prolongation of nine different SGAs.[93] Iloperidone, however, is subject to pharmacogenomic differences in metabolism, and there may be an increased risk of QTc prolongation in

CYP2D6 poor metabolizers.[27] High IV doses of haloperidol elevate the risk for QTc prolongation, resulting in a boxed warning in the FDA-approved labeling.[94] Although the precise point at which QTc prolongation becomes clinically dangerous is unclear, the risk for arrhythmia escalates when the QTc interval exceeds 500 msec, or is 60 msec above the baseline QTc.[93,94] Accordingly, it has been recommended to discontinue a medication associated with QTc prolongation if the interval consistently exceeds 500 msec. QTc intervals greater than or equal to 450 msec and/or a 30 msec increase in QTc interval from baseline may be predictors of a medication's risk to cause torsades.[93]

While QTc prolongation may predict torsade de pointes, it rarely happens in the absence of other risks factors, including patients greater than 60 years, female gender, those with preexisting cardiac or cerebrovascular disease (including bradycardia, second- or third-degree AV block, and congenital long QTc syndrome), hepatic impairment, hypokalemia, hypomagnesemia, concomitant medications that prolong the QTc interval, metabolic inhibition by another medication, or preexisting QTc prolongation.[93,94] For patients over the age of 50 years of age, a pretreatment ECG is recommended, as are baseline serum potassium and magnesium levels.

Myocarditis and Cardiomyopathy

Myocarditis is an infrequent and dose independent adverse effect that is most likely to occur with clozapine, but has been reported with quetiapine,[90] and possibly with olanzapine.[95] Eighty-seven percent of clozapine-induced myocarditis cases occur within the first 4 weeks of treatment, but cases as late as 22 weeks have been reported.[89,96] Symptoms of clozapine-induced myocarditis can be nonspecific and include: flu-like symptoms (eg, fever, myalgias), respiratory (eg, dyspnea, cough, orthopnea), and cardiac (persistent tachycardia, chest pain, syncope) symptoms. Myocarditis is considered a life-threatening event and therefore early detection is essential. While the incidence of clozapine-induced myocarditis may be as high as 3%, and the mortality rate upwards of 10% to 30%, there are no mandatory monitoring parameters.[96] 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. A baseline echocardiogram (ECHO) is recommended and repeated if myocarditis is suspected. Both CRP elevations above 100 mg/L and troponin greater than two times the upper limit of normal have been shown to be highly sensitive in detecting clozapine-induced myocarditis. Clozapine rechallenge after the occurrence of myocarditis is debated, and only a few cases have been reported. The decision to rechallenge should only be made in patients where the clinical value greatly outweighs the potential risk, and only after full resolution of the myocarditis and no signs of permanent cardiac damage. A rechallenge should be conducted in a hospital where close monitoring can occur, as myocarditis recurrence during rechallenge has been reported.[96]

Cardiomyopathy, a potentially life-threatening adverse effect, can also be seen with clozapine, which typically presents later during treatment than myocarditis, with an average time of onset of 14 months.[96,97] The current incidence of cardiomyopathy is estimated to be 0.02% to 0.1%, but this adverse effect may be under-reported,[97] as shortness of breath, palpitations, and fatigue are the most frequently reported symptoms. The diagnosis of cardiomyopathy is typically made with an ECHO with a reduction in ejection fraction (EF) being the most consistent finding. For patients with an EF less than 25%, lower recovery and higher mortality rates have been seen, whereas those with an EF greater than 40% typically fully recover.[97] In suspected cases of clozapine-induced cardiomyopathy, clozapine should be discontinued, and a rechallenge is not recommended.[98]

Sudden Cardiac Death

The risk of sudden cardiac death (SCD) with use of FGAs and SGAs is reported to be twice that of nonusers, with risk increasing with escalated dose.[89,90] Fifteen cases of SCD may occur per 10,000 years of antipsychotic exposure.[89,90] There is insufficient evidence to confer a greater risk with one class of antipsychotics over another.[89,90] A case-crossover study involving over 17,000 patients showed that antipsychotic use was associated with a 1.53-fold increase in ventricular arrhythmia or SCD. The magnitude of effect was greatest among patients who received antipsychotics for a short term (less than 28 days).[99] Nonetheless, prospectively designed studies are needed to confirm dose-dependency with antipsychotic-associated cardiovascular sudden death, and whether risk is different among antipsychotics.

Lipid Changes

Treatment with at least some SGAs and phenothiazines is associated with elevated serum triglycerides and cholesterol. Among the SGAs, olanzapine, clozapine, and quetiapine have the highest risk for dyslipidemia, with elevations in serum triglycerides being the most frequently reported abnormality.[28,30] Increased appetite and subsequent weight increase can negatively affect lipids. Independent of weight gain, antipsychotic effects on apolipoprotein B, lipoprotein oxidation, and elevations in sterol regulatory element binding protein-controlled gene expression are among possible mechanisms by which lipid changes may occur with antipsychotics.[100] As previously discussed, olanzapine is associated with greater and significant adverse effects on metabolic parameters, including lipids, blood glucose, and body weight as compared with other antipsychotics in the CATIE trial.[17]

The occurrence of weight gain, diabetes, and lipid abnormalities during antipsychotic therapy is consistent with the development of metabolic syndrome, and cohorts of patients with schizophrenia have shown elevated prevalence of metabolic syndrome as compared with general population cohorts. Prevalence rates of metabolic syndrome in US populations treated with antipsychotics range from 28% to 60%, with 40.9% reported in the prospectively designed CATIE trial.[101]

Metabolic syndrome consists of raised triglycerides (greater than or equal to 150 mg/dL [1.70 mmol/L]), low HDL cholesterol (less than or equal to 40 mg/dL [1.03 mmol/L] for males, less than or equal to 50 mg/dL [1.29 mmol/L] for females), elevated fasting glucose (greater than or equal to 100 mg/dL [5.6 mmol/L]), blood pressure elevation (greater than or equal to 130/85 mm Hg), and weight gain (abdominal circumference greater than 102 cm [40 in.] for males, greater than 89 cm [35 in.] in females).[102] A diagnosis of metabolic syndrome can be made in individuals who meet at least three of these criteria. Therefore, these abnormalities dictate an important role for general health screening and monitoring in patients with schizophrenia, and prompt intervention when such abnormalities occur. The propensity of individual antipsychotics to produce metabolic disturbances should be considered in the context of individual patient risk factors at the time of medication selection.

Thromboembolism

Compared to the general population, the risk of venous thromboembolism (VTE) is twofold higher in individuals with schizophrenia. Sedentary lifestyle, smoking, and metabolic syndrome are all potential explanations for the higher incidence. Increased rates have also been reported in stuporous catatonia and prolonged physical restraints. Additionally, both FGAs and SGAs have been associated with elevating the risk of VTE. The risk may be highest within the first 30 days of antipsychotic exposure and with higher doses. Although the mechanism for increased VTE risk is unknown, increased sedative adverse medication reactions, metabolic effects, antipsychotic effect on platelet aggregation, and hyperprolactinemia indirectly increasing venous stasis have been proposed.[103] The QThrombosis (https://qthrombosis.org/) is a validated VTE risk calculator that includes antipsychotics in the risk assessment model.[104] This tool may be helpful in identifying patients at elevated risk for VTE and can easily be implemented in clinic practice.

Anticholinergic Effects

Patients receiving antipsychotics or antipsychotics in combination with anticholinergics can experience anticholinergic adverse reactions (eg, dry mouth, constipation, tachycardia, blurred vision, inhibition or impairment of ejaculation, urinary retention, or impaired memory). These adverse medication reactions are particularly seen with low-potency FGAs, and in older adult patients who are especially sensitive to these effects. Of the SGAs, clozapine and olanzapine have moderately high rates of anticholinergic effects. Constipation, caused by slowed peristaltic movement and decreased intestinal fluid content, should be closely monitored and treated, especially in older adults. Paralytic ileus and necrotizing enterocolitis can also occur.[89,90]

Central Nervous System

Extrapyramidal System

Extrapyramidal symptoms (EPS) is an umbrella term used to describe antipsychotic-induced movement symptoms due to excess dopamine blockade in the nigrostriatal pathway. These symptoms include: dystonia, akathisia, parkinsonism, and tardive dyskinesia, which are explained in detail below.

Dystonia

Dystonia is a state of abnormal tonicity, sometimes described simplistically as a severe "muscle spasm.[105] More accurately, dystonias are prolonged tonic contractions, with a rapid onset, usually within 24 to 96 hours of initiating or increasing the dose of an antipsychotic.[106] Types of dystonic reactions include trismus, glossospasm, tongue protrusion, pharyngeal–laryngeal spasms, blepharospasm, oculogyric crisis, torticollis, and retrocollis, but can occur with any skeletal muscle group. They can be life-threatening, as in the case of pharyngeal–laryngeal dystonias, and can contribute significantly to patient medication nonadherence. Dystonic reactions occur primarily with high potency FGAs and are greatly reduced with SGAs. Risk factors for dystonia include younger patients, male sex, the use of high-potency agents, rapid titration, and high dosage. The overall incidence from the 1960s to the mid-1970s ranged from 2.3% to 10%, but as higher-potency traditional antipsychotics became more widely used, the rate increased to as high as 64%.

Intramuscular or IV anticholinergics (Table 87-8) are the treatment of choice for dystonias, with benzodiazepines being a second-line option.[106] Benztropine 2 mg or diphenhydramine 50 mg can be given IM or IV, whereas diazepam 5 to 10 mg by slow IV push or lorazepam 1 to 2 mg intramuscularly are treatment alternatives. Relief from the dystonia is typically seen within 15 to 20 minutes of an IM injection or within 5 minutes of IV administration. The antipsychotic can be continued, with concomitant short-term use of an oral anticholinergic, which is then subsequently tapered and stopped. In general, prophylactic anticholinergic medications are not recommended routinely. However, prophylaxis is reasonable when using high-potency FGAs (eg, haloperidol or fluphenazine) in young males and in patients with a history of dystonia.[105] Dystonias can also be minimized by the use of lower initial FGA doses or the use of SGAs. Anticholinergics are good choices for prophylaxis, whereas amantadine has not been proven effective for this purpose.

TABLE 87-8

Agents Used to Treat Extrapyramidal Symptoms

Generic Name	Equivalent Dose (mg)	Daily Dosage Range (mg)
Antimuscarinic		
Benztropine[a]	1	1-8[b]
Biperiden[a]	2	2-8
Trihexyphenidyl	2	2-15
Antihistamine		
Diphenhydramine[a]	50	50-400
Dopamine Agonist		
Amantadine	NA	100-400
Benzodiazepine		
Lorazepam[a]	NA	1-8
Diazepam	NA	2-20
Clonazepam	NA	2-8
β-Blocker		
Propranolol	NA	20-160

NA, Not applicable.

[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 have been reported.

Akathisia

Akathisia is defined as the inability to sit still and having functional motor restlessness. The most accurate diagnosis is made by combining subjective patient reports with objective observations (pacing, shifting, shuffling, or tapping feet). Subjectively, patients may describe a feeling of inner restlessness or disquiet or a compulsion to move or remain in constant motion that provides some relief. Akathisia occurs in 20% to 40% of patients treated with high-potency FGAs[105,107] and is frequently accompanied by dysphoria. In severe cases, akathisia may be mistaken for aggression and if left untreated, has been linked to insomnia, increased suicidality, and development of tardive dyskinesia.[107]

Akathisia generally appears early in antipsychotic treatment, but can be chronic if not appropriately addressed.[107] Risk of akathisia is greater when the antipsychotic dose is increased rapidly or multiple antipsychotics are used, as well as in antipsychotic naïve individuals.[107] Traditionally, a reduction in antipsychotic dosage has been considered the best intervention; however, this might not be a realistic goal in a patient with acute psychosis. A logical alternative is to switch to an antipsychotic with a lower risk of akathisia, or an antipsychotic the patient previously tolerated. Akathisia can occasionally occur with SGAs, particularly aripiprazole, cariprazine, lurasidone, or risperidone. Iloperidone, quetiapine, and clozapine appear to have the lowest risk of producing akathisia.[72,107]

Unlike acute dystonias, akathisia responds poorly to anticholinergics[107]; therefore, benzodiazepines have been used for treatment of akathisia, but the high prevalence of co-occurring substance use disorders in schizophrenia discourages their use.[107] The β-blockers (eg, propranolol in doses up to 160 mg daily) are effective and have the most evidence.[105,107] Additionally, 5-HT_2 receptor antagonists may be protective against akathisia and may be used for its management. Examples of such agents include mirtazapine, trazodone, and cyproheptadine, with mirtazapine having the most data to support its use.[105,107]

Parkinson Symptoms

Antipsychotic-induced parkinson symptoms resemble idiopathic Parkinson disease with symptom onset typically within 1 to 2 weeks after antipsychotic initiation or a dose increase. For some it may be delayed with 50% to 75% of cases occurring within a month and 90% within 3 months.[105,106] A patient with antipsychotic-induced parkinson symptoms can present with any of four cardinal symptoms: (a) akinesia, bradykinesia, or decreased motor activity including difficulty initiating movement, as well as extreme slowness, mask-like facial expression, micrographia, slowed speech, and decreased arm swing; (b) tremor that is predominant at rest and decreases with movement, and known as the pill-rolling type, usually involves the fingers and hands, although tremors can also be seen in the arms, legs, neck, head, and chin; (c) cogwheel rigidity, seen as the patient's limbs yielding in jerky, ratchet-like fashion when passively moved by the examiner; and (d) postural abnormalities and instability manifested as stooped posture, difficulty in maintaining stability when changing body position, and a gait that ranges from slow and shuffling to festinating. Fatigue and weakness can be noted, as well as oral abnormalities including dysphagia, dysarthria, and abnormal palmomental and glabellar reflexes. The overall incidence of FGA-induced parkinson symptoms ranges from 15.4% to 36%, depending on the medication and dose, and akinesia alone can be seen in 59% of patients on high-potency FGAs. The risk of parkinson symptoms with SGAs is low. A secondary data analysis from the CATIE study did not find marked differences in rates of EPS between perphenazine and SGAs, suggesting that a less potent FGA at modest doses may present a similar risk of parkinson symptoms as SGAs.[108] Other risk factors for the development of parkinson symptoms include increasing age and possibly female sex.

