Schizophrenia in adults: Clinical features, assessment, and diagnosis

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INTRODUCTION

Schizophrenia is a psychiatric disorder involving chronic or recurrent psychosis. It is commonly associated with impairments in social and occupational functioning [1]. It is among the most disabling and economically catastrophic medical disorders, ranked by the World Health Organization as one of the top 10 illnesses contributing to the global burden of disease [2].

This topic discusses clinical manifestations, diagnosis, and course of schizophrenia. The epidemiology and pathogenesis of schizophrenia in adults and children, and their treatment are discussed separately.

- (See "Psychosis in adults: Epidemiology, clinical manifestations, and diagnostic evaluation".)
- (See "Schizophrenia in adults: Epidemiology and pathogenesis".)
- (See "Depression in schizophrenia".)
- (See "Anxiety in schizophrenia".)
- (See "Schizophrenia in adults: Maintenance therapy and side effect management".)
- (See "Co-occurring schizophrenia and substance use disorder: Epidemiology, pathogenesis, clinical manifestations, course, assessment and diagnosis".)
- (See "Schizophrenia in adults: Psychosocial management".)
- (See "Schizophrenia in children and adolescents: Epidemiology, clinical features, assessment, and diagnosis".)

- (See "Psychosocial interventions for schizophrenia in children and adolescents".)

CLINICAL MANIFESTATIONS

Schizophrenia is a syndrome. Individuals with schizophrenia generally present with several symptom domains (ie, areas of distinct psychopathology):

- Positive symptoms
- Negative symptoms
- Cognitive impairment
- Mood and anxiety symptoms

Additionally, there are associated physical manifestations and psychological considerations relevant to the diagnosis.

Positive symptoms — This group of symptoms includes the reality distortion symptoms of hallucinations and delusions, as well as disorganized thoughts and behavior [3-5].

Hallucinations — Hallucinations are defined as the perception of a sensory process in the absence of an external source. They can be auditory, visual, somatic, olfactory, or gustatory.

- Auditory hallucinations are the most common form of hallucination, with prevalence estimates between 40 and 80 percent in people with schizophrenia [6,7]. Although auditory hallucinations are frequently voices, they can also take the form of other sounds such as music, body noises, or machinery. Some people with schizophrenia describe the sounds as coming from inside their head, whereas others can point to a specific external location from which they emanate. Auditory hallucinations are often the manifestation of the illness most responsive to antipsychotic medication. Many people with schizophrenia report antipsychotics "turn down the volume" of these hallucinations such that they can cope with them better.

- Visual hallucinations are often unformed, such as glowing orbs or flashes of color. However, some people with schizophrenia describe fully formed human figures, faces, or body parts.

- Somatic hallucinations can include feelings of being touched, of sexual intercourse, or of pain.

- Olfactory and gustatory hallucinations have not been systematically studied, but occasional patients will report a strange taste or smell.

Delusions — Delusions are defined as a fixed, false belief and are present in approximately 80 percent of people with schizophrenia [7]. Because insight into their illness may be impaired, people with schizophrenia often have delusional explanations for their hallucinations. Delusions are broadly categorized as bizarre or nonbizarre although the distinction is less important in the current diagnostic rubric.

- Bizarre delusions are clearly implausible (ie, they have no possibility of being true; eg, contradict the laws of physics). Their content is not understandable [8]. Basic concepts may be described in an unusual way (eg, how the person experiences time, space, the self, or causality) [9]. An example of a bizarre delusion is the belief that aliens have cloned a perfect body for the patient, but he must find a way to take off his head so that his spirit can flow into the new body.

- A nonbizarre delusion is one that while not true is understandable and has the possibility of being true. An example is that the Internal Revenue Service is after the patient for not paying taxes.

The content of delusions can often be categorized as ideas of reference, grandiose, paranoid, nihilistic, and erotomanic.

- Ideas/delusions of reference are beliefs that random or neutral events are not random or neutral, but include the individual in a special way. Common ideas of reference include believing that occurrences on the television or radio (certain words said or songs played) are meant to deliver a special message to the individual.

- Grandiose delusions form around the belief that the person has some special significance or power.

- Paranoid delusions are clinically important, because they may prevent the individual from cooperating with evaluation or treatment, and because they may increase the likelihood of problems, such as homelessness, as the person goes "off the grid."

