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Disease Management Project

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Physician's Guide to

Schizophrenia

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In collaboration with

BulletinHealthcare

Cleveland Clinic

Disease Management Project

Dear Healthcare Professional,

Welcome to the *Cleveland Clinic Physician's Guide to Schizophrenia*, an information-packed tool brought to you by the Cleveland Clinic's Disease Management Project (DMP) in collaboration with Bulletin Healthcare, the leading provider of medical news updates to healthcare professionals like yourself.

This guide covers a wide range of topics including signs, symptoms and causes of schizophrenia and its subtypes; treatments involving both pharmacologic and psychosocial therapies; dealing with the various phases of the disease, whether acute, stabilization, or stable; and more. And it was researched and written by leading experts in the field, Drs. Manu Mathews, George E. Tesar, Omar Fattal, and David J. Muzina.

In addition to this guide, you will receive schizophrenia news updates that provide the latest information related to various aspects of and new research on this topic.

We hope you find the *Cleveland Clinic Physician's Guide to Schizophrenia* and the updates helpful, informative, and of value in your efforts to diagnose, treat, and provide positive patient outcomes. We look forward to hearing your thoughts about this content. Please send your comments to diseasemanagement@ccf.org.

William Carey, MD
Editor-in-Chief
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Definition and Etiology

Schizophrenia is a chronic and disabling neuropsychiatric illness possibly best characterized as a syndrome rather than as a single disease entity. The abnormal, often bizarre behavior that typifies schizophrenia is a product of disturbances in cognition, perception, and volition. Clinical manifestations are believed to result from incompletely understood dysregulation of frontotemporal and limbic neurocircuitry. The National Alliance on Mental Illness (NAMI), a patient- and family-oriented self-help group, has designated schizophrenia a brain disorder, emphasizing that schizophrenia is not simply a product of dysfunctional parenting or other psychosocial stressors. Studies have consistently shown, however, that both genetic and nongenetic factors play a role in the origin of schizophrenia.

Prevalence and Risk Factors

The point prevalence of schizophrenia is 1% to 1.5%, a finding that has been fairly constant across time, cultures, races, and continents. It is equally prevalent in men and women. In the United States, about 2.5% of total annual health care expenditures are for schizophrenia. Globally, schizophrenia is a leading cause of disease burden and disability. The lifetime risk of suicide is nearly 7% compared with 14% to 15% for mood disorders such as major depression and bipolar disorder.[1]

The familial nature of the illness has long been recognized. Mounting evidence supports a strong genetic contribution, but genetic factors alone do not fully account for the variance in cause. As with other common illnesses such as hypertension, the risk of developing schizophrenia is a product of multiple genes interacting not only with one another but also with environmental factors. It is also possible that specific risk factors predict occurrence of specific schizophrenia subtypes.

Genetic Risk Factors

Accumulating evidence shows that genetic and neurodevelopmental factors are associated with greater susceptibility to schizophrenia. According to twin and adoption studies, up to 50% of identical (monozygotic) twins share a diagnosis of schizophrenia, compared with about 12% of nonidentical (dizygotic) twins. The strength of genetic factors varies across families, but approximately 10% of a patient's first-degree relatives (parents, siblings, and children) are also schizophrenic, as are 50% of the children of two schizophrenic parents. Reports indicate suggestive linkage on chromosomes 1,2, 3, 5, and 11 and on the X chromosome.

Season of Birth

The birthrate of patients with schizophrenia is 5% to 8% higher worldwide than the birthrate of the general population in the winter and spring months. No proven explanation exists for this phenomenon. A greater likelihood of viral exposure during winter months has been proposed.

Early Developmental Insults

A comparatively high rate of peripartum infant hypoxia has been associated with structural brain abnormalities (e.g., increased ventricular and decreased hippocampal volumes) in schizophrenic patients and their nonschizophrenic siblings.

Other Factors

Population density, industrialization, emigration, and low socioeconomic status at birth have been proposed as possible influences on the development of schizophrenia.

Pathophysiology and Natural History

Gross inspection of the schizophrenic brain reveals no abnormalities. Modern neuroimaging techniques, however, including computed tomography (CT), magnetic resonance imaging (MRI), functional MRI, and positron emission tomography, demonstrate evidence of nonspecific structural and metabolic abnormalities in the frontotemporal cortices, especially in the prefrontal areas and periventricular limbic structures of the schizophrenic brain. There have been some correlates of gray matter changes in the left dorsolateral prefrontal cortex in patients with predominantly negative symptoms. Detailed postmortem analysis of protein profiles and metabolic patterns in the brains of schizophrenic patients point to mitochondrial dysfunction as a distinctive feature.[2]

Neural transmission has long been an object of investigation in schizophrenia. The first agents to demonstrate promise in the pharmacologic control of schizophrenia were recognized to have dopamine-blocking properties. Several neurotransmitter systems have been implicated, but the primary focus has been on dopamine and the brain structures that are high in its content (substantia nigra, ventral tegmentum, mesolimbic structures, and the tuberoinfundibular system). Five dopamine receptor subtypes (D_1 through D_5) have been identified. Blockade of the D_2 receptor appears to have the greatest relevance to the antipsychotic efficacy as well as adverse effects of neuroleptic drugs. The site of D_2-receptor blockade is also relevant to its benefits and adverse effects. Extrapyramidal symptoms can be attributed to D_2-receptor blockade in the substantia nigra and ventral tegmentum, positive symptom suppression to D_2 blockade in mesolimbic structures, and hyperprolactinemia to D_2 blockade in the tuberoinfundibular structures (dopamine is a prolactin-inhibiting factor). The relationship to schizophrenia of serotonin, glutamate, gamma-aminobutyrate, neurotensin, and their relevant receptors is also under investigation.

Signs and Symptoms

Although not described as a separate entity in Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5),[2] acute psychosis refers to a symptom complex that includes disturbance of thought processes and behavior. The presence of psychotic symptoms usually indicates an underlying organic or psychiatric condition. Disruption of thought processes, hallucinations, delusions, agitation, and rapid deterioration in behavior are some of the common manifestations of acute psychosis. Acute psychosis can be a feature of schizophrenia, but the diagnosis of schizophrenia requires the fulfillment of a variety of other diagnostic criteria.

The median age at onset for the first psychotic episode of schizophrenia is the early to mid-20s for men and the late 20s for women. A prodromal phase that lasts months to years can precede the first psychotic episode. Acute psychosis, the hallmark of the acute phase, follows the prodrome insidiously or occurs abruptly and sometimes explosively. The natural history without treatment (and sometimes with) is for symptoms to wax and wane, punctuated by recurrent episodes of acute psychosis. The pattern of symptoms can change over time, with progressive deterioration of function and cognition in some instances and progressive improvement of psychotic symptoms and function in others. Full recovery is uncommon, especially if the illness has been present for some years. Comorbid substance abuse is common, prolongs the illness, and contributes to treatment resistance.

The prodromal phase of schizophrenia is characterized by social avoidance, emotional flattening, eccentricity or magical thinking, idiosyncratic speech, and peculiarities of attitude and behavior that fail to meet criteria for a specific psychiatric illness. Prodromal symptoms that suggest social anxiety, panic, obsessive-compulsive or major depressive disorder, and antisocial behavior or substance misuse often lead to early misdiagnosis and unsuccessful treatment efforts.

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Factor analysis has identified three main psychotic symptom dimensions in schizophrenia: positive, negative, and cognitive. The acute phase of the illness features a predominance of positive psychotic symptoms, whereas the chronic phase is typified by negative and cognitive symptoms. Unlike other types of psychosis, the positive symptoms of schizophrenia are complex and bizarre (i.e., having to do with unreal or unearthly events). Negative symptoms are believed to reflect neuroimaging evidence of reduced metabolic activity in the dorsolateral prefrontal cortex. Positive symptoms might represent abnormal temporal lobe activity. Characteristic features of positive, negative, and cognitive symptoms are outlined in Box 1.

Box 1. Schizophrenia Symptoms and Symptom Dimensions

Positive*

- Hallucinations (typically auditory but also visual)
- Delusions (paranoid delusions, nihilistic delusions, delusions of control)
- Unusual behavior (stereotypies, mannerisms)

Negative†

- Reduced emotional (affective‡‡) range
- Diminished speech production (poverty of speech)
- Loss of interest (anhedonia‡)
- Loss of drive, initiative (apathy, abulia‡)
- Indecisiveness (ambivalence‡)

Cognitive†

- Poor attention
- Working memory impairment
- Formal thought disorder (tangential thinking, loose associations)§
- Concrete thinking and impaired abstraction
- Executive function deficits¶

* Typically bizarre (i.e., unreal, other-worldly, or impossible).

† Negative and cognitive symptoms of schizophrenia correlate with neuroimaging evidence of dorsolateral prefrontal cortex dysfunction.

‡ These are the 4 As of Bleuler.

§ Formal thought disorder (a disorder of the form of thought) is also considered a positive symptom.

¶ Executive functions are the ability to initiate, regulate, plan, and sequence activities. The negative symptoms (apathy, indecision) can represent impaired executive functions.

Diagnosis

Accurate diagnosis of schizophrenia is often challenging because symptoms are nonspecific and progression to full illness is gradual. Relevant signs and symptoms must be present for at least 6 months before a diagnosis of schizophrenia can be made. Acute psychosis is a necessary but insufficient criterion for diagnosing schizophrenia. The diagnostic criteria for schizophrenia are symptomatic, functional, and time based, and they require exclusion of both medical and other psychiatric disorders that can mimic schizophrenia. Schizophrenia is largely a diagnosis of exclusion. The DSM-5 diagnostic criteria for schizophrenia require that two or more of the following be present for a significant portion of time during a 1-month period: delusions, hallucinations, disorganized speech, grossly disorganized or catatonic behavior, and negative symptoms (Box 1).[2] At least one of the two symptoms must be delusions, hallucinations, or disorganized speech. The primary symptoms are rated based on their current severity (defined as most severe in the past 7 days) on a 5 point scale ranging from 0 (not present) to 4 (present and severe).

Schizophrenia also has subtypes defined exclusively by symptom predominance. Their validity remains controversial.

DSM-5 includes two prominent changes to the diagnostic criteria for schizophrenia: 1) elimination of the need to fulfill just one symptom in Criterion A if the patient has bizarre delusions and schneiderian first rank auditory hallucinations and 2) the adoption of a dimensional approach to rating severity.[2]

Differential Diagnosis

If symptoms are not specific and signs and symptoms do not last for 6 months as required for diagnosing schizophrenia, the clinician is obliged to eliminate other important diagnostic considerations. These include psychiatric disorders, substance use, and general medical disorders (Boxes 2 and 3).

Box 2. Psychiatric and Substance Use Disorders that Can Cause Acute Psychosis[9]

Psychiatric

Bipolar disorder

Major depression with psychotic features

Schizophrenia

Schizoaffective disorder

Schizophreniform disorders

Brief psychotic disorder

Factitious disorder with psychological signs and symptoms

Side effect of antidepressant medications

Drug Abuse

Drug use
- Hallucinogens (PCP, LSD, LSD flashbacks)
- Amphetamine psychosis
- Marijuana use (with panic reactions)

Drug withdrawal
- Alcohol
- Opiates
- Sedative-hypnotic agents (barbiturates, benzodiazepines); LSD, lysergic acid diethylamide; PCP, phencyclidine.

This is the **HAT** that he wore on the day that he went to the **GAME** that made an afternoon **SPECIAL** for him and his brother.

INDICATION

FANAPT is an atypical antipsychotic agent indicated for the treatment of schizophrenia in adults. In choosing among treatments, prescribers should consider the ability of FANAPT to prolong the QT interval and the use of other drugs first. Prescribers should also consider the need to titrate FANAPT slowly to avoid orthostatic hypotension, which may lead to delayed effectiveness compared to some other drugs that do not require similar titration.

IMPORTANT SAFETY INFORMATION

WARNING: INCREASED MORTALITY IN ELDERLY PATIENTS WITH DEMENTIA-RELATED PSYCHOSIS
Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. Analysis of seventeen placebo-controlled trials (modal duration 10 weeks), largely in patients taking atypical antipsychotic drugs, revealed a risk of death in the drug-treated patients of between 1.6 to 1.7 times the risk of death in placebo-treated patients. Over the course of a typical 10-week controlled trial, the rate of death in drug-treated patients was about 4.5%, compared to a rate of about 2.6% in the placebo group. Although the causes of death were varied, most of the deaths appeared to be either cardiovascular (e.g., heart failure, sudden death) or infectious (e.g., pneumonia) in nature. Observational studies suggest that, similar to atypical antipsychotic drugs, treatment with conventional antipsychotic drugs may increase mortality. The extent to which the findings of increased mortality in observational studies may be attributed to the antipsychotic drug as opposed to some characteristic(s) of the patients is not clear. FANAPT is not approved for the treatment of patients with dementia-related psychosis.

