Collaborative Care in the Identification and Management of Psychosis in Adolescents and Young Adults

Liwei L. Hua, MD, PhD, COMMITTEE ON ADOLESCENCE

Pediatricians are often the first physicians to encounter adolescents and young adults presenting with psychotic symptoms. Although pediatricians would ideally be able to refer these patients immediately into psychiatric care, the shortage of child and adolescent psychiatry services may sometimes require pediatricians to make an initial assessment or continue care after recommendations are made by a specialist. Knowing how to identify and further evaluate these symptoms in pediatric patients and how to collaborate with and refer to specialty care is critical in helping to minimize the duration of untreated psychosis and to optimize outcomes. Because not all patients presenting with psychotic-like symptoms will convert to a psychotic disorder, pediatricians should avoid prematurely assigning a diagnosis when possible. Other contributing factors, such as co-occurring substance abuse or trauma, should also be considered. This clinical report describes psychotic and psychotic-like symptoms in the pediatric age group as well as etiology, risk factors, and recommendations for pediatricians, who may be among the first health care providers to identify youth at risk.

INTRODUCTION

Psychosis is defined as impairment in thought and behavior so severe that the ability to distinguish reality from nonreality is lost. Psychotic symptoms include delusions, fixed and false beliefs, and hallucinations or false sensory perceptions.1 Although these symptoms do not necessarily portend a primary psychotic disorder, there is a strong association with the presence or future development of other psychiatric disorders.2,3 Primary mood or anxiety disorders with concurrent psychotic symptoms often indicate a more severe form of mood or anxiety disorder, such as bipolar disorder, with psychotic features and imply more impaired functioning.4–6

abstract

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Pediatricians in the medical home may be the first point of contact for adolescents who report psychotic-like symptoms, which may be attributable in part to the ease of access to pediatricians and/or to a shortage of child and adolescent psychiatrists. Therefore, pediatricians should be familiar and comfortable with asking additional questions when patients present with vague or overt psychotic symptoms, to determine the appropriate level of care (eg, close monitoring with specialty mental health consultation with psychiatrist, psychologist, or psychotherapist, or urgent emergency department [ED] evaluation). Management decisions will depend on the severity of the psychotic-like symptoms, how deeply entrenched the beliefs are (level of insight), level of distress, functional impact, and safety of the individual and others.

This clinical report aims to provide pediatricians with a framework for identification, initial assessment, and mental health referral and consultation for youth presenting with psychotic-like symptoms. This report strongly encourages collaboration between pediatricians and mental health specialists to determine the best course of treatment of patients presenting with psychotic-like experiences or psychosis.

### EPIDEMIOLOGY

Each year, approximately 100,000 adolescents and young adults in the United States experience a first-episode psychosis (FEP). Estimates of the prevalence of early-onset schizophrenia (onset prior to 18 years of age) is approximately 0.5%, whereas the prevalence of schizophrenia in general is believed to be about 1%. In the United States, childhood-onset schizophrenia (onset prior to 13 years of age), with a more severe course and worse prognosis, is rarer, with an estimated prevalence of approximately 0.04%.

In general, the peak onset of psychotic disorders occurs between 15 and 25 years of age. Researchers in a large study of FEP found approximately 18% of adults with schizophrenia experienced their first episode before 18 years of age (53.4% male). In another study, researchers found 11% to 19% of a first-episode schizophrenia sample and 23% to 35% of a clinical high-risk syndrome sample reported onset of attenuated psychotic symptoms in childhood (manifesting at 13 years or younger). Patients who are at clinical high risk (CHR) demonstrate nonspecific and attenuated psychotic symptoms, with subtle changes in cognition, behavior, and affect that are different from their previous baseline functioning. Patients at CHR may also have a history of social isolation or withdrawal as well as odd or suspicious behavior. Family and friends may be the first to notice these symptoms, but eventually individuals themselves may begin to experience distress as well. Patients at CHR have higher likelihood of transitioning to overt psychotic symptoms, such as auditory hallucinations and/or delusions.

### CLASSIFICATION AND DEFINITIONS

The key features defining psychotic disorders are delusions, hallucinations, disorganized thinking (speech), grossly disorganized or abnormal motor behavior (including catatonia), and negative symptoms. See the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) section on schizophrenia spectrum and other psychotic disorders diagnoses for specific diagnoses and criteria.

### CORE SYMPTOMS

#### Delusions

Delusions are fixed, false beliefs. Even if evidence is shown to the contrary of the belief, the belief remains unchanged. See Table 1 for common themes of delusions.

