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Update on Psychoses and Schizophrenia

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LEARNING OBJECTIVES

Upon completion of this module, the subscriber will be able to:

1. Distinguish between schizophrenia and other psychotic disorders.
2. Explain the three broad categories of clinical symptoms commonly present in schizophrenia.
3. Recognize the risk factors for non-adherence to interventions for psychotic disorder managements.
4. List the available medications approved for psychotic disorders.
5. Identify significant adverse effects of antipsychotic medications.

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Update on Psychoses and Schizophrenia

Introduction

Schizophrenia is a chronic and debilitating mental disorder. The term, schizophrenia, was derived from the Greek root words "schizo" as split and "phrene" as mind. The term was first known to be used in the early twentieth century.[1] This name does not imply schizophrenia entails multiple personalities or multiple thinking. Additionally, schizophrenia is defined as individuals with a severe brain disorder that is characterized by withdrawal from reality, thinking in illogical patterns, and being delusional.[2,3] This mental disorder has symptoms that are also commonly associated with other psychotic disorders. These overlapping symptoms could make an accurate diagnosis challenging for health care providers. Other psychoses or schizophrenia-like disorders include schizoaffective disorder, psychotic disorder caused by a general medical condition, mood disorder with psychotic features, delusional disorder, brief psychotic disorder, and schizophreniform disorder. Despite different and overlapping symptoms between schizophrenia and other psychotic disorders, pharmacological interventions are similar for all these disease states. The goal of this module is to provide an overview of this chronic mental disorder including: epidemiology; social and economic impact; diagnosis; etiology and risk factors; and pharmacological and non-pharmacological management.

DISEASE STATE

Epidemiology

According to statistics from the National Institute of Mental Health, the prevalence of schizophrenia in the United States (U.S.) adult population is 1.1% or 2.2 million people.[4] Prevalence estimates the proportion of people living with schizophrenia at any given time. The incidence of schizophrenia or number of new cases diagnosed annually in the U.S. is estimated to be about 100,000 people. Schizophrenia affects males, females, and all ethnic groups equally. It is estimated that over 51 million people worldwide suffer from schizophrenia.[2] This number can be broken down to a rough estimate of 6-12 million people in China, 4.3 to 8.7 million people in India, 285,000 people in Australia, approximately 280,000 people in Canada, and over 250,000 diagnosed people in Great Britain.

Schizophrenia is one of the top ten causes for disability in developed countries. The age of onset is generally in young adulthood peaking around 15-25 years for males and 25-35 years for females. Onset of disease before age 10 and at older age is not common. Peak onset ages correspond with the ages when young adults are either making early career decisions or seeking training for jobs and careers. This severe disabling

brain disorder limits people from holding a job or caring for themselves. Only 28% of schizophrenic patients are able to live independently. Approximately 10% are homeless and according to the Department of Health and Human Services they make up 1/3 of the approximately 600,000 homeless population in the U.S.[2,4]

The combined direct and indirect cost of schizophrenia is staggering at an estimated $62.7 billion annually.[5] One-third of this is the financial burden incurred from treatment. These direct costs are for outpatient and inpatient care, medications, and long-term care. The indirect costs include working/productive time for patients and their caregivers, social service, and criminal justice resources. In addition, since many schizophrenic patients are unable to hold a job, they rely on the support of public assistance programs. While this condition affects only 1% of the U.S. adult population, it constitutes almost a quarter of all costs attributed to mental health.[2]

Clinical Course

The clinical course of schizophrenia can be described in multiple phases.[6] Early non-specific signs involve a slow withdrawal in all settings including social, academic, or work-related activities. The first episode may appear suddenly as the patient starts to lose touch with reality. This early disease phase includes symptoms of patient withdrawal and isolation from social contact, bizarre behavior, and not being able to maintain basic self-care skills or staying focused. The next phase is considered the "active or acute phase" and patient symptoms become more obvious with hallucinations and delusions. This is commonly the phase where families become alarmed and seek medical counsel or intervention. The residual phase is when the active phase is controlled and the patient has symptoms similar to the early phase such as withdrawal, having trouble staying focused, and listlessness. These phases may appear again in the course of the illness and the active phase sometimes is called "acute exacerbation."

Prognosis

Presently, there is no cure for this disease. Treatments for schizophrenia are focused on symptom management. The prognosis tends to be better for individuals who are diagnosed early and are treated with effective interventions. Other good prognostic signs are patients without a strong family history, stable personality preceding the onset of psychiatric symptoms, and acute onset of symptoms.[6] Poor prognostic signs include: positive family history; insidious (slow) onset; negative symptoms (described later in this module but include withdrawal, lack of motivation, etc.); abnormal or unstable personality preceding the onset of psychiatric symptoms; disrupted domestic situation and poor social adjustment; loss of affective components (emotion, mood); and delay in treatment. Studies have found that ten years after diagnosis: 25% are completely recovered; 25% report great improvement and are relatively independent; 25% report improvement but still require extensive support; 15% remain unimproved and require hospitalization; and 10% are deceased---due mostly to suicide. Thirty years after being diagnosed with schizophrenia, the statistics remain similar with the exception that 35% report great improvement and being relatively independent.[2]

The morbidity (illness) and mortality (death) for patients with schizophrenia are worse than the general population. A 25 year-long study found people with schizophrenia have a mortality risk of 2-3 times that of the general population.[7] For example, psychotic disorders are associated with high rates of nicotine dependence, poor nutrition intake, and lower rates of preventive care, resulting in increased risk for cardiovascular and pulmonary co-morbidities. Other potential risk factors such as diet, exercise, obesity, and poverty level also play an important role in these adverse outcomes. Although not included in this study, many of the antipsychotic medications have adverse metabolic effects including: weight gain, elevated blood glucose, and elevated cholesterol levels. Overall, these patients have higher incidence rates of coronary heart disease, obesity, hyperlipidemia, type 2 diabetes, hypertension, and suicide.[8]

A cohort study is an analytical observation study that has a comparison or control group.[9] Cohort studies follow at least two or more groups from exposure to outcome. These studies allow for the comparison of an exposed group with a control group to determine if the exposed group has a higher or lower incidence of an outcome than the unexposed group. Cohorts look at causes and natural history of diseases and are also useful for examining prognosis of people who already have the disease. Cohort studies have found patients diagnosed with schizophrenia shortly after onset of symptoms are at higher risk for suicide. The highest risk of suicide was found to be in the first year after a psychotic event. Suicide is 12 times higher than expected compared to the general population group. This risk continues to be elevated at four times higher than the general population group at long-term follow-up (a decade later).[10] It is important for family members and health care providers to follow these patients more

closely and frequently.

Causes of the Condition

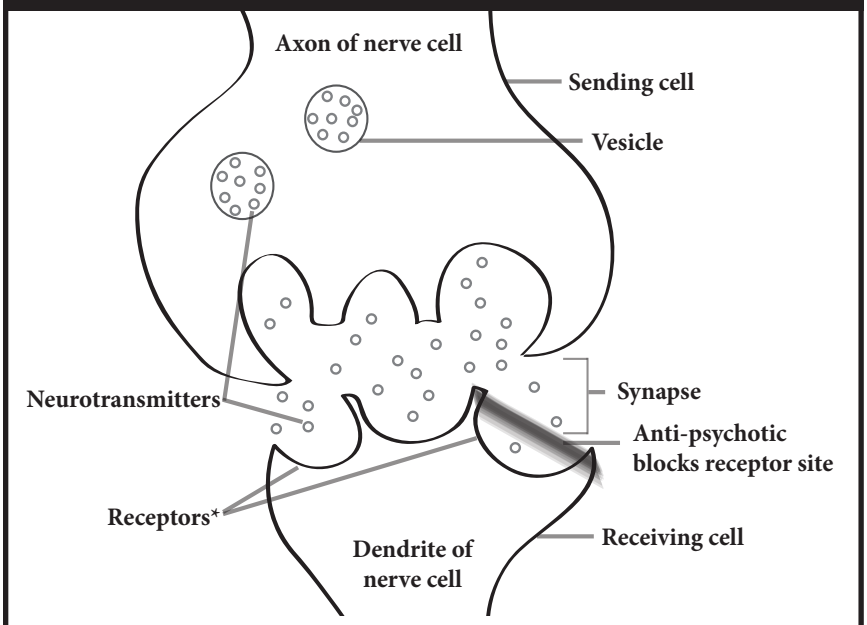
The actual cause of schizophrenia is not completely understood, though there are multiple theories. One of the theories includes genetics and environmental sources. Environmental exposure includes stresses (during pregnancy or childhood) which could contribute or aggravate this disorder. This could be an area for preventive care if identified stresses are found and the appropriate interventions are used to minimize the level of stress. Studies have found schizophrenia has a strong genetic component.[11-13] The risk for schizophrenia increases to 10% for those with a sibling who has the disease. Studies in twins have revealed the risk is 9% for dizygotic twins and up to 40% for monozygotic twins. The risk increases to 15% for children of one parent with schizophrenia and to 67% with both parents having the disease. Systematic reviews have identified that cannabis use increases the risk of psychotic outcomes.[14] In addition, a 10 year long cohort study revealed cannabis use as a risk factor for the development of psychotic symptoms. Moreover, the researchers concluded that continued cannabis use might increase the persistence of psychotic symptoms.[15] A national cohort study revealed that individuals with four out of the five following adverse social factors have a 2.7 fold increased risk for schizophrenia: living in a household receiving social welfare benefits; being unemployed; living in a single-parent household; low socioeconomic status; and living in a rented apartment.[16]

