First episode psychosis

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INTRODUCTION

Psychosis – ie, a significant impairment in reality testing, as evidenced by symptoms such as hallucinations, delusions, thought disorganization and grossly disorganized behavior – can result from medical and neurological conditions, from use of certain substances, or as a manifestations of a psychiatric disorder.

Psychosis is seen in several psychiatric disorders, including schizophrenia (and other conditions in the schizophrenia spectrum), bipolar disorder, and major depression with psychotic features. In patients ultimately diagnosed with schizophrenia or bipolar disorder, the first episode of psychosis most commonly occurs between the ages of 15 to 30 years [1]. First episode psychosis is typically preceded by subtle premorbid signs in childhood and subsyndromal prodromal symptoms.

Clinical manifestations, differential diagnosis, and initial management of psychosis in adults are reviewed separately. The epidemiology, pathogenesis, clinical manifestations, course, assessment and diagnosis of schizophrenia in adults and children are also reviewed separately. The epidemiology, pathogenesis, clinical features, assessment and diagnosis of bipolar disorder in adults and children are also reviewed separately.

- (See "Psychosis in adults: Epidemiology, clinical manifestations, and diagnostic evaluation".)
- (See "Schizophrenia in adults: Epidemiology and pathogenesis".)

- (See "Schizophrenia in adults: Clinical features, assessment, and diagnosis".)
- (See "Schizophrenia in children and adolescents: Epidemiology, clinical features, assessment, and diagnosis".)
- (See "Unipolar major depression with psychotic features: Epidemiology, clinical features, assessment, and diagnosis".)
- (See "Bipolar disorder in adults: Epidemiology and pathogenesis".)
- (See "Bipolar disorder in adults: Clinical features".)
- (See "Bipolar disorder in adults: Assessment and diagnosis".)
- (See "Pediatric bipolar disorder: Epidemiology and pathogenesis".)
- (See "Pediatric bipolar disorder: Clinical manifestations and course of illness".)
- (See "Pediatric bipolar disorder: Assessment and diagnosis".)

EPIDEMIOLOGY

The incidence of new cases of psychosis worldwide has been estimated at approximately 50 in 100,000 people, while the incidence of new cases of schizophrenia (the most frequent eventual diagnosis among cases of first episode psychosis) is approximately 15 in 100,000 per year [2].

The rate of onset of schizophrenia increases during adolescence, with the peak ages of onset ranging from 15 to 30 years. The peak age of onset is, for males, teens to mid-20s and, for females, teens to the late 20s. Eighteen percent of schizophrenia occurs before age 18 and tends to have a poorer outcome. The distribution by age of new cases of psychosis has not been well studied.

Although psychosis can occur in childhood, it is quite rare (approximately 1 in 10,000) and is more common in boys than girls [3-6]. (See "Emergency department approach to acute-onset psychosis in children" and "Schizophrenia in children and adolescents: Epidemiology, clinical features, assessment, and diagnosis" and "Pediatric bipolar disorder: Clinical manifestations and course of illness".)

PATHOGENESIS

- **Brain changes** – Studies in the first episode and prodrome of psychosis have shown reductions in multiple brain regions including prefrontal, superior, and medial temporal lobe gray matter volumes that are present in the first episode and in those high-risk individuals who go on to develop later psychosis [7]. The neuroanatomical changes in the early stages of psychosis appear to be progressive changes beyond those associated with normal development [8]. Cortical gray matter density declines normally during late adolescent development in the same brain regions implicated in the pathophysiology of schizophrenia.

- **Neurodevelopmental abnormalities** – Schizophrenia, which fully emerges during late adolescence or early adulthood with the onset of psychosis, is a neurodevelopmental disorder that most likely begins to develop in utero [9]. It is likely that pre- or perinatal neurodevelopmental abnormalities may lead to a vulnerability to postpubertal insults that contribute to the accelerated loss of gray matter and aberrant connectivity in the prefrontal regions of vulnerable individuals.