The DSM-5 generally classifies delusions as bizarre or nonbizarre. Thought withdrawal, the belief that one’s thoughts are being or have been removed; thought insertion, the belief that an outside force has placed

<table>
<thead>
<tr>
<th>Delusions</th>
<th>Definitions</th>
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<tbody>
<tr>
<td>Persecutory</td>
<td>Belief that one is being or is going to be harmed</td>
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<tr>
<td>Referential</td>
<td>Belief that certain occurrences are directed at oneself</td>
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<tr>
<td>Grandiose</td>
<td>Belief that one has special abilities</td>
</tr>
<tr>
<td>Erotomantic</td>
<td>Belief that another is in love with oneself</td>
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<tr>
<td>Nihilistic</td>
<td>Belief that a catastrophe will occur or that the world will end</td>
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<tr>
<td>Somatic</td>
<td>Intense preoccupation with health and organ function</td>
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</table>
thoughts in one’s head; and delusions of control, the belief that an outside force is controlling one’s body, are all categorized as bizarre delusions. Nonbizarre delusions are those that could be plausible, such as the belief that one is being monitored by the police or FBI or that one’s phone has been hacked by another person, despite a lack of evidence.

**Hallucinations**

The DSM-5 defines hallucinations as vivid perception-like experiences occurring in the absence of any external stimuli. Auditory hallucinations are the most common, although visual, tactile, gustatory, and olfactory hallucinations also occur. Patients report most auditory hallucinations as voices that may be familiar or unfamiliar and are distinct from one’s own thoughts. Hallucinations occurring when one is falling asleep (hypnagogic) or waking up (hypnopompic) are considered normal in the general population. Hallucinations occur more commonly in youth than delusions, and auditory hallucinations are more common than other sensory hallucinations.

**Disorganized Thinking**

Providers may assess for disorganized thinking by observing the patient’s speech. Jumping from topic to topic may be indicative of derailment or loose associations; inability to answer a question in a goal-directed manner or answering a question that was not asked may reflect tangential thinking. A speech pattern so disorganized that it may not be understood by others is known as incoherence or “word salad” (random words or phrases that are strung together in sentence form but do not make sense).1

**Disorganized Behavior**

The DSM-5 defines grossly disorganized or abnormal motor behavior as difficulty in performing goal-directed behavior, affecting functioning. Catatonia is decreased reactivity to the environment, and it may consist of a range of behaviors from negativism (not following directions) to mutism and stupor (not responding verbally or with appropriate motor responses, respectively) to catatonic excitement (purposeless and excessive motor movement). Catatonia may also include repeated stereotyped movements, echolalia, posturing, or grimacing. Catatonia is more likely to be associated with schizophrenia but can also be found with other psychiatric disorders or medical conditions, including autism spectrum disorder (ASD).1

**Negative Symptoms**

Negative symptoms consist of diminished emotional expression, avolition (lack of motivation), alogia (poverty of speech), anhedonia (inability to experience pleasure), and asociality (reduced desire or motivation to form relationships).1,16

**RISK FACTORS FOR CONVERSION TO PRIMARY PSYCHOTIC DISORDER**

The North American Prodrome Longitudinal Study (NAPLS), a consortium of 8 research centers, aimed to study CHR populations and determine mechanisms of conversion to psychosis to predict conversion in a high-risk population with an age range of participants from 12 to 35 years. In a 2.5-year follow-up, risk of conversion from CHR to full psychotic disorder was 35%, whereas approximately one-third remitted and one-third continued to demonstrate attenuated positive symptoms with poorer overall functioning.17,18 Once an individual receives a schizophrenia spectrum diagnosis, prognosis is generally poor unless they receive appropriate treatment. Researchers in 1 study using the Multi-Payer Claims Database demonstrated 12-month mortality after initial diagnosis was 1968 per 100 000 compared with the general population, in which it is 89 per 100 000 people.19 The authors also found teenagers and young adults in whom psychotic disorder is diagnosed have about a 24-times greater 12-month mortality rate than their peers, suggesting that during the year after diagnosis, it is crucial to optimize outcomes by increasing monitoring with regular follow-up and early intervention.19 An analysis of the database found it did not report cause of death, leaving the authors to speculate that the reason for death might have included suicide or substance use–related accidents.19

NAPLS described variables contributing uniquely to psychosis prediction to be genetic risk for schizophrenia with recent worsening of functioning, greater impairment in social functioning, history of substance use, increased levels of suspiciousness or paranoia, and increased levels of unusual thought content.18 In NAPLS, 92% of the CHR sample had at least 1 positive symptom, the most common of which was unusual thought content and perceptual abnormalities, followed by suspiciousness. Eighty-two percent of subjects endorsed at least 1 negative symptom, of which avolition and poor occupational functioning were the most common, and 44% demonstrated 3 or more negative symptoms. Disorganized communication occurred infrequently and grandiosity less.15 Greater levels of unusual thought content and suspiciousness, greater decline in social functioning, greater prodromal symptom severity, lower verbal learning and memory performance, more delayed processing speed, and younger age at symptom onset contributed to increased risk of conversion from CHR status to psychosis.20 Social dysfunction in early adolescence is of particular significance in conversion to psychosis in CHR individuals.21
Many children and adolescents report psychotic-like experiences, but most do not go on to develop true psychotic illness. Clinically significant psychosis usually involves mental status and behavioral changes and usually imparts a high level of distress. However, data suggest that psychotic-like experiences in childhood and adolescence can be associated with development of other psychiatric disorders in the future, and strong symptomatology in childhood may be associated with increased likelihood of psychotic disorder as adults.