Consider FANAPT for your patients in need of an improvement in overall schizophrenia symptoms

Efficacy

- FANAPT improved overall symptoms in 2 clinical trials, as measured by the PANSS (4-week trial) and the BPRS (6-week trial)[1]

Drug-induced Akathisia

- Incidence of drug-induced akathisia was similar to placebo[1*]

Drug-induced EPS

- Incidence of drug-induced EPS was similar to placebo[1*]

Tolerability

- Discontinuation rates due to adverse events were similar for FANAPT (5%) and placebo (5%)[1*]

  The most common adverse reactions were dizziness, dry mouth, fatigue, nasal congestion, somnolence, tachycardia, orthostatic hypotension, and weight increase.[1*]

Metabolics

- Mean change in weight from baseline at end point for FANAPT patients was 2.1 kg across all short-term and long-term trials[1†]

- The majority of patients taking FANAPT 24 mg/day did not experience a shift from normal to high in fasting lipid measurements in a 4-week study[1]

  Undesirable alterations in lipids have been observed in patients treated with atypical antipsychotics.

*Based on pooled data from 4 placebo-controlled, 4- or 6-week, fixed- or flexible-dose studies.

†Pooled data from 4 placebo-controlled, fixed- or flexible-dose studies show a change from baseline in body weight of 2.0 kg with FANAPT 10 to 16 mg/day (n=481), 2.7 kg with FANAPT 20 to 24 mg/day (n=391), and -0.1 kg with placebo (n=576).

BPRS, Brief Psychiatric Rating Scale; EPS, extrapyramidal symptoms; PANSS, Positive and Negative Syndrome Scale.

Atypical antipsychotic drugs have been associated with metabolic changes that may increase cardiovascular/cerebrovascular risk. These metabolic changes include hyperglycemia, dyslipidemia, and body weight gain. While all atypical antipsychotic drugs have been shown to produce some metabolic changes, each drug in the class has its own specific risk profile.

*Please see additional Important Safety Information and brief summary of Prescribing Information, including **Boxed WARNING,** on adjacent pages.*

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IMPORTANT SAFETY INFORMATION

> **WARNING: INCREASED MORTALITY IN ELDERLY PATIENTS WITH DEMENTIA-RELATED PSYCHOSIS**
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> **Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. Analysis of seventeen placebo-controlled trials (modal duration 10 weeks), largely in patients taking atypical antipsychotic drugs, revealed a risk of death in the drug-treated patients of between 1.6 to 1.7 times the risk of death in placebo-treated patients. Over the course of a typical 10-week controlled trial, the rate of death in drug-treated patients was about 4.5%, compared to a rate of about 2.6% in the placebo group. Although the causes of death were varied, most of the deaths appeared to be either cardiovascular (e.g., heart failure, sudden death) or infectious (e.g., pneumonia) in nature. Observational studies suggest that, similar to atypical antipsychotic drugs, treatment with conventional antipsychotic drugs may increase mortality. The extent to which the findings of increased mortality in observational studies may be attributed to the antipsychotic drug as opposed to some characteristic(s) of the patients is not clear. FANAPT is not approved for the treatment of patients with dementia-related psychosis.**

Contraindications: FANAPT is contraindicated in individuals with a known hypersensitivity reaction to the product. Reactions have included pruritus and urticaria.

Cerebrovascular Adverse Events, Including Stroke: In placebo-controlled trials with risperidone, aripiprazole, and olanzapine in elderly patients with dementia, there was a higher incidence of cerebrovascular adverse events (cerebrovascular accidents and transient ischemic attacks) including fatalities compared to placebo-treated patients. FANAPT is not approved for treatment of patients with dementia-related psychosis.

QT Prolongation: FANAPT was associated with QTc prolongation of 9 msec at an iloperidone dose of 12 mg twice daily. The effect of FANAPT on the QT interval was augmented by the presence of CYP450 2D6 or 3A4 metabolic inhibition (e.g., paroxetine 20 mg once daily and ketoconazole 200 mg twice daily, respectively). Under conditions of metabolic inhibition for both 2D6 and 3A4, FANAPT 12 mg twice daily was associated with a mean QTcF increase from baseline of about 19 msec. No cases of torsades de pointes or other severe cardiac arrhythmias were observed during the premarketing clinical program. FANAPT should be avoided in combination with other drugs that are known to prolong QTc. FANAPT should also be avoided in patients with congenital long QT syndrome and in patients with history of cardiac arrhythmias, and in circumstances that may increase risk of torsades de pointes and/or sudden death in association with use of drugs that prolong the QTc interval. Use caution and consider dose modification. Patients being considered for FANAPT treatment who are at risk for significant electrolyte disturbances should have baseline serum potassium and magnesium measurements with periodic monitoring. FANAPT should be discontinued in patients who are found to have persistent QTc measurements >500 msec.

Neuroleptic Malignant Syndrome (NMS): NMS, a potentially fatal symptom complex, has been reported in association with administration of antipsychotic drugs, including FANAPT. NMS can cause hyperpyrexia, muscle rigidity, altered mental status, irregular pulse or blood pressure, tachycardia, diaphoresis, and cardiac dysarrhythmia. Additional signs may include elevated creatine phosphokinase, myoglobinuria (rhabdomyolysis), and acute renal failure. Management should include immediate discontinuation of the antipsychotic drugs and other drugs not essential to concurrent therapy, intensive symptomatic treatment and medical monitoring, and treatment of any concomitant serious medical problems. If antipsychotic treatment is required after recovery from NMS, reintroduction should be carefully considered and patient should be carefully monitored.

Tardive Dyskinesia (TD): Risk of developing tardive dyskinesia, and the likelihood that it will become irreversible, may increase as the duration of treatment and the total cumulative dose increases. However, the syndrome can develop, although much less commonly, after relatively brief treatment periods at low doses. Prescribing should be consistent with the need to minimize TD. If signs and symptoms appear, drug discontinuation should be considered.

Metabolic Changes: Atypical antipsychotic drugs have been associated with metabolic changes that may increase cardiovascular/cerebrovascular risk. These metabolic changes include hyperglycemia, dyslipidemia, and body weight gain. While all atypical antipsychotic drugs have been shown to produce some metabolic changes, each drug in the class has its own specific risk profile.

Hyperglycemia and Diabetes: Hyperglycemia, in some cases extreme and associated with ketoacidosis or hyperosmolar coma or death, has been reported in patients treated with atypical antipsychotics including FANAPT. Patients with an established diagnosis of, or with risk factors for, diabetes mellitus who are starting treatment with atypical antipsychotics should undergo fasting blood glucose testing at the beginning of treatment and periodically during treatment. Any patient treated with atypical antipsychotics should be monitored for symptoms of hyperglycemia including polydipsia, polyuria, polyphagia, and weakness. Patients who develop symptoms of hyperglycemia during treatment with atypical antipsychotics should undergo fasting blood glucose testing. In some cases, hyperglycemia has resolved when the atypical antipsychotic was discontinued; however, some patients required continuation of antidiabetic treatment despite discontinuation of the antipsychotic.

Dyslipidemia: Undesirable alterations in lipids have been observed in patients treated with atypical antipsychotics.

Weight Gain: Weight gain has been observed with atypical antipsychotic use. Clinical monitoring of weight is recommended.

Seizures: As with other antipsychotics, FANAPT should be used cautiously in patients with a history of seizures or with conditions that potentially lower seizure threshold, e.g., Alzheimer's dementia.

Orthostatic Hypotension and Syncope: FANAPT must be titrated from a low starting dose to avoid orthostatic hypotension. FANAPT can induce orthostatic hypotension associated with dizziness, tachycardia, and syncope. Therefore FANAPT must be titrated as directed. Dose increases to reach the target range of 6-12 mg twice daily (12-24 mg/day) may be made with daily dosage adjustments not to exceed 2 mg twice daily (4 mg/day). The maximum recommended dose is 12 mg twice daily (24 mg/day). Control of symptoms may be delayed during the first 1 to 2 weeks of treatment. FANAPT should be used with caution in patients with known cardiovascular disease, cerebrovascular disease, or conditions that predispose the patient to hypotension. Monitoring of orthostatic vital signs should be considered in patients who are vulnerable to hypotension.

Leukopenia, Neutropenia, and Agranulocytosis: In clinical trial and postmarketing experience with antipsychotic agents, events of leukopenia/neutropenia have been reported temporally. Agranulocytosis (including death) has also been reported. Patients with a preexisting low white blood cell count or a history of drug-induced leukopenia/neutropenia should have their complete blood count (CBC) monitored frequently during the first few months of therapy and should discontinue FANAPT at the first sign of a decline in WBC in the absence of other causative factors.

Hyperprolactinemia: As with other drugs that antagonize dopamine D2 receptors, FANAPT elevates prolactin levels. Galactorrhea, amenorrhea, gynecomastia, and impotence have been reported with prolactin-elevating compounds.

Body Temperature Regulation: Appropriate care is advised when prescribing FANAPT for patients who will be experiencing conditions which may contribute to an elevation in core body temperature, e.g., exercising strenuously, exposure to extreme heat, receiving concomitant medication with anticholinergic activity, or being subject to dehydration.

Dysphagia: Esophageal dysmotility and aspiration have been associated with antipsychotic drug use. Aspiration pneumonia is a common cause of morbidity and mortality in elderly patients, in particular those with advanced Alzheimer's dementia. FANAPT and other antipsychotic drugs should be used cautiously in patients at risk for aspiration pneumonia.

Suicide: The possibility of a suicide attempt is inherent in psychotic illness, and close supervision of high-risk patients should accompany drug therapy. Prescriptions for FANAPT should be written for the smallest quantity of tablets in order to reduce the risk of overdose.

Priapism: Three cases of priapism have been reported in the premarketing FANAPT program. Severe priapism may require surgical intervention.

Cognitive and Motor Impairment: FANAPT, like other antipsychotics, has the potential to impair judgment, thinking, or motor skills. Patients should be cautioned about operating hazardous machinery, including automobiles, until they are reasonably certain that therapy with FANAPT does not affect them adversely.

Commonly observed adverse events: Commonly observed adverse reactions (incidence ≥5% and twofold greater than placebo) were: dizziness, dry mouth, fatigue, nasal congestion, orthostatic hypotension, somnolence, tachycardia, and weight increase.

Specific Populations

Pregnancy: FANAPT is Pregnancy Category C.

Hepatic Impairment: FANAPT is not recommended for patients with hepatic impairment.

Drug Interactions: Given the primary CNS effects of FANAPT, caution should be used when it is taken in combination with other centrally acting drugs and alcohol. FANAPT has the potential to enhance the effect of certain antihypertensive agents. Coadministration of FANAPT with potential CYP2D6 inhibitors (e.g., fluoxetine, paroxetine) and potential CYP3A4 inhibitors (e.g., ketoconazole) should be done with caution. FANAPT dose should be reduced by one-half. Cautiously approach coadministration of drugs mainly eliminated via CYP3A4 with FANAPT.

Fanapt®
(iloperidone) tablets

1 mg, 2 mg, 4 mg, 6 mg, 8 mg, 10 mg, 12 mg

*Please see brief summary of Prescribing Information, including **Boxed WARNING**, on adjacent pages.*

FANAPT® (iloperidone) tablets
Initial U.S. Approval: 2009
BRIEF SUMMARY: Please see package insert for full prescribing information.

**WARNING: INCREASED MORTALITY IN ELDERLY PATIENTS
WITH DEMENTIA-RELATED PSYCHOSIS**

Elderly patients with dementia-related psychosis treated with antipsy-chotic drugs are at an increased risk of death. Analysis of seventeen placebo-controlled trials (modal duration 10 weeks), largely in patients taking atypical antipsychotic drugs, revealed a risk of death in the drug-treated patients of between 1.6 to 1.7 times the risk of death in placebo-treated patients. Over the course of a typical 10-week controlled trial, the rate of death in drug-treated patients was about 4.5%, compared to a rate of about 2.6% in the placebo group. Although the causes of death were varied, most of the deaths appeared to be either cardiovascular (e.g., heart failure, sudden death) or infectious (e.g., pneumonia) in nature.