Another theory poses that the brain and its complex chemistry are responsible for schizophrenia.[6] Researchers have hypothesized that an imbalance between neurotransmitters in the brain leads to this chronic mental disease. Neurotransmitters are located in the neuron, the basic working unit of the brain and nervous system, and are messengers of neurologic information from one cell to another. We rely on this function for everything we do. In another words, these neurons communicate with one another by sending electrical impulses and chemical signals carrying messages all over the brain and between the brain and the rest of the nervous system. When the signals sent by the neurotransmitters are abnormal, they cause symptoms in various mental health disorders. For example, when the dopamine neurotransmitter is off-balance, it causes symptoms found in schizophrenia or Parkinson's disease. When other neurotransmitters are off-balance, they cause symptoms found in autism, depression, obsessive-compulsive disorder, and many others (see **Figure 1**).

Until recently, the main neurotransmitter of interest has been dopamine. Other neurotransmitters implicated in the development of schizophrenia are glutamate, norepinephrine, serotonin, gamma-aminobutyric acid (GABA), and neuropeptides. Dopamine works on multiple receptor sites in the brain and they are known as: D1, D2, D3, D4, and D5. The important roles of dopamine include behavior, cognition, voluntary movement, motivation, punishment and reward, sleep, mood, attention, and learning. An over-firing of dopamine has been suggested as a cause of schizophrenia. This discovery was formulated after the introduction of neuroleptic medications and the consequent effective responses seen in patients. This hypothesis is reinforced by drugs such as cocaine, amphetamines, and Parkinson's medication which induce psychosis through increasing synaptic dopamine availability. The pathology behind other neurotransmitters like serotonin, GABA, and others are thought to have an effect similar to dopamine. Serotonin is a neurotransmitter that regulates many important functions such as mood, appetite, and sleep.[6]

Unfortunately, the dopamine theory has failed to explain all the symptoms and defi-

Figure 1. Neurotransmission



*e.g., histimine receptors, alpha-adrenergic receptor

cits associated with schizophrenia. The glutamate hypothesis offers additional information to the possible causes of this disease. Glutamate is an excitatory neurotransmitter and is also known to play a role in brain development and neuronal survival. Glutamate also plays a role in assisting learning and memory. Conditions like autism, obsessive compulsive disorder, and schizophrenia arise in individuals when production and utilization of glutamate is not balanced. This evidence was observed in the effect of a recreational drug named phencyclidine (PCP). Phencyclidine use resulted in an off-balance of the glutamate neurotransmission and induced schizophrenia symptoms. Currently, pharmacological interventions used in schizophrenia therapy involve modulations of these neurotransmitters.[6]

There is a difference in the brain structure of healthy individuals when compared to those with schizophrenia. Scans of the brain have revealed that regions of the brain in schizophrenic patients may have more or less activity than in those without schizophrenia. There are also various amounts of neurochemical substances in the brain and this is thought to indicate evidence of progressive brain deterioration at the biochemical level. The application of scanning tests in the clinical setting is not well-known.[6]

Symptoms

The diagnosis of schizophrenia is based on the presentation of symptoms that fall into the three broad categories of positive, negative and cognitive.[3,17] Positive behaviors are psychotic behaviors not found/seen in healthy people. Often times, the positive symptoms are seen during the acute phases of the illness. Hallucinations, for instance, are a positive symptom. These can be auditory, visual, olfactory (smell) or tactile (touch) in nature. When experiencing an hallucination the patient with schizophrenia describes seeing, hearing, smelling or feeling things no one else is experiencing. Many individuals with schizophrenia hear voices that command them to perform tasks or warn them of danger and risks. Moreover, people with schizophrenia sometimes hear multiple voices that may even at times talk to one another. Other types of hallucinations include seeing objects or people not evident to anyone else; and the sensation of being touched when in fact no one is touching them. Delusions, another positive symptom, are beliefs that are proven to not be true and even bizarre to others. For instance, a delusion might entail the belief that unknown forces are controlling one's actions and thoughts. Delusions are sometimes accompanied by paranoia such as in instances where a patient becomes suspicious that others are harming them by poisoning their food or plotting against them. Thought disorder such as dysfunctional thinking is also a positive symptom of schizophrenia. Patients with dysfunctional thinking have a difficult time connecting their thoughts in a logical fashion.

Movement disorder is another positive category symptom of schizophrenia. This entails agitated body movements which may be repetitive. On the extreme end of movement disorder symptoms is catatonia---a condition where a person does not move or respond to others.

Negative symptoms encompass the exhibition of abnormal emotions and behaviors given the context the person is in. For example, when a patient presents with a flat affect and no facial expression and speaks in a monotone voice or when they take no pleasure in everyday life and are unable to begin and sustain planned interaction. Under-activity, withdrawal from others, a lack of motivation to maintain basic personal hygiene, and needing assistance to maintain normal daily activities, are additional negative symptoms. These negative symptoms are responsible for the social impairment component associated with chronic schizophrenia.

Cognitive symptoms, the third category of symptoms, include having difficulty staying focused and having poor executive functioning. Unfortunately, all areas of cognitive functions are affected including attention, language, memory, and executive function. Cognitive symptoms are the biggest barrier for psychotic patients to hold a job and lead an independent normal life. Having this category of symptoms is a strong predictor for poor functional outcomes. In addition, pharmacological intervention provides limited effectiveness in correcting these symptoms.

Diagnosis

There are no objective tests to definitely diagnose schizophrenia. The diagnosis is based mainly on symptom presentation.[17] Diagnostic work-up consists of clinical interview, family interview, physical examination, and assessment of social functioning. According to the Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV), a diagnosis of schizophrenia can be made if a patient presents with active symptoms for at least one month and has persistent disturbances in social, occupational, and self-care functioning for at least six months duration.[3] The active symptoms consist of at least two of the following: hallucinations; delusions; disorganized speech or behaviors; or negative symptoms. In addition, these symptoms should not be due to a medical disorder, mood disorder, or to substance

Table 1. Description of Schizophrenia Subtypes[3]

SCHIZOPHRENIA SUBTYPES	DESCRIPTION
Paranoid	Presence of prominent delusions or auditory hallucinations
Disorganized	Disorganized speech, behavior, and flat or inappropriate affect
Catatonic	Clinical presentation mainly includes two of the followings: motoric immobility or excessive motor activity, extreme negativism, peculiarities of voluntary movement, echolalia or echopraxia (senseless repetition of words or movements)
Undifferentiated	Symptoms meet the criteria for schizophrenia but are not met for the paranoid, disorganized, or catatonic types
Residual	Continuing evidence of disturbance or presence of negative symptoms despite absence of prominent delusions, hallucinations, disorganized speech, or grossly catatonic behavior

abuse. Schizophrenia is classified into five subtypes according to DSM-IV. The subtypes are: paranoia, disorganized, catatonia, undifferentiated, and residual. Again, the diagnosis for any particular subtype is based on patient clinical presentation at the time of evaluation and this presentation may change over time. The summary of the subtypes are presented in **Table 1**.[3]

Schizophreniform disorder is a type of psychoses and its essential diagnostic features are similar to schizophrenia. The main two differences are: that the total duration of the illness is at least one month but not longer than six months; and impaired social or occupational functioning is not required for the diagnosis.

Schizoaffective disorder is described as patients meeting the criteria for schizophrenia and mood disorders (Major Depressive episode, Manic Episode, or a Mixed Episode). These disturbances are not due to the physiological effects of a substance or a general medical condition.

Delusional disorder includes delusions that are considered non-bizarre for at least one month duration. Non-bizarre situations are those that could occur in real life (i.e. being followed, poisoned, or having a particular disease) but haven't.