Youth who report psychotic symptoms also have a higher likelihood of experiencing current mental health difficulties than those who do not; however, psychotic-like symptoms that present during childhood and/or adolescence frequently resolve. Jardri et al reported that hallucinations are common in children and may not signify psychiatric pathology; however, persistence of hallucinations into adolescence increases risk of developing psychosis five- to sixfold. In a study of adolescents with hallucinations, half reported no symptoms after 1 year. Similarly, researchers in the Philadelphia Neurodevelopmental Cohort, a 2-year prospective follow-up study, reported 51% persistence or worsening of psychotic symptoms after 2 years.

In youth presenting with delusions or hallucinations, mood disorders should be considered; although pediatric bipolar disorder is rare, early-onset schizophrenia is even rarer. Ulloa et al reported approximately 10% of youth (n = 2031) seen in a pediatric mood and anxiety disorders clinic had psychotic symptoms. Of the 10% reporting psychotic symptoms, 62% of patients had a diagnosis of a depressive disorder, 24% had a diagnosis of bipolar disorder, and 14% had a diagnosis of schizophrenia.

In a general population of youth, hallucinations were more prevalent than delusions. Youth report auditory hallucinations, often with commands and comments, more commonly than conversing voices. Visual and tactile hallucinations may occur with auditory hallucinations. True hallucinations occur when one is fully awake; they are vivid and evoke a response. Delusions may occur but are vague and are usually related to the hallucinations. Symptoms that are specific to a certain situation (such as occurring only at nighttime or only when the individual is angry), overly detailed, and not associated with disorganized thoughts or behaviors are less likely to be indicative of a true psychotic disorder as well.

Adolescents report fewer hallucinations than children do. Kelleher et al found that a median of 17% of 9- to 12-year-olds and a median of 7.5% of 13- to 18-year-olds report auditory hallucinations. An increase in lifetime history of psychiatric disorders also correlated with an increased reporting of hallucinations. Those reporting psychotic-like symptoms were more likely to have a mental health disorder, including anxiety and mood disorder, at the time of presentation and even more likely over the course of their lifetimes. In a mental health clinic sample, Kelleher et al found that patients presenting with psychotic experiences were more likely to have multiple psychiatric disorders and socio-occupational difficulties as well as a higher risk for suicidal behavior. A meta-analysis of 10 prospective cohort studies published between 2013 and 2017 found patients who reported psychotic experiences had twofold increased odds of later suicidal ideation, threefold increased odds of later suicide attempt, and fourfold increased odds of subsequent death by suicide.

In a 15-year longitudinal study that followed individuals from 11 to 26 years of age, more than 40% of patients in whom schizophreniform disorder was diagnosed in early adulthood had disclosed symptoms at younger age. Of those who reported the most severe psychotic-like symptoms in preadolescence, approximately 25% had a diagnosis of schizophreniform disorder in early adulthood, and 70% experienced at least 1 of the following: hallucinations, delusions, disorganized speech, catatonia, or anhedonia. Almost all experienced poor occupational or social functioning. When followed out to 38 years of age, those who had reported psychotic symptoms at a young age were at increased likelihood of having a diagnosis of schizophrenia and posttraumatic stress disorder and were also more likely to have attempted suicide. Very few had no psychiatric diagnosis at all.

Youth reporting psychotic symptoms appear to have worse global functioning. Approximately 75% of youth reported that the psychotic-like experiences were distressing to them. Other studies reported those with FEP have significantly slower processing speed; processing speed also predicts social functioning 1 year later. Patients with adolescent-onset psychosis did not demonstrate improvements in processing speed as they aged, which negatively affects functional outcomes. These findings support the idea that adolescent-onset psychosis is associated with a disruption in adolescent brain development, such as myelination.

In a study examining a CHR population, comparing those who developed psychosis during the course of the study versus those who did not, authors found only people with psychosis had impaired cognition, with specific impairments...
in processing speed, verbal memory, sustained attention, and executive functioning. This finding suggests cognitive deficits exist before manifestation of psychotic symptoms. Carrión et al. reported that these deficits persist but do not worsen over the course of the illness.

Although there is overlap, the risks and manifestations of psychotic-like symptoms in youth are heterogeneous. Other presentations that can be confused and/or associated with psychotic-like symptoms are described below. See Appendix 1 for sample case scenarios of psychotic and psychotic-like presentations that may occur in the pediatric ambulatory setting.