Observational studies suggest that, similar to atypical antipsychotic drugs, treatment with conventional antipsychotic drugs may increase mor-tality. The extent to which the findings of increased mortality in observa-tional studies may be attributed to the antipsychotic drug as opposed to some characteristic(s) of the patients is not clear. FANAPT is not approved for the treatment of patients with Dementia-Related Psychosis. [see Warn-ings and Precautions (5.1)]

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1 INDICATIONS AND USAGE
FANAPT® tablets are indicated for the treatment of adults with schizophre-nia. Efficacy was established in two short-term (4- and 6-week) placebo- and active-controlled studies of adult patients with schizophrenia [see Clin-ical Studies (14) in the full prescribing information].

When deciding among the alternative treatments available for this condi-tion, the prescriber should consider the finding that FANAPT is associated with prolongation of the QTc interval [see Warnings and Precautions (5.2)]. Prolongation of the QTc interval is associated in some other drugs with the ability to cause torsade de pointes-type arrhythmia, a potentially fatal poly-morphic ventricular tachycardia which can result in sudden death. In many cases this would lead to the conclusion that other drugs should be tried first. Whether FANAPT will cause torsade de pointes or increase the rate of sudden death is not yet known.

Patients must be titrated to an effective dose of FANAPT. Thus, control of symptoms may be delayed during the first 1 to 2 weeks of treatment com-pared to some other antipsychotic drugs that do not require a similar titration. Prescribers should be mindful of this delay when selecting an antipsychotic drug for the treatment of schizophrenia [see Dosage and Administration (2.1) and Clinical Studies (14) in the full prescribing information].

The effectiveness of FANAPT in long-term use, that is, for more than 6 weeks, has not been systematically evaluated in controlled trials. Therefore, the physician who elects to use FANAPT for extended periods should periodi-cally re-evaluate the long-term usefulness of the drug for the individual patient [see Dosage and Administration (2.3)].

2 DOSAGE AND ADMINISTRATION
2.1 Usual Dose
FANAPT must be titrated slowly from a low starting dose to avoid ortho-static hypotension due to its alpha-adrenergic blocking properties. The recommended starting dose for FANAPT tablets is 1 mg twice daily. Dose increases to reach the target range of 6-12 mg twice daily (12-24 mg/day) may be made with daily dosage adjustments not to exceed 2 mg twice daily (4 mg/day). The maximum recommended dose is 12 mg twice daily (24 mg/day). FANAPT doses above 24 mg/day have not been systematically evaluated in the clinical trials. Efficacy was demonstrated with FANAPT in a dose range of 6 to 12 mg twice daily. Prescribers should be mindful of the fact that patients need to be titrated to an effective dose of FANAPT. Thus, control of symptoms may be delayed during the first 1 to 2 weeks of treat-ment compared to some other antipsychotic drugs that do not require simi-lar titration. Prescribers should also be aware that some adverse effects associated with FANAPT use are dose related.

FANAPT can be administered without regard to meals.

2.2 Dosage in Special Populations
Dosage adjustments are not routinely indicated on the basis of age, gender, race, or renal impairment status [see Use in Specific Populations (8.6, 8.7)].

Dosage adjustment for patients taking FANAPT concomitantly with potential CYP2D6 inhibitors: FANAPT dose should be reduced by one-half when administered concomitantly with strong CYP2D6 inhibitors such as fluoxetine or paroxetine. When the CYP2D6 inhibitor is withdrawn from the combination therapy, FANAPT dose should then be increased to where it was before [see Drug Interactions (7.1)].

Dosage adjustment for patients taking FANAPT concomitantly with potential CYP3A4 inhibitors: FANAPT dose should be reduced by one-half when administered concomitantly with strong CYP3A4 inhibitors such as ketoconazole or clarithromycin. When the CYP3A4 inhibitor is withdrawn from the combination therapy, FANAPT dose should be increased to where it was before [see Drug Interactions (7.1)].

Dosage adjustment for patients taking FANAPT who are poor metabolizers of CYP2D6: FANAPT dose should be reduced by one-half for poor metabo-lizers of CYP2D6 [see Pharmacokinetics (12.3) in the full prescribing information].

Hepatic Impairment: FANAPT is not recommended for patients with hepatic impairment.

2.3 Maintenance Treatment
Although there is no body of evidence available to answer the question of how long the patient treated with FANAPT should be maintained, it is gener-ally recommended that responding patients be continued beyond the acute response. Patients should be periodically reassessed to determine the need for maintenance treatment.

2.4 Reinitiation of Treatment in Patients Previously Discontinued
Although there are no data to specifically address re-initiation of treatment, it is recommended that the initiation titration schedule be followed when-ever patients have had an interval off FANAPT of more than 3 days.

2.5 Switching from Other Antipsychotics
There are no specific data to address how patients with schizophrenia can be switched from other antipsychotics to FANAPT or how FANAPT can be used concomitantly with other antipsychotics. Although immediate discon-tinuation of the previous antipsychotic treatment may be acceptable for some patients with schizophrenia, more gradual discontinuation may be most appropriate for others. In all cases, the period of overlapping anti-psychotic administration should be minimized.

4 CONTRAINDICATIONS
FANAPT is contraindicated in individuals with a known hypersensitivity reaction to the product. Reactions have included pruritus and urticaria.

5 WARNINGS AND PRECAUTIONS
5.1 Increased Risks in Elderly Patients with Dementia-Related Psychosis
Increased Mortality
Elderly patients with dementia-related psychosis treated with atypical antipsychotic drugs are at an increased risk of death compared to placebo. FANAPT is not approved for the treatment of patients with dementia-related psychosis [see Boxed Warning].

Cerebrovascular Adverse Events, Including Stroke
In placebo-controlled trials with risperidone, aripiprazole, and olanzapine in elderly patients with dementia, there was a higher incidence of cerebrovas-cular adverse events (cerebrovascular accidents and transient ischemic attacks) including fatalities compared to placebo-treated patients. FANAPT is not approved for the treatment of patients with dementia-related psy-chosis [see Boxed Warning].

5.2 QT Prolongation
In an open-label QTc study in patients with schizophrenia or schizoaffective disorder (n=160), FANAPT was associated with QTc prolongation of 9 msec at an iloperidone dose of 12 mg twice daily. The effect of FANAPT on the QT interval was augmented by the presence of CYP450 2D6 or 3A4 metabolic inhibition (paroxetine 20 mg once daily and ketoconazole 200 mg twice daily, respectively). Under conditions of metabolic inhibition for both 2D6 and 3A4, FANAPT 12 mg twice daily was associated with a mean QTcF increase from baseline of about 19 msec.

No cases of torsade de pointes or other severe cardiac arrhythmias were observed during the pre-marketing clinical program.

The use of FANAPT should be avoided in combination with other drugs that are known to prolong QTc including Class 1A (e.g., quinidine, procainamide) or Class III (e.g., amiodarone, sotalol) antiarrhythmic medications, antipsy-chotic medications (e.g., chlorpromazine, thioridazine), antibiotics (e.g., gatifloxacin, moxifloxacin), or any other class of medications known to pro-long the QTc interval (e.g., pentamidine, levomethadyl acetate, methadone). FANAPT should also be avoided in patients with congenital long QT syn-drome and in patients with a history of cardiac arrhythmias.

Certain circumstances may increase the risk of torsade de pointes and/or sudden death in association with the use of drugs that prolong the QTc interval, including (1) bradycardia; (2) hypokalemia or hypomagnesemia; (3) concomitant use of other drugs that prolong the QTc interval; and (4) presence of congenital prolongation of the QT interval; (5) recent acute myocardial infarction; and/or (6) uncompensated heart failure.

Caution is warranted when prescribing FANAPT with drugs that inhibit FANAPT metabolism [see Drug Interactions (7.1)], and in patients with reduced activity of CYP2D6 [see Clinical Pharmacology (12.3) in the full prescribing information].

It is recommended that patients being considered for FANAPT treatment who are at risk for significant electrolyte disturbances have baseline serum potassium and magnesium measurements with periodic monitoring. Hypokalemia (and/or hypomagnesemia) may increase the risk of QT prolon-gation and arrhythmia. FANAPT should be avoided in patients with histories of significant cardiovascular illness, e.g., QT prolongation, recent acute myocardial infarction, uncompensated heart failure, or cardiac arrhythmia. FANAPT should be discontinued in patients who are found to have persistent QTc measurements >500 ms.

If patients taking FANAPT experience symptoms that could indicate the occurrence of cardiac arrhythmias, e.g., dizziness, palpitations, or syncope, the prescriber should initiate further evaluation, including cardiac monitoring.

5.3 Neuroleptic Malignant Syndrome (NMS)

A potentially fatal symptom complex sometimes referred to as Neuroleptic Malignant Syndrome (NMS) has been reported in association with administration of antipsychotic drugs, including FANAPT. Clinical manifestations include hyperpyrexia, muscle rigidity, altered mental status (including catatonic signs) and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis, and cardiac dysrhythmia). Additional signs may include elevated creatine phosphokinase, myoglobinuria (rhabdomyolysis), and acute renal failure.

The diagnostic evaluation of patients with this syndrome is complicated. In arriving at a diagnosis, it is important to identify cases in which the clinical presentation includes both serious medical illness (e.g., pneumonia, systemic infection, etc.) and untreated or inadequately treated extrapyramidal signs and symptoms (EPS). Other important considerations in the differential diagnosis include central anticholinergic toxicity, heat stroke, drug fever, and primary central nervous system (CNS) pathology.

The management of this syndrome should include: (1) immediate discontinuation of the antipsychotic drugs and other drugs not essential to concurrent therapy, (2) intensive symptomatic treatment and medical monitoring, and (3) treatment of any concomitant serious medical problems for which specific treatments are available. There is no general agreement about specific pharmacological treatment regimens for NMS.

If a patient requires antipsychotic drug treatment after recovery from NMS, the potential reintroduction of drug therapy should be carefully considered. The patient should be carefully monitored, since recurrences of NMS have been reported.

5.4 Tardive Dyskinesia

Tardive dyskinesia is a syndrome consisting of potentially irreversible, involuntary, dyskinetic movements, which may develop in patients treated with antipsychotic drugs. Although the prevalence of the syndrome appears to be highest among the elderly, especially elderly women, it is impossible to rely on prevalence estimates to predict, at the inception of antipsychotic treatment, which patients are likely to develop the syndrome. Whether antipsychotic drug products differ in their potential to cause tardive dyskinesia is unknown.

The risk of developing tardive dyskinesia and the likelihood that it will become irreversible are believed to increase as the duration of treatment and the total cumulative dose of antipsychotic administered increases. However, the syndrome can develop, although much less commonly, after relatively brief treatment periods at low doses.

There is no known treatment for established cases of tardive dyskinesia, although the syndrome may remit, partially or completely, if antipsychotic treatment is withdrawn. Antipsychotic treatment itself, however, may suppress (or partially suppress) the signs and symptoms of the syndrome and thereby may possibly mask the underlying process. The effect that symptomatic suppression has upon the long-term course of the syndrome is unknown.

Given these considerations, FANAPT should be prescribed in a manner that is most likely to minimize the occurrence of tardive dyskinesia. Chronic antipsychotic treatment should generally be reserved for patients who suffer from a chronic illness that (1) is known to respond to antipsychotic drugs, and (2) for whom alternative, equally effective, but potentially less harmful treatments are not available or appropriate. In patients who do require chronic treatment, the smallest dose and the shortest duration of treatment producing a satisfactory clinical response should be sought. The need for continued treatment should be reassessed periodically.

If signs and symptoms of tardive dyskinesia appear in a patient on FANAPT, drug discontinuation should be considered. However, some patients may require treatment with FANAPT despite the presence of the syndrome.

5.5 Metabolic Changes

Atypical antipsychotic drugs have been associated with metabolic changes that may increase cardiovascular/cerebrovascular risk. These metabolic changes include hyperglycemia, dyslipidemia, and body weight gain *[see Patient Counseling Information (17.3) in the full prescribing information]*. While all atypical antipsychotic drugs have been shown to produce some metabolic changes, each drug in the class has its own specific risk profile.

Hyperglycemia and Diabetes Mellitus

Hyperglycemia, in some cases extreme and associated with ketoacidosis or hyperosmolar coma or death, has been reported in patients treated with atypical antipsychotics including FANAPT. Assessment of the relationship between atypical antipsychotic use and glucose abnormalities is complicated by the possibility of an increased background risk of diabetes mellitus in patients with schizophrenia and the increasing incidence of diabetes mellitus in the general population. Given these confounders, the relationship between atypical antipsychotic use and hyperglycemia-related adverse events is not completely understood. However, epidemiological studies suggest an increased risk of treatment-emergent hyperglycemia-related adverse events in patients treated with the atypical antipsychotics included in these studies. Because FANAPT was not marketed at the time these studies were performed, it is not known if FANAPT is associated with this increased risk.