The efficacy of anticholinergic medications in treating antipsychotic-induced parkinson symptoms is well established,[105,106] although diphenhydramine produces more sedation than the other agents. Table 87-7 outlines the dosing of these medications. Symptoms typically begin to resolve within 3 to 4 days after initiation of treatment, but a minimum of at least 2 weeks of treatment is normally required for full response. Amantadine may be as efficacious for parkinson symptoms as anticholinergics, but with significantly less impact on cognition.[105,106] Prophylactic use of these agents against parkinson symptoms is less convincing compared with dystonias, and is unnecessary when using SGAs.[105,106] The long-term treatment of parkinson symptoms with antiparkinson medication is somewhat controversial. An attempt should be made to taper and discontinue these agents in 6 weeks to 3 months after symptom resolution. If symptoms reappear, then switching to an SGA should be considered. Quetiapine, aripiprazole, brexpiprazole, iloperidone, asenapine, lumateperone, and clozapine are reasonable alternatives in a patient experiencing EPS with other SGAs.[33,72,109]

Tardive Dyskinesia

Tardive dyskinesia (TD) is a syndrome characterized by abnormal involuntary hyperkinetic movements occurring late in onset in relation to initiation of antipsychotic therapy. The classic description of tardive dyskinesia is an insidious onset of oral or orofacial movements often associated with lip smacking or tongue thrusting as the disorder progresses, which can interfere with the patient's ability to chew, speak, or swallow. Other facial movements include frequent blinking, brow arching, grimacing, and upward deviation of the eyes. Involvement of the extremities sometimes occurs, and may involve any skeletal muscle group. Orofacial movements are more common in older patients, whereas the truncal axial movements are classically reported in young adults. Movements can worsen with stress, decrease with sedation, and disappear during sleep. Concentration on motor tasks or attempts to suppress the movements can increase them.[110]

Early signs of tardive dyskinesia can be reversible but if allowed to persist, can become irreversible, even with medication discontinuation. The exact time point in which TD becomes irreversible is unknown, which underscores the importance of early detection.[106] When the antipsychotic dose is decreased or tapered and discontinued, worsening of abnormal movements may occur, followed by possible slow improvement after months or years if the patient remains on lower doses or discontinues treatment. Younger age correlates with a greater chance of reversing TD.[106] No standardized diagnostic criteria for tardive dyskinesia are available. Abnormal involuntary movements can be detected early through physical assessment and the use of rating scales. Available rating scales include the Abnormal Involuntary Movement Scale (AIMS) and the Dyskinesia Identification System: Condensed User Scale (DISCUS).[109] Neither scale is diagnostic (see Chapter e81).

One of the greatest risk factors for TD is older age, with patients over 65 having a two-to-fivefold higher incidence of TD than younger adults.[111] Other possible risk factors include history of acute EPS, poor antipsychotic medication response, diagnosis of organic mental disorders, diabetes mellitus, mood disorders, female sex, use of anticholinergics, current and cumulative antipsychotic doses, and duration of antipsychotic exposure.[110] Additionally, genetic variation within CYP2D6, vesicular monoamine transporter-2 (VMAT2) gene, and D_2 receptor gene have been suggested as being associated with increased risk.[112] A systematic review of 12 studies lasting 1 year or more found the overall risk of TD with SGAs to be approximately 2.9% per year in adults under 65 years of age as compared with 7.7% for FGAs.[113] These results were confirmed with a meta-analysis which indicated that olanzapine and aripiprazole may have a small advantage over other non-clozapine SGAs.[114] Tardive dyskinesia is not always permanent, with spontaneous remission of symptoms observed in 25% of patients after 5 years of continued treatment[24]; however, overall morbidity and mortality are greater in tardive dyskinesia patients.

Prevention of TD is important, as treatment of the movements once they occur is difficult. One of the more compelling arguments for the first-line use of SGAs is their lower risk of TD.[24] Therefore, regular neurologic examinations (AIMS or other scales) should be performed at baseline, and APA guidelines recommend TD monitoring at least every 6 months for those at high risk and every 12 months for all others.[22] At the first sign of TD, the need for continuing antipsychotic treatment should be assessed, and if the patient is taking an FGA and continuing treatment is indicated, the medication should be switched to an SGA.

The VMAT2 inhibitors deutetrabenazine and valbenazine are FDA-approved medications for the treatment of TD. Both are considered first-line interventions, as they produced clinically significant decreases in AIMS scores in both short- and long-term trials.[115] However, when valbenazine treatment is discontinued, TD symptoms can rapidly return toward pretreatment levels within 4 weeks after discontinuation.[116]

Deutetrabenzine should be initiated at 6 mg twice daily with food, with weekly dose increases of 6 mg up to a maximum dose of 48 mg per day. It is primarily metabolized via CYP2D6 and a maximum daily dose of 36 mg is recommended with concomitant strong CYP2D6 inhibitors or in CYP2D6 poor metabolizers.[103] It is contraindicated in individuals with severe hepatic impairment or those taking a monoamine oxidase inhibitor. Valbenazine is initiated at 40 mg once daily and increased to 80 mg after 1 week. This medication is not recommended for use in combination with strong CYP3A4 inducers, and a maximum daily dose of 40 mg is recommended when used with CYP3A4 strong inhibitors. Use in individuals with severe renal impairment is not recommended. Labeling for both deutetrabenzine and valbenazine includes warnings about suicidality, depression, and QTc prolongation.[115,116]

Numerous other medications have been used to treat tardive dyskinesia. In two controlled trials lasting 22 to 52 weeks, clozapine decreased abnormal involuntary movement[24]; therefore, switching to clozapine has been recommended as a treatment for moderate-to-severe TD.[14,22-24] A 2013 guideline developed by the American Academy of Neurology (AAN) recommended short-term treatment of TD with either clonazepam (up to 4.5 mg daily) or ginkgo biloba extract 240 mg daily based upon randomized clinical trial data. However, long-term treatment data are lacking.[117] The AAN guideline was developed before the availability of the two VMAT2 inhibitors. However, in patients who do not have access to these agents, or do not tolerate or respond with their use, clonazepam or ginkgo biloba can be considered.[115]

Seizures

An increased risk of medication-induced seizures can occur in patients receiving antipsychotics as these agents decrease the seizure threshold. However, this risk is greater if the following predisposing factors are present: preexisting seizure disorder, history of medication-induced seizure, abnormal electroencephalogram (EEG), and preexisting CNS pathology or head trauma. Seizures are more closely associated with high plasma concentrations, rapid dosage titration, and treatment initiation. The exact mechanism is unknown, but involvement of D_2 and D_s receptors has been proposed.[90] When an isolated seizure occurs, a dosage reduction of the antipsychotic is first recommended, and routine prophylactic use of antiseizure medication is not recommended. Although spontaneously occurring seizures have been reported with most

antipsychotics, the highest potential risk for an antipsychotic-related seizure is with clozapine or chlorpromazine. If a change in antipsychotic therapy is required because of a medication-induced seizure, aripiprazole, risperidone, thioridazine, haloperidol, pimozide, trifluoperazine, and fluphenazine are associated with the lowest potential.[90]

Thermoregulation

Poikilothermia, the body temperature adjusting to the ambient temperature, can be a serious adverse reaction in temperature extremes.[118] Hyperpyrexia can be a danger in hot weather or during exercise. Additionally, inhibition of sweating, a result of anticholinergic properties impairing the peripheral mechanisms of heat dissipation can contribute to this problem, which in its severest form can lead to heat stroke. Hypothermia is a risk in cold temperatures, particularly in older adults. All patients receiving antipsychotics should be educated about these potential problems. Thermoregulatory problems are reportedly more common with the use of low-potency FGAs, but can occur with the more anticholinergic SGAs.

Neuroleptic Malignant Syndrome

Neuroleptic malignant syndrome (NMS) occurs in <1% of patients and is reported with both FGAs and SGAs, with the highest incidence occurring with high-potency FGAs.[90] High antipsychotic doses, rapid parenteral administration, use of multiple antipsychotics, previous history of NMS, dehydration, physical restraints, and older age all increase the risk.[90] Symptoms are most likely to occur within the first week of antipsychotic initiation and develop rapidly over the course of 24 to 72 hours. The mortality rates associated with NMS is high at approximately 10%, with premorbid dehydration elevating the risk of mortality.

Possible mechanisms of NMS include disruption of the central thermoregulatory processes or excess production of heat secondary to skeletal muscle contractions, including the involvement of proinflammatory cytokines. Regardless of the mechanism, the differential diagnoses for NMS include: heat stroke, lethal catatonia, malignant hyperthermia, anticholinergic toxicity, and serotonin toxicity. The cardinal signs and symptoms of NMS are body temperature exceeding 38°C (100.4°F) on at least two occasions, mental status changes, autonomic instability (tachycardia, blood pressure, diaphoresis, tachypnea, or urinary or fecal incontinence), and rigidity.[119] Laboratory evaluation, although nonspecific, frequently shows leukocytosis with or without a left shift, and increases in creatine kinase, aspartate aminotransferase, alanine aminotransferase, lactate dehydrogenase, and myoglobinuria.[118,119] Importantly, NMS treatment should begin with antipsychotic discontinuation and supportive care (eg, IV fluid hydration and benzodiazepines). Dantrolene, bromocriptine, or amantadine may be useful in severe cases as all three agents have reports of reduced time to clinical improvement and reduction in mortality rates.[118]

Many patients with schizophrenia, despite having had NMS, will require future antipsychotic pharmacotherapy. The literature suggests that the risk of rechallenge is acceptable in most patients, provided that the patient is observed for an extended period of time (2 weeks or more is suggested) without antipsychotics, that there is careful monitoring, slow dose titration, and that the patient is maintained on the lowest possible dose.[118,119] A different antipsychotic, an SGA or a low-potency FGA, should be used for rechallenge following an episode of NMS.

Psychiatric Adverse Medication Reactions

Aripiprazole has been associated with impulse control disorders, including pathological gambling, uncontrolled sexual urges, uncontrolled spending, binge or compulsive eating, and other intense urges. This led to an FDA safety announcement in 2016 and subsequent update to the warnings in the package labeling for all aripiprazole products.[120] Mechanistically the D_2 partial agonist activity and possible D_3 receptor activity seen with aripiprazole have been implicated as potential pathways for these reactions.[120] Clinicians are encouraged to monitor for changes in impulse control behaviors and reduce the dose or stop aripiprazole should urges develop or worsen.

Ophthalmologic Effects

Anticholinergic effects of antipsychotics or concomitant antiparkinson medications can exacerbate narrow-angle (angle-closure) glaucoma. Therefore, antipsychotics with low anticholinergic effects should be used in such individuals, and they should be appropriately monitored.[121]

Opaque deposits in the cornea and lens can occur with chronic phenothiazine treatment, with this adverse event occurring most frequently with chlorpromazine. Although visual acuity is not usually affected, periodic ophthalmologic examinations are frequently recommended in patients receiving long-term treatment with phenothiazines, as fully formed cataracts are possible.[121]

Because of cataract development and lenticular changes in animals, baseline and periodic eye examinations are recommended in quetiapine product labeling. However, the effect of quetiapine on lens opacity was found to be no different than risperidone in a 2-year comparative trial.[122] Lastly, retinitis pigmentosa can result from use of thioridazine doses greater than 800 mg daily, due to melanin deposits that can result in permanent visual impairment or blindness.

Genitourinary System

Urinary hesitancy and retention, secondary to antipsychotic anticholinergic effects are reported with low-potency FGAs and with clozapine; those with benign prostatic hypertrophy are especially prone to this effect.[90] Reducing the antipsychotic dose or switching to an antipsychotic with less anticholinergic activity may help. Alternatively, bethanecol can be used to treat antipsychotic-induced urinary hesitancy and retention.

Urinary incontinence is thought to be caused by α-blockade, and among the SGAs, it appears to be particularly problematic with clozapine.[90] The incidence has been reported to be as high as 44%, and it can be persistent in 25% of patients. Female sex and previous urinary incontinence can be risk factors for developing incontinence.[90]

Although inadequately studied, multiple mechanisms are likely responsible for sexual dysfunction seen with antipsychotic use, including dopaminergic blockade, hyperprolactinemia, histaminergic blockade, anticholinergic effects, and α-adrenergic blockade. However, unmedicated individuals with schizophrenia also report decreased libido. Most, but not all, studies show a relationship between hyperprolactinemia and sexual dysfunction, including decreased libido, erectile dysfunction, difficulty achieving orgasm, and ejaculatory abnormalities. Risperidone and paliperidone produce at least as much sexual dysfunction as FGAs, while other SGAs, with weak effects on prolactin, produce less sexual dysfunction. Patients experiencing sexual dysfunction with FGAs or risperidone or paliperidone should be switched to an SGA with less effect on prolactin.[123]

Priapism, a sustained and painful erection that is unprovoked and persists for longer than an hour, is increasingly reported with antipsychotic medication use. This is believed to occur because of α_1-adrenergic receptor blockade, leading to intracavernosal blood stasis.[124] This can evolve into a urologic emergency, due to the ischemic nature of the priapism, and as such patients experiencing this adverse event require emergency treatment. If left untreated, priapism may lead to permanent impotence.

Hematologic System

Transient leukopenia can occur during initial treatment with antipsychotics; however, it typically does not progress to be clinically significant.[125] Agranulocytosis reportedly occurs in 0.01% of patients receiving FGAs, and more frequently with chlorpromazine and thioridazine. The three antipsychotics with the highest relative risk for neutropenia in rank order are clozapine, chlorpromazine, and olanzapine.[125] The onset is usually within the first 8 weeks of therapy. If the absolute neutrophil count (ANC) is less than 500/μL (0.5×10^9/L), the antipsychotic should be discontinued and the ANC monitored closely until it returns to normal and the

patient monitored for the development of secondary infections. Agranulocytosis can initially manifest as a local infection, with sore throat, leukoplakia, erythema, and ulcerations of the pharynx. These symptoms in any patient receiving antipsychotics should signal the immediate need for an ANC. Additionally, isolated rare cases of thrombocytopenia and eosinophilia have been reported.