- Nihilistic delusions are uncommon beliefs that are defined in the American Psychiatric Association's Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, Text Revision (DSM-5-TR) as the conviction that a major catastrophe will occur. However, other definitions of nihilistic delusions include the delusional belief of being dead, decomposed or annihilated, having lost one's own internal organs or even not existing entirely as a human being.

- In erotomanic delusions, the person erroneously believes that they have a special relationship with someone. These delusions can lead to legal problems, such as restraining orders and trespass charges.

Disorganization — People with schizophrenia typically display some disorganization in behavior and/or thinking. Disorganized behaviors are directly observed while disorganized thoughts must be inferred from the speech of the person. Disjointed, disconnected speech patterns reflect a disruption in the organization of person's thoughts. The most commonly observed forms of abnormal speech are tangentiality and circumstantiality, while more severe thought disorder includes derailment, neologisms, and word salad. The symptoms of disorganization are independent of the severity of hallucinations or delusions [10].

- Tangential speech – The person gets increasingly further off the topic without appropriately answering a question.
- Circumstantial speech – The person will eventually answer a question, but in a markedly roundabout manner.
- Derailment – The person suddenly switches topic without any logic or segue.
- Neologisms – The creation of new, idiosyncratic words.
- Word salad – Words are thrown together without any sensible meaning.

Negative symptoms — Negative symptoms are conceptualized as an absence or diminution of normal processes. Negative symptoms are usually one of the first manifestations of schizophrenia; up to 70 percent of patients experience negative symptoms prior to their first positive symptom [11].

- **Negative symptoms may be primary or secondary** – Primary, enduring negative symptoms represent a core feature of schizophrenia. These are also referred to as deficit symptoms.

  Primary negative symptoms are very resistant to treatment [12-14] and closely related to functional outcome [15,16]. The severity of negative symptoms is independent of the reality distortion positive symptoms (ie, hallucinations and delusions) [17]. A person may simultaneously have deficit symptoms and be quite psychotic, or have deficit symptoms in the absence of positive symptoms.

  Alternatively, negative symptoms may be secondary to other manifestations of the illness or its treatment. As examples, paranoia may lead to social isolation, and depression may

lead to anergy. An unchanging facial expression may be due to extrapyramidal symptoms of an antipsychotic medication.

Negative symptoms appear to cluster into two main components: a diminished expression component, which includes blunted affect and alogia, and an avolition-apathy component, which includes anhedonia, avolition, and asociality [11,18-20]. Individual patients may present with any of the five symptoms, which make up these two components. A table lists negative symptoms (table 1).

The recognition of these two components may facilitate understanding of the pathophysiology of negative symptoms and lead to the development of novel therapeutics. For example, the symptom of anhedonia can be conceptualized as representing two distinct aspects: "liking" something that is pleasurable (consummatory pleasure) and "wanting" something pleasurable (seeking or anticipating pleasure). Studies have indicated that people with schizophrenia do not show consistent deficits in experiencing pleasure; rather, the deficit appears to be in pleasure seeking [21]. This may reflect cognitive impairment (ie, a failure to accurately represent pleasurable activities in memory) or avolition [21]. Avolition is a reduction of goal-directed activities due to a lack of interest or drive [22]. This lack of drive may affect activities of daily living such as decreased hygiene as well as more complex behaviors such as work [22]. Development of treatments targeted to avolition has the potential to both increase quality of life and decrease the economic burden of the illness.

- **Deficit schizophrenia** – While not a recognized DSM-5-TR subtype of schizophrenia, people with schizophrenia who have prominent negative (or deficit) symptoms as a primary manifestation of the illness (eg, not akinesia due to antipsychotic-related parkinsonism or social isolation secondary to paranoia), appear to represent a distinct subgroup [17]. People with deficit schizophrenia are less likely to have delusions with high emotional content (eg, jealous delusions), to have a depressive disorder, or to have a substance use disorder compared with nondeficit schizophrenia [16,23,24]. People categorized as deficit are least likely to show improvement and recovery over the course of the illness. (See "Schizophrenia in adults: Epidemiology and pathogenesis", section on 'Deficit schizophrenia'.)

Cognitive impairment — Areas of cognition that seem to be the most affected in schizophrenia are described below [25]. It is not known whether these areas reflect multiple unique impairments, or a generalized impairment that affects multiple areas of cognition [26,27].

