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Schizophrenia: Ensuring an accurate Dx, optimizing treatment

First rule out secondary psychosis with appropriate lab tests and imaging studies, as needed. Give an antipsychotic for at least 4 weeks to judge its effectiveness.

THE CASE

Steven R,* a 21-year-old man, visited the clinic accompanied by his mother. He did not speak much, and his mother provided his history. Over the previous 2 months, she had overheard him whispering in an agitated voice, even though no one else was nearby. And, lately, he refused to answer or make calls on his cell phone, claiming that if he did it would activate a deadly chip that had been implanted in his brain by evil aliens. He also stopped attending classes at the community college. He occasionally had a few beers with his friends, but he had never been known to abuse alcohol or use other recreational drugs.

HOW WOULD YOU PROCEED WITH THIS PATIENT?

**The patient's name has been changed to protect his identity.*

CHARACTERISTICS AND SCOPE OF SCHIZOPHRENIA

Schizophrenia is a psychotic illness in which the individual loses contact with reality and often experiences hallucinations, delusions, or thought disorders. Criteria for schizophrenia described in the *Diagnostic and Statistical Manual of Mental Disorders 5th edition* (DSM-5) include signs and symptoms of at least 6 months' duration, as well as at least one month of active-phase positive and negative symptoms.[1]

Delusions, hallucinations, disorganized speech, and disorganized behavior are examples of positive symptoms. Negative symptoms include a decrease in the range and intensity of expressed emotions (ie, affective flattening) and a diminished initiation of goal-directed activities (ie, avolition).

Approximately 7 in 1000 people will develop the disorder in their lifetime.[2] Schizophrenia is considered a "serious mental illness" because of its chronic course and often poor long-term social and vocational outcomes.[3,4] Symptom onset is generally between late adolescence and the mid-30s.[5]

Getting closer to understanding its origin

Both genetic susceptibility and environmental factors influence the incidence of schizophrenia.[4] Newer models of the disease have identified genes (*ZDHHC8* and *DTNBP1*) whose mutations may increase the risk of schizophrenia.[6] Physiologic insults during fetal life—hypoxia, maternal infection, maternal stress, and maternal malnutrition—account for a small portion of schizophrenia cases.[6]

Abnormalities in neurotransmission are the basis for theories on the pathophysiology of schizophrenia. Most of these theories center on either an excess or a deficiency of neurotransmitters, including dopamine, serotonin, and glutamate. Other theories implicate aspartate, glycine, and gamma-aminobutyric acid as part of the neurochemical imbalance of schizophrenia.[7]

ESTABLISHING A DIAGNOSIS

Although psychotic symptoms may be a prominent part of schizophrenia, not all psychoses indicate a primary psychiatric disorder such as schizophrenia. Broadly, psychoses can be categorized as primary or secondary.

Primary psychoses include schizophrenia, schizoaffective disorder, schizophreniform disorder, brief psychotic disorder, delusional disorder, and mood disorders (major depressive disorder and borderline personality disorder) with psychotic features.[1] Difficulty in distinguishing between these entities can necessitate referral to a psychiatrist.

Secondary psychoses arise from a precursor such as delirium, dementia, medical illness, or adverse effects of medications or illicit substances. Medical illnesses that cause psychotic symptoms include:[5,8]

- seizures (especially temporal lobe epilepsy),
- cerebrovascular accidents,
- intracranial space-occupying lesions,
- neuropsychiatric disorders (eg, Wilson's or Parkinson's disease),
- endocrine disorders (eg, thyroid or adrenal disease),
- autoimmune disease (eg, systemic lupus erythematosus, Hashimoto encephalopathy),
- deficiencies of vitamins A, B_1, B_{12}, or niacin,
- infections (eg, human immunodeficiency virus [HIV], encephalitis, parasites, and prion disease),
- narcolepsy, and
- metabolic disease (eg, acute intermittent porphyria, Tay-Sach's disease, Niemann-Pick disease).

Several recreational drugs can cause psychotic symptoms: cocaine, amphetamines, cannabis, synthetic cannabinoids, inhalants, opioids, and hallucinogens. Psychotic symptoms can also appear during withdrawal from alcohol (delirium tremens) and from sedative hypnotics such as benzodiazepines. Prescribed medications such as anticholinergics, corticosteroids, dopaminergic agents (L-dopa), stimulants (amphetamines), and interferons can also induce psychotic symptoms.