Agranulocytosis with clozapine has significantly inhibited use of this agent, and it is only available in the United States through the Clozapine REMS Program.[32] The risk of developing neutropenia or agranulocytosis with clozapine is approximately 3% and 0.8%, respectively,[124] and most cases occur between 6 weeks and 6 months. The baseline ANC must be at least 1,500/μL (1.5×10^9/L) to start clozapine, and weekly ANC monitoring for the first 6 months of therapy is mandated in the FDA-approved product labeling. After this time, if the patient's ANC remains greater than 1,500/μL (1.5×10^9/L), the labeling allows monitoring to be decreased to every 2 weeks for the next 6 months. After this, monitoring can be decreased to monthly if all ANCs remain greater than 1,500/μL (1.5×10^9/L). 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 1,500/μL (1.5×10^9/L). The FDA-approved product labeling should be consulted for more detailed information regarding ANC monitoring, including monitoring for mild and moderate leukopenia and recommendations for patients with benign ethnic neutropenia.[32]

Dermatologic System

Allergic reactions are rare and usually occur within 8 weeks of initiating therapy, manifesting as maculopapular, erythematous, pruritic rashes that are evident on the face, neck, trunk, or extremities. Contact dermatitis, including the oral mucosa, has been reported in patients and medical personnel exposed to FGA liquid formulations. The risk of oral mucosal reactions can be decreased by mixing the FGA concentrate in a sufficient quantity of a nonacidic liquid and swallowing it quickly. Care should be taken in the handling and preparation of liquid FGAs. Ziprasidone's FDA-approved label contains a warning regarding the risk of a rare but fatal skin reaction called *Drug Reaction with Eosinophilia and Systemic Symptoms* (DRESS).[126]

Phenothiazines can absorb ultraviolet light, resulting in the formation of free radicals, which can have damaging effects on the skin. All antipsychotics can cause photosensitivity resulting in erythema and sunburn; therefore, exposure to sunlight should be limited, and patients should be educated about the use of a maximally blocking sunscreen, hats, protective clothing, and sunglasses.[125]

Blue-gray or purplish skin coloration in areas exposed to sunlight occurs in patients receiving higher doses of low-potency phenothiazines during long-term administration, especially with chlorpromazine. This adverse event commonly occurs with concurrent corneal or lens pigmentation.

Miscellaneous Adverse Effects

Clozapine-induced sialorrhea (drooling), which is typically prominent at night,[125] affects up to 54% of patients receiving clozapine. The mechanism behind this drooling is unclear; however, two theories exist. The first involves muscarinic receptor activity and clozapine's imbalanced binding affinity to this receptor. The other involves clozapine's α-antagonist activity at the salivary glands leaving unopposed beta-receptor stimulation and hence hyper-salivation.[125] Anticholinergics such as benztropine and atropine, and α-agonists such as clonidine have been used to treat clozapine-related sialorrhea.[127]

Use in Pregnancy and Lactation

The reproductive health of females with schizophrenia has historically received little attention from clinicians or researchers, partly due to reports of lower fertility rates in individuals with schizophrenia. However, with the introduction of more prolactin sparing SGAs (exceptions being risperidone and paliperidone), fertility rates in schizophrenia are increasing.[128] While data on the safety of antipsychotic medication use during pregnancy and lactation are limited, greater than 50% of individuals with schizophrenia who discontinue their medication will experience relapse.[129] Additionally, pregnant individuals with untreated schizophrenia are more likely to use alcohol, tobacco and other substances and are less likely to engage in prenatal care visits.[127] Therefore, these factors may put pregnant individuals and their offspring at greater risk, outweighing any potential risks associated with antipsychotic use.

The risk of teratogenesis with FGAs has not been sufficiently studied, and a specific pattern of teratogenicity has not been found.[130,131] The use of phenothiazines and low dose haloperidol to treat hyperemesis gravidarum provides additional reassurance that FGAs are not major teratogens.[132] Haloperidol is the best studied FGA with approximately 400 reported exposures.[127] With regard to labor and delivery complications, one small study found greater than a twofold elevated risk of preterm birth in pregnant individuals with schizophrenia taking FGAs as compared with those not taking antipsychotics, but did not find an association between FGA exposure and low birth weight or small for gestational age.[133] A major limitation in interpreting this study are the confounding variables such as disease severity, concurrent substance use or other concurrent medications that were not addressed.

Data regarding the safety of SGAs in pregnancy are rapidly increasing but also limited. All SGAs cross the blood-placenta barrier, but to varying degrees. In one study sample, the highest rates of transfer were for olanzapine (72.1%), followed by haloperidol (65.5%) and risperidone (49.2%), with quetiapine being the lowest (24.1%).[134] Among the SGAs, safety data are most abundant for olanzapine, quetiapine, aripiprazole, and risperidone. As a class, SGAs are not thought to be major teratogens. Results from the largest database study to date (9,258 pregnant females with SGA exposure in the first trimester) suggest that the SGAs aripiprazole, olanzapine, quetiapine, risperidone, and ziprasidone collectively do not increase the risk of congenital malformations or cardiac malformation. This finding held true when evaluating each agent individually, except for a small, but statistically significant increase of congenital malformations with risperidone (RR, 1.26; 95% CI, 1.02-1.56).[135-138] A meta-analysis of 12 studies (which did not include the previous study) found a greater risk of congenital malformations with SGA exposure in early pregnancy, but no specific abnormality was identified. In this same study, an increased risk of preterm birth was present in the SGA-treated group. However, healthy females composed the control group in these studies, and the underlying disease state being treated with an SGA is an important confounder.[139] Data on pregnancy exposure with the newer SGAs (eg, asenapine, lurasidone, brexpiprazole, lumateperone, and cariprazine) are minimal or absent. While large, well-controlled studies are still needed to determine the safety of all SGAs during pregnancy, the British Association for Psychopharmacology Consensus Guidelines do not currently consider them major teratogens.[127]

The potential for antipsychotic-related postnatal and gestational complications is of interest. Weight gain associated with SGAs and the potential risk of gestational diabetes should be considered in medication selection. A systematic review that included 10 studies did not find an association between SGAs collectively and gestational diabetes.[140] A retrospective cohort study reported an increased risk of gestational diabetes in individuals who continued quetiapine or olanzapine during the first 20 weeks of pregnancy versus those who discontinued those agents.[141] An increased risk was not observed with risperidone, aripiprazole, or ziprasidone which indicates that risk may differ among SGAs.[127] An increased risk of hypertension in individuals taking antipsychotics during pregnancy as well as venous thromboembolism have also been reported.[128]

Risk of neonatal EPS is increased with in utero exposure to FGAs, with effects in the infant lasting for 3 to 12 months after birth. In 2011, the FDA issued a safety announcement informing healthcare professionals that the pregnancy section of medication labels had been updated for the entire antipsychotic class, highlighting the potential risk for EPS and withdrawal symptoms in newborns exposed to antipsychotics in utero during the third trimester.[142] Symptoms of neonatal withdrawal reported to the FDA included agitation, hypertonia, hypotonia, tremor, somnolence, respiratory distress, and feeding disorder.

To date, little is known about in utero exposure to antipsychotics and neurodevelopmental teratology with most data being derived from case reports and case-series. One case-control study ($n = 76$) reported a transient delay in cognitive, motor, social-emotional, and adaptive behavior in SGA-exposed infants at 2 months of age that resolved by 12 months.[143] One prospective study reported in utero exposure to antipsychotics ($n=22$) was associated with lower neuromotor screening measures at 6 months of age compared to either antidepressant-exposed infants or no psychotropic exposure.[144] A population-based cohort study of 411,251 children did not find an elevated risk of autism spectrum disorder or attention deficit hyperactivity disorder with in utero exposure to SGAs.[145]

For many individuals with schizophrenia, discontinuing the antipsychotic during pregnancy may not be recommended, despite the lack of safety data. The risk of antipsychotic use must be weighed against the

benefits of pharmacotherapy in pregnant individuals experiencing disorganized thoughts, delusions about change in body image or pregnancy, or who are unable to engage in prenatal care.[133] A national pregnancy exposure registry monitors pregnancy outcomes in those exposed to SGAs during pregnancy. Clinicians are encouraged to report SGA use in pregnancy through the registry to assist in gathering safety information. This registry can be accessed at: http://womensmentalhealth.org/clinical-and-research-programs/pregnancyregistry/atypicalantipsychotic.

Data regarding the antipsychotics and human milk are even more limited than their use during pregnancy. Olanzapine is the most studied antipsychotic in lactation ($n = 170$ exposures), followed by quetiapine ($n = 14$), risperidone ($n = 8$), and aripiprazole ($n = 4$). Overall, olanzapine and quetiapine have reported relative infant doses (RIDs) of less than 2%, meaning that with continued exposure to human milk, infants would only be exposed to 2% of maternal dosage overall.[146] Risperidone (+ 9-OH-risperidone) and aripiprazole have reports of slightly higher RID ranges (2.8-9.1 and 0.7-8.3, respectively).[146] Of note, treatment with aripiprazole may lead to reduced milk production as a result of reduced prolactin release.[147] Breastfeeding while on clozapine is not recommended due to the risk of severe neutropenia and seizures in the infant.[127] For all of the FGAs, the overall RID is thought to be less than 10%, which is a common threshold indicating that these medications are safe when feeding infants human milk.

Data evaluating long-term outcomes in infants exposed to antipsychotics through human milk are minimal to absent. The coadministration of chlorpromazine and haloperidol is reported to result in developmental delays at 12 to 18 months of age; however, these were not controlled studies.[127] Although most antipsychotics are not contraindicated in lactation, the lowest antipsychotic dosage should be used, and the infant carefully monitored for antipsychotic adverse events such as EPS, sedation, seizures, and developmental delays.[127,146,147] Additional studies evaluating short- and long-term adverse effects, including developmental outcomes, of infants exposed to antipsychotics via human milk are warranted.

Medication Interactions

Most medication interactions occur because of pharmacodynamic or pharmacokinetic interactions (Tables 87-9 and 87-10). Common examples of pharmacodynamic interactions resulting in enhanced effect include the excess sedation that can occur when antipsychotics are used concomitantly with other medications that have sedative adverse effects. Additive antimuscarinic effects can also be seen when antipsychotics are used with other medications possessing antimuscarinic effects, potentially resulting in urinary retention, constipation, blurred vision, or other anticholinergic adverse effects.[148] Both combined sedative and anticholinergic effects from multiple medications can result in impaired cognition or delirium, particularly in older adults and other patients predisposed to such problems.[148] Patients are more likely to experience symptomatic orthostatic hypotension when an antipsychotic is used with other medications that cause orthostasis. Metoclopramide, a DA antagonist, is prescribed for treating esophageal reflux or gastroparesis, and patients may be more likely to experience akathisia and other EPS (including TD) if it is used concomitantly with antipsychotics.[149] Although some selective serotonin reuptake inhibitors (SSRIs) can interact with antipsychotics through enzyme inhibition, they can also interact through pharmacodynamic mechanisms. Since 5-HT_2 receptors are present on the presynaptic dopaminergic neuron, their activation leads to decreased DA release from the presynaptic terminal. Increased availability of 5-HT through the SSRI's effect can activate these receptors, which in turn results in decreased DA release, and adds to the dopaminolytic effects of antipsychotics.[57] In the absence of enzyme inhibition, SSRIs can still precipitate akathisia or EPS when added to a patient stabilized on an antipsychotic. Several cases of serotonin syndrome have been reported with SGAs used in combination with serotonergic agents, such as SSRIs or tramadol.[57] Another potentially dangerous interaction can occur when medications that slow myocardial conduction, and thus prolong the QTc interval, are used in combination with antipsychotics having the same effect.[57] Careful monitoring should occur with medications that prolong the QTc interval, as well as when antipsychotics with this effect are combined with diuretics.[57]

Food enhances the absorption of both ziprasidone and lurasidone, with the product labels noting a greater than twofold increase in bioavailability when the agents are given with food (Table 87-10). The exact mechanism for the impact of food on absorption is not fully understood[30,150] but simply doubling the dose in a fasted state will not necessarily double the level.[150] Therefore, ziprasidone requires administration with a 500 kcal (2,100 kJ) meal and 350 kcals (1,460 kJ) with lurasidone.[30,150] Asenapine, on the other hand, requires that food and drink be avoided for at least 10 minutes after administration to reduce the chance of the patient swallowing the medication instead of allowing for sublingual absorption, which as previously discussed, impacts bioavailability.[28,66]

TABLE 87-9

Common Potential Pharmacodynamic Interactions with Antipsychotic Medications

Mechanism of Interaction		Examples of Interacting Drugs or Other Substances		Clinical Effect
Muscarinic receptor blockade		Anticholinergics Benztropine Diphenhydramine Trihexyphenidyl		Increased risk of anticholinergic adverse reactions
Additive or synergistic sedation		*Sedatives* Benzodiazepines Concomitant AP Diphenhydramine Melatonin and melatonin agonists Mirtazapine Trazodone TCAs Hypnotics Opiates	*Anticholinergics* Benztropine Diphenhydramine Trihexyphenidyl Mirtazapine	Increased risk of sedation Lethargy Impaired cognition Impaired psychomotor activity Risk of accidents
DA antagonist use for different indication		Metoclopramide		Increased risk of EPS
Cardiovascular interactions				
	QTc prolongation	Amitriptyline Clomipramine Imipramine Citalopram Fluorquinolone antibiotics	Procainamide Quinidine	Increased risk of ECG changes and dysrhythmias
	Electrolyte changes	Diuretics		Increased risk of ECG changes and dysrhythmias
Stimulation of presynaptic 5-HT receptors on DA neuron		SSRIs		Increased EPS
Sympatholytics: α-blockade decreases NE release		Clonidine Methyldopa Prazosin Nitric oxide containing products		Increased hypotension
Increased DA receptor binding		Antipsychotics		Increased adverse medication reactions particularly EPS

DA, dopamine; ECG, electrocardiogram; EPS, extrapyramidal symptoms; 5-HT, serotonin; SSRI, serotonin selective reuptake inhibitor; TCAs, tricyclic antidepressants; NE, norepinephrine.

Data from References 27-30, 32, 37, 148, and 149.