- Processing speed
- Attention
- Working memory
- Verbal learning and memory
- Visual learning and memory
- Reasoning/executive functioning
- Verbal comprehension
- Social cognition

These impairments are reflected in the performance on neuropsychological tests among people with schizophrenia. On average, the neuropsychological test performance of someone with schizophrenia is one to two standard deviations lower than the performance of healthy controls [26,28]. If an individual tests within the normal range on any given neuropsychological battery, then their premorbid performance was very likely to have been above average. People with schizophrenia who appear to lack cognitive impairment, when matched to healthy controls on age, education, and intelligence quotient (IQ), may actually show a unique pattern of performance impairments in memory and processing speed [29,30].

Cognitive impairments usually precede the onset of positive symptoms [31]. Impairment in the performance of cognitive tasks in people with first-episode schizophrenia is usually of a similar magnitude as that seen in people with multiple episodes [32]. The same pattern of cognitive impairment is observed in the family members of people with schizophrenia, though the magnitude of impairment is less [33]. In a study of monozygotic twins discordant for the disorder, affected twins performed worse on tests of memory and vigilance than the unaffected siblings [34].

Although antipsychotic and anticholinergic medications can impair cognition [35,36], reports of memory disturbances in schizophrenia frequently predate the advent of pharmacologic treatment [37]. The same pattern of cognitive dysfunction in people with schizophrenia is seen in both treated groups and those who have never been exposed to antipsychotics [38].

Older individuals with schizophrenia have an increased risk of receiving a diagnosis of dementia [39]. In a retrospective study using United States Medicare data, over 74,000 individuals with a diagnosis of schizophrenia were compared with 7.9 million individuals without serious mental illness [39]. At 66 years of age, the prevalence of dementia diagnosis in individuals with schizophrenia was greater than in the comparator group (28 versus 1 percent). At 80 years of age, the prevalence was 70 versus 11 percent, respectively. While the cause of the increased rate of dementia among these individuals is not fully understood, the association of schizophrenia with other risk factors for dementia, such as cardiovascular disease,

hyperlipidemia, smoking, and substance use may play a role. Additionally, the role of decreased cognitive reserve and the use of psychotropic medications may be contributory.

Mood and anxiety symptoms — Mood and anxiety symptoms are common in schizophrenia; mood and anxiety disorders appear to occur at a higher rate than in the general population. The epidemiology, clinical manifestations, diagnosis, and treatment of mood and anxiety symptoms in schizophrenia are discussed separately. (See "Depression in schizophrenia" and "Anxiety in schizophrenia".)

Insight — It is common for people with schizophrenia to demonstrate a lack of awareness of their illness. This can result in difficulties forming a therapeutic alliance with clinicians and in adhering to prescribed treatment. A meta-analysis of 21 studies including over 3000 patients with psychotic disorders confirmed that insight can be improved with treatment [40]. However, improved insight can be associated with increased perceived stigma. A meta-analysis of 20 studies including over 1000 patients with schizophrenia showed insight was inversely related to reported quality of life [41].

- **Stigma** – In the course of assessment and ongoing clinical care, we are an important source of compassion and education for the patient and family. Along with treatment for symptoms and medication side effects, the patient may need help coping with disabilities, associated losses, and the stigma associated with the diagnosis of schizophrenia. The experience of stigmatizing attitudes towards people with schizophrenia is common [42] and may be internalized, leading to "self-stigma" [43]. Internalized stigma can be as damaging as the direct effects of the illness. In a five-month longitudinal study of 78 people with schizophrenia, internalized stigma was associated with poorer response to vocational rehabilitation [44]. A discriminant function analysis of 105 people with schizophrenia found that self-stigma was a predictor of decreased treatment adherence [45,46].

Associated physical manifestations — There are several physical manifestations associated with schizophrenia, including neurological disturbances, catatonia, sleep disturbances, and metabolic disturbances.

Neurological disturbances — Neurological "soft signs" involve subtle impairments of sensory integration, motor coordination, and sequencing [47]. Examples of neurological soft signs are right-left confusion, agraphesthesia (the inability to recognize letters or numbers traced on the skin, usually on the palm of the hand), and astereognosia (the inability to identify familiar objects by touch alone). These neurological soft signs are observed in schizophrenia, are relatively stable, and are largely unrelated to medication [47-50].

Research findings have linked certain symptom domains to neurological signs (ie, sensory integration problems have been correlated with deficit symptoms, disorganization, and cognitive impairment), while impaired sequencing of complex motor behaviors has been correlated with disorganization [49,50].