- **Neuropathological mechanisms in early psychosis –** Epigenetic factors, such as substance abuse, stress, and maternal infection, may contribute to a later neurodegenerative process [8,10,11]. While disturbances of neurodevelopment early in life may be necessary for the future emergence of psychosis, environmental influences during the late adolescent period may contribute to the emergence of first episode of psychosis via a range of possible interconnected neuropathological mechanisms, including increased hypothalamic pituitary axis activity, neuroinflammation, N-methyl-D-aspartate receptor hypofunction, glutamatergic or dopaminergic transmission abnormalities and reduced neuroplasticity, all of which are potential targets for early intervention in the prodrome or first episode of psychosis.

  Increasing evidence suggests that the neuropathological changes in the prodrome and first episode of psychosis are dynamic and different than what is observed in the more chronic forms of the illness. This neuroplasticity in early psychosis offers a window of opportunity to alter the course of the illness.

CLINICAL MANIFESTATIONS

Psychotic symptoms — Symptoms of psychosis, including hallucinations, delusions, thought disorganization, agitation, and aggression, are reviewed separately. (See "Psychosis in adults: Epidemiology, clinical manifestations, and diagnostic evaluation".)

Neurocognitive impairment — Neurocognitive deficits are prominent even prior to the onset of psychotic illness and are predictive of a later development of psychotic illness in individuals who demonstrate subsyndromal psychotic symptoms characterizing the psychosis prodrome [12-15]. The following domains of dysfunction are most commonly noted in early psychosis:

- **Memory** – Problems with ability to use information after learning it
- **Attention** – Trouble focusing or paying attention
- **Processing speed** – Speed of information processing
- **Executive function** – The ability to understand information and use it to make decisions

Depression and suicide — Depressive symptoms, including dysphoria, anhedonia, amotivation, sleep disturbance, and suicidal thoughts, may be the presenting symptoms in the prodrome or first episode of psychosis. Depressive symptoms are associated with a less favorable outcome. (See "Depression in schizophrenia".)

At the onset of a first episode psychosis, before it is known whether psychosis is a manifestation of schizophrenia or a psychotic mood disorder, depressive symptoms must be differentiated from negative symptoms or extrapyramidal symptoms and dysphoria from antipsychotic drugs.

The risk of suicide is especially high at the onset of schizophrenia, which has a lifetime risk of suicide of approximately 5 percent. Risk factors for suicide include [16] (see "Depression in schizophrenia", section on 'Course'):

- Young
- Male
- Highly educated
- Number of prior attempts
- Depressive symptoms
- Active hallucinations and delusions
- Family history of suicide
- Comorbid substance misuse
- Presence of insight

Functional impairment — Functional impairment is present even before the onset of psychosis and linked to neurocognitive impairment. Functional impairment in the prodrome is a predictor of which individuals will go on to develop a full psychotic episode. Early psychosis treatment programs are designed to target the significant functional impairment early in the course of illness using recovery-based service.

Agitation/aggression — Prior to receiving treatment, patients with first episode psychosis are four times more likely to commit acts of violence compared with the general population [17,18]. (See "Psychosis in adults: Epidemiology, clinical manifestations, and diagnostic evaluation", section on 'Agitation/aggression'.)

Metabolic abnormalities — Metabolic abnormalities, have traditionally been considered a manifestation of chronic psychotic illness, secondary to antipsychotic medication and unhealthy lifestyles [19]. However, they have also been reported in drug-naïve patients with first episode schizophrenia [20-22], suggesting that chronic psychotic disorders may be systemic diseases in which metabolic abnormalities are intertwined with psychopathological features in a complex network that may even precede the onset of the illness. (See "Metabolic syndrome in patients with severe mental illness: Epidemiology, contributing factors, pathogenesis, and clinical implications".)

COURSE

Premorbid — Children who go on to develop schizophrenia later in life have been shown to have subtle neuromotor abnormalities, developmental delays, socioemotional abnormalities, and neurocognitive impairment prior to the onset of illness [23,24]. In addition to delays or abnormalities in speech, children in the premorbid phase often experience a delay in developmental milestones such as sitting, standing, and walking alone. The premorbid phase is also characterized by clumsiness, odd movements, and slower reaction time (eg, unbalanced, involuntary, or unusual movements like heel-to-toe standing).