**Benign Hallucinations**

Some adolescents may mention hearing their name called with no other concerning symptoms. The Washington University in St Louis Kiddie Schedule for Affective Disorders and Schizophrenia, which assesses for hallucinations that are benign or pathologic, defines these as “benign hallucinations,” because they do not impair functioning, are nonthreatening in content, and occur infrequently. Pathologic hallucinations, such as a voice telling one to harm oneself or others, do impair functioning. A recent review of “healthy voice-hearer” literature found there appeared to be a continuum of voice hearing from healthy controls (no auditory hallucinations) to “healthy voice-hearers” (low frequency, low distress) to “clinical voice-hearers” (high frequency, high distress). Although healthy voice hearers seem to be at higher risk of transitioning to mental health disorders, only a minority end up transitioning. Illusions are distinct from hallucinations but warrant mention. Illusions are defined as a misperception and/or misinterpretation of an actual stimulus, such as seeing a rope on the ground and thinking it is a snake for an instant, whereas hallucinations consist of perceiving something that is not actually there. Illusions are not necessarily pathologic and can be experienced by people with no psychiatric disorders. In a white noise speech illusion study (hearing speech when only white noise was being played) in adults, there was no association of white noise speech illusion with psychosis in a nonclinical population.

**Imaginary Friends**

Imaginary friends, which could also be called “hallucination-like phenomenon,” are reported in 28% to 65% of children 5 to 12 years of age, and up to 65% of children 7 years of age and younger have imaginary companions. There is scarce literature on imaginary companions and association with psychotic symptoms. An imaginary companion could be invisible or embodied by a doll or stuffed animal. Imaginary companions during childhood are normative and are thought to help with development of appropriate social interactions and emotional regulation. Children can identify that imaginary companions are not real. Youth are usually able to make imaginary friends go away, unlike hallucinations. Because of concerns for prognosis and relevance to future mental health disorders, a longitudinal study of “high-risk” middle school students 11 to 14 years of age with imaginary companions, described by their teachers as having the most “problem behaviors” (as assessed by the Child Behavior Checklist 4–18) in school, was performed. The researchers found that although these children had the most behavioral issues and the least social acceptance, they were not at higher risk for any psychiatric disorders and seemed to have greater positive adjustment.

**Cultural and Religious Considerations and Bereavement**

It is important for pediatricians to consider cultural issues or family background when asking about psychotic-like symptoms, because some symptoms that sound pathologic may be normal cultural or developmental responses. For example, if a youth describing a presence or shadow in their room at night comes from a family that believes strongly in spirits or ghosts, such an experience may not reflect an actual visual hallucination. During bereavement and mourning, youth may report auditory or visual hallucinations of the deceased person. In these situations, the individual’s degree of distress can be helpful in determining the pediatrician’s next step. When symptoms are described as comforting or neutral, they are less likely to be an indication of a psychotic disorder. Distress would indicate something more problematic, and referral to a psychotherapist would be recommended.

**Intellectual Disability**

People with intellectual disability (ID) may report psychotic-like symptoms, and pediatricians and developmental and behavioral pediatricians can assist with providing a differential diagnosis for youth with ID and ASD and help coordinate a plan of care related to special educational needs and therapies. Providers may consider using a neurodevelopmental framework to assess psychotic-like symptoms. Symptoms suggestive of psychosis in this population could instead reflect self-talk, imaginary friends, or fantasies, depending on an individual’s developmental level. Stressful experiences, such as the loss of a loved one, may trigger or exacerbate psychotic-like symptoms. When assessing adolescents or young adults with ID, it is important to determine if they understand the questions being asked.
to ensure a valid assessment. Individuals with intellectual limitations and delayed emotional development may feel pressured to answer a question a certain way to please the interviewer or blame negative behaviors on voices in their head to avoid getting in trouble.44

Co-occurring mental disorder and ID in youth is common and often persists through the life span.48 Relative to children and adolescents without ID, the rate of co-occurrence of mental disorders in youth with ID is 3 to 4 times greater.

ASD

Core features of ASD consist of social communication and social interaction deficits as well as restricted interests, stereotyped or repetitive behaviors, and sensory sensitivities. Some of these symptoms may overlap with those occurring in schizophrenia spectrum disorders (SSDs). In addition, a number of individuals with ASD may experience transient hallucinations and engage in vivid fantasies, which may be mistaken for true psychotic symptoms. Although there is a level of co-occurrence of ASD and SSDs, one must be careful to distinguish the overlapping symptoms before giving both diagnoses.49 Common genetic regions and brain regions may contribute to the comorbidity of ASD and SSDs.50

Co-occurring ASD and SSD should be considered when perceptual abnormalities and beliefs or behaviors are noted to be different from those at baseline, especially with associated change in functioning.50 Thorough developmental, medical, and psychiatric history, as well as any other useful collateral information, is important when assessing for co-occurring conditions. In addition, genetic testing should be considered if not already completed. Clinicians should also monitor for catatonia.