Antipsychotic dopamine blockade can cause extrapyramidal symptoms, such as tremor and bradykinesia, acute dystonias, akathisia (a subjective sense of restlessness or actual restlessness), or tardive (meaning 'late') dyskinesia (which includes abnormal peri-oral and other movements). However, descriptions of movement disorders including signs of pseudoparkinsonism, choreiform movements, and myoclonic jerking are common in the descriptions of schizophrenia that predate the development of antipsychotics [38].

- (See "First-generation antipsychotic medications: Pharmacology, administration, and comparative side effects".)
- (See "Second-generation antipsychotic medications: Pharmacology, administration, and side effects".)
- (See "Tardive dyskinesia: Etiology, risk factors, clinical features, and diagnosis", section on 'Clinical spectrum'.)
- (See "Schizophrenia in adults: Maintenance therapy and side effect management", section on 'Side effect management'.)

Catatonia — Catatonia can present in schizophrenia as either extreme negativism (eg, motiveless motor resistance to instruction or attempts to move the person or mutism) or catatonic excitement (eg, excessive, purposeless motor activity). Catatonia is reviewed in more detail separately. (See "Catatonia in adults: Epidemiology, clinical features, assessment, and diagnosis".)

Sleep disturbances — Sleep disturbances are reported by up to 80 percent of people with schizophrenia [51]. Per some patients and caregivers, poor sleep may be a marker of impending relapse. Poor sleep may be more than an epiphenomenon of the illness; it may have a causative role in exacerbations of psychosis and cognitive impairment [51,52]. Types of sleep disturbances in schizophrenia range from obstructive sleep apnea (which may be related to body habitus secondary to metabolic disturbances) to disruptions of sleep architecture and circadian rhythms [51]. Although factors such as duration of illness and medication may impact findings, people with schizophrenia have been observed to exhibit increased stage 2 latency, decreased rapid eye movement latency, and reduced sleep spindle density [52,53]. There is speculation that dopamine and gamma amino butyric acid (GABA) receptor abnormalities observed in schizophrenia may inappropriately promote wakefulness (ie, increased activity at D2 receptors and decreased activity at GABA receptors) [53].

Metabolic disturbances — Schizophrenia is associated with diabetes, hyperlipidemia, and hypertension. Although many antipsychotic medications cause metabolic disturbances, including weight gain and diabetes, people with schizophrenia often have other risk factors for these conditions, including a sedentary lifestyle and smoking. The life expectancy of people with schizophrenia is reduced by more than a decade compared with the general population. This excess medical mortality is largely mediated by heart disease [54]. (See "Schizophrenia in adults: Maintenance therapy and side effect management", section on 'Metabolic dysregulation'.)

Schizophrenia, independent of treatment with antipsychotic medication, is associated with altered glucose homeostasis, indicating an increased risk of diabetes. A meta-analysis examined 16 case-control studies of glucose homeostasis in 731 antipsychotic-naive individuals with first-episode schizophrenia compared with 614 healthy controls [55]. Higher levels of fasting plasma glucose (Hedges' g 0.20, 95% CI 0.02-0.38) and fasting plasma insulin (0.41, 95% CI 0.09-0.72) were seen as well as lower glucose tolerance (0.61, 95% CI 0.16-1.05) and greater insulin resistance (0.35, 95% CI 0.14-0.55) in people with schizophrenia compared with controls. Hemoglobin A1c levels did not differ between the two groups.

There is also evidence from the pre-antipsychotic era and insulin coma treatments that schizophrenia itself is associated with insulin resistance [56].

COMORBID GENERAL MEDICAL DISORDERS

People diagnosed with schizophrenia are at increased risk of developing several co-occurring medical conditions. In a Danish national registry study, investigators compared people carrying a diagnosis of schizophrenia with age- and sex-matched controls who did not have a diagnosis of schizophrenia (sample sizes not reported) [57]. People with schizophrenia had an increased risk for circulatory, endocrine, gastrointestinal, hematological, pulmonary, and urogenital disorders (hazard ratios ranging from approximately 1.2 to 1.7). In other studies, schizophrenia has been prominently associated with greater rates of cardiovascular disease, dyslipidemia, dementia [39,58], and type 2 diabetes compared with the general population, with a resulting decrease in average lifespan of up to 20 years [59,60]. Although some diabetes risk is attributable to medications, increased rates of diabetes and insulin resistance in people with schizophrenia predate antipsychotics, and may also be related to shared genetics, lifestyle, and/or diet [56,61].