Brief psychotic disorder has symptoms that occur for at least one day but no longer in duration than one month. The symptoms include one to two of the following: delusions, hallucinations, disorganized speech, gross disorganization, or catatonic behavior.

Although it is difficult to establish a definitive relationship, many medications could cause psychotic symptoms. It is important to assess drug-induced psychosis in newly diagnosed patients with no history of this mental disorder and to suspect agents recently initiated. Medications could cause bizarre behaviors like hallucinations, paranoia, agitation, anxiety, mania, delusions, and confusion. The most common causes are either with medication overdose or abrupt withdrawal from medications that are being discontinued.[18, 19] For example, substance or drug-induced psychosis typically has a quick onset but is short-lived. Psychotic symptoms could be seen in patients with alcohol withdrawal or sedative-hypnotic medication withdrawal. In addition, before a definite diagnosis of schizophrenia is made, other illnesses associated with psychosis should be ruled out. Medical conditions ranging from metabolic abnormality to viral infections sometimes cause hallucinations and delusions.[20] The list of medications and medical conditions that can cause psychotic symptoms is vast. **Tables 2 and 3** summarize a sample of possible offending medications and medical conditions that may cause psychotic symptoms.[18-20]

Assessment

A complete assessment by a health care provider is crucial to making the appropriate diagnosis and to rule out other causes for any psychotic symptoms. An accurate diagnosis is necessary to optimize medical intervention. The patient assessment entails the following: complete history of all events to identify delusions, hallucinations, and thought disorders; mental state examination; physical examination; urine drug screen; an accurate medication list to identify or exclude drug induced psychosis; electroencephalogram to check for

Table 2. Selected Medications Associated with Psychotic Symptoms[18-20]

DRUG CLASS	SYMPTOMS	COMMENTS
Amphetamine-like drugs	Hallucination, paranoia, agitation, anxiety, mania, nightmares, insomnia	Usually with overdose
Anabolic steroids	Psychosis, depression, aggressiveness, paranoia	Most data based on abuse cases
Anticholinergics	Confusion, disorientation, delirium, visual hallucination, fear, agitation, anxiety	More common in the elderly and in children on high doses
Tricyclic antidepressants	Hallucination, delirium, suicidality, irritability, paranoia	Seen in withdrawal cases or due to anticholinergic effects in the elderly
Antiepileptics	Agitation, confusion, delirium, psychosis, suicidality, mania	Usually seen in high doses
Benzodiazepines	Hallucination, hostility, amnesia, delirium, nightmares	More common in the elderly, during treatment or withdrawal from therapy
Beta-adrenergic blockers	Psychosis, delirium, anxiety, nightmares, hallucination	
Corticosteroids	Psychosis, delirium, mania, depression	May be due to dosage strength or duration of therapy
Fluoroquinolone antibiotics	Acute psychosis, confusion, agitation, hallucination, mania	Case reports
Antihistamines	Hallucination, confusion, agitation	Mostly with first generation drugs. Elderly at higher risk with either generation
Nonsteroidal anti-inflammatory drugs (NSAIDs)	Psychosis, confusion, anxiety, depression	
Opioids	Psychosis, hallucination, dementia, agitation, euphoria	More common with high doses, especially in the elderly (intrathecal morphine)
Selective serotonin reuptake inhibitors	Mania, hallucination, suicidality	Sudden withdrawal from therapy

Table 3. Selected Medical Conditions Associated with Psychotic Symptoms[18,20]

Alcohol intoxication/withdrawal	Head trauma	Rheumatic fever
Brain tumor	HIV infection	Stroke
Dementia /Alzeimer's Disease	Metabolic disturbances	Substance Abuse /Toxicity
Endocrine disorders	Nutritional deficiencies	Systemic infections
Epilepsy	Parkinson's disease	

epilepsy; brain imaging to identify brain injury; and social assessment (i.e. work, home). Furthermore, a complete assessment should also identify possible barriers to implement any recommended treatment plans. A patient's social support system should also be ascertained.[21]

Rating Scales

Since the diagnosis of schizophrenia and psychotic disorders are based on symptoms, treatment interventions and their outcome effectiveness will also be based on a patient's clinical presentation. Validated rating scales are used to translate these observable and subjective symptoms (i.e. patient's thoughts, feelings, and behaviors) into objective measurable values.[22] A number of these rating scales have been developed to assist health care providers in assessing patient responses, adverse reactions to medications or non-drug interventions, cognitive functions, and a patient's quality of life. The common validated scales are: Positive and Negative Syndrome Scale; Psychotic Symptom Rating Scale; Quality of Life Scale; Beck Depression Inventory; Schizophrenia Cognition Rating Scale; Drug Attitude Inventory; and Abnormal Involuntary Movement Scale. **Table 4** provides details of the commonly used rating scales for measuring the effectiveness/outcomes of treatment intervention.[22]

TREATMENT

Medications for Schizophrenia and Other Psychoses

Medications have been the mainstay of treatment for schizophrenia and other psychoses since they were introduced more than 50 years ago. Pharmacotherapy maintains an essential role in the management of acute psychotic symptoms, induction of symptom remission, and prevention of symptom relapse. In addition to early diagnosis, implementing the most appropriate drug regimen is the cornerstone to ensure successful outcomes. The first antipsychotic drug was discovered by a surgeon who was trying to find a medical intervention to minimize surgical shock complications.[23] Chlorpromazine (Thorazine®) was used to reduce the dose of an anesthetic and patients were found to be less anxious and "indifferent" by the surgeon. Currently, there are many antipsychotic agents available in the U.S. (see **Table 5**).[24-26] They are commonly classified under the categories of "typical" or "atypical" antipsychotic medications. The older (first) generation antipsychotics are termed typical antipsychotic agents and the newer (second) generation antipsychotics as atypical agents. Overall, with the exception of clozapine, these agents are equally effective in the treatment of symptoms of psychoses.[27-32] The main differences between the drugs are their side effect profiles. The choice of medication depends on the medication potency, history of patient response, side effect profile, formulation (oral vs. injection), patient co-morbidity, and cost.

Indications for Antipsychotic Medications

Medications approved by the U.S. Food and Drug Administration (FDA) for schizophrenia may have other indications.[24,25,33] Many are approved by the FDA to treat conditions such as bipolar disease, acute agitation or manic episodes, hyperactivity, intractable hiccups, nausea and vomiting, tetanus, and Tourette's disorder. Many atypical antipsychotics have been studied for off-label uses (i.e. non FDA-approved uses).[33] Among those studied include: depression, obsessive-compulsive disorder, insomnia, post-traumatic stress disorder, generalized anxiety disorder, per-

Table 4. Description of Rating Scales[21]

RATING SCALE	DETAILS	COMMENTS
Positive and Negative Syndrome Scale (PANSS)	• 30 items total: 7 covering positive symptoms, 7 covering negative symptoms, 16 covering general psychopathology (anxiety, depression, etc.) • Symptoms are rated along a 7 point continuum (1=absent to 7=extreme) Likert scale	• Commonly used for assessing clinical outcome in treatment studies of schizophrenia and other psychotic disorders • Recommended to use regularly to assess symptom improvements or exacerbations • Time needed for assessment = 30-40 minutes
Psychotic Symptom Rating Scale (PSYRATS)	• A broad scale to measure the multiple dimensions of common psychotic symptoms • 17 items on a 5 point Likert scale	• Widely used in cognitive behavioral therapy (CBT) studies • Recommended to use multiple times during CBT therapy to monitor progress
Quality of Life Scale (QLS)	• Assess patient's day to day functioning, occupational attainment, social relationship, and overall quality of life. • 21 items to assess: interpersonal relations, instrumental role functioning, intrapsychic foundations, and common objects and activities on a 7 point Likert scale	• Some items are based on patient's perspective exclusively and some are from the standpoint of family members or clinicians • Time needed for assessment = less than 45 minutes
Schizophrenia Cognition Rating Scale (SCoRS)	• 18 items to assess cognitive deficits and the degree to which it affects day to day function • 4 point scale	• Fairly new, not well adapted in clinical practice yet • Recommended to use as an annual assessment
Drug Attitude Inventory (DAI-10)	• 10 items to assess patient's adherence and attitudes toward taking medication	• Recommended to use at every visit • Time needed for assessment = less than 10 minutes
Abnormal Involuntary Movement Scale (AIMS)	• 12 items to assess abnormal movement adverse effects potentially from antipsychotic medications	• Recommended to assess patient every 3-6 months while on antipsychotic medications • Time needed for assessment = less than 10 minutes
Beck Depression Inventory (BDI)	• 21 items to assess both cognitive and neurovegetative symptoms of depression	• Brief and reliable assessment for depression

sonality disorder, and psychosis and agitation in patients with dementia or Alzheimer's disease. Off-label antipsychotic use has also been studied in children with autism and Tourette's syndrome. As such, patients could be on antipsychotic medications without a medical history of schizophrenia or other psychoses.