TABLE 87-10

Common Potential Pharmacokinetic Interactions with Antipsychotic Medications

Substrate Antipsychotic and Mechanism of Interaction	Interacting Medication or Substance			Clinical Effect
Aripiprazole, brexpiprazole, cariprazine, and iloperidone				
Inhibition of AP metabolism (CYP2D6, CYP3A4)	*Antidepressants* Bupropion Clomipramine Doxepin Duloxetine Fluoxetine Fluvoxamine Paroxetine Sertraline *HIV protease inhibitors* Indinavir Nelfinavir Ritonavir	*Anti-infectives* Ciprofloxacin Clarithromycin Erythromycin Fluconazole Ketoconazole Itraconazole *Antipsychotics* Asenapine Chlorpromazine Haloperidol Perphenazine Thioridazine	*Miscellaneous* Chlorpheniramine Cimetidine Cocaine Diltiazem Diphenhydramine Cimetidine Grapefruit juice Hydroxyzine Methadone Quinidine Ticlopidine Verapamil	Increased AP effect and risk of adverse medication reactions
Induction of AP metabolism	*Antiseizure Medications* Carbamazepine Oxcarbazepine	*Anti-infectives* Rifampin *Miscellaneous*	*Herbals* St. John's wort	Decreased AP effect

	Phenobarbital Phenytoin	Glucocorticoids Modafinil		
Asenapine				
Inhibition of AP metabolism (CYP1A2)	*Antidepressants* Fluvoxamine	*Anti-infectives* Ciprofloxacin Fluroquinolones	*Miscellaneous* Amidarone Cimetidine	Increased AP effect and risk of adverse medication reactions
Induction of AP metabolism	*Anti-infectives* Nafcillin	*Miscellaneous* Broccoli Brussels sprouts Chargrilled meat Smoking tobacco	*Miscellaneous* Insulin Modafinil Omeprazole	Decreased AP effect
NOTE: Eating food or drinking liquids within 10 minutes of asenapine sublingual administration will decrease bioavailability				
Clozapine				
Inhibition of AP metabolism (CYP3A4, CYP1A2, CYP2D6)	*Antidepressants* Fluoxetine Fluvoxamine *HIV protease inhibitors* Indinavir Nelfinavir Ritonavir	*Anti-infectives* Ciprofloxacin Clarithromycin Erythromycin Fluconazole Fluroquinolones Ketoconazole Itraconazole Nafcillin	*Miscellaneous* Amidarone Cimetidine Diltiazem Grapefruit juice Haloperidol Ticlopidine Verapamil Cimetidine	Increased AP effect and risk of adverse medication reactions
Induction of AP metabolism	*Antiseizure Medications* Carbamazepine Phenobarbital Phenytoin	*Miscellaneous* Glucocorticoids Insulin Modafinil Omeprazole Smoking tobacco	*Herbals* St. John's wort *Anti-infectives* Rifampin	Decreased AP effect
Haloperidol				
Inhibition of AP metabolism (CYP2D6, CYP3A4, CYP1A2)	*Antidepressants* Bupropion Doxepin Duloxetine Fluoxetine Fluvoxamine Paroxetine Sertraline *HIV protease inhibitors* Indinavir Nelfinavir Ritonavir Sequinavir	*Anti-infectives* Ciprofloxacin Clarithromycin Erythromycin Fluoconazole Fluoroquinolones Ketoconazole Itraconazole *Antipsychotics* Chlorpromazine Perphenazine	*Miscellaneous* Amiodarone Chlorpheniramine Cimetidine Diltiazem Diphenhydramine Quinidine Diphenhydramine Cimetidine Grapefruit juice Hydroxyzine Methadone Quinidine Verapamil	Increased AP effect and risk of adverse medication reactions
Induction of AP metabolism	*Antiseizure Medications* Carbamazepine Oxcarbazepine Phenobarbital Phenytoin	*Anti-infectives* Nafcillin Rifampin *Miscellaneous* Broccoli Brussels sprouts Chargrilled meat Glucocorticoids Insulin Modafinil Omeprazole	*Herbals* St. John's wort Tobacco smoking	Decreased AP effect
Olanzapine				
Inhibition of AP metabolism (CYP3A4 and CYP1A2)	*Antidepressants* Fluoxetine Fluvoxamine *HIV protease inhibitors*	*Anti-infectives* Ciprofloxacin Clarithromycin Erythromycin	*Miscellaneous* Amiodarone Cimetidine Diltiazem	Increased AP effect and risk of adverse medication reactions

	Indinavir Nelfinavir Ritonavir	Fluoconazole Fluoroquinolones Ketoconazole Itraconazole	Cimetidine Grapefruit juice Verapamil	
Induction of AP metabolism	*Antiseizure Medications* Carbamazepine Oxcarbazepine Phenobarbital Phenytoin *Anti-infectives* Nafcillin Rifampin	*Miscellaneous* Broccoli Brussels sprouts Chargrilled meat Glucocorticoids Insulin Modafinil Omeprazole	*Herbals* St. John's wort Smoking tobacco *HIV protease inhibitors* Efavirenz Nevirapine	Decreased AP effect
Paliperidone				
The bioavailability of paliperidone is significantly increased when it is taken with food. Although this could increase paliperidone effect, including adverse effects, the clinical significance is undetermined. Only potent CYP3A4 (eg, carbamazepine, rifampin, St. John's wort) inducers appear to increase paliperidone metabolism and affect dose requirements.				
Lurasidone, lumateperone, and quetiapine				
Inhibition of AP metabolism (CYP3A4)	*Antidepressants* Fluoxetine Fluvoxamine Nefazodone *HIV protease inhibitors* Indinavir Nelfinavir Ritonavir Sequinavir	*Anti-infectives* Ciprofloxacin Clarithromycin Erythromycin Fluoconazole Ketoconazole Itraconazole	*Miscellaneous* Amiodarone Cimetidine Diltiazem Grapefruit juice Verapamil	Increased AP effect and risk of adverse medication reactions
Induction of AP metabolism	*Antiseizure Medications* Carbamazepine Oxcarbazepine Phenobarbital Phenytoin	*Anti-infectives* Rifampin *Miscellaneous* Glucocorticoids Modafinil	*Herbals* St. John's wort *HIV protease inhibitors* Efavirenz Nevirapine	Decreased AP effect
NOTE: Lurasidone AUC and Cmax increase by two- and threefold when given with at least 350 calories (1,460 J) of food regardless of fat content. NOTE: Lumateperone is metabolized through multiple different pathways, but interactions have been found with moderate to potent CYP3A4 inhibitors and a CYP3A4 inducer.				
Perphenazine and risperidone				
Inhibition of AP metabolism (CYP2D6)	*Antidepressants* Bupropion Clomipramine Doxepin Duloxetine Fluoxetine Paroxetine Sertraline *Antipsychotics* Chlorpromazine Haloperidol (reduced haloperidol) Perphenazine	*Miscellaneous* Amiodarone Cimetidine Chlorpheniramine Cocaine Diphenhydramine Cimetidine Hydroxyzine Methadone Quinidine		Increased AP effect and risk of adverse medication reactions
Induction of AP metabolism (via CYP3A34, a minor pathway for risperidone)	*Miscellaneous* Dexamethasone	*Anti-infectives* Rifampin		Decreased AP effect
NOTE: Because risperidone's metabolite formed through CYP2D6 metabolism is active (paliperidone), the clinical significance of pharmacokinetic interactions with risperidone is unclear.				
Ziprasidone				
The bioavailability of ziprasidone is increased twofold when it is taken with food. Consistent administration with food is recommended.				

AP, antipsychotic; AUC, Area Under the Curve; Cmax, maximum plasma concentration.

Data from References 27-33, 57, and 148-150.

Asenapine inhibits CYP2D6, and is the only SGA that has been shown to significantly affect the pharmacokinetics of other medications.[28] Table 87-6 lists the known major pathways involved in the metabolism of SGAs. Risperidone is largely metabolized by CYP2D6 to its active metabolite, 9-OH-risperidone (paliperidone), which is thought to have a similar pharmacodynamic profile.[57] Although paliperidone is primarily eliminated renally unchanged, potent inducers of CYP3A4 can cause a potential need for dosage adjustment.[57,66] For asenapine, CYP1A2 is the primary isoenzyme responsible for metabolism with CYP3A4 also being a significant

pathway.[57,66]

Based on current information, inhibitors of CYP1A2 have the greatest potential for causing interactions with clozapine and olanzapine, and some concern with asenapine.[57] Examples include cimetidine, fluvoxamine, and fluoroquinolone antibiotics (ie, ciprofloxacin) to varying degrees. To date, however, no serious inhibition interactions have been reported with olanzapine, which may be a result of olanzapine's wide therapeutic index; however, carbamazepine has been reported to increase olanzapine elimination by as much as 50%.[57] Cigarette smoking is a potent inducer of CYP1A2, and one would expect lower mean olanzapine serum concentrations in smokers compared with those in nonsmokers.

Because of the risk of seizures with higher clozapine tissue concentrations, interactions that inhibit clozapine's metabolism are potentially significant. In particular, fluvoxamine increases clozapine serum concentrations by an average of two- to threefold and up to fivefold.[57] Ciprofloxacin, other fluroquinolones, fluoxetine, and erythromycin can also increase clozapine serum concentrations.[57] As smoking has been associated with a 33% to 55% increase in clozapine clearance,[57] smoking cessation can result in increased clozapine serum concentration that may increase the risk of seizures.[66] Carbamazepine can also induce clozapine metabolism and lead to lower serum concentrations.[57]

A study with the potent CYP3A4 inhibitor ketoconazole showed minimal effects on ziprasidone single-dose pharmacokinetics, with only a 33% mean increase in the ziprasidone area under the time-versus-concentration curve.[57] These results are consistent with data suggesting that aldehyde oxidase is the major metabolic pathway for ziprasidone, with only 30% to 35% being metabolized by CYP3A4.[57]

Modest elevations of aripiprazole serum concentrations occur in the presence of ketoconazole or quinidine, which inhibit CYP3A4 and 2D6, respectively. Ketoconazole has a profound effect on decreasing lurasidone metabolism, and it is recommended that they not be used concomitantly.[30,57] Carbamazepine has been reported to decrease aripiprazole serum concentrations.[57]

Since iloperidone is metabolized through CYP2D6 and 3A4, its clearance can be impaired by inhibitors of these pathways. These types of interactions have the potential to be clinically significant. For example, it is recommended that the iloperidone dose be decreased by 50% when used with CYP2D6 inhibitors such as fluoxetine or paroxetine.[27,57]

Multiple enzymes are responsible for the metabolism of lumateperone. AKR1C1 is the predominant enzyme metabolizing lumateperone to the alcohol metabolite IC200131.[151] Multiple other enzymes are involved in its metabolism including CYP3A4. Dosage adjustments should occur in patients taking moderate to strong CYP3A4 inhibitors or inducers.[33]

Personalized Pharmacotherapy

Pharmacotherapy must be individualized for each person with schizophrenia. Apart from iloperidone, no laboratory tests are generally available that will predict a patient's response to treatment. Past response to treatment, potential adverse effects, patient personal preference, and medication price are the primary variables that should be used in selecting an antipsychotic that is included in stages 1A, 1B, or 2 of the treatment algorithm. In the CATIE study, the number one reason for medication discontinuation was the patient not wanting to take that medication any more, and the second most common reason was adverse effects.[17] These two factors should be carefully considered in antipsychotic selection and medication dosage must be individualized within the usual dose ranges. Careful consideration must also be given to concomitant medications that may interact with the antipsychotic and necessitate a change in dosage.

Preliminary data suggest a relationship between different genetic markers and clinical improvement as well as QTc prolongation in patients treated with iloperidone.[27,64] Substantial interest exists regarding the potential utility of pharmacogenetic monitoring in the pharmacotherapy of schizophrenia. Increasing relationships are being identified between specific genetic variation in relation to both the pharmacodynamics and pharmacokinetics of different antipsychotics. However, no convincing data have demonstrated that clinical outcomes are superior when using routine pharmacogenetic monitoring in the pharmacotherapy of schizophrenia, nor have cost-effectiveness studies of its use been performed.[64,65] Although promising for the future, routine pharmacogenetic monitoring in all patients with schizophrenia is not currently recommended. However, it may be useful in select patients. For example, if a patient appears particularly sensitive to developing EPS when treated with antipsychotics metabolized through CYP2D6, it might be useful to perform pharmacogenetic testing to determine whether the patient is a poor CYP2D6 metabolizer. If so, antipsychotics metabolized through CYP2D6 should be used at lower doses, or the patient switched to an antipsychotic not metabolized by CYP2D6.[64] Clinicians should consult accepted guidelines, such as those by the Clinical Pharmacogenetics Implementation Consortium (https://cpicpgx.org/), before utilizing pharmacogenetic data.[67]

Given that no antipsychotic has proven superiority regarding efficacy in the treatment of schizophrenia (with the exception of clozapine in treatment resistance), cost should be a factor in antipsychotic selection. Many antipsychotics have generic equivalents available, and this should be a factor in selecting an antipsychotic (Table 87-9).

Evaluation of Therapeutic Outcomes

10 Assessment of response has traditionally been done subjectively or empirically (a relative sense of how the clinician feels the patient is doing). A formal mental status exam (MSE) is used to structure the patient interview and focus on items related to appearance, mood, sensorium, intellectual functioning, and thought processes. However, the MSE is neither specific nor quantitative for the measurement of medication response. Clinicians should be trained to use simple, standardized psychiatric rating scales to assist in objectively rating patient medication responses.[152] The Brief Psychiatric Rating Scale (BPRS) and the Positive and Negative Syndrome Scale (PANSS) were developed for use in clinical trials as research tools to quantify symptom improvement seen with antipsychotic treatment (see Chapter e81). Objectively, a numeric indicator (eg, 20%, 30%, or 40% reduction in BPRS score) has been used to quantify overall symptom reduction and classify patients according to different degrees of response. However, these types of rating scales are too long and unwieldy to be routinely used within the time constraints of most clinical practices. Symptom scales used in clinical practice must be sufficiently brief to be used during an ordinary clinic visit (eg, 15-30 minutes) while measuring both positive and negative symptoms, and being sufficiently representative of overall symptomatology. The four-item Positive Symptom Rating Scale (PSRS) and the four-item Brief Negative Symptom Assessment (BNSA) are brief scales that meet such criteria (Table 87-11).[152] A brief rating scale of positive symptoms, such as the PSRS, should be used at baseline before starting pharmacotherapy, and at each time response to pharmacotherapy is assessed.