COURSE OF ILLNESS

Heterogeneity — Although earlier descriptions of schizophrenia suggested that the course was quite poor, the course actually shows considerable heterogeneity. One of the first and most influential longitudinal studies described eight course types, which differ in several ways [62]:

- Onset – Abrupt versus insidious
- Symptom presentation – Continuous versus intermittent
- Outcome – Poor versus nonpoor

Most people with schizophrenia in the study had an acute onset, intermittent symptoms, and later had no or only mild symptoms. Only approximately 20 percent had the stereotypical insidious onset, continuous symptoms, and poor outcome. In a re-examination of these data, participants were re-diagnosed with more stringent criteria, and the results among those retaining a schizophrenia diagnosis were largely unchanged from the original course observations [63].

Other influential longitudinal studies of schizophrenia demonstrate that the course of schizophrenia is not uniform and that there are subsets of individuals with fairly good outcome [64-66]. A 15- to 25-year follow-up of 644 participants with schizophrenia who participated in World Health Organization studies (including the International Pilot Study of Schizophrenia and the Determinants of Outcome of Severe Mental Disorders study) found that approximately half had favorable outcomes (minimal or no symptoms, employment, Global Assessment of Functioning scores greater than 60) [66,67].

Though the course of schizophrenia may be heterogenous, functional recovery tends to be less common earlier in the illness. In a medication algorithm study, only approximately 14 percent of 118 people with a first episode of schizophrenia or schizoaffective disorder met recovery criteria for two or more years during the first five years of the illness [68]. Recovery in this study was defined as no more than mild psychotic symptoms, no more than moderate negative symptoms, adequate role function (student, employment, homemaker), attention to hygiene, and independence in daily chores.

Factors influencing course — The course of illness is affected by numerous factors, including early intervention and utilization of a multidisciplinary care approach, symptom types, level of stressors, socioeconomic factors, and effectiveness and adherence to medication regimen.

Early intervention and multidisciplinary treatment — Timely, intensive treatment can positively impact psychosocial functioning early in the illness. Treatment programs offering multicomponent interventions have been associated with lower rehospitalization rates, lower core illness symptoms, and improved interpersonal and everyday living skills in patients recovering from first episode of psychosis [69-71].

Comprehensive review of pharmacologic and psychosocial management of patients with schizophrenia is discussed elsewhere. (See "Schizophrenia in adults: Maintenance therapy and side effect management", section on 'Multidisciplinary care' and "Schizophrenia in adults: Psychosocial management", section on 'Multimodal interventions'.)

Substance use — Numerous epidemiological studies have implicated co-occurring substance use disorders in poorer prognosis in schizophrenia [72-74]. (See "Co-occurring schizophrenia and substance use disorder: Epidemiology, pathogenesis, clinical manifestations, course, assessment and diagnosis".)

Stressors — External stressors may have an impact on the course of schizophrenia. A systematic review of observational and retrospective studies suggested that stressful events such as trauma, bereavement, financial problems, and interpersonal conflict are associated with relapse of psychosis [75].

Deficit schizophrenia — Persons with the deficit form of schizophrenia (eg, with primary and enduring negative symptoms) seem to have a more consistently poor prognosis compared with their nondeficit peers [15,16]. (See "Schizophrenia in adults: Epidemiology and pathogenesis", section on 'Deficit schizophrenia' and 'Insight' above.)

Effects of adherence to medication — Effectiveness of medications and assessment and treatment of nonadherence to medications are discussed in detail elsewhere. (See "Psychosis in adults: Initial management", section on 'Antipsychotic therapy' and "Schizophrenia in adults: Maintenance therapy and side effect management", section on 'Nonadherence'.)

Suicide — The rate of suicide among people with schizophrenia is much higher than in the general population. In a retrospective study including over 668,000 individuals with schizophrenia using United States Medicare data, the rate of suicide was found to be over four times higher than the general population (standardized mortality ratio 4.5, 95% CI 4.4-4.7) [76]. The rate of suicide was highest in the youngest age group (18 to 34 years; standardized mortality ratio 10.2, 95% CI 9.3-11.2) and declined with age (≥65 years; standardized mortality ratio 1.5, 95% CI 1.3-1.8). Approximately 5 percent of people with schizophrenia commit suicide over their lifetime [77]. Among all completed suicides, approximately 10 percent occur in people with schizophrenia [78,79].