Effectiveness

Studies have demonstrated no difference between the first and second generation antipsychotics with regard to adherence, quality of life, and effectiveness.[30,31,34] Furthermore, no one antipsychotic agent has been proven to be effective and toler-

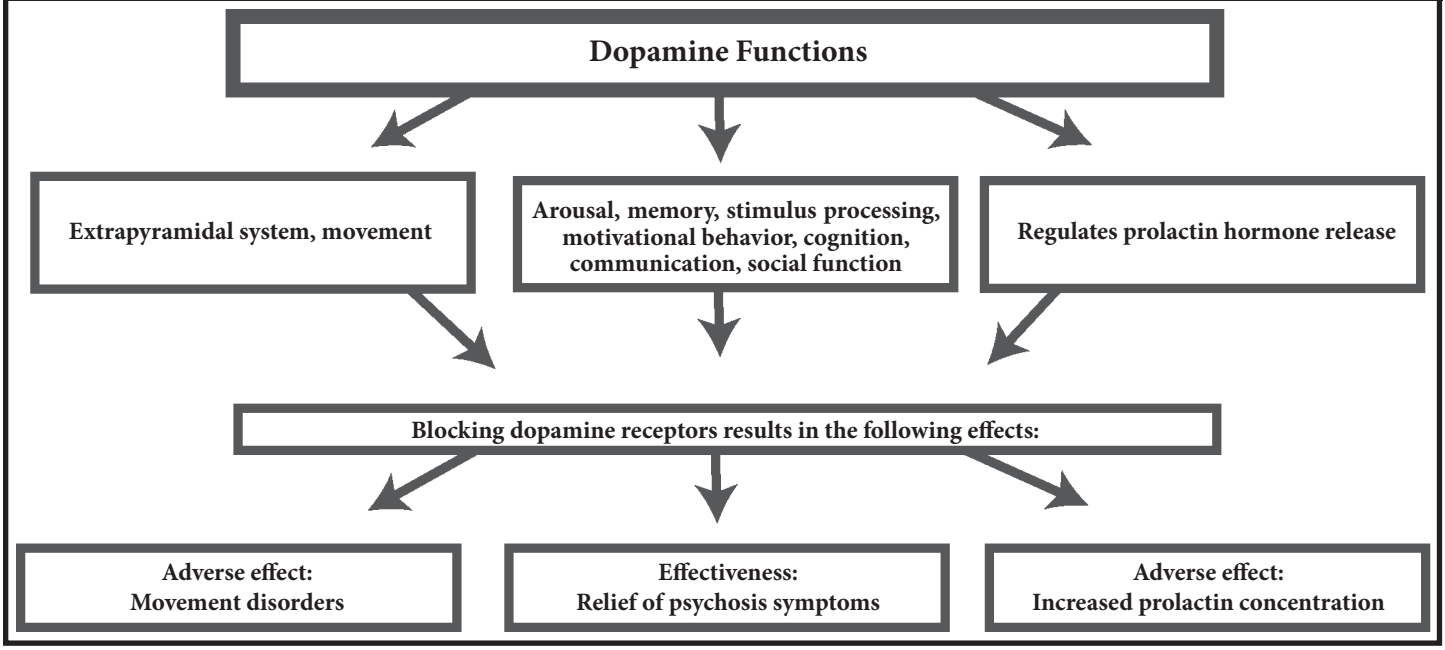
Table 5. Antipsychotic Medications[24-26]

GENERIC NAME (BRAND NAME)	DOSAGE FORMS (**)	USUAL ADULT DOSING RANGE (mg/day unless otherwise specified)
Typical agents		
Chlorpromazine (Thorazine)	T, L, C, S	30-800
Trifluoperazine (Stelazine)	T, L, C, I	2-15
Pimozide (Orap)	T	1-10
Loxapine (Loxitane)	C, L	20-250
Thioridazine (Mellaril)	T, L	150-800
Perphenazine (Trilafon)	T, L, C, I	12-64
Prochlorperazine (Compro)	T, I, S	15-150
Fluphenazine (Prolixin)	T, L, C, I	1-40
Fluphenazine decanoate (Prolixin Decanoate)	LI	12.5-100 mg every 3-4 weeks
Haloperidol (Haldol)	T, L, C, I	1-30
Haloperidol decanoate (Haldol Decanoate)	LI	100-200 every 3-4 weeks
Thiothixine (Navane)	C, L	6-60
Atypical agents		
Risperidone (Risperdal)	T, L, O	4-16
Risperidone Long-Acting (Risperdal Consta)	LI	25-50 mg every 2 weeks
Olanzapine (Zyprexa)	T, I, O	5-20
Quetiapine (Seroquel)	T	50-800
Ziprasidone (Geodon)	C, I	40-200
Aripiprazole (Abilify)	T, O, L	15-30
Paliperidone Extended-Release (Invega)	T	3-12
Paliperidone palmitate (Invega Sustenna)	LI	39-234 mg every 4 weeks
Clozapine (Clozaril)	T, O	300-900
New agents		
Asenapine (Saphris)	T (sublingual)	10-20
Iloperidone (Fanapt)	T	12-24
Lurasidone (Latuda)	T	40-80

****Formulations: T=tablet, C=capsule, L=liquid, R=rectal suppository, I=injectable, LI=long-acting injectable, O=oral disintegrating tablet**

able for all patients. It is important to be aware that 10-30% of patients might not respond to medication.[34] Another 30% have only a partial response to these agents. Antipsychotic medications are effective in reducing positive symptoms for patients during acute psychotic episodes. Unfortunately, the benefit is less for negative symptoms. Although studies have found comparable efficacy for psychotic symptoms among antipsychotic agents, these results should be interpreted with caution. In general, clinical trials were of short duration with a large patient drop-out rate (i.e. >60%).[30] Systematic reviews found high attrition (drop out) rates which could lead to a problematic interpretation of results.[32] Moreover, the major-

Figure 2. Dopamine Functions



ity of these clinical trials were sponsored by pharmaceutical companies, which could be a source of bias. One of the largest trials initiated by the National Institute of Mental Health--Clinical Antipsychotic Trials of Intervention Effectiveness trial (CATIE)---compared the two classes of medications and found a modest improvement in PANSS score, QLS, and Global Assessment; however, these differences were not statistically significant.[30] There were also no preferences for either class of drug based on the DAI scale. Discontinuation rates remained high (74%) before the 18 month long duration for one trial and only 50-60% of patients remained in the allocated treatment group by the end of one year for another trial. Lack of efficacy is one of the reasons for drug discontinuation for 24% of patients.

Mechanism of Action

The main mechanism of action for the typical antipsychotic medications is to block dopamine neurotransmitters in the brain, predominantly at the D2 receptors.[26] Since dopamine exists in various parts of the brain and plays an important role in regulating many functions other than mood, unwanted effects can occur when dopamine is modulated by pharmacological agents (see **Figure 2**). Typical antipsychotics also affect non-dopamine neurotransmitter receptor systems. They block the muscarinic, alpha-1 adrenergic, and histaminic receptors. Each medication's binding capacity varies to some degree at these receptor sites, but the trend is that lower-potency antipsychotic agents tend to block other sites as well. This translates to clinically significant unwanted effects. Some common side effects are dry mouth, constipation, tachycardia, and orthostatic hypotension. An uncommon cardiac side effect is the induction of irregularity of the electrical activity of the heart that places patients at risk for ventricular arrhythmias. **Table 6** provides a summary of side effects from receptor blockade.[26,35]

In addition to exerting its mechanism of action through blocking dopamine (D2) neurotransmitter sites, dopamine subtype (e.g., D1, D3, D4, and D5) receptor sites are also blocked by second generation antipsychotics. Additionally, this class of medication has a higher affinity for serotonin receptor blockade. As a result the dopamine and serotonin ratio might be the reason for decreased risk of extra-pyramidal symptoms (EPS) and hyper-prolactinemia seen with the first generation antipsychotics. One of the advantages of atypical agents is that they have a low incidence of causing extrapyramidal symptoms or movement disorders (described later in monograph). Similar to the first generation drugs, receptor blockade takes place at the histamine-1, muscarinic, and alpha-1 adrenergic sites (see **Figure 1**).