TABLE 87-11

Brief Clinical Assessments for Monitoring Antipsychotic Response in Schizophrenia

Four-Item Positive Symptom Rating Scale (PSRS)								
Use each item's anchor points to rate the patient								
1. Suspiciousness	NA	1	2	3	4	5	6	7
2. Unusual thought content	NA	1	2	3	4	5	6	7
3. Hallucinations	NA	1	2	3	4	5	6	7
4. Conceptual disorganization	NA	1	2	3	4	5	6	7
Each item is scored from 1 (not present) to 7 (extremely severe)	SCORE:							
Brief Negative Symptom Assessment (BNSA)								
Use each item's anchor points to rate the patient								
1. Prolonged time to respond	1	2	3	4	5	6		
2. Emotion: Unchanging facial expression, blank, expressionless face	1	2	3	4	5	6		
3. Reduced social drive	1	2	3	4	5	6		
4. Poor grooming and hygiene	1	2	3	4	5	6		
Each item is scored from 1 (normal) to 6 (severe)	SCORE:							

[a]NA, not able to be assessed.

Data from Reference 152.

Similarly, the pharmacotherapeutic plan should include specific monitoring parameters for adverse medication reactions (Table 87-12). The plan should include how the potential reactions will be evaluated, and the frequency of assessment. Given the risk of weight gain, diabetes, and lipid abnormalities associated with many of the SGAs, a consensus task force led by the American Diabetes Association recommends the following baseline parameters before beginning antipsychotics: family history, weight, height, BMI, waist circumference, blood pressure, fasting plasma glucose, and fasting lipid profile.[83] They also recommend follow-up monitoring of these parameters after beginning or changing SGAs. Weight should be monitored monthly for the first 3 months and quarterly thereafter. The other parameters should be assessed at the end of 3 months, and if normal, then at least annually. Self-assessments can be a useful adjunct in treating the patient. Although the patient with schizophrenia may not always be accurate in evaluating symptom severity, the use of patient self-assessments increases patient engagement in care, enhances therapeutic alliance, and gives the clinician an opportunity to identify misconceptions the patient may have regarding symptoms associated with the illness, adverse medication reactions, and the like.[55] Traditionally, clinicians have often accepted partial symptom response in schizophrenia as success, and have not been aggressive in attempting to achieve greater symptomatic remission. The advent of multiple different SGAs with varying tolerability profiles should encourage clinicians to be more assertive in attempting to achieve symptom remission. This is consistent with an increasing focus on remission as a goal of treatment and the evolving emphasis on consumerism in the care of patients with severe mental illness.[54]

TABLE 87-12

Antipsychotic Adverse Reactions and Monitoring Parameters

Adverse Reaction	Monitoring Parameter	Frequency	Comments
Adverse Reaction 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 adverse 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 females, ask about expression of milk from the breast and menstrual irregularities. In males, 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 6 months for FGAs and every 12 months for SGAs	
Weight gain	Measure body weight, BMI, and waist circumference	BMI every visit for 6 months and at least quarterly thereafter	Waist circumference is the single best predictor of cardiac morbidity
Adverse Reaction Monitoring Parameters for Specific Antipsychotics			
Agranulocytosis	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, patients must be screened 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 medication 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
Post injection sedation/delirium syndrome	Observation of the patient for at least 3 hours after medication 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

FBS, fasting blood sugar; AIMS, Abnormal Involuntary Movement Scale; DISCUS, dyskinesia identification system condensed user scale; FGA, first-generation antipsychotic; SGA, second-generation antipsychotic.

CONCLUSION

Schizophrenia is a neurodevelopmental disorder whose etiology is currently unknown. A multitude of medications, primarily working through dopamine, serotonin, and glutamatergic antagonism, have been developed to treat symptoms associated with this syndrome. Although there is no cure for schizophrenia, lifelong antipsychotic use combined with comprehensive psychosocial services can allow many of these

individuals to function. However, medication adherence can be challenging, and the use of long-acting injectable antipsychotics combined with psychosocial services designed to address engagement with treatment can promote adherence. Antipsychotic medications have a multitude of potential adverse reactions, and prudent monitoring is necessary. As the common core symptoms associated with schizophrenia (positive, negative, and cognitive) vary among person to person, continual evaluation of therapeutic outcomes focusing on overall functioning and quality of life is necessary.

ABBREVIATIONS

α_1	alpha one adrenergic receptor
α_2	alpha two adrenergic receptor
AAN	American Academy of Neurology
ACHIEVE	Randomized Trial of Achieving Healthy Lifestyles in Psychiatric Rehabilitation
ACT	active community treatment
ADTA2A	adrenoreceptor alpha-2a
AIMS	Abnormal Involuntary Movement Scale
AIWG	antipsychotic-induced weight gain
ANC	absolute neutrophil count
AP	antipsychotic
APA	American Psychiatric Association
ASD	autism spectrum disorder
AUC	area under the curve
β_2	beta-2 adrenergic receptor
BDNF	brain-derived neurotrophic factor
BLM	buccal–lingual–masticatory
BMI	body mass index
BP	blood pressure
BNSA	Brief Negative Symptom Assessment
BPRS	Brief Psychiatric Rating Scale
C4	complement component 4 genes
CACN1A2	voltage-dependent calcium channel 1A2
CATIE	Clinical Antipsychotic Trials of Intervention Effectiveness
CK	creatine kinase
CNS	central nervous system
CNV	copy number variant
C_{max}	maximum plasma concentration
CRP	C-reactive protein
CYP	cytochrome P450
D_1	dopamine-1 receptor
D_2	dopamine-2 receptor
D_3	dopamine-3 receptor
D_4	dopamine-4 receptor

DA	dopamine
DISCUS	Dyskinesia Identification System: Condensed User Scale
DKA	diabetic ketoacidosis
DRESS	Drug Reaction with Eosinophilia and Systemic Symptoms
DSM-5	*Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition*
ECG	electrocardiogram or electrocardiographic
ECHO	echocardiogram
ECT	electroconvulsive therapy
EEG	electroencephalogram
EF	ejection fraction
EPS	extrapyramidal side effect
FBS	fasting blood sugar
FDA	Food and Drug Administration
FGA	first-generation antipsychotic
FMO3	flavin containing monooxygenase 3 gene
GABA	gamma-aminobutyric acid
GNB3	guanine nucleotide binding protein
GWAS	genome-wide association studies
HgA1c	hemoglobin A1c
5-HT	serotonin or 5-hydroxytryptamine
5-HT_{1A}	serotonin-1A receptor
5-HT_{2}	serotonin-2 receptor
5-HT_{2A}	serotonin-2A receptor
5-HT_{2C}	serotonin-2C receptor
5-HT_{6}	serotonin-6 receptor
5-HT_{7}	serotonin-7 receptor
HR	heart rate
ICD	impulse control disorder
IM	intramuscular
INSIG2	insulin-induced gene 2
IV	intravenous
LAIA	long-acting injectable antipsychotic
LBW	low birth weight
MC4R	melanocortin-4-receptor
1MPP	1-month paliperidone palmitate (Invega Sustenna)
3MPP	3-month paliperidone palmitate (Invega Trinza)
mRNA	microribonucleic acid

MTHFR	methylenetetrahydrofolate reductase
MSE	mental status examination
NAMI	National Alliance on Mental Illness
NE	norepinephrine
NIMH	National Institute of Mental Health
NMDA	*N*-methyl-D-aspartate
NMS	neuroleptic malignant syndrome
NRG1	neuregulin 1
NRXN1	synaptic protein neurexin 1
PANSS	Positive and Negative Symptom Scale
PDSS	post injection delirium/sedation syndrome
PET	positron emission tomography
PORT	Patient Outcomes Research Team
PSRS	Positive Symptom Rating Scale
RAISE	Recovery After Initial Schizophrenia Episode
REMS	Risk Evaluation and Mitigation Strategy
RID	relative infant dose
RNA	ribonucleic acid
SCD	sudden cardiac death
SEs	side effects
SGA	second-generation antipsychotic
SNP	single nucleotide polymorphism
SSRI	selective serotonin reuptake inhibitor
STRIDE	Reducing Weight and Diabetes Risk in an Underserved Population
T2DM	type 2 diabetes mellitus
TCA	tricyclic antidepressant
TD	tardive dyskinesia
UK	United Kingdom
VMAT2	vesicular monoamine transporter-2
VTE	venous thromboembolism
WBC	white blood cell

REFERENCES

1. American Psychiatric Association. Schizophrenia spectrum and other psychotic disorders. In: *Diagnostic and Statistical Manual of Mental Disorders*. 5th ed. Arlington, VA: American Psychiatric Association; 2013:87–122.

2. Charlson FJ, Ferrari AJ, Santomauro DF, et al. Global epidemiology and burden of schizophrenia: findings from the global burden of disease study 2016. *Schizophr Bull*. 2018;44:1195–1203. [PubMed: 29762765]

3. Milan ML, Andrieux A, Bartzokis G, et al. Altering the course of schizophrenia: progress and perspectives. *Nat Rev Drug Discov*. 2016;15:485–515. [PubMed: 26939910]

4. Price AJ, Jaffe AE, Weinberger DR. Cortical cellular diversity and development in schizophrenia. *Mol Psychiatry*. 2021;26(1):203–217. 10.1038/s41380-020-0775-8 [PubMed: 32404946] .

5. Dalmau J, Graus F. Antibody-mediated encephalitis. *N Engl J Med.* 2018;378:840–851. [PubMed: 29490181]

6. Howes OD, Murray RM. Schizophrenia: an integrated sociodevelopmental cognitive model. *Lancet*. 2014;383:1677–1687. [PubMed: 24315522]

7. Arsalan A, Kowalec K. Genetic architecture of schizophrenia: a review of major advancements. *Psychol Med.* 2021;51(13):2168–2177. 10.1017/S0033291720005334 [PubMed: 33550997] .

8. Sekar A, Bialas AR, de Rivera H, et al. Schizophrenia risk from complex variation of complement component 4. *Nature*. 2016;530:177–183. doi: 10.1038/nature16549.

9. Cannon TD, Chung Y, He G, et al. North American Prodrome Longitudinal Study Consortium. Progressive reduction in cortical thickness as psychosis develops: a multisite longitudinal neuroimaging study of youth at elevated clinical risk. *Biol Psychiatry*. 2015;77(2):147–157. [PubMed: 25034946]

10. McCutcheon RA, Reis Marques T, Howes OD. Schizophrenia—an overview. *JAMA Psychiatry*. 2020;77(2):201–210. 10.1001/jamapsychiatry.2019.3360 [PubMed: 31664453] .

11. Howes OD, Kambeitz J, Kim E, et al. The nature of dopamine dysfunction in schizophrenia and what this means for treatment. *Arch Gen Psychiatry*. 2012;69:776–786. [PubMed: 22474070]

12. Krystal JH, Anticevic A. Toward illness phase-specific pharmacotherapy for schizophrenia. *Biol Psychiatry*. 2015;78:738–740. [PubMed: 26542740]

13. Wright R, Rethelyi JM, Gage FG. Enhancing induced pluripotent stem cell models of schizophrenia. *JAMA Psychiatry*. 2014;71(3):334–335. [PubMed: 24382673]

14. Hasan A, Palkai P, Wobrock T, et al. World Federation of Societies of Biological Psychiatry (WFSBP) guidelines for biological treatment of schizophrenia—short version for primary care. *Int J Psychiatry Clin Pract.* 2017;21:82–90. [PubMed: 28498090]

15. Evins AE, Green AI, Kane JM, Murray RM. Does using marijuana increase the risk for developing schizophrenia? *J Clin Psychiatry*. 2013;74:e08. doi: 10.4088/JCP.12012tx2c.

16. Lieberman JA, First MB. Psychotic disorders. *New Engl J Med.* 2018;379:270–180.

17. Lieberman JA, Stroup S. The NIMH-CATIE schizophrenia study: what did we learn? *Am J Psychiatry*. 2011;168:770–775. [PubMed: 21813492]

18. Addington D, Anderson E, Kelly M, et al. Canadian practice guidelines for comprehensive community treatment for schizophrenia and schizophrenia spectrum disorder. *Can J Psychiatry*. 2017;62:662–672. [PubMed: 28886669]

19. McGorry PD. The next stage for diagnosis: validity through utility. *World Psychiatry*. 2013;12(3):213–214. [PubMed: 24096779]

20. Kane JM, Robinson DG, Schooler NR, et al. Comprehensive versus usual community care for first-episode psychosis: 2-year outcomes from the NIMH RAISE early treatment program. *Am J Psychiatry*. 2015;173:362–372. doi: 10.1176/appi.ajp.2015.15050632.

21. Saperstein AM, Kurtz MM. Current trends in the empirical study of cognitive remediation for schizophrenia. *Can J Psychiatry*. 2013;58(6):311–318. [PubMed: 23768258]

22. Keepers GA, Fochtmann LJ, Anzia JM, et al. The American Psychiatric Association Practice Guideline for the Treatment of Patients with Schizophrenia. *Focus (Am Psychiatr Publ).* 2020;18(4):493–497. 10.1176/appi.focus.18402 [PubMed: 33343262] .

23. Osser DN, Jalali-Roudsari M, Manschreck T. Schizophrenia. Psychopharmacology algorithms, from the Psychopharmacology Algorithm Project at the Harvard Medical School Dept. of Psychiatry, South Shore Program. Available at: http://psychopharm.mobi/algo_live/. Accessed December 26, 2018.

24. Hazari N, Kate N, Grover S, et al. Clozapine and tardive movement disorders: a review. *Asian J Psychiatr.* 2013;6(6):439–51. 10.1016/j.ajp.2013.08.067 [PubMed: 24309853] .