Trauma

In addition to serving as a risk factor for psychotic disorder, trauma can result in posttraumatic symptoms that can be mistaken for psychotic symptoms. For instance, flashbacks can be mistaken for visual and/or auditory hallucinations, and hypervigilance or hyperarousal can be mistaken for paranoid delusions. Withdrawal and avoidance could be mistaken for negative symptoms.51 Assessment to determine if symptoms are psychotic-like or truly psychotic in nature may need to take place over time to determine the most appropriate course of treatment. Dissociative episodes can also be associated with trauma and may serve as a protective mechanism to mentally or emotionally escape physical trauma. Dissociation is a detachment from reality, whereas psychosis is a loss of reality. Although the two are distinct, some researchers hypothesize that dissociation may mediate the relationship between traumatic life events and the development of attenuated positive psychotic symptoms.52

ETIOLOGY OF PSYCHOTIC SYMPTOMS AND DISORDERS

Neuroanatomical Abnormalities

Schizophrenia is a heterogeneous disorder, but disruptions in brain connectivity and synaptic functioning likely underlie the development of schizophrenia.53 These disruptions appear to occur first in neural circuits involved in referencing occurrences by time, place, and saliency, potentially resulting in an inability to recognize that certain thoughts have been self-generated, which could eventually contribute to loss of reality testing. Axonal pathology, such as disruption in myelination, may also be involved.53 Excessive synaptic pruning may also be a factor, possibly associated with the immune system, namely upregulation of complement genes and activation of microglia.54 Scientists have found abnormalities in brain structure, likely progressive, including bilateral enlargement of lateral ventricles and volume decreases in the frontal lobe, hippocampus, and thalamus.55,56 Rapoport et al57 demonstrated reduced frontal and temporal gray matter volume compared with healthy controls. People with childhood-onset schizophrenia seem to lose more gray matter in the cortex than do children who report brief psychotic episodes.57 Those with early-onset schizophrenia also show significant gray matter volume decrease and decrease in cortical folding.55,58

Neurotransmitters

Schizophrenia is primarily associated with dopamine dysfunction, with increased dopamine synthesis and release leading to psychosis; however, multiple other neurotransmitters and pathways are believed to be involved.59,60 Olney and Farber found that animals given N-methyl-D-aspartate receptor antagonists develop neurototoxic changes similar to those observed in brains of patients with schizophrenia.61 Administration of agents that increase glutamate, such as phencyclidine or ketamine, increase the likelihood of psychotic symptoms.62 Serotonin antagonism, as found in some second-generation antipsychotic medications, appears to provide some benefit for extrapyramidal symptoms and for mood symptoms associated with schizophrenia.63 Serotonergic antagonists also show promise for treatment of negative and cognitive symptoms of schizophrenia.60,63,64 The muscarinic cholinergic system may play a role in schizophrenia, because blockade of acetylcholine receptors can result in psychotic symptomatology.60,65 In addition, alterations in the γ-aminobutyric acid neurotransmitter system may also have a role in schizophrenia.60 Abnormalities in these neurotransmitter systems form the
basis for pharmacologic treatment of psychotic disorders and/or schizophrenia.

**Genetic Factors**

Family, twin, and adoption studies indicate genetic involvement in schizophrenia. The risk of developing schizophrenia is 5 to 20 times higher in first-degree relatives of patients with schizophrenia.\(^{55,66}\) Concordance rates are 40% to 60% between monozygotic twins and 5% to 15% in dizygotic twins and other siblings.\(^{55,66}\) A number of genomic disorders resulting from duplication or deletion of genetic material have been associated with ID, ASD, and schizophrenia. See Table 2 for a list of medical illnesses for which symptoms can include psychosis.\(^{67-69}\)

**Environmental Exposure**

Environmental exposure can cause direct neurologic damage or may mediate risk of future development of psychosis with new mutations or epigenetic effects.\(^{55}\) Environmental exposures include exposure in utero, like maternal starvation, obesity, or infection (such as *Toxoplasma gondii*); obstetric complications (such as hypoxia, pregnancy bleeding, preeclampsia); substance exposure (marijuana, tobacco, alcohol); and advanced paternal age.\(^{55,70-73}\) The effect of in utero stressors on the development of a psychotic disorder and other psychiatric disorders may be mediated by inflammation, although substances are believed to have negative effects on brain development, neurotransmitters, and cognition.\(^{73-75}\) Substances that have been most studied are tobacco, alcohol, and marijuana, all of which have been associated with later development of psychosis in offspring exposed in utero.\(^{75-77}\)

**Trauma**

Childhood trauma experienced from 0 to 17 years of age, including emotional neglect, physical abuse, sexual abuse, emotional abuse, domestic violence, or bullying, increase the odds of psychotic experiences at 18 years or older.\(^{78}\) Exposure to more than 1 type of trauma or experience of repeated trauma over multiple age periods further increase the odds of psychotic experiences.\(^{78}\) Evidence suggests adverse childhood experiences can interact with genetic risk factors to contribute to the development of psychotic disorders or other psychiatric disorders. In a recent review of trauma and stressful life events in a population at high risk for psychosis, up to 80% of adolescents