Minor physical anomalies, suggestive of neurodevelopment abnormalities, are also commonly noted prior to the onset of psychotic illness and include evidence of facial dysmorphia, such as a wide skull base or abnormal size of facial features. The socioemotional difficulties that characterize the premorbid phase include behavioral problems such as antisocial externalizing behavior and evidence of social isolation by age 11. As a group, individuals who later develop schizophrenia have global intellectual impairments compared with the general population [23,25,26].

Prodrome of psychosis — There has been increasing interest in identifying individuals at high-risk psychosis so that it is possible to intervene early and perhaps prevent the development of a full psychotic syndrome. Individuals who develop psychosis typically experience a prodromal period of illness that can last from a few weeks to a few years. It is characterized by subsyndromal psychotic symptoms, negative symptoms, and a deterioration in functioning. Because the true prodrome can only be diagnosed retrospectively, other terms have been

developed to describe a syndrome that is at high risk, but not inevitable risk, for developing psychosis. Various terms have been developed to describe this prodromal syndrome (see 'Early indentification and intervention' below):

- Clinical high risk for psychosis.
- Ultra-high risk for psychosis.
- Attenuated psychosis syndrome – Attenuated psychosis syndrome is DSM-5's characterization of the prodromal phase. The syndrome is included under "Conditions for Further Study" to facilitate research into this at risk population.

Eventual diagnosis — Research on the eventual diagnoses among patients initially assessed with prodromal symptom is limited. In a sample of 89 clinical high-risk subjects from the North American Prodrome Longitudinal Study consortium, the conversion diagnoses in the former prodromal patients were [27]:

- Schizophrenia-spectrum psychoses in 56 percent
- Affective psychoses in 10 percent
- Other psychoses, principally psychosis not otherwise specified, in 34 percent

Co-occurring conditions — Early psychotic illness is characterized by multiple comorbid diagnoses in the premorbid, prodromal, and first episode. A detailed developmental history and differential diagnosis is critical in the early stages of illness given the significant overlap with other problems often requiring attention. (See 'Child developmental history' below and "Psychosis in adults: Epidemiology, clinical manifestations, and diagnostic evaluation".)

Substance use disorders (SUDs) — Patients with first episode psychosis have been found to have higher rates of co-occurring SUDs compared with the general population.

As an example, structured diagnostic interviews were conducted with 404 patients with first episode psychosis at 34 community mental health centers across the United States, enrolled in a first episode study and compared with the young adult general population [28]:

- **Any lifetime SUD** – 50 percent in first episode psychosis.
- **Cannabis use disorder** – 34.7 in first episode psychosis versus 11.0 percent in general population.

- **Stimulant use disorder** – Stimulant use disorder was found to be 4 to 5 percent in first episode psychosis versus 2 percent in general population.

- **Opioid use disorders** – 4.5 in first episode psychosis versus 3 percent in general population.

In contrast, the rate of lifetime alcohol use disorder in first episode psychosis was found to be similar to that in the young adult general population (34.7 versus 37.0 percent) [29].

Patients meeting criteria for attenuated psychosis syndrome have been found to have a relatively high prevalence of SUDs compared with the general population. In a review of 10 published studies, cannabis, alcohol, and nicotine were found to be the most commonly used substances in the attenuated psychosis syndrome samples, with the use of cannabis (range 33 to 54 percent) and nicotine (16 to 34 percent) being higher than in healthy controls and similar to individuals in their first episode of psychosis [30,31]. The rate of alcohol misuse ranged from 17 to 44 percent across studies. (See 'Prodrome of psychosis' above.)

Epidemiologic studies have found associations between substance use, generally cannabis use, and increased risk of developing psychotic symptoms [32]. Some experts believe that early cannabis use is a causal factor in developing schizophrenia. As an example, in a sample of 291 individuals meeting the criteria for attenuated psychotic syndrome, a history of any substance use disorder was one of five predictors of conversion to psychosis [33].