Patients with an established diagnosis of diabetes mellitus who are started on atypical antipsychotics should be monitored regularly for worsening of glucose control. Patients with risk factors for diabetes mellitus (e.g., obesity,

family history of diabetes) who are starting treatment with atypical antipsychotics should undergo fasting blood glucose testing at the beginning of treatment and periodically during treatment. Any patient treated with atypical antipsychotics should be monitored for symptoms of hyperglycemia including polydipsia, polyuria, polyphagia, and weakness. Patients who develop symptoms of hyperglycemia during treatment with atypical antipsychotics should undergo fasting blood glucose testing. In some cases, hyperglycemia has resolved when the atypical antipsychotic was discontinued; however, some patients required continuation of antidiabetic treatment despite discontinuation of the suspect drug.

Data from a 4-week, fixed-dose study in adult subjects with schizophrenia, in which fasting blood samples were drawn, are presented in Table 1.

Table 1: Change in Fasting Glucose

	Placebo	FANAPT® 24 mg/day
	Mean Change from Baseline (mg/dL)	
	n=114	**n=228**
Serum Glucose Change from Baseline	-0.5	6.6
	Proportion of Patients with Shifts	
Serum Glucose Normal to High (<100 mg/dL to ≥126 mg/dL)	2.5% (2/80)	10.7% (18/169)

Pooled analyses of glucose data from clinical studies including longer term trials are shown in Table 2.

Table 2: Change in Glucose

	Mean Change from Baseline (mg/dL)		
	3-6 months	**6-12 months**	**>12 months**
FANAPT 10-16 mg/day	1.8 (N=773)	5.4 (N=723)	5.4 (N=425)
FANAPT 20-24 mg/day	-3.6 (N=34)	-9.0 (N=31)	-18.0 (N=20)

Dyslipidemia

Undesirable alterations in lipids have been observed in patients treated with atypical antipsychotics.

Data from a placebo-controlled, 4-week, fixed-dose study, in which fasting blood samples were drawn, in adult subjects with schizophrenia are presented in Table 3.

Table 3: Change in Fasting Lipids

	Placebo	FANAPT® 24 mg/day
	Mean Change from Baseline (mg/dL)	
Cholesterol	**n= 114**	**n=228**
Change from baseline	-2.17	8.18
LDL	**n=109**	**n=217**
Change from baseline	-1.41	9.03
HDL	**n= 114**	**n=228**
Change from baseline	-3.35	0.55
Triglycerides	**n= 114**	**n=228**
Change from baseline	16.47	-0.83
	Proportion of Patients with Shifts	
Cholesterol		
Normal to High (<200 mg/dL to ≥240 mg/dL)	1.4% (1/72)	3.6% (5/141)
LDL		
Normal to High (<100 mg/dL to ≥160 mg/dL)	2.4% (1/42)	1.1% (1/90)
HDL		
Normal to Low (≥40 mg/dL to <40 mg/dL)	23.8% (19/80)	12.1% (20/166)
Triglycerides		
Normal to High (<150 mg/dL to ≥200 mg/dL)	8.3% (6/72)	10.1% (15/148)

Pooled analyses of cholesterol and triglyceride data from clinical studies including longer term trials are shown in Tables 4 and 5.

Table 4: Change in Cholesterol

	Mean Change from Baseline (mg/dL)		
	3-6 months	**6-12 months**	**>12 months**
FANAPT 10-16 mg/day	-3.9 (N=783)	-3.9 (N=726)	-7.7 (N=428)
FANAPT 20-24 mg/day	-19.4 (N=34)	-23.2 (N=31)	-19.4 (N=20)

Table 5: Change in Triglycerides

	Mean Change from Baseline (mg/dL)		
	3-6 months	**6-12 months**	**>12 months**
FANAPT 10-16 mg/day	-8.9 (N=783)	-8.9 (N=726)	-17.7 (N=428)
FANAPT 20-24 mg/day	-26.6 (N=34)	-35.4 (N=31)	-17.7 (N=20)

Weight Gain

Weight gain has been observed with atypical antipsychotic use. Clinical monitoring of weight is recommended.

Across all short- and long-term studies, the overall mean change from baseline at endpoint was 2.1 kg.

Changes in body weight (kg) and the proportion of subjects with ≥7% gain in body weight from four placebo-controlled, 4- or 6-week, fixed- or flexible-dose studies in adult subjects are presented in Table 6.

Table 6: Change in Body Weight

	Placebo	FANAPT 10-16 mg/day	FANAPT 20-24 mg/day
	n=576	n=481	n=391
Weight (kg) Change from Baseline	-0.1	2.0	2.7
Weight Gain ≥7% increase from Baseline	4%	12%	18%

5.6 Seizures

In short-term placebo-controlled trials (4- to 6-weeks), seizures occurred in 0.1% (1/1344) of patients treated with FANAPT compared to 0.3% (2/587) on placebo. As with other antipsychotics, FANAPT should be used cautiously in patients with a history of seizures or with conditions that potentially lower the seizure threshold, e.g., Alzheimer's dementia. Conditions that lower the seizure threshold may be more prevalent in a population of 65 years or older.

5.7 Orthostatic Hypotension and Syncope

FANAPT can induce orthostatic hypotension associated with dizziness, tachycardia, and syncope. This reflects its alpha1-adrenergic antagonist properties. In double-blind placebo-controlled short-term studies, where the dose was increased slowly, as recommended above, syncope was reported in 0.4% (5/1344) of patients treated with FANAPT, compared with 0.2% (1/587) on placebo. Orthostatic hypotension was reported in 5% of patients given 20-24 mg/day, 3% of patients given 10-16 mg/day, and 1% of patients given placebo. More rapid titration would be expected to increase the rate of orthostatic hypotension and syncope.

FANAPT should be used with caution in patients with known cardiovascular disease (e.g., heart failure, history of myocardial infarction, ischemia, or conduction abnormalities), cerebrovascular disease, or conditions that predispose the patient to hypotension (dehydration, hypovolemia, and treatment with antihypertensive medications). Monitoring of orthostatic vital signs should be considered in patients who are vulnerable to hypotension.

5.8 Leukopenia, Neutropenia and Agranulocytosis

In clinical trial and postmarketing experience, events of leukopenia/neutropenia have been reported temporally related to antipsychotic agents. Agranulocytosis (including fatal cases) has also been reported.

Possible risk factors for leukopenia/neutropenia include preexisting low white blood cell count (WBC) and history of drug induced leukopenia/neutropenia. Patients with a pre-existing low WBC or a history of drug induced leukopenia/neutropenia should have their complete blood count (CBC) monitored frequently during the first few months of therapy and should discontinue FANAPT at the first sign of a decline in WBC in the absence of other causative factors.

Patients with neutropenia should be carefully monitored for fever or other symptoms or signs of infection and treated promptly if such symptoms or signs occur. Patients with severe neutropenia (absolute neutrophil count <1000/mm³) should discontinue FANAPT and have their WBC followed until recovery.

5.9 Hyperprolactinemia

As with other drugs that antagonize dopamine D2 receptors, FANAPT elevates prolactin levels.

Hyperprolactinemia may suppress hypothalamic GnRH, resulting in reduced pituitary gonadotropin secretion. This, in turn, may inhibit reproductive function by impairing gonadal steroidogenesis in both female and male patients. Galactorrhea, amenorrhea, gynecomastia, and impotence have been reported with prolactin-elevating compounds. Long-standing hyperprolactinemia when associated with hypogonadism may lead to decreased bone density in both female and male patients.

Tissue culture experiments indicate that approximately one-third of human breast cancers are prolactin-dependent *in vitro*, a factor of potential importance if the prescription of these drugs is contemplated in a patient with previously detected breast cancer. Mammary gland proliferative changes and increases in serum prolactin were seen in mice and rats treated with FANAPT *[see Nonclinical Toxicology (13.1) in the full prescribing information]*. Neither clinical studies nor epidemiologic studies conducted to date have shown an association between chronic administration of this class of drugs and tumorigenesis in humans; the available evidence is considered too limited to be conclusive at this time.

In a short-term placebo-controlled trial (4-weeks), the mean change from baseline to endpoint in plasma prolactin levels for the FANAPT 24 mg/day-treated group was an increase of 2.6 ng/mL compared to a decrease of 6.3 ng/mL in the placebo-group. In this trial, elevated plasma prolactin levels were observed in 26% of adults treated with FANAPT compared to 12% in the placebo group. In the short-term trials, FANAPT was associated with modest levels of prolactin elevation compared to greater prolactin elevations observed with some other antipsychotic agents. In pooled analysis from clinical studies including longer term trials, in 3210 adults treated with iloperidone, gynecomastia was reported in 2 male subjects (0.1%) compared to 0% in placebo-treated patients, and galactorrhea was reported in 8 female subjects (0.2%) compared to 3 female subjects (0.5%) in placebo-treated patients.

5.10 Body Temperature Regulation

Disruption of the body's ability to reduce core body temperature has been attributed to antipsychotic agents. Appropriate care is advised when prescribing FANAPT for patients who will be experiencing conditions which may contribute to an elevation in core body temperature, e.g., exercising strenuously, exposure to extreme heat, receiving concomitant medication with anticholinergic activity, or being subject to dehydration.

5.11 Dysphagia

Esophageal dysmotility and aspiration have been associated with antipsychotic drug use. Aspiration pneumonia is a common cause of morbidity and mortality in elderly patients, in particular those with advanced Alzheimer's dementia. FANAPT and other antipsychotic drugs should be used cautiously in patients at risk for aspiration pneumonia *[see Boxed Warning]*.

5.12 Suicide

The possibility of a suicide attempt is inherent in psychotic illness, and close supervision of high-risk patients should accompany drug therapy. Prescriptions for FANAPT should be written for the smallest quantity of tablets consistent with good patient management in order to reduce the risk of overdose.

5.13 Priapism

Three cases of priapism were reported in the pre-marketing FANAPT program. Drugs with alpha-adrenergic blocking effects have been reported to induce priapism. FANAPT shares this pharmacologic activity. Severe priapism may require surgical intervention.

5.14 Potential for Cognitive and Motor Impairment

FANAPT, like other antipsychotics, has the potential to impair judgment, thinking or motor skills. In short-term, placebo-controlled trials, somnolence (including sedation) was reported in 11.9% (104/874) of adult patients treated with FANAPT at doses of 10 mg/day or greater versus 5.3% (31/587) treated with placebo. Patients should be cautioned about operating hazardous machinery, including automobiles, until they are reasonably certain that therapy with FANAPT does not affect them adversely.

6 ADVERSE REACTIONS

6.1 Clinical Studies Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trial of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice. The information below is derived from a clinical trial database for FANAPT consisting of 2070 patients exposed to FANAPT at doses of 10 mg/day or greater, for the treatment of schizophrenia. Of these, 806 received FANAPT for at least 6 months, with 463 exposed to FANAPT for at least 12 months. All of these patients who received FANAPT were participating in multiple-dose clinical trials. The conditions and duration of treatment with FANAPT varied greatly and included (in overlapping categories), open-label and double-blind phases of studies, inpatients and outpatients, fixed-dose and flexible-dose studies, and short-term and longer-term exposure.

Adverse reactions during exposure were obtained by general inquiry and recorded by clinical investigators using their own terminology. Consequently, to provide a meaningful estimate of the proportion of individuals experiencing adverse reactions, reactions were grouped in standardized categories using MedDRA terminology.

The stated frequencies of adverse reactions represent the proportions of individuals who experienced a treatment-emergent adverse reaction of the type listed. A reaction was considered treatment emergent if it occurred for the first time or worsened while receiving therapy following baseline evaluation.

The information presented in these sections was derived from pooled data from four placebo-controlled, 4- or 6-week, fixed- or flexible-dose studies in patients who received FANAPT at daily doses within a range of 10 to 24 mg (n=874).

Adverse Reactions Occurring at an Incidence of 2% or More among FANAPT-Treated Patients and More Frequent than Placebo

Table 7 enumerates the pooled incidences of treatment-emergent adverse reactions that were spontaneously reported in four placebo-controlled, 4- or 6-week, fixed- or flexible-dose studies, listing those reactions that occurred in 2% or more of patients treated with FANAPT in any of the dose groups, and for which the incidence in FANAPT-treated patients in any dose group was greater than the incidence in patients treated with placebo.