However, treatment can decrease the risk of suicide [80]. In a two-year randomized trial that compared clozapine with olanzapine in patients with schizophrenia and schizoaffective disorder (n = 980), fewer suicide attempts occurred with clozapine (34 versus 55) [81]. (See "Schizophrenia in adults: Guidelines for prescribing clozapine".)

In addition, treatment with antipsychotic medication may decrease the long-term risk of suicide mortality. A national registry study identified patients with schizophrenia (n >60,000) who were followed for a median of 14 years, and compared the rate of suicide during periods of antipsychotic use with the rate during periods of nonuse [82]. After adjusting for some potential confounding factors (eg, age, duration of illness, and comorbidities), the analyses found that fewer suicide deaths occurred during antipsychotic use than during nonuse (adjusted hazard ratio 0.5, 95% CI 0.4-0.6). The analyses also found that the cumulative all-cause mortality rates were lower during antipsychotic use than nonuse (26 versus 46 percent). However, not every antipsychotic was associated with a similar reduction in mortality.

Remission and recovery — Remission of schizophrenia refers to a state in which the individual has no symptoms, or minimal symptoms which do not interfere with behavior, for a period of at least six months [83,84].

Over the past decade, consumer advocacy has drawn attention to the concept of recovery from schizophrenia. The model of recovery that has emerged differs from a strictly clinical model of recovery (eg, no or mild symptoms, restored functioning). The consumer-driven model is a blend of function, life-satisfaction, and independence. Despite scientific efforts to capture this outcome, there are no accepted scales to measure recovery [85].

ASSESSMENT

The assessment of individuals with psychosis (including schizophrenia and other medical or psychiatric causes) are described separately. (See "Psychosis in adults: Epidemiology, clinical manifestations, and diagnostic evaluation", section on 'Diagnostic evaluation' and 'Differential diagnosis' below.)

DIAGNOSIS

The diagnosis of schizophrenia requires the presence of "characteristic symptoms" of the disorder (delusions, hallucinations, disorganized speech or behavior, and/or negative symptoms) coupled with social and/or occupational dysfunction for at least six months in the absence of another diagnosis that would better account for the presentation.

DSM-5-TR diagnostic criteria for schizophrenia are described in more detail below [1].

- A. Two or more of the characteristic symptoms below are present for a significant portion of time during a one-month period (or less if successfully treated):

  - 1. Delusions
  - 2. Hallucinations
  - 3. Disorganized speech (eg, frequent derailment or incoherence)
  - 4. Grossly disorganized or catatonic behavior
  - 5. Negative symptoms (ie, affective flattening, alogia, or avolition)

- B. For a significant portion of the time since the onset of the disturbance, one or more major areas of functioning such as work, interpersonal relations, or self-care are markedly below the level achieved prior to the onset. When the onset is in childhood or adolescence: failure to achieve expected level of interpersonal, academic, or occupational achievement.

- C. Continuous signs of the disturbance persist for at least six months. The six-month period must include at least one month of symptoms (or less if successfully treated) that meet Criterion A (ie, active-phase symptoms) and may include periods of prodromal or residual symptoms. During these prodromal or residual periods, the signs of the disturbance may be manifested by only negative symptoms or two or more symptoms listed in Criterion A that present in an attenuated form (eg, odd beliefs, unusual perceptual experiences).

- D. Schizoaffective disorder and mood disorder with psychotic features have been ruled out because either: (1) no major depressive, manic, or mixed episodes have occurred concurrently with the active-phase symptoms; or (2) if mood episodes have occurred during active-phase symptoms, their total duration has been brief relative to the duration of the active and residual periods.

- E. The disturbance is not due to the direct physiological effects of a substance (eg, a drug of abuse or medication) or a general medical condition.

- F. If the patient has a history of autistic disorder or another pervasive developmental disorder, the additional diagnosis of schizophrenia is made only if prominent delusions or hallucinations are also present for at least a month (or less if successfully treated).

Specifiers for schizophrenia in DSM-5-TR — The following course specifiers can be applied only after at least one year has elapsed since the initial onset of the disorder.

Specify if:

- First episode, currently in acute episode
- First episode, currently in partial remission
- First episode, currently in full remission

- Multiple episodes, currently in acute episode
- Multiple episodes, currently in partial remission
- Multiple episodes, currently in full remission
- Continuous
- Unspecified

Specify if: with catatonia

Specify current severity: Each of the following symptoms may be rated for its highest severity in the last seven days. A five-point scale is used: from 0 (not present) to 4 (present and severe).