First rule out causes of secondary psychosis

Rule out causes of secondary psychosis by conducting a detailed history and physical examination and ordering appropriate lab tests and imaging studies. If the patient's psychosis is of recent onset, make sure the laboratory work-up includes a complete blood count (CBC), renal function testing, urine culture and sensitivity and urine toxicology, and measures of electrolytes, blood glucose, thyroid-stimulating hormone (TSH), vitamin B_{12}, folic acid, erythrocyte sedimentation rate (ESR), antinuclear antibodies (ANA), HIV antibody, and serum fluorescent treponemal antibody absorption (FTA-ABS).[9]

Consider cranial computed tomography or magnetic resonance imaging if there are focal neurologic deficits or if the patient's presentation is atypical (eg, new onset psychosis in old age).[9] Clinical presentation may also indicate a need for electroencephalography, ceruloplasmin measurement, a dexamethasone suppression test, a corticotropin stimulation test, 24-hour urine porphyrin and copper assays, chest radiography, or cerebrospinal fluid analysis.[9]

FACTORS TO CONSIDER IN TREATMENT DECISIONS

Although primary care physicians may encounter individuals experiencing their first episode of psychosis, it's more likely that patients presenting with signs and symptoms of the disorder have been experiencing them for some time and have received no psychiatric care. In both instances, schizophrenia is best managed in conjunction with a psychiatrist until symptoms are stabilized.[5] Psychosis does

All antipsychotic agents are comparably effective, but adverse effects differ.

Patients with schizophrenia have a higher incidence of medical illness—particularly cardiovascular disease—than the general population.

TABLE 1

Antipsychotic agents and recommended dosages[5,8]

Drug	Dosage (mg/d)
First-generation antipsychotics	
Chlorpromazine	300-1000
Haloperidol	5-20
Perphenazine	16-64
Second-generation antipsychotics	
Aripiprazole	10-30
Asenapine	5
Clozapine	150-600
Lurasidone	40-160
Olanzapine	10-30
Paliperidone	3-12
Quetiapine	300-800
Risperidone	2-8
Ziprasidone	120-200

not always require hospitalization. But urgent psychiatry referral is recommended, if possible. Consider admission to a psychiatric inpatient unit for anyone who poses a danger to self or others.[8,10]

Treatment for schizophrenia is most effective with an interprofessional and collaborative approach that includes medication, psychological treatment, social supports, and primary care clinical management.[11,12] The last aspect takes on particular importance given that people with schizophrenia, compared with the general population, have a higher incidence of medical illness, particularly cardiovascular disease.[13]

Medications (TABLE 1[5,8]) are grouped into first-generation antipsychotics (FGAs) and second-generation, or atypical, antipsychotics (SGAs), with the 2 classes being equally effective.[14-16] Quality of life is also similar at one year for patients treated with either drug class.[14]

Adverse effects can differ. The main difference between these medications is their adverse effect profiles. FGAs cause extrapyramidal symptoms (dystonia, akathisia, and tardive dyskinesia) more often than SGAs. Among the SGAs, olanzapine, asenapine, paliperidone, clozapine, and quetiapine cause significant weight gain, glucose dysregulation, and lipid abnormalities.[5,8,12,17] Clozapine is associated with agranulocytosis, as well. Risperidone causes mild to moderate weight gain.[5,8,12,17] Aripiprazole, lurasidone, and ziprasidone are considered weight neutral and cause no significant glucose dysregulation or lipid abnormalities.[5,8,12,17] All antipsychotics can cause QT prolongation and neuroleptic malignant syndrome.[5,8,12,17]

Keys to successful treatment. Antipsychotics are most effective in treating positive symptoms of schizophrenia and show limited, if any, effect on negative or cognitive symptoms.[18,19] Give patients an adequate trial of therapy (at least 4 weeks at a therapeutic dose) before discontinuing the drug or offering a different medication.[20] All patients who report symptom relief while receiving antipsychotics should receive maintenance therapy.[12]

TABLE 2

Long-acting injectable antipsychotics[21]

Generic name	Dose (mg)	Frequency (weeks)
Risperidone	25-50	Q 2
Paliperidone palmitate	34-234	Q 4
	273-819	Q 12
Olanzapine pamoate	150-405	Q 2-4
Aripiprazole	300-400	Q 4
	441-882	Q 4
Haloperidol decanoate	50-200	Q 4
Fluphenazine decanoate	12.5-100	Q 2

TABLE 3

Monitor these parameters when treating patients with antipsychotics[23-27]

Parameter	Baseline	6 weeks	12 weeks	Quarterly	Annually
Medical history	x				x
Blood pressure	x	x	x	x	x
Body mass index	x	x	x	x	x
Waist circumference	x	x			x
Fasting glucose level	x	x	x		x
Fasting lipid levels	x	x	x		x
Lifestyle choices	x	x	x	x	x
Smoking status	x	x	x	x	x
Electrocardiogram (EKG)	No consensus. Consider an EKG when: using other QT-prolonging medications, increasing the dosage of an antipsychotic agent, or when the patient has baseline CVD risk factors or a history of syncope.				

CVD, cardiovascular disease.