25. Correll CU, Robinson DG, Schooler NR et al. Cardiometabolic risk in patients with first-episode schizophrenia spectrum disorders: baseline results from the RAISE-ETP Study. *JAMA Psychiatry*. 2014;71(12):1350–1363. [PubMed: 25321337]

26. de Berardis D, Fornaro M, Orsolini L, et al. The role of inhaled loxapine in the treatment of acute agitation in patients with psychiatric disorders: a clinical review. *Int J Molo Sci.* 2017;18:349. doi: 10.3390/ijms18020349.

27. Citrome L. Iloperidone for schizophrenia: a review of the efficacy and safety profile for this newly commercialized second-generation antipsychotic. *Int J Clin Pract.* 2009;63:1237–1248. [PubMed: 19624791]

28. Citrome L. Asenapine for schizophrenia and bipolar disorder: a review of the efficacy and safety profile for this newly approved sublingually absorbed second-generation antipsychotic. *Int J Clin Pract.* 2009;63:1762–1784. [PubMed: 19840150]

29. McCormack PL. Cariprazine: first global approval. *Drugs*. 2015;75:2035–2043. [PubMed: 26510944]

30. Citrome L. Lurasidone for schizophrenia: a review of the efficacy and safety profile for this newly approved second-generation antipsychotic. *Int J Clin Pract.* 2011;65:189–210. [PubMed: 21129135]

31. Frankel JS, Schwartz TL. Brexpiprazole and cariprazine: distinguishing two new antipsychotics from the original dopamine stabilizer aripiprazole. *Ther Adv Psychopharmacol.* 2017;7:29–41. doi: 10.1177/2045125316672136.

32. Prescribing information. *Clozaril*. Rosemont, PA: HLS Therapeutics (USA), Inc. HLS Therapeutics, Inc.; 2017.

33. Greenwood J, Acharya RB, Marcellus V, et al. Lumateperone: a novel antipsychotic for schizophrenia. *Ann Pharmacother.* 2021;55(1):98–104. 10.1177/1060028020936597 [PubMed: 32590907] .

34. Goldman R, Loebel A, Cucchiaro J, et al. Efficacy and safety of lurasidone in adolescents with schizophrenia: a 6-week, randomized placebo-controlled study. *J Child Adolesc Psychopharmacol.* 2017;27:516–525. [PubMed: 28475373]

35. Subotnik KL, Casaus LR, Ventura J, et al. Long-acting injectable risperidone for relapse prevention and control of breakthrough symptoms after a recent first episode of schizophrenia. *JAMA Psychiatry*. 2015;72:822–829. [PubMed: 26107752]

36. Patchan K, Vyas G, Hackman AL, et al. Clozapine in reducing aggression and violence in forensic populations. *Psychiatr Q.* 2018;89:157–168. [PubMed: 28643049]

37. Van Putten T, Marder SR. Behavioral toxicity of antipsychotic drugs. *J Clin Psychiatry*. 1987;48(suppl 9):13–19. [PubMed: 2887552]

38. Samara MT, Leucht C, Leeflang MM, et al. Early improvement as a predictor of later response to antipsychotics in schizophrenia: a diagnostic test review. *Am J Psychiatry*. 2015;172:617–629. [PubMed: 26046338]

39. Sajatovic M, Ross R, Legacy SN, et al. Initiating/maintaining long-acting injectable antipsychotics in schizophrenia/schizoaffective or bipolar disorder—expert consensus survey part 2. *Neuropsychiatr Dis Treat.* 2018;14:1475–1492. [PubMed: 29922063]

40. Kishimoto T, Hagi K, Kurokawa S, et al. Long-acting injectable versus oral antipsychotics for the maintenance treatment of schizophrenia: a systematic review and comparative meta-analysis of randomised, cohort, and pre-post studies. *Lancet Psychiatry*. 2021;8(5):387–404. 10.1016/S2215-0366(21)00039-0 [PubMed: 33862018] .

41. Parellada E, Bioque M. Barriers to the use of long-acting injectable antipsychotics in the management of schizophrenia. *CNS Drugs*. 2016;30:689–701. [PubMed: 27255405]

42. Buckley PF. Treatment-resistant schizophrenia. *Focus (Am Psychiatr Publ)*. 2020;18(4):364–367. 10.1176/appi.focus.20200025 [PubMed: 33343247] .

43. Citrome L. New second-generation long-acting injectable antipsychotics for the treatment of schizophrenia. *Expert Rev Neurother.* 2013;13:767–783. [PubMed: 23898849]

44. Prescribing information. *PERSERIS.* North Chesterfield, VA: Indivior Inc.; 2018.

45. Prescribing information. *INVEGA SUSTENNA.* Titusville, NJ: Janssen Pharmaceuticals Inc.; 2017.

46. Prescribing information. *Invega Trinza.* Titusville, NJ: Janssen Pharmaceuticals Inc.; 2018.

47. Prescribing information. *Aristada Initio.* Waltham, MA: Alkermes, Inc.; 2018.

48. Meyer JM. Understanding the depot antipsychotics: sn illustrated guide to kinetics. *CNS Spectrums*. 2013;18:58–68. [PubMed: 24345710]

49. Prescribing information. *ABILIFT MYCITE.* Rockville, MD: Otsuka America Pharmaceutical Inc.; 2017.

50. Prescribing information. *Zyprexa Relprevv.* Indianapolis, IN: Lilly USA; 2018.

51. Samalin L, Garay R, Ameg A, Llorca PM. Olanzapine pamoate for the treatment of schizophrenia: an safety evaluation. *Expert Opin Drug Saf.* 2016;15(3):403–411. doi: 10.1517/14740338.2016.1141893.

52. Jann MW, Penzak SR. Long-acting injectable second-generation antipsychotics: an update and comparison between agents. *CNS Drugs*. 2018;32:241–257. https://doi.org/10.1007/s40263-018-0508-6. [PubMed: 29569082]

53. Howes OD, McCutcheon R, Agid O, de Bartolomeis A, et al. Treatment resistant schizophrenia: treatment response and resistance in psychosis (TRRIP) working groups consensus guidelines on diagnosis and terminology. *Am J Psychiatry*. 2017;174(3):216–229. [PubMed: 27919182]

54. Barkhof E, Meijer CJ, de Sonneville LMJ, et al. Interventions to improve adherence to antipsychotic medications in patients with schizophrenia—a review of the past decade. *Eur Psychiatry*. 2012;27:9–18. [PubMed: 21561742]

55. Velligan DI, Weiden PJ, Sajatovic M, et al. The expert consensus guideline series: adherence problems in patients with serious and persistent mental illness. *J Clin Psychiatry*. 2009;70:1–48. [PubMed: 19686636]

56. Kane J, Honigfeld G, Singer J et al. Clozapine for the treatment-resistant schizophrenic: a double-blind comparison with chlorpromazine. *Arch Gen Psychiatry*. 1988;45:789–796. [PubMed: 3046553]

57. Kennedy WK, Jann MW, Kutscher EC. Clinically significant drug interactions with atypical antipsychotics. *CNS Drugs*. 2013;27:1021–1048. [PubMed: 24170642]

58. Tiihonen J, Taipale H, Mehtälä J, et al. Association of antipsychotic polypharmacy vs monotherapy with psychiatric rehospitalization among adults with schizophrenia. *JAMA Psychiatry*. 2019;76(5):499–507. 10.1001/jamapsychiatry.2018.4320 [PubMed: 30785608] .

59. Miyamoto S, Miyake N, Jarskog LF, Fleischhacker WW, Lieberman JA. Pharmacological treatment of schizophrenia: a critical review of the pharmacology and clinical effects of current and future therapeutic agents. *Mol Psychiatry*. 2012;17:1206–1227. [PubMed: 22584864]

60. Maeda K, Sugino H, Akazawa H, et al. Brexpiprazole I: in vitro and in vivo characterization of a novel serotonin-dopamine activity modulator. *J Pharmacol Exp Ther.* 2014;350:589–604. [PubMed: 24947465]

61. Nucifora FC, Miohaljevic M, Lee BJ, Sawa A. Clozapine as a model for antipsychotic development. *Neurotherapeutics*. 2017;14:750–761. [PubMed: 28653280]

62. Snyder GL, Vanover KE, Davis RE, et al. A review of the pharmacology and clinical profile of lumateperone for the treatment of schizophrenia. *Adv Pharmacol.* 2021;90:253–276. 10.1016/bs.apha.2020.09.001 [PubMed: 33706936] .

63. Mauri MC, Volonteri LS, Colasanti A et al. Clinical pharmacokinetics of atypical antipsychotics: a critical review of the relationship between plasma concentrations and clinical response. *Clin Pharmacokinet.* 2007;46:359–388. [PubMed: 17465637]

64. Eum S, Lee AM, Bishop JR. Pharmacogenetic tests for antipsychotic medications: clinical implications and considerations. *Dialogues Clin Neurosci.* 2016;18:323–337. [PubMed: 27757066]

65. Pouget JG, Shams TA, Tiwari AK, Muller DJ. Pharmacogenetics and outcome with antipsychotic drugs. *Dialogues Clin Neurosci.* 2014;16:555–566. [PubMed: 25733959]

66. Preskorn SH. Clinically important differences in the pharmacokinetics of the ten newer atypical antipsychotics: Part 2. Metabolism and elimination. *J Psychiatr Pract.* 2012;18:361–368. [PubMed: 22995963]

67. Clinical Pharmacogenetics Implementation Consortium. Available at: https://cpicpgx.org/. Accessed December 1, 2018.

68. Tewksbury A, Olander A. Management of antipsychotic induced hyperprolactinemia. *Ment Health Clin.* 2016;6(4):185–190. doi: 10.9740/mhc.2016.7.185.

69. Wong-Anuchit C. Clinical management of antipsychotic-induced hyperprolactinemia. *Perspect Psychiatr Care*. 2015;52:145–152. doi: 10.1111/ppc.12111.

70. Kinon BJ, Liu-Seifert H, Stauffer VL, Jacob J. Bone loss associated with hyperprolactinemia in schizophrenia. *Clin Schizophr Relat Psychoses*. 2013;7:114–123.

71. Peuskens J, Pani L, Detraux J, De Hert M. The effects of novel and newly approved antipsychotics on serum prolactin levels: a comprehensive review. *CNS Drugs*. 2014;28:421–453. [PubMed: 24677189]

72. Huhn M, Nikolakopoulou A, Schneider-Thoma J, et al. Comparative efficacy and tolerability of 32 oral antipsychotics for the acute treatment of adults with multi-episode schizophrenia: a systematic review and network meta-analysis. *Lancet*. 2019;394(10202):939–951. 10.1016/S0140-6736(19)31135-3
[PubMed: 31303314] .

73. Kane JM, Durgam S, Satlin A, et al. Safety and tolerability of lumateperone for the treatment of schizophrenia: a pooled analysis of late-phase placebo- and active-controlled clinical trials. *Int Clin Psychopharmacol.* 2021;36(5):244–250. 10.1097/YIC.0000000000000371
[PubMed: 34054112] .

74. Meng M, Li W, Zhang S et al. Using aripiprazole to reduce antipsychotic-induced hyperprolactinemia: meta-analysis of currently available randomized controlled trials. *Shanghai Arch Psychiatry*. 2015;27(1):4–17. [PubMed: 25852251]

75. Bo QJ, Wang ZM, Li XB, Ma X, Wang CY, de Leon J. Adjunctive metformin for antipsychotic-induced hyperprolactinemia: a systematic review. *Psychiatr Res.* 2016;237:257–263.

76. Musil R, Obermeier M, Russ P, Haerle M. Weight gain and antipsychotics: a drug safety review. *Expert Opin Drug Saf.* 2015;14(1):73–96. [PubMed: 25400109]

77. Jeon SW, Kim YK. Unresolved issues for utilization of atypical antipsychotics in schizophrenia: antipsychotic polypharmacy and metabolic syndrome. *Int J Mol Sci.* 2017;18(10):E2174. doi: 10.3390/ijms18102174.9e.

78. Reynolds GP, McGowan OO. Mechanism underlying metabolic disturbances associated with psychosis and antipsychotic drug treatment. *J Psychopharmacol.* 2017;31(11):1430–1436. doi: 10.1177/0269881117722987.

79. Whicher CA, Price H, Holt RIG. Mechanisms in endocrinology: antipsychotic medication and diabetes and impaired glucose regulation. *Eur J Endocrinol.* 2018;178(6):R245–R258. doi: 10.1530/EJE-18-0022.

80. Shams TA, Muller DJ. Antipsychotic induced weight gain: genetics, epigenetics and biomarkers reviewed. *Curr Psychiatry Rep.* 2014;16:473–481. doi: 10.1007/s11920-014-0473-9.

81. Zhang JP, Lencz T, Zhang RX, et al. Pharmacogenetic associations of antipsychotic drug-related weight gain: a systematic review and meta-analysis. *Schizophr Bull*. 2016;42(6):1415–1437. doi: 10.1093/schlbulk/sbw058.

82. Correll CU, Newcomer JW, Silverman B, et al. Effects of olanzapine combined with samidorphan on weight gain in schizophrenia: a 24-week phase 3 study. *Am J Psychiatry*. 2020;177(12):1168–1178. 10.1176/appi.ajp.2020.19121279
[PubMed: 32791894] .

83. American Diabetes Association. Consensus development conference on antipsychotic drugs and obesity and diabetes. *Diabetes Care*. 2004;27:596–601. [PubMed: 14747245]

84. Mizuno Y, Suzuki T, Nakagawa A et al. Pharmacological strategies to counteract antipsychotic-induced weight gain and metabolic adverse effects in schizophrenia: a systematic review and meta-analysis. *Schizophr Bull*. 2014;1385–13403.

85. Wani RA, Dar MA, Margoob MA, Rather YH, Haq I, Shah MS. Diabetes mellitus and impaired glucose tolerance in patients with schizophrenia, before and after antipsychotic treatment. *J Neurosci Rural Pract.* 2015;6(1):17–22. [PubMed: 25552846]

86. Green CA, Yarborough BJ, Leo MC, et al. The STRIDE weight loss and lifestyle intervention for individuals taking antipsychotic medications: a randomized trial. *Am J Psychiatry*. 2015;172(1):71–81. [PubMed: 25219423]

87. Correll CU, Sikich L, Reeves G, et al. Metformin add-on vs. antipsychotic switch vs. continued antipsychotic treatment plus healthy lifestyle education in overweight or obese youth with severe mental illness: results from the IMPACT trial. *World Psychiatry*. 2020;19(1):69–80. 10.1002/wps.20714
[PubMed: 31922663] .