- Delusions
- Hallucinations
- Disorganized speech
- Abnormal psychomotor behavior
- Negative symptoms

Differential diagnosis — In the differential diagnosis of schizophrenia, the most common psychiatric disorders include schizophreniform disorder, schizoaffective disorder, bipolar disorder, major depression with psychotic features, and substance-induced psychotic disorders. Psychosis due to a general medical condition should be ruled out. Characteristics of disorders informing the differential diagnosis of schizophrenia are described below. An algorithm describes the differential diagnosis of psychosis (algorithm 1).

Psychiatric

- **Schizophreniform disorder** all the criteria for schizophrenia are met, but the total duration of the disorder is less than six months.

- **Schizoaffective disorder, bipolar disorder, and major depression with psychotic features** all differ from schizophrenia in that there is a prominent mood component to the patient's presentation. Schizoaffective disorder is essentially schizophrenia with manic episodes or a significant depressive component. The validity and reliability of schizoaffective disorder remains unresolved [86].

  The difference between mood disorders with psychosis and schizoaffective disorder is the timing of symptoms:

  - In **schizoaffective disorder**, psychosis occurs in the absence of a mood episode.

- In **psychotic mood disorders** the psychosis is only observed in the presence of a mood episode.

- In **substance-induced psychotic disorders** the symptoms are a manifestation of intoxication or acute withdrawal and do not persist after the individual is sober.

- **Delusional disorder** is present if the individual has a delusion, but criteria for schizophrenia have never been met. An exception to this is that the person may have olfactory or tactile hallucinations consistent with the delusion, but not auditory hallucinations.

- **Schizotypal personality disorder** is a long-standing pattern of odd or eccentric beliefs and/or perceptual disturbances that do not rise to the level of delusions or hallucinations. People with this presentation may eventually transition to a psychotic disorder, but many do not [87].

- **Schizoid personality disorder** is a long-standing pattern of little interest in social relationships or intimacy. There is overlap with the negative symptoms seen in schizoid personality disorder and schizophrenia, but schizoid personality disorder does not present with psychosis.

- **Pervasive developmental disorders** may present with psychosis or negative symptoms. An additional diagnosis of schizophrenia should only be made in a patient with an autism spectrum disorder if psychotic symptoms last more than one month.

The diagnoses of schizophreniform disorder, schizophrenia, schizoaffective disorder, schizotypal personality disorder, and schizoid personality disorder are described collectively as 'schizophrenia spectrum' disorders. Although most researchers believe schizophrenia is likely a syndrome of distinct disease entities, the concept of schizophrenia spectrum disorders is useful for epidemiological research.

In many cases, repeated assessment longitudinally is necessary to definitively diagnose a patient presenting with a schizophrenia spectrum disorder.

General medical

- **Psychosis due to previous cerebrovascular accident or traumatic brain injury** can often be established with the medical history supplemented by neuroimaging studies.

- **Psychosis associated with a major neurocognitive disorder** (eg, Alzheimer disease, Parkinson disease) can often be established with the medical history and physical

examination. People with major cognitive disorders typically experience psychosis late in their illness and usually present earlier with other illness manifestations (eg, memory complaints, tremor).

- **Psychosis due to metabolic errors or infection** (eg, Wilson disease, porphyria, syphilis, or HIV infection) may be suspected from the medical history and physical examination and can be tested for via laboratory studies (eg, ceruloplasmin, rapid plasma reagin).

- **Psychosis due to known genetic disorders** is rare. DiGeorge syndrome (also known as 22q11.2 deletion syndrome) occurs in approximately 1 of every 6000 births. The syndrome can present with a variety of physical (eg, cardiac anomalies, cleft lip/palate) and psychiatric (eg, attention deficit hyperactivity disorder, autism spectrum disorder) manifestations [88]. Up to 25 percent of these individuals will develop schizophrenia that is indistinguishable from schizophrenia in non-DiGeorge populations. Because the treatment for schizophrenia does not differ between DiGeorge-related and non-DiGeorge-related cases, testing for 22q11 deletions in people with schizophrenia is only recommended if DiGeorge is suspected based on medical history or physical examination [89].