Table 7: Treatment-Emergent Adverse Reactions in Short-Term, Fixed- or Flexible-Dose, Placebo-Controlled Trials in Adult Patients*

Body System or Organ Class Dictionary-derived Term	Percentage of Patients Reporting Reaction		
	Placebo (N=587)	FANAPT 10-16 mg/day (N=483)	FANAPT 20-24 mg/day (N=391)
Body as a Whole			
Arthralgia	2	3	3
Fatigue	3	4	6
Musculoskeletal Stiffness	1	1	3
Weight Increased	1	1	9
Cardiac Disorders			
Tachycardia	1	3	12
Eye Disorders			
Vision Blurred	2	3	1
Gastrointestinal Disorders			
Nausea	8	7	10
Dry Mouth	1	8	10
Diarrhea	4	5	7
Abdominal Discomfort	1	1	3
Infections			
Nasopharyngitis	3	4	3
Upper Respiratory Tract Infection	1	2	3
Nervous System Disorders			
Dizziness	7	10	20
Somnolence	5	9	15
Extrapyramidal Disorder	4	5	4
Tremor	2	3	3
Lethargy	1	3	1
Reproductive System			
Ejaculation Failure	<1	2	2
Respiratory			
Nasal Congestion	2	5	8
Dyspnea	<1	2	2
Skin			
Rash	2	3	2
Vascular Disorders			
Orthostatic Hypotension	1	3	5
Hypotension	<1	<1	3

*Table includes adverse reactions that were reported in 2% or more of patients in any of the FANAPT dose groups and which occurred at greater incidence than in the placebo group. Figures rounded to the nearest integer.

Dose-Related Adverse Reactions in Clinical Trials
Based on the pooled data from four placebo-controlled, 4- or 6-week, fixed- or flexible-dose studies, adverse reactions that occurred with a greater than 2% incidence in the patients treated with FANAPT, and for which the incidence in patients treated with FANAPT 20-24 mg/day were twice than the incidence in patients treated with FANAPT 10-16 mg/day were: abdominal discomfort, dizziness, hypotension, musculoskeletal stiffness, tachycardia, and weight increased.

Common and Drug-Related Adverse Reactions in Clinical Trials
Based on the pooled data from four placebo-controlled, 4- or 6-week, fixed- or flexible-dose studies, the following adverse reactions occurred in ≥5% incidence in the patients treated with FANAPT and at least twice the placebo rate for at least one dose: dizziness, dry mouth, fatigue, nasal congestion, somnolence, tachycardia, orthostatic hypotension, and weight increased. Dizziness, tachycardia, and weight increased were at least twice as common on 20-24 mg/day as on 10-16 mg/day.

Extrapyramidal Symptoms (EPS) in Clinical Trials
Pooled data from the four placebo-controlled, 4- or 6-week, fixed- or flexible-dose studies provided information regarding treatment-emergent EPS. Adverse event data collected from those trials showed the following rates of EPS-related adverse events as shown in Table 8.

Table 8: Percentage of EPS Compared to Placebo

Adverse Event Term	Placebo (%) (N=587)	FANAPT 10-16 mg/day (%) (N=483)	FANAPT 20-24 mg/day (%) (N=391)
All EPS events	**11.6**	**13.5**	**15.1**
Akathisia	2.7	1.7	2.3
Bradykinesia	0	0.6	0.5
Dyskinesia	1.5	1.7	1.0
Dystonia	0.7	1.0	0.8
Parkinsonism	0	0.2	0.3
Tremor	1.9	2.5	3.1

Adverse Reactions Associated with Discontinuation of Treatment in Clinical Trials
Based on the pooled data from four placebo-controlled, 4- or 6-week, fixed- or flexible-dose studies, there was no difference in the incidence of discontinuation due to adverse events between FANAPT-treated (5%) and placebo-treated (5%) patients. The types of adverse events that led to discontinuation were similar for the FANAPT- and placebo-treated patients.

Demographic Differences in Adverse Reactions in Clinical Trials
An examination of population subgroups in the four placebo-controlled, 4- or 6-week, fixed- or flexible-dose studies did not reveal any evidence of differences in safety on the basis of age, gender or race [see Warnings and Precautions (5.1)].

Laboratory Test Abnormalities in Clinical Trials
There were no differences between FANAPT and placebo in the incidence of discontinuation due to changes in hematology, urinalysis, or serum chemistry.

In short-term placebo-controlled trials (4- to 6-weeks), there were 1.0% (13/1342) iloperidone-treated patients with hematocrit at least one time below the extended normal range during post-randomization treatment, compared to 0.3% (2/585) on placebo. The extended normal range for lowered hematocrit was defined in each of these trials as the value 15% below the normal range for the centralized laboratory that was used in the trial.

Other Reactions During the Pre-marketing Evaluation of FANAPT
The following is a list of MedDRA terms that reflect treatment-emergent adverse reactions in patients treated with FANAPT at multiple doses ≥ 4 mg/day during any phase of a trial with the database of 3210 FANAPT-treated patients. All reported reactions are included except those already listed in Table 7, or other parts of the Adverse Reactions (6) section, those considered in the Warnings and Precautions (5), those reaction terms which were so general as to be uninformative, reactions reported in fewer than 3 patients and which were neither serious nor life-threatening, reactions that are otherwise common as background reactions, and reactions considered unlikely to be drug related. It is important to emphasize that, although the reactions reported occurred during treatment with FANAPT, they were not necessarily caused by it.

Reactions are further categorized by MedDRA system organ class and listed in order of decreasing frequency according to the following definitions: frequent adverse events are those occurring in at least 1/100 patients (only those not listed in Table 7 appear in this listing); infrequent adverse reactions are those occurring in 1/100 to 1/1000 patients; rare events are those occurring in fewer than 1/1000 patients.

Blood and Lymphatic Disorders: Infrequent – anemia, iron deficiency anemia; Rare – leukopenia

Cardiac Disorders: Frequent – palpitations; Rare – arrhythmia, atrioventricular block first degree, cardiac failure (including congestive and acute)

Ear and Labyrinth Disorders: Infrequent – vertigo, tinnitus

Endocrine Disorders: Infrequent – hypothyroidism

Eye Disorders: Frequent - conjunctivitis (including allergic); Infrequent – dry eye, blepharitis, eyelid edema, eye swelling, lenticular opacities, cataract, hyperemia (including conjunctival)

Gastrointestinal Disorders: Infrequent – gastritis, salivary hypersecretion, fecal incontinence, mouth ulceration; Rare - aphthous stomatitis, duodenal ulcer, hiatus hernia, hyperchlorhydria, lip ulceration, reflux esophagitis, stomatitis

General Disorders and Administrative Site Conditions: Infrequent – edema (general, pitting, due to cardiac disease), difficulty in walking, thirst; Rare - hyperthermia

Hepatobiliary Disorders: Infrequent – cholelithiasis

Investigations: Frequent: weight decreased; Infrequent – hemoglobin decreased, neutrophil count increased, hematocrit decreased

Metabolism and Nutrition Disorders: Infrequent – increased appetite, dehydration, hypokalemia, fluid retention

Musculoskeletal and Connective Tissue Disorders: Frequent – myalgia, muscle spasms; Rare – torticollis

Nervous System Disorders: Infrequent – paresthesia, psychomotor hyperactivity, restlessness, amnesia, nystagmus; Rare – restless legs syndrome

Psychiatric Disorders: Frequent – restlessness, aggression, delusion; Infrequent – hostility, libido decreased, paranoia, anorgasmia, confusional state, mania, catatonia, mood swings, panic attack, obsessive-compulsive disorder, bulimia nervosa, delirium, polydipsia psychogenic, impulse-control disorder, major depression

Renal and Urinary Disorders: Frequent – urinary incontinence; Infrequent – dysuria, pollakiuria, enuresis, nephrolithiasis; Rare – urinary retention, renal failure acute

Reproductive System and Breast Disorders: Frequent – erectile dysfunction; Infrequent – testicular pain, amenorrhea, breast pain; Rare – menstruation irregular, gynecomastia, menorrhagia, metrorrhagia, postmenopausal hemorrhage, prostatitis.

Respiratory, Thoracic and Mediastinal Disorders: Infrequent – epistaxis, asthma, rhinorrhea, sinus congestion, nasal dryness; Rare – dry throat, sleep apnea syndrome, dyspnea exertional

6.2 Postmarketing Experience
The following adverse reactions have been identified during postapproval use of Fanapt: retrograde ejaculation. Because these reactions were reported voluntarily from a population of uncertain size, it is not possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

7 DRUG INTERACTIONS

Given the primary CNS effects of FANAPT, caution should be used when it is taken in combination with other centrally acting drugs and alcohol. Due to its α1-adrenergic receptor antagonism, FANAPT has the potential to enhance the effect of certain antihypertensive agents.

7.1 Potential for Other Drugs to Affect FANAPT

Iloperidone is not a substrate for CYP1A1, CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, or CYP2E1 enzymes. This suggests that an interaction of iloperidone with inhibitors or inducers of these enzymes, or other factors, like smoking, is unlikely.

Both CYP3A4 and CYP2D6 are responsible for iloperidone metabolism. Inhibitors of CYP3A4 (e.g., ketoconazole) or CYP2D6 (e.g., fluoxetine, paroxetine) can inhibit iloperidone elimination and cause increased blood levels.

Ketoconazole: Co-administration of ketoconazole (200 mg twice daily for 4 days), a potent inhibitor of CYP3A4, with a 3 mg single dose of iloperidone to 19 healthy volunteers, ages 18-45, increased the AUC of iloperidone and its metabolites P88 and P95 by 57%, 55% and 35%, respectively. Iloperidone doses should be reduced by about one-half when administered with ketoconazole or other strong inhibitors of CYP3A4 (e.g., itraconazole). Weaker inhibitors (e.g., erythromycin, grapefruit juice) have not been studied. When the CYP3A4 inhibitor is withdrawn from the combination therapy, the iloperidone dose should be returned to the previous level.

Fluoxetine: Co-administration of fluoxetine (20 mg twice daily for 21 days), a potent inhibitor of CYP2D6, with a single 3 mg dose of iloperidone to 23 healthy volunteers, ages 29-44, who were classified as CYP2D6 extensive metabolizers, increased the AUC of iloperidone and its metabolite P88, by about 2-3 fold, and decreased the AUC of its metabolite P95 by one-half. Iloperidone doses should be reduced by one-half when administered with fluoxetine. When fluoxetine is withdrawn from the combination therapy, the iloperidone dose should be returned to the previous level. Other strong inhibitors of CYP2D6 would be expected to have similar effects and would need appropriate dose reductions. When the CYP2D6 inhibitor is withdrawn from the combination therapy, iloperidone dose could then be increased to the previous level.

Paroxetine: Co-administration of paroxetine (20 mg/day for 5-8 days), a potent inhibitor of CYP2D6, with multiple doses of iloperidone (8 or 12 mg twice daily) to patients with schizophrenia ages 18-65 resulted in increased mean steady-state peak concentrations of iloperidone and its metabolite P88, by about 1.6 fold, and decreased mean steady-state peak concentrations of its metabolite P95 by one-half. Iloperidone doses should be reduced by one-half when administered with paroxetine. When paroxetine is withdrawn from the combination therapy, the iloperidone dose should be returned to the previous level. Other strong inhibitors of CYP2D6 would be expected to have similar effects and would need appropriate dose reductions. When the CYP2D6 inhibitor is withdrawn from the combination therapy, iloperidone dose could then be increased to previous levels.

Paroxetine and Ketoconazole: Co-administration of paroxetine (20 mg once daily for 10 days), a CYP2D6 inhibitor, and ketoconazole (200 mg twice daily) with multiple doses of iloperidone (8 or 12 mg twice daily) to patients with schizophrenia ages 18-65 resulted in a 1.4 fold increase in steady-state concentrations of iloperidone and its metabolite P88 and a 1.4 fold decrease in the P95 in the presence of paroxetine. So giving iloperidone with inhibitors of both of its metabolic pathways did not add to the effect of either inhibitor given alone. Iloperidone doses should therefore be reduced by about one-half if administered concomitantly with both a CYP2D6 and CYP3A4 inhibitor.