As with all chronic illnesses, success in managing schizophrenia requires patient adherence to the medication regimen. Discontinuation of antipsychotics is a common problem in schizophrenia, resulting in relapse. Long-acting injectable agents (LAIs) were developed to address this problem (**TABLE 2**).[21] Although LAIs are typically used to ensure adherence during maintenance treatment, recent research has suggested they may also be effective for patients with early-phase or first-episode disease.[22]

What to watch for. Patients on SGAs may develop metabolic abnormalities, and ongoing monitoring of relevant parameters is key (**TABLE 3**[23-27]). More frequent monitoring may be necessary in patients with cardiovascular risk factors. Continue antipsychotics for at least 6 months to prevent relapse.[12] Also keep in mind the "Choosing Wisely" recommendation from the American Psychiatric Association of not prescribing 2 or more antipsychotics concurrently.[28]

Adjunctive treatment should also be offered

In addition to receiving medication, patients with schizophrenia should be offered adjunctive therapies such as cognitive behavioral therapy, family intervention, and social skills training.[10-12] Among patients with schizophrenia, the incidences of anxiety disorder, panic symptoms, posttraumatic stress disorder, and obsessive compulsive disorder are higher than in the general population.[29] To address these conditions, medications such as selective serotonin reuptake inhibitors and anxiolytics can be used simultaneously with antipsychotic agents.

CLINICAL COURSE AND PROGNOSIS CAN VARY

Schizophrenia can have a variable clinical course that includes remissions and exacerbations, or it can follow a more persistently chronic course.

Mortality for patients with schizophrenia is 2 to 3 times higher than that of the general population.[30] Most deaths are due to an increased incidence of cardiovascular disease, respiratory illness, cancer, stroke, and other thromboembolic events.[30]

The lifetime prevalence of suicide attempts among individuals with schizophrenia is 20% to 40%,[31] and approximately 5% complete suicide.[32] Risk factors include command hallucinations, a history of suicide attempts, intoxication with substances, anxiety, and physical pain.[32] Clozapine has been shown to reduce suicide risk and may be considered for patients who are at high risk for suicide.[32]

Therapeutic response varies among patients with schizophrenia, with one-third remaining symptomatic despite adequate treatment regimens.[4]

CONTINUED

Consider a long-acting agent if patient adherence to treatment is uncertain.

CARE MANAGERS CAN HELP ADDRESS BARRIERS TO CARE

Certain patient, provider, and health care system factors can hamper the provision of primary care to people with schizophrenia. Symptoms of the illness may disrupt the patient's ability to engage with a provider or clinic. Access to mental health services may be limited based on geography. Even when primary care and mental health services are available, a patient with schizophrenia can find it challenging to schedule appointments. Reducing such barriers by using care managers may be an effective way to improve the overall quality and effectiveness of primary care for patients with schizophrenia.[33]

A review of the literature suggests that up to one-third of individuals with serious mental illnesses who have had some contact with the mental health system disengage from care.[12] Poor engagement may lead to worse clinical outcomes, with symptom relapse and rehospitalizations. Disengagement from treatment may indicate a patient's belief that treatment is not necessary, is not meeting his or her needs, or is not being provided in a collaborative manner.

Although shared decision-making is difficult with patients who have schizophrenia, emerging evidence suggests that this approach coupled with patient-centered care will improve engagement with mental health treatment.[12] Models of integrated care are being developed and have shown promise in ensuring access to behavioral health for these patients.[34]

CASE ▶

The primary care physician talked with Mr. R and his mother about the diagnosis of schizophrenia. He screened for suicide risk, and the patient denied having suicidal thoughts. Both the patient and his mother agreed to his starting medication.

Blood and urine samples were collected for a CBC and ESR, as well as to evaluate renal function, electrolytes, glucose, TSH, vitamin B_{12}, folic acid, ANAs, and HIV antibodies. A serum FTA-ABS test was done, as was a urine culture and sensitivity test and a toxicology screen. Because of the patient's obesity, the physician decided to prescribe a weight-neutral SGA, aripiprazole 10 mg/d. The physician spoke with the clinic's care coordinator to schedule an appointment with the psychiatry intake department and to follow up on the phone with the patient and his mother. He also scheduled a follow-up appointment for 2 weeks later.

At the follow-up visit, the patient showed no improvement. His blood and urine test results revealed no metabolic abnormalities or infectious or inflammatory illnesses. His urine toxicology result showed no illicit substances. The physician increased the dosage of aripiprazole to 15 mg/d and asked the patient to return in 2 weeks.

At the next follow-up visit, the patient was more verbal and said he was not hearing voices. His mother also acknowledged an improvement. He had already been scheduled for a psychiatry intake appointment, and he and his mother were reminded about this. Mr. R was also asked to make a follow-up primary care appointment for one month from the current visit. JFP

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