Mood disorders — Comorbid depression is common in first episode psychosis, occurring in 80 percent of patients at one or more phases of first episode psychosis; a combination of depression and suicidal thinking was present in 63 percent [34]. Depression in the prodromal phase is a significant predictor of future depression and acts of self-harm.

Anxiety disorders — Anxiety disorders are prevalent in early psychosis in the premorbid and prodromal phases, and first episode of illness. In a large sample of first episode patients from the McLean-Harvard International First-Episode Project, 17 percent of their sample met criteria for an anxiety disorder [35]. In a sample of 744 prodromal phase patients, the prevalence of DSM-5 anxiety disorders was 47 percent, with an additional 9 percent meeting criteria for obsessive compulsive disorder or posttraumatic stress disorder [30].

Attention deficit hyperactivity disorder (ADHD) — A premorbid history of ADHD is present in approximately 17 to 50 percent of patients presenting with a first episode of psychosis across multiple studies [36-38].

Among individuals who meet the criteria for attenuated psychosis syndrome, the prevalence of ADHD is similar to that observed in a first episode patients, with 17 percent reported to have a current diagnosis of ADHD in the 744 patient sample with prodromal symptoms [30].

DIAGNOSTIC EVALUATION

Interview — The initial assessment should focus on establishing a timeline of symptoms, a psychiatric history including premorbid and prodromal symptoms, prior diagnoses and treatments, a psychiatric review of symptoms including affective and anxiety disorders, substance use history, a family history for psychiatric illness, a childhood developmental history, and a complete medical history. The clinician should seek corroborative sources of information, whenever possible, for evidence of delusional or referential thinking or other unusual behaviors.

Child developmental history — Features of childhood development that should be determined include the presence or absence of associated childhood problems such as learning disabilities, mood or anxiety symptoms, and/or a history of maltreatment or other comorbid conditions before the onset of psychosis.

Mental status examination — A complete mental status examination should be conducted, paying particular attention to the patient's appearance (grooming, hygiene) and general behaviors, mood and affect, thought processes (evidence of disorganization), evidence for perceptual disturbances (responding to internal stimuli), unusual thought content such as ideas of reference or delusions, suicidal or homicidal behavior, attention, memory function, insight, and judgment.

Initial medical work-up

- **Physical and neurologic exam**.
- **Laboratory –** Complete blood count with differential to rule out infection, serum electrolytes to rule out metabolic disturbance, renal panel (blood urea nitrogen, creatinine), liver panel, thyroid stimulating hormone, blood glucose, blood calcium and phosphate, urinalysis, and drug screen.
- **Also consider** – HIV test, syphilis screen (venereal disease research laboratory, rapid plasma reagin), hepatitis panel, copper studies, serum folate/B12, urine porphyrins, serum cortisol, anti-nuclear antibody, sedimentation rate, heavy metal screen, *anti-N-methyl-D-aspartate* receptor (NR1) immunoglobulin antibodies.

- **Neuroimaging** – Computed tomography brain or magnetic resonance imaging to evaluate for space-occupying lesions, demyelinating disorders, or stroke.
- **Electroencephalogram** – To rule out seizure disorder if there is a history consistent with possible seizure activity.
- **Neuropsychological testing –** To assess neurocognitive functioning.
- **Lumbar puncture** – A lumbar puncture is indicated to rule out meningitis or other evidence of infection if there is evidence of delirium, fever, leukocytosis, or change in level of consciousness.

DIFFERENTIAL DIAGNOSIS

A primary psychiatric disorder is considered when substances, medications, and nonpsychiatric underlying medical conditions have been ruled out as causes for psychotic symptoms. The differential diagnosis for psychosis is reviewed in greater detail separately. (See "Psychosis in adults: Epidemiology, clinical manifestations, and diagnostic evaluation".)