7.2 Potential for FANAPT to Affect Other Drugs

In vitro studies in human liver microsomes showed that iloperidone does not substantially inhibit the metabolism of drugs metabolized by the following cytochrome P450 isozymes: CYP1A1, CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, or CYP2E1. Based on *in vitro* studies, iloperidone is a time-dependent inhibitor of CYP3A at therapeutic exposure levels. Co-administration of iloperidone may lead to an increase in plasma levels of drugs that are predominantly eliminated by CYP3A. Furthermore, *in vitro* studies in human liver microsomes showed that iloperidone does not have enzyme inducing properties, specifically for the following cytochrome P450 isozymes: CYP1A2, CYP2C8, CYP2C9, CYP2C19, CYP3A4 and CYP3A5.

Dextromethorphan: A study in healthy volunteers showed that changes in the pharmacokinetics of dextromethorphan (80 mg dose) when a 3 mg dose of iloperidone was co-administered resulted in a 17% increase in total exposure and a 26% increase in C_{max} of dextromethorphan. Thus, an interaction between iloperidone and other CYP2D6 substrates is unlikely.

Fluoxetine: A single 3 mg dose of iloperidone had no effect on the pharmacokinetics of fluoxetine (20 mg twice daily).

7.3 Drugs that Prolong the QT Interval

FANAPT should not be used with any other drugs that prolong the QT interval *[see Warnings and Precautions (5.2)]*.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C

FANAPT caused developmental toxicity, but was not teratogenic, in rats and rabbits.

In an embryo-fetal development study, pregnant rats were given 4, 16, or 64 mg/kg/day (1.6, 6.5, and 26 times the maximum recommended human dose [MRHD] of 24 mg/day on a mg/m2 basis) of iloperidone orally during the period of organogenesis. The highest dose caused increased early intrauterine deaths, decreased fetal weight and length, decreased fetal skeletal ossification, and an increased incidence of minor fetal skeletal anomalies and variations; this dose also caused decreased maternal food consumption and weight gain.

In an embryo-fetal development study, pregnant rabbits were given 4, 10, or 25 mg/kg/day (3, 8, and 20 times the MRHD on a mg/m2 basis) of iloperidone during the period of organogenesis. The highest dose caused increased early intrauterine deaths and decreased fetal viability at term; this dose also caused maternal toxicity.

In additional studies in which rats were given iloperidone at doses similar to the above beginning from either pre-conception or from day 17 of gestation and continuing through weaning, adverse reproductive effects included prolonged pregnancy and parturition, increased stillbirth rates, increased incidence of fetal visceral variations, decreased fetal and pup weights, and decreased post-partum pup survival. There were no drug effects on the neurobehavioral or reproductive development of the surviving pups. No-effect doses ranged from 4 to 12 mg/kg except for the increase in stillbirth rates which occurred at the lowest dose tested of 4 mg/kg, which is 1.6 times the MRHD on a mg/m2 basis. Maternal toxicity was seen at the higher doses in these studies.

The iloperidone metabolite P95, which is a major circulating metabolite of iloperidone in humans but is not present in significant amounts in rats, was given to pregnant rats during the period of organogenesis at oral doses of 20, 80, or 200 mg/kg/day. No teratogenic effects were seen. Delayed skeletal ossification occurred at all doses. No significant maternal toxicity was produced. Plasma levels of P95 (AUC) at the highest dose tested were 2 times those in humans receiving the MRHD of iloperidone.

There are no adequate and well-controlled studies in pregnant women.

Non-Teratogenic Effects

Neonates exposed to antipsychotic drugs, during the third trimester of pregnancy are at risk for extrapyramidal and/or withdrawal symptoms following delivery. There have been reports of agitation, hypertonia, hypotonia, tremor, somnolence, respiratory distress and feeding disorder in these neonates. These complications have varied in severity; while in some cases symptoms have been self-limited, in other cases neonates have required intensive care unit support and prolonged hospitalization.

FANAPT should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

8.2 Labor and Delivery

The effect of FANAPT on labor and delivery in humans is unknown.

8.3 Nursing Mothers

FANAPT was excreted in milk of rats during lactation. It is not known whether FANAPT or its metabolites are excreted in human milk. It is recommended that women receiving FANAPT should not breast feed.

8.4 Pediatric Use

Safety and effectiveness in pediatric and adolescent patients have not been established.

8.5 Geriatric Use

Clinical Studies of FANAPT in the treatment of schizophrenia did not include sufficient numbers of patients aged 65 years and over to determine whether or not they respond differently than younger adult patients. Of the 3210 patients treated with FANAPT in pre-marketing trials, 25 (0.5%) were ≥65 years old and there were no patients ≥75 years old.

Studies of elderly patients with psychosis associated with Alzheimer's disease have suggested that there may be a different tolerability profile (i.e., increased risk in mortality and cerebrovascular events including stroke) in this population compared to younger patients with schizophrenia *[see Boxed Warning and Warnings and Precautions (5.1)]*. The safety and efficacy of FANAPT in the treatment of patients with psychosis associated with Alzheimer's disease has not been established. If the prescriber elects to treat such patients with FANAPT, vigilance should be exercised.

8.6 Renal Impairment

Because FANAPT is highly metabolized, with less than 1% of the drug excreted unchanged, renal impairment alone is unlikely to have a significant impact on the pharmacokinetics of FANAPT. Renal impairment (creatinine clearance <30 mL/min) had minimal effect on maximum plasma concentrations (C_{max}) of iloperidone (given in a single dose of 3 mg) and its metabolites P88 and P95 in any of the three analytes measured. $AUC_{0-\infty}$ was increased by 24%, decreased by 6%, and increased by 52% for iloperidone, P88 and P95, respectively, in subjects with renal impairment.

8.7 Hepatic Impairment

A study in mild and moderate liver impairment has not been conducted. FANAPT is not recommended for patients with hepatic impairment.

8.8 Smoking Status

Based on *in vitro* studies utilizing human liver enzymes, FANAPT is not a substrate for CYP1A2; smoking should therefore not have an effect on the pharmacokinetics of FANAPT.

9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

FANAPT is not a controlled substance.

9.2 Abuse

FANAPT has not been systematically studied in animals or humans for its potential for abuse, tolerance, or physical dependence. While the clinical trials did not reveal any tendency for drug-seeking behavior, these observations were not systematic and it is not possible to predict on the basis of this experience the extent to which a CNS active drug, FANAPT, will be misused, diverted, and/or abused once marketed. Consequently, patients should be evaluated carefully for a history of drug abuse, and such patients should be observed closely for signs of FANAPT misuse or abuse (e.g. development of tolerance, increases in dose, drug-seeking behavior).

10 OVERDOSAGE

10.1 Human Experience

In pre-marketing trials involving over 3210 patients, accidental or intentional overdose of FANAPT was documented in eight patients ranging from 48 mg to 576 mg taken at once and 292 mg taken over a three-day period. No fatalities were reported from these cases. The largest confirmed single ingestion of FANAPT was 576 mg; no adverse physical effects were noted for this patient. The next largest confirmed ingestion of FANAPT was 438 mg over a four-day period; extrapyramidal symptoms and a QTc interval of 507 msec were reported for this patient with no cardiac sequelae. This patient resumed FANAPT treatment for an additional 11 months. In general, reported signs and symptoms were those resulting from an exaggeration of the known pharmacological effects (e.g., drowsiness and sedation, tachycardia and hypotension) of FANAPT.

10.2 Management of Overdose

There is no specific antidote for FANAPT. Therefore appropriate supportive measures should be instituted. In case of acute overdose, the physician should establish and maintain an airway and ensure adequate oxygenation and ventilation. Gastric lavage (after intubation, if patient is unconscious) and administration of activated charcoal together with a laxative should be considered. The possibility of obtundation, seizures or dystonic reaction of the head and neck following overdose may create a risk of aspiration with induced emesis. Cardiovascular monitoring should commence immediately and should include continuous ECG monitoring to detect possible arrhythmias. If antiarrhythmic therapy is administered, disopyramide, procainamide and quinidine should not be used, as they have the potential for QT-prolonging effects that might be additive to those of FANAPT. Similarly, it is reasonable to expect that the alpha-blocking properties of bretylium might be additive to those of FANAPT, resulting in problematic hypotension. Hypotension and circulatory collapse should be treated with appropriate measures such as intravenous fluids or sympathomimetic agents (epinephrine and dopamine should not be used, since beta stimulation may worsen hypotension in the setting of FANAPT-induced alpha blockade). In cases of severe extrapyramidal symptoms, anticholinergic medication should be administered. Close medical supervision should continue until the patient recovers.

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Box 3. General Medical Conditions that Can Cause Acute Psychosis[9]

Industrial Exposures
Acute intermittent porphyria
Carbon disulfide
Cushing's syndrome
Heavy metals
Hypocalcemia and hypercalcemia
Hypoglycemia
Hypothyroidism and hyperthyroidism

Neurologic Disorders
Central nervous system neoplasm
Early Alzheimer's disease
Encephalitis, meningitis, brain abscess
Huntington's disease
Neurosyphilis
Seizure disorder (temporal lobe epilepsy, postictal psychosis)
Stroke (right thalamic, Wernicke's aphasia)
Wilson's disease

Nutritional Deficiencies
Korsakoff's psychosis (thiamine deficiency)
Pellagra (niacin deficiency)
Vitamin B_{12} deficiency
Wernicke's encephalopathy (thiamine deficiency)

Systemic Illness with Central Nervous System Effects
Hepatic encephalopathy
HIV/AIDS encephalopathy
Hypoxic encephalopathy
Lupus cerebritis
Pancreatic encephalopathy
Paraneoplastic syndrome

Toxic Reactions to Medications
ACE inhibitors
Anticholinergic agents
Antihistamines
Digitalis
Dopaminergic agents (bromocriptine, levodopa, ropinirole, mirapex)
Glucocorticoids
Isoniazid
NSAIDs (indomethacin, sulindac)
Over-the-counter sleep aids
Stimulants (methylphenidate [Concerta, Focalin, Metadate, Ritalin], dextroamphetamine [Dexedrine, Adderall])ACE, angiotensin-converting enzyme

AIDS, autoimmune deficiency syndrome; HIV, human immunodeficiency virus; NSAID, nonsteroidal anti-inflammatory drug.

Cleveland Clinic

Acute psychosis, although not recognized as a diagnostic term in DSM-5 is commonly used to describe a rapid deterioration of behavior associated with hallucinations and delusions. Schizophreniform disorder, brief psychotic disorder, and organic psychoses fall under this rubric. The DSM-5 diagnosis of schizophreniform disorder depends on the persistence of schizophrenia-like symptoms for at least 1 month and exclusion of other causes of acute psychosis. Brief psychotic disorder (often referred to as brief reactive psychosis) lasts less than 1 month, but more than 1 day. It is typically regarded as a reaction to marked stress in persons with borderline or antisocial personality disorders.

Schizoaffective disorder is a chronic mental illness that includes prominent features of both schizophrenia and a mood disorder. The diagnostic criteria for schizoaffective disorder are characteristic symptoms of schizophrenia concurrent with a major mood disturbance (major depressive or manic episode). Although mood symptoms and episodes must be present for a substantial portion of the total course of the illness, a diagnosis of schizoaffective disorder also requires that psychotic symptoms, such as delusions or hallucinations, have been present for a minimum of 2 weeks in the absence of an active mood disturbance.

Delusional disorder is distinguished from schizophrenia by delusions (e.g., erotomanic, grandiose, jealous, persecutory, somatic, mixed) that are not bizarre and functioning that is not markedly impaired. Hallucinations are generally not present.

A diagnosis of mood disorder with psychotic features is made if psychotic symptoms occur solely during episodes of mood disturbance.

Acute psychosis caused by substance use or medication toxicity is distinguished from schizophrenia by clear-cut evidence of substance use leading to symptoms.

Treatment

General Approach

The successful treatment of schizophrenia requires simultaneous attention to medical variables and psychosocial factors relevant to the patient. A multimodal approach encompassing biologic and psychosocial therapies as well as programs that offer rehabilitation and social reintegration has been found to be most effective. Schizophrenia generally does not occur in isolation but rather with other comorbid conditions, commonly alcohol or drug abuse, or both. Failure to recognize and treat comorbid substance abuse is a common cause of treatment resistance in schizophrenia. Comprehensive management of schizophrenia, therefore, typically requires the involvement of a multidisciplinary team including a psychiatrist, social worker, case manager, individual or family therapist, and one or more family members. Episodes of illness can require treatment in multiple settings, including outpatient, intensive outpatient, hospital, and residential.

The primary care physician's principal role is to recognize the illness, initiate treatment, and refer to a psychiatrist.