General Pharmacokinetics

Both generations of antipsychotics are generally highly lipophilic (fat soluble) and protein bound. They tend to

accumulate in the brain, lung, and tissue.[24,26] These medications also enter fetal circulation and breast milk, increasing the potential for drug exposure to a fetus and/or infant. Although these agents might possess a short plasma half-life, many have a long biological half-life which allows for once a day dosing. This favorable kinetic profile makes it easier for patients to take their medication. Patients usually start on smaller, multiple doses per day to minimize side effects. Once a patient is doing well with the assigned medication dose, the dose is increased slowly and finally dosed once daily for most medications. Many antipsychotic drugs are metabolized (broken down) through the liver. This can lead to potential interactions with other medications. In other words, the level of an antipsychotic could significantly be elevated if a patient is taking another medication which could inhibit the liver enzymes which break down the antipsychotic medication. This elevated antipsychotic level could lead to clinically significant side effects. Examples of medications which could decrease the metabolism of antipsychotics are erythromycin, ketoconazole, ritonavir, cimetidine, fluoxetine, and paroxetine. On the other hand, there are medications or substances which could potentially increase the metabolism of antipsychotic drugs and result in a lower level/effect of the antipsychotic medication. Examples are carbamazepine and cigarette smoking. It is important to monitor patients closely to adjust therapy to minimize unwanted effects.

A unique oral formulation is the oral disintegrating tablet. The medication is formulated in wafers which dissolve on the tongue in seconds. This formulation is an option for patients who cannot swallow pills or have significant nausea and vomiting. In addition to oral formulations of antipsychotics, some medications are available in injectable form such as depot (long-acting) and short-acting forms (see **Table 7**).[24, 26] A short-acting injectable formulation has a quick onset of action and its main role is for use in agitated and uncooperative patients when immediate intervention is needed. The depot formulation has a long half-life and is engineered for intramuscular injection by suspending the medication in seed oil. Once injected into the muscle, the medication is slowly released into the circulation. A single injection will provide an effective level of medication for a duration of days to weeks. This formulation is used when a patient is stabilized on antipsychotic therapy. The injection is administered by health care providers in out-patient settings. The obvious advantages of this formulation are there is no need for the patient to take the medication on a daily basis and the patient has regular contact with the health care team. Candidates for this formulation are individuals with a history of non-adherence to taking their medication daily. Long-acting injections are not appropriate for patients who refuse to be on this formulation or for patients who are unable to tolerate or respond to the long-acting injectable medication.

Adverse Reactions and Management

The strongest predictor for non-adherence to therapy is side effects that are unacceptable to patients. Adverse reactions associated with antipsychotics are plentiful and relatively unavoidable. There are some clinically significant side effects among the two generations of drugs.[24,26,35] It is crucial for health care providers to have a good understanding of these side effects as part of the treatment plan. The typical or first generation agents vary in severity with relatively few chances for causing side effects such as sedation, hypotension, and movement disorders. The typical antipsychotics are further divided into either low or high potency groups. Low potency medications require a higher dose to achieve an equivalent effect as a smaller dose of higher potency medications. The side effects are more sedating, anticholinergic related (i.e. dry mouth, urinary retention, constipation), but less likely to cause extrapyramidal symptoms (EPS) or movement disorders in the low potency group. On the contrary, the high potency agents tend to cause less sedation and anticholinergic side effects, but are more likely to cause EPS or movement disorders because of greater dopamine blockade. Patients should be assessed for side effects at every visit, preferably using the self-assessment side effects rating scale. If intolerable side effects are detected, it is best to work with patients to find either an alternative medication or adjust the dosage to minimize these side effects. In general, the higher the dose, the higher the risk for adverse reactions. Many of these side effects are reversible once the medications are discontinued, with the exception of tardive dyskinesia (see below). Atypical or second generation agents are less likely to cause EPS. However, this newer class of medications is more likely to be associated with weight gain, glucose intolerance or diabetes, and increased lipid levels. Additional side effects associated with antipsychotics are abnormal heartbeat (QTc prolongation), seizures, sexual dysfunction, liver impairment, and vision defects. These side effects are presented in **Table 8**.[24,26,35]

Extrapyramidal Symptoms (EPS)

Extrapyramidal symptoms include movement disorders such as dystonia, akathisia, pseudo-parkinsonism, and tar-

Table 6. Antipsychotics Side Effects[26,35]

RECEPTOR BLOCKADE	SIDE EFFECTS
Histamine-1	Sedation, weight gain, worsening effects of other central nervous system depressant medications
Muscarinic	Urinary retention, cognition and memory effects, tachycardia, dry mouth, blurred vision, constipation
Alpha-1 adrenergic	Orthostatic hypotension, reflex tachycardia, worsening effects of blood pressure lowering medications
Dopamine D2	Extrapyramidal symptoms, increased prolactin hormone level
Serotonin	Orthostatic hypotension, sedation, weight gain
Increased prolactin hormone concentration	Galactorrhea (milky nipple discharge) in both males and females, amenorrhea

Table 7. Commonly Used Antipsychotics[24-26]

DRUG	HALF-LIFE (hours unless otherwise specified)	POTENCY	COST (**)
Typical agents			
Haloperidol	18	High	+ to ++
Haloperidol decanoate (injection)	21 **days**	High	++
Fluphenazine	14	High	+
Fluphenazine decanoate (injection)	14 **days**	High	+
Thiothixene	24	High	+
Perphenazine	19	Low	++
Loxapine	19	Low	++
Thioridazine	25	Low	+
Chlorpromazine	30	Low	++
Atypical agents			
Ziprasidone	2-7	High potency and blocks more than one dopamine receptor	++++
Risperidone	20		++ to +++
Risperidone Long-Acting (injection)	3-6 **days**		+++++
Paliperidone	23		+++++
Paliperidone (injection)	25-49 **days**		+++ to ++++
Iloperidone	18-26		++++ to +++++
Aripiprazole	75-94		+++++
Olanzapine	21-54		+++++
Quetiapine	7		+++ to +++++
Clozapine	12		++++ to +++++

****Average Wholesale Cost/Year (at time of publication):**
+ (<$500) ++ ($500-2,500) +++ ($2,500-4,500) ++++ ($4,500-6,500) +++++(>$6,500)

Table 8. Side Effects of Selected Typical and Atypical Antipsychotics[24,26,35]

DRUG	EPS	ORTHOSTATIC HYPOTENSION	SEDATION	ANTICHOLINERGIC EFFECTS	WEIGHT GAIN
Typical agents					
Haloperidol	++++	+	+	+	
Fluphenazine	++++	+	+	+	
Thiothixene	+++	+	+	+	
Perphenazine	++	+	++	+	
Loxapine	++	+	+	+	
Thioridazine	+	+++	+++	+++	
Chlorpromazine	++	+++	+++	++	
Atypical agents					
Ziprasidone	++	++	++	+	+
Risperidone	++	++	+	0 to +	+++
Paliperidone			+	0 to +	
Iloperidone					
Aripiprazole	0	+	+	0 to +	+
Olanzapine	+	++	++	++	++++
Quetiapine	0	++	++	0 to +	+++
Clozapine	0	+++	+++	+++	++++

0 (none to minimal effect) +(minimal effect) ++ to +++ (moderate effect) ++++(severe effect)

Table 9. Extrapyramidal Symptoms[35]

SIDE EFFECT	TIME OF ONSET	RISK FACTOR	TREATMENT
Dystonia	1-5 days	Young, never on antipsychotic therapy, high potency antipsychotics	Anti-parkinsonian agents (benztropine, trihexyphenidyl)
Akathisia	5-60 days	High potency antipsychotics	Reduce antipsychotic dose or change drug; use benzodiazepines (clonazepam, diazepam, lorazepam); or propranolol
Pseudoparkinsonism	5-30 days	Elderly	Reduce antipsychotic dose or change drug; anti-parkinsonian agents (benztropine, trihexyphenidyl)
Tardive dyskinesia	Months to years	Elderly, high dose or high potency antipsychotics	May be reversible if detected early and antipsychotic agent discontinued

dive dyskinesia. These movement disorders are the result of dopamine blockade or super-sensitivity to dopamine effects after long-term use of antipsychotics. The onset of these abnormal movements can be as quick as a few days or up to years after initiation of medication therapy. Dystonia is described as abnormal movement involving the head and neck muscles, the tongue, and the back. These side effects can manifest themselves after a day of therapy in response to an abrupt decrease in dopamine levels. This is frightening to patients; therefore, it is important to educate patients about this potential side effect. Individuals who are at high risk for this side effect are young patients and those who have never been on antipsychotics. Akathisia includes symptoms such as restlessness or the inability to sit still. Up to 40% of patients treated with high potency antipsychotics experience this side effect. The onset for this side effect could be a week to two months of therapy. Pseudo-parkinsonism is a set of symptoms that resemble Parkinson's disease. These are generalized slow movements, reduced arm movements during walking, and sometimes rigidity and tremor at rest. Elderly patients are at greatest risk for this adverse effect and the onset is after a week to a month into antipsychotic therapy. Another movement side effect is tardive dyskinesia and this is the result of super-sensitivity to dopamine neurotransmitters at a different region of the brain. The symptoms are abnormal involuntary movements involving the mouth and face. An example of this side effect is repetitive, tic-like movements of the face, eyelids, mouth, tongue, and extremities. Risk factors for tardive dyskinesia are dependent on the antipsychotic agents, duration of therapy, medication dosage, age (older is worse), and history of EPS. The best treatment is preventive care since no treatment is available for this side effect. **Table 9** provides a summary of these extrapyramidal adverse reactions and treatment strategies.[35]