ICD-11 diagnosis — The World Health Organization's International Statistical Classification of Disease and Related Health Problems, 11th Revision (ICD-11) is primarily a coding source text and not a diagnostic manual (ie, there is minimal guidance on making a diagnosis) [90]. Psychiatric diseases are listed with a short, prototypical description. The schizophrenia or other psychotic disorders section includes schizophrenia, schizoaffective disorder, schizotypal disorder, acute and transient psychotic disorder, delusional disorder, symptomatic manifestations of primary psychotic disorders, substance-induced psychotic disorder, and schizophrenia or other primary psychotic disorder, unspecified.

SOCIETY GUIDELINE LINKS

Links to society and government-sponsored guidelines from selected countries and regions around the world are provided separately. (See "Society guideline links: Psychotic disorders".)

INFORMATION FOR PATIENTS

UpToDate offers two types of patient education materials, "The Basics" and "Beyond the Basics." The Basics patient education pieces are written in plain language, at the 5th to 6th grade reading level, and they answer the four or five key questions a patient might have about a given condition. These articles are best for patients who want a general overview and who prefer

short, easy-to-read materials. Beyond the Basics patient education pieces are longer, more sophisticated, and more detailed. These articles are written at the 10th to 12th grade reading level and are best for patients who want in-depth information and are comfortable with some medical jargon.

Here are the patient education articles that are relevant to this topic. We encourage you to print or e-mail these topics to your patients. (You can also locate patient education articles on a variety of subjects by searching on "patient info" and the keyword(s) of interest.)

- Basics topics (see "Patient education: Schizophrenia (The Basics)" and "Patient education: Schizoaffective disorder (The Basics)")

SUMMARY AND RECOMMENDATIONS

- **Clinical manifestations** – Clinical manifestations of schizophrenia include positive and negative symptoms, cognitive impairment, and mood or anxiety symptoms. (See 'Clinical manifestations' above.)
  - **Positive symptoms** – Positive symptoms include hallucinations, delusions, and disorganization. (See 'Positive symptoms' above.)
    - Hallucinations are defined as the perception of a sensory process in the absence of an external source. They can be auditory, visual, somatic, olfactory, or gustatory. (See 'Hallucinations' above.)
    - Delusions are defined as a fixed, false belief. They can be bizarre or nonbizarre. Their content can often be categorized as grandiose, paranoid, nihilistic, or erotomanic. (See 'Delusions' above.)
    - Disorganization can typically be seen in both behavior and speech. The most commonly observed forms of abnormal speech are tangentiality and circumstantiality, while more severe thought disorder includes derailment, neologisms, and word salad. (See 'Disorganization' above.)
  - **Negative symptoms** – Primary, enduring negative symptoms (ie, deficit symptoms) represent a core feature of schizophrenia. Examples of negative symptoms include a flat affect, poverty of speech, and a lack of interest or motivation. A table lists other negative symptoms (table 1). Secondary negative symptoms can be caused by antipsychotic medications. (See 'Negative symptoms' above.)

- **Cognitive impairment** – Areas of cognitive impairment that seem to be the most affected in schizophrenia include processing speed, attention, working memory, executive functioning, and social cognition. (See 'Cognitive impairment' above.)

- **Mood and anxiety symptoms** – Mood and anxiety symptoms are common in schizophrenia. Mood and anxiety disorders appear to occur at a higher rate than in the general population. (See 'Mood and anxiety symptoms' above.)

- **Physical manifestations** – Physical manifestations of schizophrenia include neurological "soft signs," catatonia, and metabolic disturbances. Metabolic abnormalities and movement disorders can be caused by schizophrenia itself as well as by antipsychotic medications. (See 'Associated physical manifestations' above.)

- **Course** – The course of schizophrenia shows considerable heterogeneity. The course may be affected by early intervention and utilization of a multidisciplinary care approach, symptom types, level of stressors, socioeconomic factors, and effectiveness and adherence to medication regimen.

- **Suicide** – The rate of suicide among people with schizophrenia is much higher than in the general population. (See 'Suicide' above.)

- **Diagnosis** – The diagnosis of schizophrenia (table 2) requires the presence of two of the five characteristic symptoms below coupled with social and/or occupational dysfunction for at least six months, and the absence of another diagnosis that would better account for the presentation (such as drug use, certain medical conditions, or psychotic mood disorders). (See 'Diagnosis' above.)

  - Delusions
  - Hallucinations
  - Disorganized speech
  - Disorganized or catatonic behavior
  - Negative symptoms

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