Treatment of schizophrenia is divided into three phases: acute, stabilization, and stable.[3] Generally, the illness first comes to medical attention with the presentation of an acute psychotic episode. Acute psychosis, like schizophrenia, has a differential diagnosis that includes general medical, psychiatric, and substanceuse disorders, (see Boxes 2 and 3). At this point the primary care physician's role may be to ensure safe transfer of the acutely psychotic patient to an emergency facility where appropriate evaluation and stabilization can be conducted. Once the proper treatment regimen for a schizophrenic patient has been identified, the primary care physician may be called on to prescribe maintenance medication, with specialist referral for assistance in managing recurrent illness episodes.

Proper medical care is another important consideration in the comprehensive management of the schizophrenic patient. The patient's idiosyncratic behavior, poor hygiene, or nonadherence to medical recommendations often interferes with attention to and successful management of medical problems. Schizophrenic patients have a high incidence of cardiovascular problems such as hypertension and coronary artery disease, diabetes, and tobacco-related disorders. Given that many schizophrenic patients are homeless, higher rates of tuberculosis, HIV infection, and problems associated with poor foot care are also common in this population.

Acute Phase: Treatment of Acute Psychosis

The first priority in management of acute psychosis is the safety of patient and staff. This includes simultaneous attention to potentially life-endangering causes of acute psychosis or delirium (Box 4) and other psychiatric, substance-use (see Box 2), and general medical (see Box 3) causes. Identification of the underlying cause of the acute psychosis requires a thorough evaluation that includes the patient's psychiatric and medical histories; collateral information from the family, workplace, school, and other sources; physical and mental status examinations; and laboratory investigation. Typically, much of this information is either unavailable or difficult to obtain, and the clinician is forced to rely on rapid observation, clinical intuition, and laboratory measures (Table 1). A commonly raised question is whether or not to obtain brain neuroimaging. Most experts recommend CT or MRI during a first psychotic episode. An electroencephalogram should be obtained if one suspects organic psychosis such as delirium (encephalopathy). If an underlying cause of psychosis is discovered, it should be corrected (e.g., hypoglycemia, cerebral vasculitis, seizures). In the absence of a definitive cause, the focus can shift to pharmacologic intervention. Voluntary or involuntary hospitalization is often necessary for the first episode of psychosis in schizophrenia.

Box 4. Life-Endangering Causes of Acute Psychosis or Delirium: WWHHHIMPS

Withdrawal from alcohol or barbiturates

Wernicke's encephalopathy

Hypertensive crisis

Hypoglycemia

Hypoxemia (cerebral)

Intracranial process (tumor, stroke)

Meningitis or encephalitis

Poisoning (overdose, heavy metal toxicity)

Seizures (postictal state, temporal lobe epilepsy)

Table 1. Laboratory Investigation in Acute Psychosis and Chronic Schizophrenia

Test	Acute Psychosis*	Chronic Schizophrenia†
Blood glucose	×	‡
Blood glucose, fasting		×
Brain MRI or CT	×	‡
BUN	×	‡
CBC	×	‡
Creatinine	×	‡
ECG	×	‡
EEG	‡	
Electrolytes	×	‡
Hepatitis B and C	‡	‡
HIV	‡	‡
Lipid profile		×
Liver function	×	‡
Pregnancy (women with childbearing potential)	×	‡
Syphilis (RPR, VDRL)	×	‡
Toxicology (serum and urine)	×	‡
Vitamin B$_{12}$ and folic acid blood levels	×	

BUN, blood urea nitrogen; CBC, complete blood count; CT, computed tomography; ECG, electrocardiogram; EEG, electroencephalogram; HIV, human immunodeficiency virus; MRI, magnetic resonance imaging; RPR, rapid plasma reagin; VDRL, Venereal Disease Research Laboratory.

*For all first-episode psychoses or acute psychoses in which the patient's history is unknown.

†Patients who have an existing diagnosis of schizophrenia and require regular monitoring of medical status.

‡Order only if the clinical situation warrants it or if the test result is considered important for routine monitoring of physical status.

The traditionally accepted regimen for rapid control of agitation associated with acute psychosis is oral or intramuscular (IM) lorazepam (Ativan) 1 to 2 mg, alone or in combination with haloperidol (Haldol) 2 to 5 mg. Rapidly acting alternatives include oral or IM olanzapine (Zyprexa) 5 to 10 mg or ziprasidone (Geodon) 20 mg IM or 60 to 80 mg oral. Oral dispersible forms of olanzapine (Zyprexa Zydis) 5 to 10 mg and risperidone (Risperdal M-Tab) 1 to 2 mg are useful when rapid absorption is desired and for noncompliant patients who seek medication. Simultaneous administration of IM olanzapine and lorazepam is not recommended because the combination has been associated with respiratory failure. An algorithm for treating acute psychosis is presented in Figure 1.

Pharmacologic Treatment of Schizophrenia

Antipsychotics are considered to be the first line of therapy in the pharmacologic treatment of schizophrenia. They are generally categorized as first-generation (typical) antipsychotics (FGAs) or second-generation (atypical) antipsychotics (SGAs). Typical starting and therapeutic doses of FGAs and SGAs are listed in Tables 2 and 3.

A guideline for the pharmacologic management of schizophrenia is presented in Figure 2. The choice of antipsychotic drug, dosage, and desired route of administration is based on phase of treatment, intensity of agitation, adherence to treatment recommendations, history of response to antipsychotic medications, and antipsychotic side-effect profile.
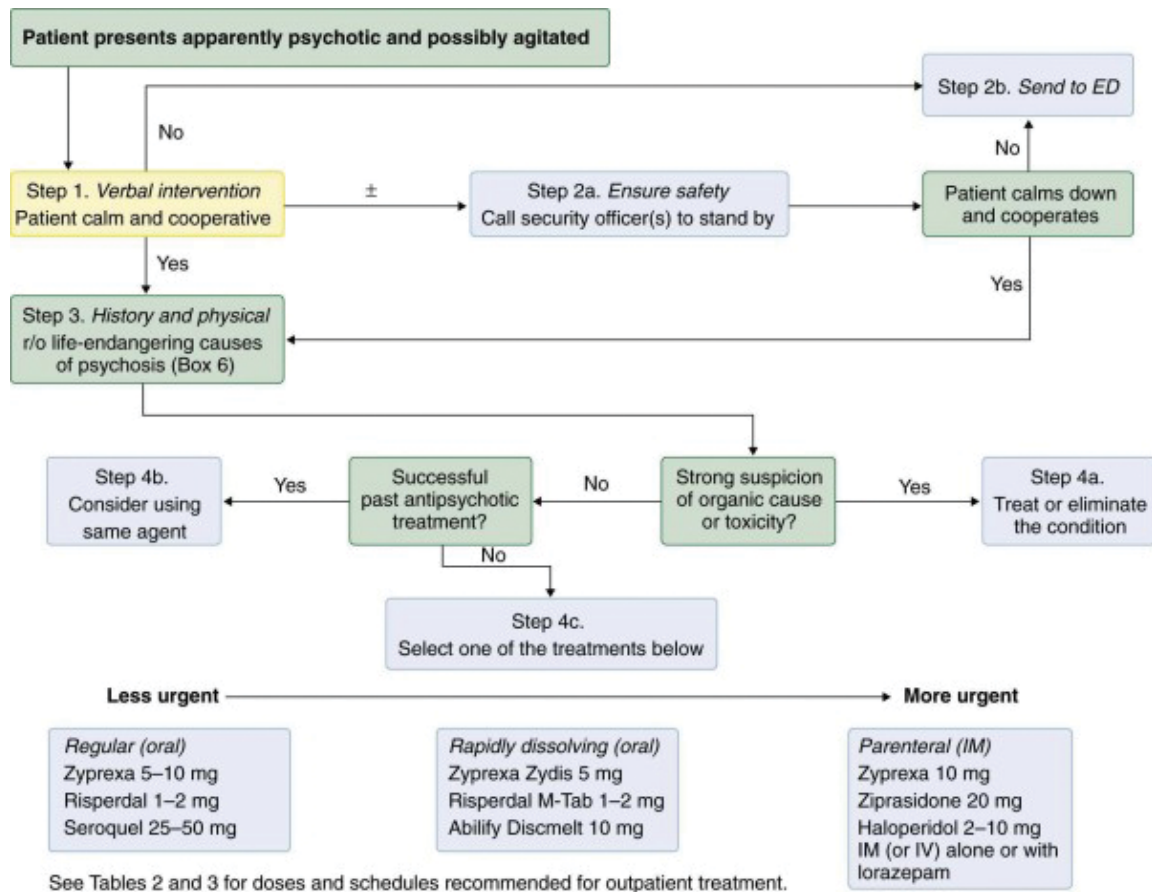
Figure 1. Algorithm for managing acute psychosis. ED, emergency department; r/o, rule out.

Table 2. First-Generation (Atypical) Antipsychotics

Drug	Daily Dosage				Preparations				
	Starting (mg/day)	Range (mg/day)	Maximum (mg/day)	Schedule	Pill, Capsule	Elixir	IM Short Acting	IM Long Acting	IV
Chlorpromazine	50-100	400-800	1000	bid	×				
Thioridazine	50-100	150-300	800	bid-qid	×				
Trifluoperazine	2-4	5-10	40	bid	×				
Fluphenazine	0.5-1	5-10		bid	×				
Fluphenazine decanoate	12.5	25-50	100	q 3-6 wk				×	
Perphenazine	12-24	32-64	64	tid-qid	×				
Molindone (Moban)	50-75	50-200	225	tid-qid	×	×			
Loxapine	10-20	60-100	250	bid	×				
Thiothixene (Navane)	6-10	5-15	60	bid-tid	×				
Haloperidol	2-10	5-15	100	bid-tid	×				
Haloperidol lactate	1-5	5-10	100	bid-tid			×		×[a]
Haloperidol decanoate (Haldol Decanoate)	25	50-100	450	q mo				×	

Note: First-generation antipsychotics are no longer considered first-line treatment for schizophrenia unless an atypical antipsychotic is not available, and then either haloperidol or chlorpromazine should be considered.

a Not approved by U.S. Food and Drug Administration for IV use, but off-label use is common when IV access is available.

The FGAs are broadly classified into the phenothiazines (e.g., chlorpromazine) and butyrophenones (e.g., haloperidol). The phenothiazines are more anticholinergic, cause more weight gain, and are more likely than butyrophenones to cause postural hypotension. Overdose is more likely to be fatal with phenothiazines than with butyrophenones. Haloperidol, the most widely prescribed butyrophenone, is associated with a high risk of all types of extrapyramidal symptoms (EPS). Although effective, the FGAs have fallen out of favor because of their side-effect profiles, especially their propensity to cause EPS (Box 5).

The SGAs affect several receptor types—serotonin, histamine, noradrenergic, and muscarinic—in addition to the D_2 receptors.[4] The multiplicity of receptors targeted by SGAs contributes to their efficacy and side-effect profiles. The results of the oft-cited Clinical Antipsychotic Trials of Interven-tion Effectiveness (CATIE) demonstrated that FGAs and SGAs have similar efficacy, but both groups have potentially troublesome side effects that warrant careful monitoring and can disrupt otherwise effective treatment.[4-7] Although SGAs are less likely to cause EPS, they are not risk free. Quetiapine is the least likely to cause EPS. The risk of other adverse effects varies among individual SGAs. Clozapine (Clozaril), the first SGA to be developed and marketed, has retained its reputation for being the most effective of all antipsychotics at treating negative symptoms. Unfortunately, its tendency to cause bone marrow suppression, weight gain, and metabolic syndrome also distinguishes it from the other SGAs. It is therefore used only selectively.