Histamine-1 Blockade

The two major clinically significant adverse effects associated with histamine-1 blockade are sedation and weight gain. These medications are often prescribed at bedtime to minimize daytime drowsiness and to help a patient sleep. Tolerance to the sedative effects occurs with continued use of the offending antipsychotic agent. If the decision is made to switch agents, one must taper the patient off the first agent slowly to prevent rebound insomnia. Weight gain due to appetite stimulation is a concern for patients. Additional risk factors are sedentary lifestyle and poor caloric intake. It is very important to counsel patients during every office visit about behavioral strategies to minimize weight gain.

Muscarinic Blockade

Anticholinergic effects are the result of muscarinic receptor blockade. Low potency antipsychotics tend to have significant anticholinergic side effects. Common adverse effects include dry mouth, constipation, blurred vision, urinary retention, confusion, and memory impairment. Initial management of these side effects is to reduce the dose of antipsychotic slowly to the lowest tolerable dose for the patient. If these adverse effects remain troublesome for patients despite dose reduction, pharmacological intervention can be included. Side effects such as constipation can be prevented with stool softeners and/or by incorporating more dietary fiber foods. Patients with dementia or urinary retention should avoid these antipsychotics and switch to agents with less anticholinergic effects.

Alpha-1 Adrenergic Blockade

Orthostatic hypotension from alpha-1 adrenergic blockade is defined as greater than a 20mmHg drop in systolic blood pressure when the patient rises from a sitting position. Patients experience light-headedness or syncope (fainting). Patients should be educated to change positions in posture slowly (i.e. stand up slowly; dangle feet over the edge of the bed before getting up out of bed). Tolerance to this side effect develops in some patients over 2-3 months of therapy. For patients with cardiovascular disease or the very elderly, agents with alpha-1 adrenergic blockade should be used with caution.

Metabolic Adverse Effects

The major metabolic side effects seen with atypical antipsychotics are weight gain and metabolic syndrome. Weight gain is prevalent with both the typical and atypical antipsychotics. The exact mechanism of action is not known but is thought to be due to blocking histamine-1 and serotonin (5-HT2c) receptors. The blocking of these receptors results in the interference of normal appetite regulation and metabolism. Most of the weight gain occurs in the early course of treatment but weight gain can be substantial in some patients. Other potential factors leading to weight gain include inactivity due to the sedative effects of some medication, lack of motivation to exercise, and poor food choices. Metabolic syndrome is a constellation of risk factors including: overweight with excessive fat tissue around the abdominal area, abnormal cholesterol levels (high triglycerides, low-HDL and high LDL-cholesterol), high blood pressure, and

impaired glucose levels. This negative effect can be seen in as little as a few weeks of therapy with the offending medications. The prevalence of type 2 diabetes is found to be 2-3 times higher in these patients than in the general population. In addition, patients with metabolic syndrome are at an increased risk for cardiovascular disease, stroke, and peripheral vascular disease. It is recommended to monitor for these potential complications in patients on atypical antipsychotics at the beginning of therapy and every three months to annually.[8,35] The main prevention and treatment of these metabolic side effects are lifestyle modification and using pharmacological interventions to control cholesterol, blood pressure, and blood glucose.

Neuroleptic Malignant Syndrome

Neuroleptic malignant syndrome (NMS) is a potentially fatal adverse event associated with antipsychotics. The incidence is low (<1%) in patients taking the first generation antipsychotics and this rate is even lower with the second generation medications.[35] NMS is described as body temperature exceeding 100.4°F, mental status changes, muscle rigidity, and abnormal heart rate. Laboratory findings have revealed abnormal blood cell counts, muscle enzyme activities, and liver enzymes. The onset of this syndrome varies from early in the treatment to months of therapy. Treatment intervention is to discontinue the antipsychotic medication as quickly as possible and to provide supportive care. This poses a challenge for health care providers to treat psychotic patients with a history of NMS in the future. Only second generation agents are recommended and patients should be monitored closely.

Pharmacological Intervention and Duration of Therapy

Pharmacological interventions are classified into two broad categories, acute and chronic. The treatment goals for patients with schizophrenia are improvement in quality of life, symptom control and prevention of disease relapse, and minimizing adverse effects. Ideal clinical outcomes should include complete symptom improvement as well as what matters most to the patient. Unfortunately, complete remission is not a realistic outcome with current treatment plans. A more pragmatic goal is to minimize symptoms, prevent recurrence and intensity of symptoms, and improve the quality of life.

In addition to different side effect profiles, the typical antipsychotics are relatively inexpensive and have been found to be cost-effective.[21,24,34,35] In general, the effectiveness of most antipsychotics is equivalent and medication selection should be guided by clinical presentation; a patient's previous response to antipsychotics and drug side effects; comorbidities; and patient preference.[21,36] Many health care providers prefer atypical agents because of the lower risk of EPS. Not all patients will respond to one particular agent or particular class of agents. If the patient does not respond to the initial antipsychotic within a reasonable treatment duration, it is recommended for the patient to try another agent.

The acute symptoms of schizophrenia can be reversed rapidly but chronic schizophrenia symptoms can take weeks to improve. For acute management, the immediate goal is to reverse acute psychotic symptoms. The onset of medication action is an important factor to consider, especially if a patient is acting violently and could pose a danger to themselves or others. Short-acting injectable formulations have quick onset (within 15 minutes) and clinical benefit.[17,21,33] For instance, haloperidol can be administered every 30-120 minutes if needed to control agitation. In addition, benzodiazepines such as lorazepam can be given to stabilize patients. Most patients can be stabilized in less than 24 hours. This is likely due to the sedating effects of the drugs. Within a week of drug therapy, acute symptoms such as agitation and insomnia should diminish and socialization skills should recover within the next four to six weeks. Thought disorder symptoms can take weeks to months to see an impact. If the negative symptoms do not improve after three weeks of therapy, the medication dose should be adjusted. Once a patient is stabilized on the initial dose, the regimen should be continued for a few months to minimize relapse. The goal of chronic disease management is to maintain control of psychotic symptoms. Most patients will require long-term therapy. Unfortunately, long-term therapy may result in the development of side effects. Medication doses should be tapered slowly to the lowest possible dose needed to control symptoms and minimize side effects (see **Table 9**). Relapse rates are high and systematic reviews have found that 16-21% of patients relapse while on medications compared to 33-55% on placebo.[34] Although it remains controversial when therapy should be discontinued, if a patient remains stable and maintains good psychosocial functioning (working, attends medication groups, keeps close contact with social workers), treatment may be discontinued after one to two years of therapy. The consensus is that prevention of disease relapse is the principal priority. Life-long therapy is recommended if there are more than two psychotic episodes within five years or multiple episodes over time.[17,21,34,36]

Table 10. Sound-Alike Medication Name Pairs[62]

ANTIPSYCHOTIC MEDICATION	CONFUSED DRUG NAME
aripiprazole	proton pump inhibitors (i.e. omeprazole, esomeprazole, rabeprazole, lansoprazole, pantoprazole)
Fanapt®	Xanax®
Loxitane®	Lexapro®, soriatane
Risperdal®	Restoril®
risperidone	ropinirole
Seroquel®	Serzone®, Sinequan®
Zyprexa®	Celexa®, Reprexain®, Zestril®, Zyrtec®

Drug Level Monitoring and Follow-Up Tests

Monitoring drug levels of most antipsychotics is not recommended. Routine testing provides little clinical benefit for most patients since the levels do not correlate well with clinical response. Levels can provide dosage adjustment guidance when a patient fails to respond to conventional dosages. Other scenarios for using level monitoring are when a patient is taking multiple medications with potential drug interactions or to assess adherence to medication regimens.