88. Koalchuk C, Castenllani L, Chintoh A, Remington G, Giacca A, Hahn M. Antipsychotics and glucose metabolism: how brain and body collide. *Am J Physiol Endocrino Metab.* 2018. doi: 10.1152/ajpendo.00164.2018.

89. Orsolini L, Tomasetti C, Valchera A, et al. An update of the safety of clinically used atypical antipsychotics. *Expert Opin Drug Saf.* 2016;15(10):1329–1347. doi: 10.1080/14740338.2016.1201475.

90. Solmi M, Murru A, Pacciarotti I, et al. Safety, tolerability and risks associated with first- and second-generation antipsychotics: a state-of-the-art review. *Ther Clin Risk Manag.* 2017;13:757–777. [PubMed: 28721057]

91. Leung JY, Barr AM, Procyshyn RM, Honer WG, Pang CC. Cardiovascular side-effects of antipsychotic drugs: the role of the autonomic nervous system. *Pharmacol Ther.* 2012;135(2):113–122. [PubMed: 22565090]

92. Harrigan EP, Miceli JJ, Anziano R, et al. A randomized evaluation of the effects of six antipsychotic agents on QTc, in the absence and presence of metabolic inhibition. *J Clin Psychopharmacol.* 2004;24:62–69. [PubMed: 14709949]

93. Hasnain M, Vieweg WVR. QTc interval prolongation and torsades de pointes associated with second generation antipsychotics and antidepressants: a comprehensive review. *CNS Drugs*. 2014;28:887–920. [PubMed: 25168784]

94. Wenzel-Seifert K, Wittmann M, Haen E. QTc prolongation by psychotropic drugs and the risk of torsade de pointes. *Dtsch Arztebl Int.* 2011;108:687–693. [PubMed: 22114630]

95. Vang T, Rosenzweig M, Bruhn CH, et al. Eosinophilic myocarditis during treatment with olanzapine: report of two possible cases. *BMC Psychiatry*. 2016;16:70. doi: 10.1186/s12888-016-0776-y.

96. Curto M, Girardi N, Lionetto L, Ciavarella GM, Ferracuti S, Balderssarini RJ. Systematic review of clozapine cardiotoxicity. *Curr Psychiatry Rep.* 2016;18:68. doi: 10.1007/s11920-0704-3.

97. Alawani M, Wasywich C, Cicovic A, Kenedi C. A systematic review of clozapine induced cardiomyopathy. *Int J Cardiol.* 2014;176:315–320. [PubMed: 25131906]

98. Nielsen J, Correll CU, Manu P, Kane JM. Termination of clozapine due to medical reasons: when is it warranted and how can it be avoided? *J Clin Psychiatry*. 2013;74:603–613. [PubMed: 23842012]

99. Wu CS, Tsai YT, Tsai HJ. Antipsychotic drugs and the risk of ventricular arrhythmia and/or sudden cardiac death: a nationwide case-crossover study. *J Am Heart Assoc.* 2015;4(2). pii: e001568. doi: 10.1161/JAHA.114.001568.

100. Ballon JS, Pajvani UB, Mayer LES, et al. Pathophysiology of drug induced weight gain and metabolic effects: findings from an RCT in healthy volunteers treated with olanzapine, iloperidone, or placebo. *Psychopharmacol.* 2018;32:533–540. doi: 10.1177/0269881118754708.

101. McEvoy JP, Meyer JM, Goff DC et al. Prevalence of the metabolic syndrome in patients with schizophrenia: baseline results from the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) schizophrenia trial and comparison with national estimates from NHANES III. *Schizophr Res.* 2005;80(1):19–32. [PubMed: 16137860]

102. Monteleone P, Martiadis V, Maj M. Management of schizophrenia with obesity, metabolic and endocrinological disorders. *Psychiatr Clin North Am.* 2009;32:775–794. [PubMed: 19944883]

103. Hsu WY, Lane HY, Lin CL, Kao CH. A population-based cohort study on deep vein thrombosis and pulmonary embolism among schizophrenia patients. *Schizophr Res.* 2015;162(1-3):248–252. doi: 10.1016/j.schres.2015.01.012.

104. Hippisley-Cox J, Coupland C. Development and validation of risk prediction algorithm (QThrombosis) to estimate future risk of venous thromboembolism: prospective cohort study. *BMJ.* 2011;343:d4656. doi: https://doi.org/10.1136/bmj.d4656.

105. Burkhard PR. Acute and subacute drug-induced movement disorders. *Parkinsonism Relat Disord.* 2014;20S1:S108–S112.

106. Caroff SN, Campbell EC. Drug-induced extrapyramidal syndromes: implications for contemporary practice. *Psychiatr Clin North Am.* 2016;39(3):391–411. doi: 10.1016/j.psc.2016.04.003.

107. Pringsheim T, Gardner D, Addington D, et al. Assessment and treatment of antipsychotic-induced akathisia. *Can J Psychiatry*. 2018. doi: 10.1177/0706743718760288.

108. Peluso M, Lewis S, Barnes T, et al. Extrapyramidal motor side-effects of first and second-generation antipsychotic drugs. *Br J Psychiatry*. 2012;200:387–392. [PubMed: 22442101]

109. Sprague RL, Kalachnik JE. Reliability, validity, and a total score cutoff for the Dyskinesia Identification System Condensed User Scale (DISCUS) with mentally ill and mentally retarded populations. *Psychopharmacol Bull*. 1991;27:51–58. [PubMed: 1862206]

110. Ricciardi L, Pringsheim T, Barnes TRE. Treatment recommendations for tardive dyskinesia. *Can J Psychiatry*. 2019;64(6):388–399. 10.1177/0706743719828968 [PubMed: 30791698] .

111. Solmi M, Pigato G, Kane JM, Correll CU. Clinical risk factors for the development of tardive dyskinesia. *J Neurol Sci.* 2018;389:21–27. doi: 10.1016/j.jns.2018.02.012.

112. Zai CC, Maes MS, Tiwari AK, Zai GC, Remington G, Kennedy JL. Genetics of tardive dyskinesia: promising leads and ways forward. *J Neurol Sci.* 2018;389:28–34. doi: 10.1016/j.jns.2018.02.011.

113. Correll CU, Schenk EM. Tardive dyskinesia and new antipsychotics. *Curr Opin Psychiatry*. 2008;21:151–156. [PubMed: 18332662]

114. Carbon M, Kane JM, Leucht S, Correll CU. Tardive dyskinesia risk with first-generation and second-generation antipsychotics in comparative randomized controlled trials: a meta-analysis. *World Psychiatry*. 2018;17:330–340. doi: 10.1002/wps.20579.

115. Bhidayasiri R, Jitkritsadakul O, Friedman JH, Fahn S. Updating the recommendations for treatment of tardive syndromes: a systematic review of new evidence and practical treatment algorithm. *J Neurol Sci.* 2018;389:67–75. 10.1016/j.jns.2018.02.010 [PubMed: 29454493] .

116. Correll CU, Josiassen RC, Liang GS, Burke J, O'Brien CF. Efficacy of valbenazine (NBI-98854) in treating subjects with tardive dyskinesia and mood disorder. *Psychopharmacol Bull*. 2017;47:53–60. [PubMed: 28839340]

117. Bhidayasiri R, Fahn S, Gronseth GS, et al. Evidence-based guideline: Treatment of tardive syndromes—report of the guideline development subcommittee of the American Academy of Neurology. *Neurology*. 2013;81:463–469. [PubMed: 23897874]

118. Wilson MP, Vilke GM, Hayden SR, Nordstrom K. Psychiatric emergencies for clinicians: emergency department management of neuroleptic malignant syndrome. *J Emerg Med.* 2016;51:66–69. [PubMed: 27247083]

119. Gurrera RJ, Caroff SN, Cohen A, et al. An international consensus study of neuroleptic malignant syndrome diagnostic criteria using the Delphi method. *J Clin Psychiatry*. 2011;72:1222–1228. [PubMed: 21733489]

120. Citrome L. Agitation in schizophrenia: origins and evidence-based treatment. *Curr Opin Psychiatry*. 2021;34(3):216–221. 10.1097/YCO.0000000000000685 [PubMed: 33395103] .

121. Li J, Tripathi RC, Tripathi BJ. Drug-induced ocular disorders. *Drug Saf.* 2008;31:127–141. [PubMed: 18217789]

122. Laties AM, Flach AJ, Baldycheva I, et al. Cataractogenic potential of quetiapine versus risperidone in long-term treatment of patients with schizophrenia or schizoaffective disorder: a randomized open-label, ophthalmologist-masked, flexible-dose, non-inferiority trial. *J Psychopharmacol.* 2015;29:69–79. [PubMed: 25315830]

123. Rettenbacher MA, Hofer A, Ebenbichler C, et al. Prolactin levels and sexual adverse effects in patients with schizophrenia during antipsychotic treatment. *J Clin Psychopharmacol.* 2010;30:711–715. [PubMed: 21105287]

124. Andersohn F, Schmedt N, Weinmann S, et al. Priapism associated with antipsychotics: role of alpha1 adrenoceptor affinity. *J Clin Psychopharmacol.* 2010;30:68–71. [PubMed: 20075651]

125. Hasan A, Falkai P, Wobrock T, et al. World Federation of Societies of Biological Psychiatry (WFSBP) guidelines for biological treatment of schizophrenia, part 2: update 2012 on the long-term treatment of schizophrenia and management of antipsychotic induced side effects. *World J Biol Psychiatry*. 2013;14:2–44. [PubMed: 23216388]

126. FDA Drug Safety Communication: FDA reporting mental health drug ziprasidone (Geodon) associated with rare but potentially fatal skin reactions: 2014. Available at: http://www.fda.gov/Drugs/DrugSafety/ucm426391.htm. Accessed June 1, 2015.

127. Ben-Sheetrit J, Huller-Harari L, Rasner M, et al. Psychiatric disorders and compliance with prenatal care: a 10-year retrospective cohort compared to controls. *Eur Psychiatry*. 2018;49:23–29. 10.1016/j.eurpsy.2017.11.011 [PubMed: 29353177] .

128. Vigod SN, Seeman MV, Ray JG, et al. Temporal trends in general and age-specific fertility rates among women with schizophrenia (1996–2009): a population-based study in Ontario, Canada. *Schizophr Res.* 2012;139:169–175. [PubMed: 22658526]

129. Damkier P, Videnbech P. The safety of second-generation antipsychotics during pregnancy: a clinically focused review. *CNS Drugs*. 2018;32:351–366. [PubMed: 29637530]

130. Einarson A, Boskovic R. Use and safety of antipsychotic drugs during pregnancy. *J Psychiatr Pract.* 2009;15(3):183–92. 10.1097/01.pra.0000351878.45260.94 [PubMed: 19461391] .

131. Huybrechts KF, Hernández-Díaz S, Patorno E, et al. Antipsychotic use in pregnancy and the risk for congenital malformations. *JAMA Psychiatry*. 2016;73(9):938–46. 10.1001/jamapsychiatry.2016.1520 [PubMed: 27540849] .

132. Arsenault MY, Lane CA, MacKinnon CJ, et al. The management of nausea and vomiting of pregnancy. *J Obstet Gynaecol Can.*, 2002;24(817–831); quiz 832-3. [PubMed: 12405123]

133. Lin HC, Chen IJ, Chen YH, et al. Maternal schizophrenia and pregnancy outcome: does the use of antipsychotics make a difference? *Schizophr Res.* 2010;116(1):55–60. [PubMed: 19896335]

134. Newport DJ, Calamaras MR, DeVane CL, et al. Atypical antipsychotic administration during late pregnancy: placental passage and obstetrical outcomes. *Am J Psychiatry*. 2007;164(8):1214–1220. 10.1176/appi.ajp.2007.06111886 [PubMed: 17671284] .

135. Huybrechts KF, Hernandez-Diaz S, Patorno E, et al. Antipsychotic use in pregnancy and the risk for congenital malformations. *JAMA Psychiatry*. 2016;73:938–946. doi: 10.1001/jamapsychiatry.2016.1520.

136. Coughlin CG, Blackwell KA, Bartley C, et al. Obstetric and neonatal outcomes after antipsychotic medication exposure in pregnancy. *Obstet Gynecol.* 2015;125(5):1224–1235. 10.1097/AOG.0000000000000759 [PubMed: 25932852] .

137. Ellfolk M, Leinonen MK, Gissler M, et al. Second-generation antipsychotic use during pregnancy and risk of congenital malformations. *Eur J Clin Pharmacol.* 2021;77(11):1737–1745. 10.1007/s00228-021-03169-y [PubMed: 34100993] .

138. Viguera AC, Freeman MP, Góez-Mogollón L, et al. Reproductive safety of second-generation antipsychotics: updated data from the Massachusetts General Hospital National Pregnancy Registry for Atypical Antipsychotics. *J Clin Psychiatry*. 2021;82(4):20m13745. 10.4088/JCP.20m13745. [PubMed: PMID: 34352165] .

139. Terrana N, Koren G, Pivovarov J, Etwel F, Nulman I. Pregnancy outcomes following in utero exposure to second-generation antipsychotics: a systematic review and meta-analysis. *J Clin Psychopharmacol.* 2015;35:559–565. [PubMed: 26274044]

140. Uguz F. Antipsychotic use during pregnancy and the risk of gestational diabetes mellitus: a systematic review. *J Clin Psychopharmacol.* 2019;39(2):162–167. 10.1097/JCP.0000000000001002 [PubMed: 30624301] .

141. Park Y, Hernandez-Diaz S, Bateman BT, et al. Continuation of atypical antipsychotic medication during early pregnancy and the risk of gestational diabetes. *Am J Psychiatry*. 2018;175:564–874. doi: 10.1176/appi.ajp.2018.17040393.

142. FDA Drug Safety Communication: Antipsychotic drug labels updated on use during pregnancy and risk of abnormal muscle movements and withdrawal symptoms in newborns. U.S. Food and Drug Administration, February 22, 2011. Available at: http://www.fda.gov/Drugs/DrugSafety/ucm243903.htm. Accessed September 9, 2018.