Table. 3 Second-Generation (Atypical) Antipsychotics

| Drug | Daily Dosage | | | | Preparations | | | | |
	Starting (mg/day)	Range (mg/day)	Maximum (mg/day)	Schedule	Pill, Capsule	Rapidly Dissolving	Elixir	IM Short Acting	IM Long Acting
Clozapine (Clozaril)[a]	25	300-600	900	bid	×				
Risperidone (Risperdal)	1-2	4-8	16	qd-bid	×	×			
Risperidone (Risperdal M-Tab)	1-2	4-8	16	qd-bid		×			
Risperidone (Risperdal Consta)	12.5[b]	25[b]	50[b]	q 2 wk					×
Paliperidone (Invega)	3-6	6-12	12	qd	×				
Paliperidone palmitate (Invega Sustenna)	234[c]	117[c]		qmo					×
Olanzapine (Zyprexa)	5-10	15-20	20	qd-bid	×			×	
Olanzapine (Zyprexa Zydis)	5-10	15-20	20	qd-bid		×			
Ziprasidone (Geodon)	40-80	80-160	160	bid	×			×	
Quetiapine (Seroquel)	50-100	400-800	750	bid	×				
Aripiprazole (Abilify)	5-10	15-30	30	qd	×				
Lurasidone (Latuda)	40	40-160	160	qd	×				
Asenapine maleate (Saphris)	10	20	20	bid		×			
Iloperidone (Fanapt)	2mg	12-24	24	bid	×				

Note: All second-generation (atypical) antipsychotics have U.S. Food and Drug Administration approval for use in schizophrenia.

a Not considered a first-line agent. Requires weekly monitoring of white blood cell count (WBC) for the first 6 months of treatment and then biweekly thereafter for the duration of use.

b Initial dose, administered at recommended intervals.

c Initial dose with 156 mg administered 1 week later; maintenance doses (117 mg) administered monthly.
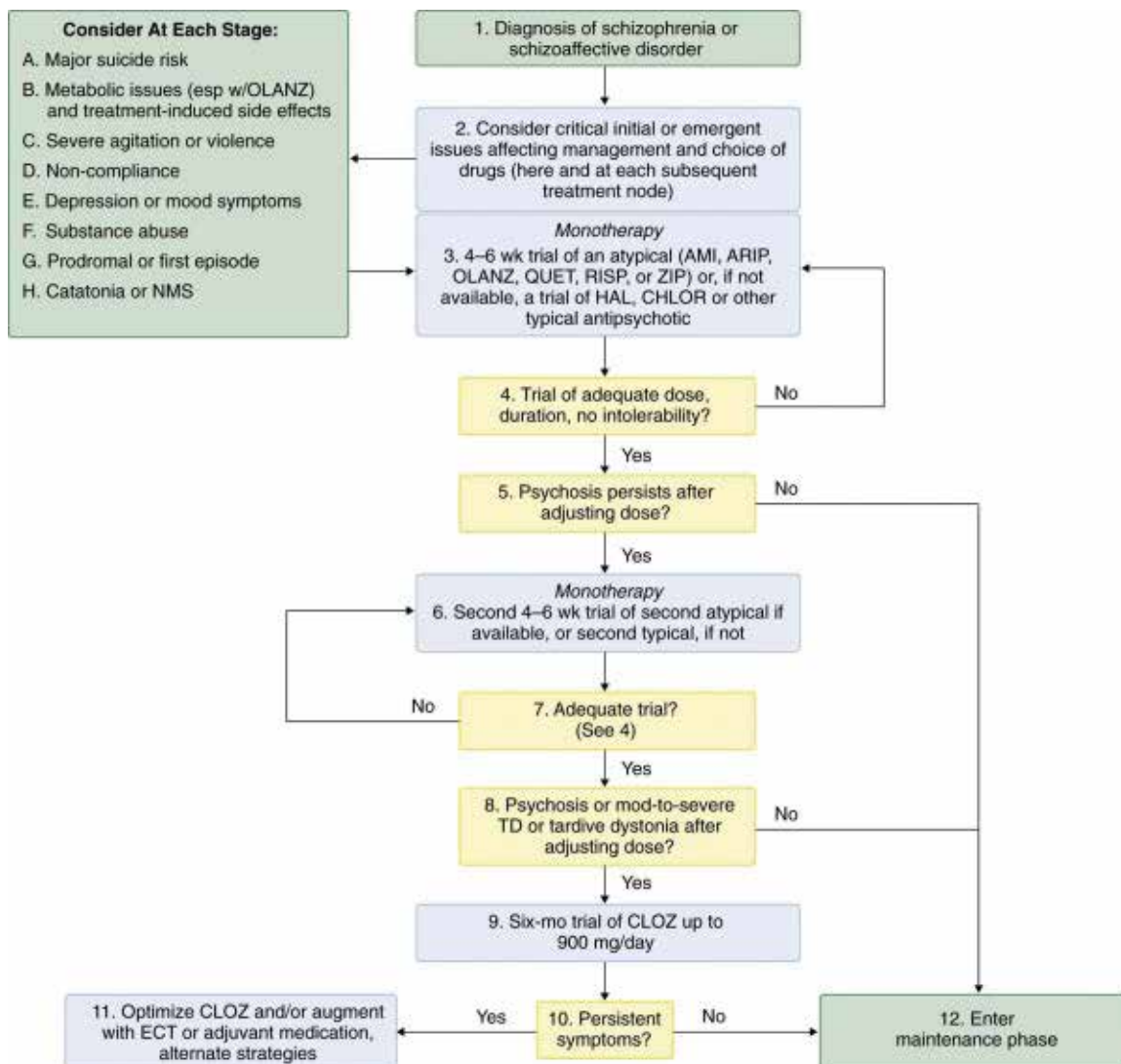
Figure 2. International Psychopharmacology Algorithm Project algorithm for schizophrenia. For descriptive not prescriptive purposes. AMI, amisulpride; ARIP, aripiprazole; CHLOR, chlorpromazine; CLOZ, clozapine; ECT, electroconvulsive therapy; esp, especially; HAL, haloperidol; NMS, neuroleptic malignant syndrome; OLANZ, olanzapine; QUET, quetiapine; RISP, risperidone; TD, tardive dyskinesia; ZIP, ziprasidone. Reprinted with permission from The International Psychopharmacology Algorithm Project. Copyright © 2004-2006 International Psychopharmacology Algorithm Project (IPAP) www.ipap.org.

Box 5. Treatment of Extrapyramidal Symptoms

Acute Dystonia
Benzotropine mesylate (Cogentin) 2 mg PO/IM/IV bid
Diphenhydramine (Benadryl) 25-50 mg IM/IV
Trihexyphenidyl (Artane) 2-5 mg PO bid-tid

Akathisia
Clonazepam 0.5 mg PO bid
Lorazepam 1 mg PO tid
Pramipexole 0.125-0.5 mg PO qd
Propranolol 10-30 mg tid
Ropinirole 1-4 mg PO qd

Neuroleptic Malignant Syndrome
Anticholinergics (benztropine, trihexyphenidyl)
Dantrolene sodium
Dopamine agonists (amantadine, bromocriptine, ropinirole, pramipexole)

Parkinsonism
Amantadine 100 mg PO bid
Anticholinergics (benztropine, trihexyphenidyl)
Pramipexole 0.125-0.5 mg PO qd
Ropinirole 1-4 mg PO qd

Tardive Dyskinesia
No uniformly effective treatment; tetrabenazine may be tried

Tardive Dystonia
Anticholinergics are sometimes helpful

Withdrawal Dyskinesia
Resume same antipsychotic agent

Neuroleptic-induced catatonia
Anticholinergics (benztropine, trihexyphenidyl)
Bromocriptine 10 mg PO tid
Dopamine agonists (amantadine, bromocriptine, ropinirole, pramipexole)

The use of antipsychotics in elderly patients with dementia-related psychosis has been associated with a 1.7-fold increase in risk of death. Most deaths are related to cardiovascular, cerebrovascular, or infectious (i.e., pneumonia) causes. This was initially thought to be an atypical antipsychotic–specific phenomenon, but studies have shown that FGAs may pose a similar risk.

Stabilization Phase

The dosage of medication used to achieve remission or optimal control in the acute phase should be continued for at least 6 months to prevent relapse. Psychotherapeutic interventions remain supportive. Patients should be helped with the transition to life in the community and helped to adjust to their lives outside the hospital through realistic goal setting.

Table 4. Abnormal Involuntary Movement Scale[8]

Assessment

1. Observe the patient's gait on the way into the room.
2. Have the patient remove gum or dentures if they do not fit properly.
3. Determine if the patient is aware of any abnormal movements.
4. Have the patient sit on a firm, armless chair with hands on knees, legs slightly apart, and feet flat on the floor. Now and throughout the examination, look at the entire body for movements.
5. Have the patient sit with hands unsupported, dangling over the knees.
6. Ask the patient to open the mouth twice. Look for tongue movements.
7. Ask the patient to protrude the tongue twice.
8. Ask the patient to tap the thumb against each finger for 15 sec with each hand. Observe face and legs.
9. Have the patient stand with arms extended forward.

Rating

Rate each item on a 0 to 4 scale for the greatest severity observed. Movements that occur only on activation merit 1 point less than those that occur spontaneously.

Score

Movement	None	Minimal*	Mild	Moderate	Severe
Face and Mouth					
Muscles of facial expression	0	1	2	3	4
Lips and perioral area	0	1	2	3	4
Jaw	0	1	2	3	4
Tongue	0	1	2	3	4
Extremities					
Arms	0	1	2	3	4
Legs	0	1	2	3	4
Trunk					
Neck	0	1	2	3	4
Shoulders	0	1	2	3	4
Hips	0	1	2	3	4
Global					
Severity of abnormal movements	0	1	2	3	4
Incapacitation due to abnormal movements	0	1	2	3	4
Patient's awareness of abnormal movements (0 = unaware; 4 = severe distress)	0	1	2	3	4

*May be the extreme of normal.

Stable Phase

The goals of the stable phase are sustained symptom control or remission. Monthly to semiannual monitoring for treatment adherence, relapse, and intolerance to medications is recommended. Signs and symptoms of weight gain, increasing waist circumference, hyperlipidemia, and hyperglycemia should be monitored, as well as evidence of abnormal involuntary movements.[7] The Abnormal Involuntary Movement Scale (AIMS) (Table 4) should be used serially to rate presence and intensity of movement disorder.

Continued antipsychotic treatment reduces the risk of symptom relapse. There are no strict guidelines for the minimum antipsychotic dose required to prevent relapse. For FGAs, the optimal dose is regarded as the minimum dose at which mild EPS are detectable on physical examination. SGAs can be administered at therapeutic doses well below their EPS threshold.

Pharmacologic treatment of schizophrenia is essential but insufficient. Optimal outcome requires additional use of psychosocial therapies and programs that foster recovery through vocational rehabilitation and social reintegration.

Psychosocial Interventions

Assertive Community Treatment

Developed in the late 1960s, assertive community treatment provides the patient with around-the-clock support in the community, thereby significantly reducing the time spent in hospitals. A team composed of a social worker, nurse, and case manager provides treatment in community settings. Services delivered include case management, initial and ongoing assessments, access to psychiatric services, employment and housing assistance, family support and education, substance-abuse services, and any other services and support critical to successful adaptation in the community.

Psychotherapy

The quality of the therapeutic alliance may be the best predictor of compliance and outcome. The emphasis is on education, support, and problem solving, rather than on developing insight. Therapy of this type can be provided on an individual or group basis.

Family Therapy

The schizophrenic patient's behavior can trigger a vicious cycle of conflict between the patient and family. Anger, criticism, and devaluing comments directed by family members at the patient—referred to in the literature as high expressed emotion—are associated with a greater increase of relapse even when pharmacologic management is optimal. A therapist works with the family to reduce expressed emotion by educating them about schizophrenia and helping to modify the behaviors and attitudes that undermine the patient.

Social Skills Training

The principles of learning theory are used to improve social skills such as interpersonal relationships, employment, and leisure. Behaviors such as odd facial expressions, lack of spontaneity, and inappropriate perception of others' emotional states are targeted and modified.

Vocational Rehabilitation

Workshops and part-time employment programs help the patient acquire greater functionality.

Screening and Prevention

Most prevention efforts are in the realm of secondary and tertiary prevention, or reducing the number and severity of episodes. Public health education on schizophrenia helps to reduce stigma and resistance to seeking treatment. Family history of schizophrenia is an important indicator of risk that should increase vigilance for early detection and treatment of prodromal symptoms. Once the diagnosis is made, the team should develop a comprehensive treatment plan that includes family involvement with goals of adhering to treatment and reducing symptoms. Assertive community treatment has been very effective at maintaining community and keeping patients out of the hospital. Assiduous attention to substance abuse and abstinence is a key to a good outcome in schizophrenia.

Considerations In Special Populations

Populations with special needs include patients with pervasive developmental disorders and mental retardation, women with childbearing potential, children, the elderly, and the homeless.

Summary

- Schizophrenia is a treatable neuropsychiatric disorder present in approximately 1% of the general population.
- The etiology is multifactorial and includes genetic, developmental, and possibly environmental causes.
- The signs and symptoms of schizophrenia are nonspecific, warranting a thorough evaluation for other medical and psychiatric disorders that can manifest with psychosis.
- The primary care physician should be familiar with the use, benefits, and potential adverse effects of antipsychotic medications used to treat schizophrenia.
- Metabolic syndrome is a common comorbidity, especially since the introduction of atypical (second-generation) antipsychotics.

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Suggested Readings

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