### TABLE 2 Medical Causes Associated With Psychotic Episodes

<table>
<thead>
<tr>
<th>Causes</th>
<th>Testing to Consider</th>
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<tbody>
<tr>
<td>Infections or fever</td>
<td>CBC, lumbar puncture</td>
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<tr>
<td>Viruses (HSV, HPV, HIV, CMV, measles, mumps, rubella, etc)</td>
<td>And serum titer, HIV ELISA/PCR</td>
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<tr>
<td>Bacteria ( <em>Treponema pallidum</em>, <em>Mycoplasma pneumoniae</em>, Lyme disease, etc)</td>
<td>And antitreponemal IgG, serum titer, lumbar puncture</td>
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<tr>
<td>Parasitic infections ( <em>Toxoplasma gondii</em>, malaria, TB)</td>
<td>And MRI, skin test</td>
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<tr>
<td>Encephalitis (viral, bacterial)</td>
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<tr>
<td>Neurologic</td>
<td>MRI</td>
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<tr>
<td>Migraine</td>
<td>And history</td>
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<tr>
<td>Seizures and epilepsy</td>
<td>And EEG</td>
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<tr>
<td>Neoplasms</td>
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<td>Metabolic</td>
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<tr>
<td>Thyroid disorders</td>
<td>And thyroid function tests</td>
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<td>Parathyroid disorders</td>
<td>And thyroid function tests, PTH</td>
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<tr>
<td>Adrenal disorders</td>
<td>And ACTH stimulation test, morning cortisol, CRH stim test</td>
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<td>Beriberi</td>
<td>And blood and urine tests for thiamine</td>
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<td>Electrolyte disturbances</td>
<td>And testing for specific electrolytes</td>
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<tr>
<td>Genetic</td>
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<tr>
<td>Fragile X syndrome</td>
<td>Genetic testing</td>
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<td>Klinefelter syndrome (47, XXX)</td>
<td>And blood and urine tests</td>
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<tr>
<td>Metachromatic leukodystrophy</td>
<td>And urine porphyrins</td>
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<td>Porphyria</td>
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<td>Prader–Willi syndrome</td>
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<tr>
<td>Velocardiofacial syndrome (22q11.2 deletion)</td>
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<tr>
<td>Wilson disease</td>
<td>And eye exam (silt lamp for Kayser-Fleischer rings)</td>
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<td>Nutritional deficiencies</td>
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<td>Sleep disorders</td>
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<td>Narcolepsy</td>
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<tr>
<td>Hypnopompic and hypnagogic hallucinations</td>
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<td>Medications</td>
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<td>Steroids</td>
<td>Urine toxicology</td>
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<td>Stimulants</td>
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<td>Anticholinergics</td>
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<td>Drug intoxication and abuse</td>
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<td>Hallucinogens</td>
<td>Urine toxicology</td>
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<td>Cannabis</td>
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<tr>
<td>Ecstasy (3,4-methyleneoxymethamphetamine)</td>
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<td>Cocaine</td>
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<td>Amphetamines</td>
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<td>Barbiturates</td>
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<td>Opiates</td>
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<tr>
<td>Toxicological causes</td>
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<tr>
<td>Carbon monoxide poisoning</td>
<td>Carboxyhemoglobin</td>
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<tr>
<td>Heavy metal poisoning (eg, lead, mercury)</td>
<td>Physical examination, blood or urine mercury levels, lead levels</td>
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Sources: refs 30, 44, 67, 111, 115. ACTH, adrenocorticotropic hormone; BMP, basic metabolic panel; CBC, complete blood cell count; CMV, cytomegalovirus; CRH, corticotropin-releasing hormone; ELISA, enzyme-linked immunosorbent assay; HPV, human papillomavirus; HSV, herpes simplex virus; IgG, immunoglobulin G; PCR, polymerase chain reaction; PTH, parathyroid hormone; TB, tuberculosis.
and young adults reported a history of childhood trauma, including bullying.79 In adolescents and young adults with history of trauma, the overall odds of experiencing psychotic symptoms or developing a psychotic disorder range between 2.8 and 11.5.80 A large-scale twin study in England and Wales with mental health assessments performed at 11 and 16 years of age found that bullying resulted in anxiety, mood, and conduct problems, and paranoid thoughts and cognitive disorganization persisted for 5 years.81 Sexual trauma has the highest risk of conversion to psychosis, followed by physical trauma (e.g., abuse, bullying, neglect).79 Researchers in studies of people with CHR and FEP found both groups showed higher rates of suicide attempts and hospitalizations and generally demonstrated poorer functioning.79 In the CHR population, there is a higher likelihood of comorbid posttraumatic stress disorder as compared with the healthy control population.

Some longitudinal studies found traumatic life experiences may predict the development of psychotic symptoms.80–82 People presenting with psychosis who have a history of trauma have increased severity of psychotic symptoms, more frequent hospitalizations, increased number of comorbid disorders, more cognitive deficits, and increased treatment resistance.80 In a longitudinal cohort study of a CHR population, researchers found a positive association between sexual abuse in childhood and conversion to a psychotic disorder.83 Therefore, for patients who report a history of trauma, including physical or sexual abuse or bullying, providers may consider inquiring about any experience of psychotic symptoms.