On initial assessment of a first psychotic episode, it is often difficult to determine the primary diagnosis and only longitudinal follow-up and careful history will help to sort out the most likely diagnosis. The associated symptoms, time course of illness, and family history provide valuable information for the differential diagnosis [39].

If the psychotic symptoms are more attenuated, an attenuated psychosis syndrome should be considered along with other DSM-5 diagnoses that present with psychotic-like symptoms (schizotypal personality disorder, autism spectrum, posttraumatic stress disorder, obsessive compulsive disorder). (See 'Prodrome of psychosis' above.)

Autism, characterized by social communication dysfunction and bizarre behavior, is typically evident from childhood and does not include positive psychotic symptoms. Posttraumatic stress disorder is characterized by a history of trauma and reexperiencing the trauma. Obsessive compulsive disorder includes obsessions and compulsions.

INITIAL MANAGEMENT

Goals for the initial management of patients with first episode psychosis are to assure safety, improve symptoms, and promote functional recovery. Interventions to achieve these goals are reviewed separately. Treatment of children and adolescents with schizophrenia, a disorder often

eventually diagnosed in many patients with first psychotic episode, is also reviewed separately. Treatment of substance use co-occurring with schizophrenia is also reviewed separately. (See "Psychosis in adults: Epidemiology, clinical manifestations, and diagnostic evaluation" and "Schizophrenia in children and adolescents: Treatment overview" and "Pharmacotherapy for co-occurring schizophrenia and substance use disorder" and "Co-occurring schizophrenia and substance use disorder: Psychosocial interventions".)

EARLY INDENTIFICATION AND INTERVENTION

Early identification and intervention efforts seek to identify individuals with first episode psychosis or during the prodrome of psychosis, a period associated with high risk for psychosis, and to intervene to treat or perhaps prevent the development of a full psychotic syndrome. (See 'Prodrome of psychosis' above.)

Early identification and intervention efforts were developed to reduce what have been, on average, lengthy, years-long delays from psychosis onset to detection and treatment. Such delays have been associated with poorer treatment responses in analyses of patients ultimately diagnosed with schizophrenia or other psychotic disorders [40], suggesting that earlier intervention may improve clinical outcomes.

Components — Early identification and intervention programs have been implemented worldwide, first in Australia, North America, and Europe, and more recently, throughout Asia and Latin America. Components of the programs include:

- Methods for early identification include education and community outreach with mental health professionals, secondary schools, and colleges, as well as education of primary care providers and encouraging referral to specialty programs for diagnosis and treatment.
- Screening age-appropriate populations for prodromal symptoms has been studied, but has resulted in high rates of false positive results.
- Multidisciplinary teams of mental health professionals who work in an integrated fashion (instead of referring patients to different health care providers for each service) and follow patients over time.
- Provision of diagnosis-specific, multimodal treatments including different psychosocial and psychopharmacologic interventions that are tailored to the needs of each patient. Early intervention treatments for schizophrenia are reviewed separately. (See

"Psychosocial interventions for schizophrenia in children and adolescents", section on 'For high clinical risk' and "Schizophrenia in children and adolescents: Treatment overview".)

- A focus on functional recovery and the aims of decreasing psychotic symptoms, improving functional outcomes, and reducing long-term disability.
- Recovery-based services that seek to integrate the input of, and achieve the outcomes prioritized by, first episode patients and their family. In this model, clinicians remain optimistic for recovery and individualize care based on the individual's experience.
- Psychological assessments that focus on a strengths and resilience framework, emphasizing empowerment, collaborative decision making, self-determination, choice, and risk-taking in individualized, person-centered, recovery planning.

Efficacy — A meta-analysis of randomized clinical trials found that early intervention services led to better clinical outcomes for patients with first episode psychosis compared with treatment as usual [41]. The ten trials randomly assigned 2176 patients to receive early intervention services or treatment as usual. Patients assigned to early intervention services had superior results on all meta-analyzable outcomes studied, including any psychiatric hospitalization (relative risk = 0.74; 95% CI, 0.61-0.90), involvement in school or work (relative risk = 1.13; 95% CI 1.03-1.24), and total symptom severity (standardized mean difference = -0.32; 95% CI -0.47 to -0.17).