Consensus from several different health discipline organizations provides guidance on how to monitor patients on second generation antipsychotics for the potential development of metabolic side effects.[8] Weight should be measured at baseline, monthly for three months, and then every three months thereafter. Fasting blood glucose and blood pressure should be checked at baseline, three months, and then annually. Blood cholesterol should be checked at baseline, at three months, and then every five years.

Hospitalization

Admission to the hospital for treatment is not a necessity for every schizophrenic patient. One reason for patients to be treated at the hospital is when symptoms of schizophrenia are harmful behaviors to either themselves or to others.[6] Other reasons for hospitalization are: 1) new onset of illness, to rule out alternative diagnoses, and/or to stabilize the medication dose; 2) special medical procedures; 3) when a patient is suicidal; 4) when a patient cannot care for him or herself; and 5) when there are life-threatening side effects. Treatment in the hospital setting is usually relatively short and once the patient is stabilized, he or she will be discharged and be treated and monitored in the outpatient/clinic setting.

Combination Therapy

Limited data from clinical trials support the use of two or more antipsychotic agents concurrently in a single patient. Clinical practice commonly uses dual or multiple agents for patients with only partial response from single agents in both outpatient and inpatient settings.[37-39] Recent estimates have found that at least 33% of schizophrenic patients receive two antipsychotics and 10% receive three antipsychotics. Antipsychotic polypharmacy is prescribed for up to 50% of patients in the inpatient setting. The rationale behind combination therapy is to increase neurotransmitter receptor coverage and to increase the dopamine subtypes receptor blockade by using different classes of antipsychotics. No high quality studies have shown better clinical outcomes with polypharmacy vs. monotherapy. On the other hand, additive risk for side effects can occur with multiple agents and this regimen should be used with caution. Currently, treatment algorithms recommend two different trials of a single agent be used as the initial therapy.[21,36] If the result is undesirable, the next therapy should be clozapine as a single agent. Combination therapy should be the last resort strategy if trials of single agents fail to control symptoms per algorithm.

Treatment for Refractory Patients

Clozapine is the drug of choice for 30% of patients who do not respond to conventional antipsychotic medications.[28,29,36] Review of study data has found that clozapine provides more clinical improvements, fewer relapses, and is more tolerable than conventional antipsychotics. Most of the trials were less than 13 weeks in duration. The review found no difference between agents in mortality or ability to work. The mechanism of action for clozapine is that it is a relatively weak inhibitor at the dopamine receptor sites. It also has the capacity to block serotonin, alpha-adrenergic, histamine, and cholinergic receptors. Clozapine resulted in fewer motor side effects but more patients experienced sedation, hyper-salivation, weight gain, and blood cell count problems. Another unique side effect associated with clozapine is seizure induction. Patients with a history of seizure should be monitored closely if clozapine therapy is indicated. The clozapine dose should also be titrated slowly to minimize the risk of orthostatic hypotension. Additional clozapine side effects are gastrointestinal effects, sedation, weight gain, diabetes, and hyperlipidemia.

Agranulocytosis (decreased white blood cells) is a side effect which occurs in 1-2% of patients taking clozapine and is a potentially fatal side effect. The U.S. Food and Drug Administration requires blood test monitoring for patients taking clozapine. The blood test monitoring schedule is intense with weekly blood levels for months of therapy, moving to twice weekly and then to monthly for the duration of therapy.[24,26] Therapy is discontinued at the first sign of decreasing white blood cell counts. The Clozaril National Registry program was developed to monitor these potential side effects. Pharmacies must have a record of patients' blood cell count results before dispensing this medication to patients.[40]

Electroconvulsive therapy (ECT), while most often used to treat severe depression, has also been used for the treatment of refractory schizophrenia. During ECT, a brief electrical current is applied through the scalp to the brain of a patient under general anesthesia to induce a seizure. A recent review of the literature found that the combination of ECT and antipsychotic drugs could be options for patients with schizophrenia. There appears to be short-term benefit in patients and even in patients with limited response to medication alone.[34] Drawbacks to ECT include short-term memory loss, the number of ECT sessions needed, and the availability of ECT centers.

OTHER CONSIDERATIONS AND TREATMENT METHODS

Special Populations

Women

There are unique factors to consider when treating women with schizophrenia. The two main categories are: 1) fertility; and 2) medication use safety during pregnancy and breastfeeding. In general, the fertility rate is lower in females with schizophrenia when compared to the general population. Antipsychotic agents induce side effects such as prolactin hormone elevation which can increase the risk of infertility.[34] Regardless of the high risk of infertility in this population, pregnancies do occur. A rough estimate is 500,000 pregnancies annually in the United States in females with psychiatric medical conditions including major depression, bipolar disorder, anxiety disorder, and schizophrenia.[41] Many of the pregnancies in schizophrenic patients are unplanned. Schizophrenic female patients are also more likely to be smokers, have poor nutrition, and have limited social support. Higher rates of low birth weight, poor neonatal conditions, and stillbirths were found in this patient population.[41,42] Females with schizophrenia are considered a high-risk pregnancy category and close monitoring is necessary.

A teratogenic medication is defined as any medication that can cause a disturbance to embryo or fetus development.[43] Such disturbances could lead to terminating a pregnancy or producing a congenital malformation or birth defect. The majority of antipsychotic agents have the FDA-assigned "pregnancy category of C."44 This category does not exclude pregnant females from receiving these medications. It means these medications have not been studied in pregnant women. Both classes of medications have been used during pregnancy for a number of medical conditions such as nausea/vomiting, mania, bipolar disorder, and schizophrenia. Clinical trials testing for the safety of these medications during pregnancy is limited. One limitation is the ethical considerations involved with testing the safety of medications in pregnant individuals. Hence, the information available is often based on case reports and medication registries. Data available has revealed no clinically significant increased risk of birth defects in patients on antipsychotics compared to the general population. Most databases identified no differences in rates of birth defects, perinatal mortality, and birth weight.[42,45,46,47] One small study found a higher incidence of infants with larger gestational size and higher birth weight in the groups exposed to second generation antipsychotics compared to

first generation antipsychotics.[43] In February 2011, the U.S. Food and Drug Administration informed health care providers that the labeling for all antipsychotics was updated to include information about the potential risk for abnormal muscle movement (EPS) and withdrawal symptoms in newborns whose mothers were treated with these medications during their third trimester of pregnancy.[49] These abnormal muscle movements can include agitation, increased or decreased muscle tremor, sleepiness, severe difficulty breathing, and difficulty in feeding. Some newborns recovered within hours or days without specific treatment. Others required longer care at the hospital. It is important to remind patients not to stop taking antipsychotics once they become pregnant. Patients should first contact their physician because abruptly discontinuing the medication could lead to significant complications for treatment. Therefore, the use of antipsychotics during pregnancy should be individualized and a risk-benefit analysis done. The American College of Obstetricians and Gynecologists recommends a multidisciplinary team approach involving a patient's primary care provider, mental health clinician, obstetrician, and pediatrician to care for the patient and manage the pregnancy. Moreover, a single medication should be used at all times before prescribing multiple medications for the management of the patient's psychiatric illness.[45]

The safety profile of antipsychotic medications used during breastfeeding has not been established.[39,45,50] Antipsychotics do excrete into the breast milk. Available literature is mostly from case reports and reveals no conclusions that can be made about the safety profile of these medications. Authors recommend avoiding the use of clozapine and olanzapine during breast-feeding because of potential serious adverse effects induced in breast-fed babies.[49] The following precautions should be taken in weighing the benefits/risks when deciding which antipsychotic to use during breastfeeding: 1) evaluate the risk/benefit ratio of neonatal drug exposure; 2) evaluate the severity of maternal psychiatric illness; and 3) balance the drug choice by balancing its safety and efficacy profile.