History of trauma is associated with increased risk for future development of borderline personality disorder.84 Borderline personality disorder can also present with psychotic-like experiences and/or psychotic symptoms and dissociative episodes. In a European study of adolescents 15 to 18 years of age, those with full threshold borderline personality disorder were more likely to experience psychotic symptoms; these symptoms predicted severity of borderline personality disorder.85 Auditory and visual hallucinations, paranoia, and thought problems, like strange thoughts and confusion, were common and presented early in the course of the disorder. Another study suggested that borderline traits mediate the relationship between history of trauma and psychotic-like experiences in the context of high stress.86

Substance Use

The ingestion or use of multiple illicit substances, such as hallucinogens and stimulants, can result in psychotic experiences, although no causal link has been established. In a study of help-seeking youth, those at risk for developing a psychotic disorder had higher rates of tobacco, alcohol, and cannabis use than those individuals who were not.87 In a study of 404 participants from the Recovery After an Initial Schizophrenia Episode–Early Treatment Program (RAISE-ETP), up to half of adolescents and young adults with FEP reported use of alcohol or cannabis within the month before starting treatment.88 In addition, about half of this population also reported use of tobacco at the time of enrollment in RAISE-ETP. Authors found that cigarette smoking was associated with reports of more psychiatric symptoms and poorer functioning, more missed pills, and decreased quality of life. Use of alcohol was associated with decreased adherence to medication regimen, and cannabis use was related to increased severity of illness and positive symptoms of schizophrenia.89 Other meta-analyses of observational and longitudinal studies have demonstrated that daily tobacco use is associated with increased psychosis risk as well as earlier age when psychotic symptoms begin; researchers in these studies concluded that a causal link between tobacco smoking and development of psychosis should be considered and that further studies should be performed.89–91

Most studies suggest a consistent association between marijuana use in adolescence and development of psychosis, and persistent use after an initial psychotic episode is associated with poorer prognoses.82–94 There is also evidence suggesting earlier age at first marijuana use correlates with earlier age at onset of psychotic symptoms, regardless of whether or when marijuana users discontinued use; therefore, cannabis use is a preventable risk factor in psychosis.93,95,96 There remains controversy over the level of risk for development of psychosis attributed to the use of cannabis and the level to which cannabis use can precipitate people without genetic predisposition to psychosis into illness.92 One recent multisite study in Europe and Brazil demonstrated daily cannabis use and use of high-potency cannabis were the strongest independent predictors of having a psychotic disorder.97 The odds of having a psychotic disorder for individuals using cannabis daily was 3.2 times higher than for those who never used cannabis (“never-users”). The odds of having a psychotic disorder in those who used high-potency cannabis versus never-users was 1.6 times higher. Because of the multiple sites and knowledge of incidence rates of psychotic disorders at those sites, researchers of this study were able to demonstrate that the association between use of cannabis and risk of psychosis varies by location depending on how and what kind of cannabis is used in that region. The authors report that in regions where cannabis is used daily and where high-potency cannabis tends to be
used more frequently, there are more cases of psychotic disorders. Synthetic cannabinoids (K2, spice) can also induce psychotic symptoms. Routine urine toxicology screens do not screen for synthetic cannabinoids.

In a study in Denmark following patients with substance-induced psychosis, researchers found that more than 30% converted to bipolar disorder or primary psychotic disorder. In the case of cannabis-induced psychosis, almost half converted. Approximately half of those patients who transitioned to schizophrenia did so within 2 years of diagnosis. A Scottish longitudinal study reported a 15.5-year cumulative hazard rate of 17.3% for diagnosis of schizophrenia after an initial hospital admission with substance-induced psychotic disorder (including cannabis, stimulants, and alcohol). Approximately half of these patients transitioned to schizophrenia within 2 years (80% by 5 years). These studies suggest that follow-up of patients in whom substance-induced psychosis is initially diagnosed could benefit from follow-up of 2 to 5 years to optimize early intervention and mitigate negative outcomes.

Perhaps of particular relevance to pediatricians, because they may be more likely to prescribe stimulants for children with attention-deficit/hyperactivity disorder (ADHD), researchers of a recent study using data from 2 commercial insurance claims databases compared the diagnosis of new-onset psychosis in adolescents and young adults with a diagnosis of ADHD treated with either a methylphenidate or amphetamine formulation. Although both classes of stimulants increase overall dopamine, amphetamines potently increase dopamine release from neurons (similar to neurotransmission in a primary psychotic disorder), whereas methylphenidates inhibit dopamine transport, thereby decreasing reuptake of dopamine into the presynaptic terminal. In this large-scale study of adolescents and young adults with stimulant prescriptions, researchers determined that 0.1% in the methylphenidate group and 0.2% in the amphetamine group required treatment of stimulant-induced psychosis. On the basis of this study, authors determined that approximately 1 in 660 patients with ADHD who are treated with a stimulant will develop a new-onset psychosis. Analyses of data from the US Food and Drug Administration (FDA) and case reports demonstrated that stimulant-induced psychotic symptoms generally did not last long and often resolved with cessation of stimulant alone. Cathinones (bath salts) fall under the category of stimulants and can also induce psychosis. Cathinones do not show up on routine urine drug screens.