As an example, a clinical trial randomly assigned 120 patients with first episode psychosis to receive specialized treatment (medication, family education, cognitive-behavioral therapy, case management, and employment or educational support) or treatment as usual [41]. After one year, specialized treatment participants were more likely have no inpatient hospitalizations compared with those in usual treatment (77 versus 56 percent; risk ratio = 1.38, 95% CI 1.08-1.58) and better vocational engagement (91.7 versus 66.7 percent; risk ratio = 1.40, 95% CI 1.18-1.48). The two groups did not differ in global functioning.

A network meta-analysis comparing interventions in first episode psychosis did not find any one intervention to be superior to any other [42].

Meta-analyses are mixed for the efficacy of early intervention to prevent the development of psychosis in patients with attenuated psychosis syndrome [43]. Cognitive-behavioral therapy has shown evidence of reducing symptoms of attenuated psychotic syndrome in multiple trials [44].

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".)

SUMMARY

- Psychosis is a condition of the mind broadly defined as a loss of contact with reality, which presents with delusions, hallucinations, thought disorganization, and/or unusual behaviors. (See 'Introduction' above.)
- Approximately 1 percent of the population is affected by psychotic illnesses such as schizophrenia. The incidence of new cases of psychosis has been estimated to be approximately 50 in 100,000 people worldwide [2]. (See 'Epidemiology' above.)
- Psychotic symptoms can present in a variety of psychiatric and medical illnesses; clinical features are not pathognomonic for particular diagnoses. (See 'Clinical manifestations' above.)
- It is important to perform a thorough history – including child developmental history – physical examination, mental status examination, and workup in order to assess the clinical status and provisional diagnosis, rule out treatable underlying causes of psychosis, and guide appropriate therapy. (See 'Diagnostic evaluation' above.)
- Children who go on to develop schizophrenia have subtle neuromotor abnormalities, developmental delays, socioemotional abnormalities, and neurocognitive impairment prior to onset of the illness (ie, during the premorbid phase). In addition to delays or abnormalities in speech, they often experience a delay in developmental milestones such as sitting, standing, and walking alone. (See 'Premorbid' above.)
- Individuals who develop psychosis typically experience a prodromal period that can last from a few weeks to a few years. It is characterized by subsyndromal psychotic symptoms, negative symptoms, and a deterioration in functioning. Patients manifesting this syndrome are at high risk, but not inevitable risk, for developing psychosis. (See 'Prodrome of psychosis' above.)
- If substances, medications, and nonpsychiatric underlying medical conditions have been ruled out as causes for psychotic symptoms, a primary psychiatric disorder should be considered. The differential diagnosis for psychosis is reviewed in detail separately. (See

"Psychosis in adults: Epidemiology, clinical manifestations, and diagnostic evaluation" and 'Differential diagnosis' above.)

- Goals for the initial management of patients with first episode psychosis are to assure safety, improve symptoms, and promote functional recovery. Interventions to achieve these goals are reviewed separately. Treatment of children and adolescents with schizophrenia, a disorder often eventually diagnosed in many patients with first psychotic episode, is also reviewed separately. Treatment of substance use co-occurring with schizophrenia is also reviewed separately. (See "Psychosis in adults: Epidemiology, clinical manifestations, and diagnostic evaluation" and "Schizophrenia in children and adolescents: Treatment overview" and "Pharmacotherapy for co-occurring schizophrenia and substance use disorder" and "Co-occurring schizophrenia and substance use disorder: Psychosocial interventions".)

- Early identification and intervention efforts seek to identify individuals with first episode psychosis or during the prodrome of psychosis, a period associated with high risk for psychosis, and to intervene to treat or perhaps prevent the development of a full psychotic syndrome. Clinical trials of these services have found evidence of efficacy in patients with first episode psychosis and mixed results in patients with prodromal symptoms. (See 'Early indentification and intervention' above.)

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