143. Peng M, Gao K, Ding Y, et al. Effects of prenatal exposure to atypical antipsychotics on postnatal development and growth of infants: a case-controlled, prospective study. *Psychopharmacology (Berl)*. 2013;228(4):577–84. 10.1007/s00213-013-3060-6 [PubMed: 23559219] .

144. Johnson KC, LaPrairie JL, Brennan PA, et al. Prenatal antipsychotic exposure and neuromotor performance during infancy. *Arch Gen Psychiatry*. 2012;69(8):787–794. 10.1001/archgenpsychiatry.2012.160 [PubMed: 22474072] .

145. Wang Z, Chan AYL, Coghill D, et al. Association between prenatal exposure to antipsychotics and attention-deficit/hyperactivity disorder, autism spectrum disorder, preterm birth, and small for gestational age. *JAMA Intern Med.* 2021;181(10):1332–1340. 10.1001/jamainternmed.2021.4571 [PubMed: 34398171] .

146. Uguz F. Second generation antipsychotics during the lactation period. A comparative systematic review on infant safety. *J Clin Psychopharmcol.* 2016;36:244–252.

147. Cuomo A, Goracci A, Fagiolini A. Aripiprazole use during pregnancy, peripartum and lactation. A systematic literature search and review to inform clinical practice. *J Affect Disord.* 2018;228:229–237. [PubMed: 29275156]

148. Ereshefsky L. Drug–drug interactions with the use of psychotropic medications. *CNS Spectr.* 2009;14(suppl 8):1–8. [PubMed: 20085108]

149. Gaertner J, Ruberg K, Schlesiger G, Frechan S, Voltz R. Drug interactions in palliative care—it's more than cytochrome P450. *Palliat Med.* 2012;26:813–825. [PubMed: 21737479]

150. Citrome L. Using oral ziprasidone effectively: the food effect and dose-response. *Adv Ther.* 2009;26(8):739–748. [PubMed: 19669631]

151. Center for Drug Evaluation and Research.Administrative and correspondence documents. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2019/209500Orig1s000OtherR.pdf. Accessed December 20, 2021.

152. Velligan DI, Lopez L, Castillo DA, et al. Interrater reliability of using brief standardized outcome measures in a community mental health setting. *Psychiatr Serv.* 2011;62:558–560. [PubMed: 21532087]

SELF-ASSESSMENT QUESTIONS

1. Which of the following is the *most accurate* statement regarding the potential etiology of schizophrenia?
   A. Schizophrenia is likely caused by the affected individual having an oppressive mother during early childhood development.
   B. Genetics studies suggest a Mendelian genetic relationship for developing schizophrenia.
   C. PET studies indicate that schizophrenia is a degenerative brain disorder.
   D. Schizophrenia may be caused by variety of genetic polymorphisms in combination with an environmental assault in utero.
2. A theory regarding the pathophysiology of schizophrenia suggests that the predrome phase of the illness is associated with
   A. Excessive synthesis and release of serotonin from presynaptic receptors
   B. Decreased density of D_2 receptors in the mesocaudate
   C. Glutamatergic synaptic dysfunction resulting in a glutamatergic signaling defect
   D. Hyperactivity of gamma-amino-butyric acid (GABA) pathways
3. Symptom domains that are characteristic of a diagnosis of schizophrenia include all of the following *except*:
   A. Cognitive impairment
   B. Depression
   C. Negative symptoms
   D. Positive symptoms
4. The four core interventions that have been shown to improve the quality of life in individuals with early schizophrenia include all of the following *except*:
   A. Family psychoeducation
   B. Psychoanalysis
   C. Resilience-focused individual therapy
   D. Supported employment and education
5. Which of the following *most accurately* reflects the initial workup (ie, evaluation) of a patient suspected of having schizophrenia?
   A. Mental status exam, physical exam, neurological exam, social history, laboratory workup, and PET scan
   B. Mental status exam, physical exam, neurological exam, social history, laboratory workup, and MRI scan
   C. Mental status exam, physical exam, neurological exam, social history, family history, and a CSF homovanillic acid (HVA) level
   D. Mental status exam, physical exam, neurological exam, family history, social history, and laboratory workup
6. Based upon both efficacy and safety, which of the following are evidence-based first-line pharmacotherapy options in a patient experiencing the first psychotic episode associated with schizophrenia?
   A. Aripiprazole, risperidone, and ziprasidone
   B. Perphenazine, quetiapine, and risperidone

C. Haloperidol, olanzapine, and quetiapine

D. Aripiprazole, lurasidone, and ziprasidone

7. O.Y. is a 27-year-old with schizophrenia admitted for their second psychiatric hospitalization. Treated with risperidone, the patient presents in an acute psychotic episode with fulminate suicidal ideation and a serious suicide attempt prior to hospitalization. Based on this information, which of the following antipsychotics would be the *best choice* for this patient at the present time?

A. Clozapine

B. Haloperidol

C. Lurasidone

D. Risperidone

8. Which of the following are interventions that may increase the treatment adherence of individuals with schizophrenia?

A. Cognitive behavioral therapy

B. Involvement of families

C. Patient information about the disorder and treatment

D. All of the above may be helpful

9. B.W. is a 33-year-old with schizophrenia in an acute exacerbation who has had previous unsuccessful medication courses with risperidone and olanzapine. The risperidone was at a maximum dose of 6 mg/day for 6 months, and olanzapine was for a maximum dose of 20 mg daily for 9 months. Patient adherence with treatment was deemed to be adequate during the previous medication trials. Based on the available information, which of the following is the *most appropriate* medication intervention at the present time?

A. Asenapine

B. Cariprazine

C. Clozapine

D. Lumateperone

10. The rapid on, rapid off theory of atypicality is *best associated* with which of the following antipsychotics?

A. Aripiprazole

B. Olanzapine

C. Quetiapine

D. Risperidone

11. C.H. is a 25-year-old with a diagnosis of schizophrenia previously treated with haloperidol and risperidone. Since starting risperidone, the patient has gained about 8 pounds and inquires about a change in medication to an antipsychotic that is less likely to cause weight gain. Based on this request, which of the following would be the *best* choice?

A. Ziprasidone

B. Chlorpromazine

C. Clozapine

D. Olanzapine

12. J.B. is a 34-year-old with a diagnosis of schizophrenia previously treated with monotherapy trials of haloperidol, perphenazine, and fluphenazine decanoate. J.B. has had persistent difficulty with extrapyramidal side effects, including parkinsonian symptoms and dystonic reactions. These symptoms have been treated with benztropine and diphenhydramine, but breakthrough EPS symptoms still occur. Which of the following would be the *poorest* antipsychotic treatment option for this patient?

A. Risperidone

B. Olanzapine

C. Quetiapine

D. Brexpiprazole

13. B.C. is a 35-year-old with a diagnosis of schizophrenia. In the past, B.C. has taken haloperidol and risperidone and experienced parkinsonian symptoms on both of these medications. After taking olanzapine 15 mg daily for the past 6 months, B.C. presented to primary care for complaints of fatigue, excessive thirst, and frequent urination. Fasting blood glucose is 180 mg/dL (10.0 mmol/L). Although psychotic symptoms are reasonably well controlled, the clinician deems that it is best to change antipsychotic medication. Based on the information above, which of the following would be the *best* choice?

A. Aripiprazole

B. Clozapine

C. Haloperidol

D. Quetiapine

14. D.D. is a 66-year-old with a diagnosis of schizophrenia, hypertension, and gastroesophageal reflux disorder (GERD) and medication regimen includes quetiapine, hydrochlorothiazide, metoclopramide, and ranitidine. Over the past 3 months, D.D. has developed a shuffling gait, drooling, and a resting tremor. In screening the patient's profile, which of the following might represent a drug interaction?

    A. Ranitidine is inhibiting the metabolism of quetiapine, causing the patient to develop Parkinson's symptoms.

    B. Hydrochlorothiazide alteration of quetiapine elimination in the kidneys is resulting in Parkinson's symptoms.

    C. Metoclopramide's dopaminergic blockade in combination with quetiapine is producing Parkinson's symptoms.

    D. Metoclopramide alteration of quetiapine metabolism is causing Parkinson's symptoms.

15. After initiating a new antipsychotic in a patient with schizophrenia, appropriate routine monitoring parameters are *best* reflected by:

    A. Brief standardized clinical rating scales, weight, blood pressure, waist circumference, blood glucose, serum lipids

    B. Positive and Negative Symptom Rating Scale, weight, antipsychotic serum concentration, waist circumference, blood glucose, serum lipids

    C. Brief standardized clinical rating scales, weight, blood pressure, blood glucose, serum lipids, electrocardiogram

    D. Positive and Negative Symptom Rating Scale, weight, blood pressure, blood glucose, serum lipids, white blood cell count, electrocardiogram

SELF-ASSESSMENT QUESTION-ANSWERS

1. **D.** Schizophrenia is a neurodevelopmental disorder that is associated with genetic polymorphism of multiple different genes combined with an unknown environmental risk factor. The environmental risk likely occurs in utero or in the perinatal period (see "Etiology" section).

2. **C.** The predrome phase is a high-risk period for the development of schizophrenia. Glutamatergic dysfunction may precede abnormalities in dopaminergic dysfunction. Glutamatergic dysfunction results in decreased GABA activity (prodrome phase), and this results in decreased inhibition of dopaminergic transmission. The actual increase in dopaminergic transmission may be associated with onset of the first psychotic episode (see "Pathophysiology" section).

3. **B.** Although depression is commonly seen in individuals with schizophrenia, it is not one of the core symptoms required for the diagnosis of the syndrome (see "Clinical Presentation" section).

4. **B.** Effective psychosocial interventions focus on improving the individuals' ability to function on a daily basis, including methods to promote adherence with medication and other treatment regimens. Therapy is typically focused on improving the person's resilience, daily psychosocial functioning, and treatment adherence. However, cognitive therapy that focuses on the needs of a person with schizophrenia may be of benefit. Classic psychoanalysis has no evidence to support its use in individuals with schizophrenia (see Table 87-4).

5. **D.** The initial workup for an individual suspected of having schizophrenia is focused on eliminating other potential causes of psychosis (eg, medical disorder, substance use), and establishing a baseline for medical monitoring of the patient. The mental status and history focus on making sure that the clinical features are consistent with the *DSM-5* criteria for schizophrenia. There are no laboratory tests or imagining studies that are diagnostic for schizophrenia.

6. **A.** Aripiprazole, risperidone, and ziprasidone have all been studied during the initial or first episode of schizophrenia, and all have similar efficacy. The one study with quetiapine during the first episode showed a higher relapse rate than in the studies with the other three medications. While olanzapine has good efficacy during the first episode, it has the highest incidence of weight gain and other metabolic side effects and is not recommended for first episode. The other medications listed have not been studied during first episode (see Fig. 87-1).

7. **A.** The general recommendation is to use clozapine in a patient who has failed to have adequate improvement in symptoms after two adequate monotherapy trials (dose and duration) with other antipsychotics. However, clozapine is the only antipsychotic that has evidence of decreasing suicide in highly suicidal patients, and its use is indicated earlier in treatment for treating suicidality associated with schizophrenia. Clozapine would be the best choice for this particular patient (see Fig. 87-1).

8. **D.** All of the listed psychosocial interventions have evidence for improving treatment adherence in individuals with schizophrenia, and outcomes are thought to be better when they are used in combination. Comprehensive psychosocial services in combination with appropriate medication are necessary to achieve the best clinical outcomes in persons with schizophrenia (see Table 87-4).

9. **C.** Clozapine is the only antipsychotic that has evidence for efficacy in individuals with "treatment-resistant schizophrenia." Treatment resistance is most commonly defined as inadequate improvement in clinical symptoms with adequate monotherapy trials (dose and duration) with two different antipsychotics.

10. **C.** All available antipsychotics bind to D_2 receptors rapidly (rapid on). However, of available antipsychotics only clozapine and quetiapine have evidence for rapid disassociation from the D_2 receptor (rapid off). Based on this theory, only relatively brief binding to dopaminergic D_2 receptors is necessary for antipsychotic effect while longer binding (slow off) is thought to be associated with greater risk of extrapyramidal side effects. While there is some evidence in humans, utilizing PET scan technology, to support this theory, it is important to emphasize that it is still largely theoretical (see Table 87-5).

11. **A.** Of the listed antipsychotics, ziprasidone is associated with the least weight gain. Olanzapine causes the most weight gain, and both chlorpromazine and quetiapine are associated with more weight gain than ziprasidone (see Table 87-7).

12. **A.** Of the second-generation antipsychotics listed, risperidone has the greatest risk of extrapyramidal side effects. The risk of EPS with risperidone is dose related, and at doses greater than 6 mg daily, risperidone loses most of its atypical antipsychotic profile (see Table 87-7).

13. **A.** Patient B.C. is experiencing glucose intolerance, possibly associated with olanzapine. With a history of EPS with the use of haloperidol and risperidone, both of those medications would be a poor choice of antipsychotics. B.C. does not appear to have treatment-resistant symptoms, and clozapine is also associated with significant weight gain and metabolic disturbances. Of the antipsychotics listed, aripiprazole has the least risk of both causing EPS and producing metabolic disturbances.

14. **E.** Metoclopramide is a D_2 receptor antagonist and can cause EPS, including pseudoparkinsonism. The risk of this is higher in older individuals. Since both metoclopramide and quetiapine have D_2 receptor antagonist properties, the two medications could have a pharmacodynamic additive effect increasing the risk for Parkinson's symptoms. Given that there are a number of therapeutic alternatives available for treating GERD, the use of metoclopramide should be avoided in older individuals and in combination with antipsychotics

15. **A.** The use of brief objective rating scales helps in evaluating clinical response to antipsychotics. In particular, brief rating scales can be useful in monitoring partial response and changes in symptoms with changes in the pharmacological regimen. The other rating scales listed are longer rating scales primarily used in clinical research. Because of the effects of antipsychotics on weight and other metabolic parameters, it is important to monitor weight, blood pressure, waist circumference, blood glucose, serum lipids. These parameters need to be monitored at baseline before starting medications, as well as periodically after medications are started. If base line monitoring parameters are not obtained, it is challenging to determine whether changes are drug related (see Table 87-11).