Elderly

The prevalence rates of psychotic symptoms in the elderly varies from as low as <5% in the community to as high as 60% in nursing homes.[51] Elders are more likely to be affected by many other health conditions. Some of these underlying conditions may induce psychotic symptoms. Health conditions contributing to the risk of psychotic symptoms in the elderly are: chronic medical conditions, psychiatric disorders, Alzheimer's disease, dementia, Parkinson' disease, social isolation, cognitive decline, and medications. Treating elderly patients with antipsychotic agents poses a number of challenges for health care providers. Due to physiologic changes associated with aging, the elderly can have variable and unpredictable responses to medications. For example, organ function declines as a process of aging. The kidneys and liver are the common pathways to break down and eliminate medications. As a result of these changes, antipsychotics can be retained and accumulate in the elderly patient. Elderly patients are also more sensitive to the effects and side effects of medications. Many of the adverse effects associated with antipsychotics would also be more pronounced in the elderly. For instance, the chance for developing tardive dyskinesia was found to be 5-6 times higher in the elderly.[51] Another study performed by the manufacturer found cerebrovascular side effects were two times more common in patients with dementia treated with risperidone than those on placebo.[52] The general safety precaution strategy is to start elderly patients on low doses and adjust the doses slowly to minimize unwanted or unpredictable effects. The Food and Drug Administration (FDA) has requested a black box warning to be added to antipsychotics. The warning states that the use of these medications for behavioral problems in demented elderly is associated with a higher risk of death.[52]

Psychosocial Therapies

An effective comprehensive treatment plan includes both pharmacotherapy and psychosocial interventions. Psychosocial interventions involve individual psychotherapy and cognitive-behavioral therapy.[17] The goals are to build support and to reduce stress for patients. The benefits for patients whose treatment plan includes psychosocial intervention are significant. Studies have revealed that treatment regimens including both pharmacotherapy and psychosocial interventions provide better patient outcomes compared to pharmacotherapy alone. By the end of a one year trial, early-stage schizophrenic patients treated with a combination regimen had a lower rate of treatment discontinuation, a lower risk of relapse, and improved insight, quality of life, and social functioning.[53] To maximize the effectiveness of these interventions, psychosocial therapy must be tailored to an individual patient's needs. For example, the plan could focus on problem solving and social stimulation for a patient who is living alone while another patient might benefit from family therapy if living at home with his/her family.

Cognitive-behavioral therapy (CBT) focuses on helping patients to connect their thoughts and feelings and their reactions to those feelings. Often times, their reactions are emotions such as fear, depression, or dysfunctional behaviors. CBT increases patients' awareness of these abnormal thinking patterns as well as learning techniques and behaviors to minimize the adverse impact they impose on their lives.[17]

Social rehabilitation focuses on social and vocational training to help patients function as productive citizens in the community. These programs work with patients on job training, financial planning and management, public transportation navigation, and communication skills.

Family education emphasizes empowering family members to learn and understand the disease as much as possible. While a multi-disciplinary team is available to help patients with schizophrenia find housing for those in need, family members are often times the primary caregivers for schizophrenic patients. Therapists work with family members on coping strategies, problem-solving skills, and learning how to help patients during the course of the treatment plan.

Support groups or self-help groups are support meetings without a professional therapist. These group meetings are made up of members/patients providing support and networking for each other.

Diets/Supplements

There is insufficient evidence to support the effects of fatty acid or vitamin supplementation for the treatment of schizophrenia. No specific diet has been found to replace conventional therapy such as antipsychotics or to be effective in treating patients with schizophrenia. Chinese herbal medicine has been used to treat patients with schizophrenia in China for a long time. Limited data has found additional benefits in combining Chinese herbal medicine with antipsychotics compared to antipsychotics alone.[54] The challenge for many western providers in using Chinese herbal medicine is the medication availability. The traditional Chinese medicine herbal formula is made based on a patient's specific symptoms.

Medication Adherence

The best medical intervention is useless if not correctly implemented. Medication adherence is defined as "the extent to which a person's behavior coincides with medical advice."[55] Adherence rates to antipsychotic medication has been found to be around less than 50%.[56] There are no differences in adherence rates among both generations of antipsychotics. Studies have identified characteristics that increase the risk for non-adherence to antipsychotic medications. These characteristics are patients with: prior non-adherence status; recent illicit drug and alcohol use; poor insight and negative attitude towards the illness; poor discharge planning and aftercare; and medication-related adverse effects.[57,58] Non-adherence to medication regimens was found to be associated with poorer functional outcomes; increased psychiatric hospitalizations; increased emergency psychiatric needs, arrests, violence, and victimizations; poorer mental functioning; poorer life satisfaction; greater substance use; and more alcohol-related problems.[59] In addition, non-adherence in the first year is a predictor of poorer outcomes in the remaining two study years. Effective interventions to improve antipsychotic medication adherence involves a comprehensive approach including educational, behavioral, and affective strategies.[60] An educational approach alone was the least effective strategy at increasing medication adherence. It is important for health care providers to recognize risk factors and barriers for an individual patient to be adherent to medical interventions and take appropriate action to minimize non-adherence.

Risk Evaluation and Mitigation Strategy (REMS)

The FDA requires a REMS from manufacturers to ensure that the benefits of a drug or biological product outweigh its risks.[61] Antipsychotic medications that have a REMS requirement are clozapine and olanzapine extended release injection. For clozapine, the REMS includes having prescribers, pharmacies and patients recorded in a registry as well as the monitoring and reporting of the patient's white blood cell count and absolute neutrophil count on a weekly, biweekly or monthly basis as required by the registry before dispensing. For olanzapine extended release injection, the REMS components include a medication guide, communication plan, elements to assure safe use, and implementation system.

Medication Stability

The general principle to protect and ensure medication stability is to keep medications in a dry environment. For oral medications, it is recommended to store them at room

temperature at 25°C or 77°F. For short distance travel, the recommended storage temperature ranges from 15° to 30°C (59° to 86°F). The elixir or oral liquid formulation should not be placed in a freezer. In addition, injectable medications in either powder or solution formulation should also be kept away from direct light.[24]

Medication Sound-Alike Names

One area for potential medication errors is miscommunication resulting from sound-alike drug names. The Institute for Safe Medication Practices (ISMP) collects these reported events and shares them with providers and patients with the intent to minimize any future drug errors. The Institute also provides the following recommendations to reduce the risks of these medication errors: 1) encouraging health care providers to use both brand and generic names for prescribing and dispensing medications; 2) programming the computer to avoid sound-alike drugs from appearing consecutively; and 3) changing the appearance and the shelving location of these medications in the pharmacy. **Table 10** provides the list of antipsychotics with sound-alike drug names.[62]

Drug Splitting or Crushing

There are many potential reasons for patients to inquire about antipsychotic medication splitting or crushing before use. One reason is to minimize cost by splitting a higher dosage strength into smaller ones since this strategy will reduce the quantity of pills a patient has to pay for each month. Another common reason is to reduce the size of the pill so that it is easier for the patient to swallow. Some patients might need to crush the medication in order to swallow it or to sprinkle it on food to make it more palatable. There are also patients who require a feeding tube for all nutritious needs. These patients will require crushable medications or liquid medications for the feeding tube. Unfortunately, not all drugs are crushable or can be split. The concerns are that incorrect doses could result from pill splitting and this could lead to loss of drug effectiveness and increased risk for drug toxicity. The following drug formulations are generally not recommended for splitting or crushing: 1) sustained-release medications; 2) enteric-coated medications; 3) buccal tablets; and 4) sublingual tablets.[57]

Patient Education

Patient education is the key to empowering patients to better self-management. They need to learn about their disease and treatment interventions as much as possible. Recognition of side effects and symptom deterioration by the patient is the first step to seeking assistance. Patients should be guided to learn about the signs and symptoms of EPS and other side effects of medications. Many medications potentially cause drowsiness, impaired thinking and impaired motor skills. Patients should be counseled not to drink alcohol. Patients should be advised to be extra cautious with driving automobiles or operating heavy machinery. Patients should be advised by the pharmacist not to discontinue or adjust their medications without consulting their health care providers. If a patient misses a dose of medication, it's important to inform the patient to take the missed pill as soon as he/she remembers it. If the timing is close to the next pill schedule, the patient should skip the dose and take the next dose at the scheduled time. Due to potential drug-drug or drug-herbal interactions, patients should also be cautious and discuss it with their doctors before taking any over-the-counter medications or nutritional/herbal supplements. Patients should also be encouraged to inquire and learn about potential side effects associated with his/her antipsychotics and understand what actions need to be taken should side effects occur. The National Institute of Mental Health is an agency under the United States Department of Health and Human Services. It is also the largest research organization in mental illness and provides a wealth of information for patients, researchers, and health care providers. The educational resources department provides video and audio health literature on mental illnesses, health topics, image library, and publications for patients and family. The web site is available at: www.nimh.nih.gov. Pharmacy technicians should encourage patients to talk with their pharmacist about their medications.

Conclusion

Schizophrenia is one of the top ten causes of disability in developed countries. While schizophrenia affects only 1.1% or 2.2 million U.S. adults at any given time, it accounts for almost 25% of all costs attributed to mental illness. Presenting symptoms are used to diagnose schizophrenia---there is no objective test to provide a definitive diagnosis. Medications are the mainstay of treatment for schizophrenia and improvement in quality of life is the main treatment goal for patients with schizophrenia. Nevertheless, treatment regimens including both pharmacotherapy and psychosocial interventions provide both better patient outcomes compared to pharmacotherapy alone.

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