These data indicate that substance use increases vulnerability for those who are at risk for developing psychotic symptoms.

**EVALUATION OF PATIENTS WITH PSYCHOTIC-LIKE SYMPTOMS**

The presentation of adolescents and young adults with psychotic-like symptoms can be varied, and a wide differential diagnosis should be considered, including psychiatric disorders, physical illness, and intoxication (see Tables 2 and 3). Pediatricians may initially encounter a patient presenting with vague feelings that something is wrong or “off,” with a correlating drop in grades and/or work performance or increased isolation, which may be attributable to suspicions and mistrust of others. Patients may also present with decrease in hygiene and/or self-care, difficulty communicating or confused speech, and new-onset difficulty in concentrating. Additionally, adolescents may present with difficulty separating fantasy from reality. Early-onset schizophrenia can also present with cognitive delays. One of these symptoms merits consideration of referral to a mental health specialist for further evaluation and monitoring and therapy (eg, cognitive behavioral therapy [CBT]), and multiple symptoms warrant referral to a child and adolescent psychiatrist and a therapist. Collaboration with developmental and behavioral pediatricians should also be considered, especially in the context of ID and ASD. If symptoms are more overtly psychotic and could potentially lead to unsafe behavior with possible suicidal or homicidal ideation, pediatricians should arrange for immediate safety evaluation in a mental health facility or ED with resources to stabilize and evaluate children and adolescents with mental health problems.

Screening for psychosis with validated screens, such as the Prodromal Questionnaire—Brief, the PRIME early psychosis screen, and the Youth Psychosis At-Risk Questionnaire, can be helpful to screen for psychotic symptoms.
regularly because they are relatively short and have high specificity. Other longer screens are mostly used in research settings, such as the Structured Interview for Prodromal Symptoms (SIPS), the gold standard for psychosis risk, and the Comprehensive Assessment of At-Risk Mental States (CAARMS), both of which are labor-intensive and require special training by the administrator of the screen.104,105

In the case of an adolescent presenting with an acute psychotic break, additional concerns may be relevant, and there should be consultation with a child and adolescent psychiatrist if available. Although the below recommendations and suggestions for interviewing and examination of the patient remain important, pediatricians will also likely have more concern for trauma or signs of intoxication or withdrawal. There may also be more concern for agitation. Early signs of agitation include restlessness, irritability, and inappropriate or aggressive behaviors, which could require pharmacologic interventions, such as an antipsychotic (haloperidol is often used) and/or a benzodiazepine, such as lorazepam. It is best to offer these medications orally to allow the patient to feel that he or she has some control in the situation.106 Because of safety concerns, these patients may ultimately be admitted to psychiatric inpatient units. If other physical or medical issues are discovered and the adolescent must be hospitalized in a pediatric unit, consultation with a psychiatrist may be helpful to manage agitation.

**Interviewing Patients With Psychotic Symptoms**

Pediatricians should interview patients in a quiet and private setting, with as few distractions as possible. Parents and guardians may be able to provide more information and a better time line than the patient, depending on the patient’s mental status. Attempting to construct a timeline of symptom progression is also useful and includes asking about recent stressors or possible precipitating or exacerbating events, such as trauma in the form of physical or sexual abuse, bullying, or the loss of a loved one (or anniversary of such a loss).105

Although it is essential to gather history from parents or guardians, it is also important to talk alone with the adolescent. Careful attention to and documentation of the mental status of the adolescent is necessary (such as his or her presentation and hygiene, engagement, response to internal stimuli). When asking about possible psychotic symptoms, it is important for providers to normalize the symptoms if possible. Asking when these symptoms occur (when one is stressed or depressed, at night when one is alone) and how often they occur (randomly, only in stressful situations, constantly) is also helpful. In addition to asking about specific symptoms, it is helpful and important to ask reality-testing questions (testing how valid the patient’s beliefs are and trying to differentiate the patient’s internal experience from that of real life), which indicate how entrenched the belief is. If patients report hearing voices of others talking about them but feel that the voices could actually be their own thoughts or that there could be other explanations for the feeling that they are being watched, this would be less acutely concerning. Other important information including medical history (birth history, including age of parents, and developmental history); family psychiatric history; history of abuse or other trauma, including bullying; and history of substance use can shed light on possible risk factors and etiology. Although understanding of current symptoms is critical, it is also important to assess premorbid functioning to understand the patient’s degree of change from baseline.

Pediatricians also may consider gathering collateral information from teachers, counselors, or coaches, with consent, after the initial interview to gain different perspectives on the adolescent’s behavior and functioning. For example, if parents notice increased isolation and withdrawal as well as refusal to engage in regular hygiene, but the teacher states that grades continue to be good and the adolescent continues to engage in appropriate social interactions with peers (who also do not shower regularly), this might be less concerning for a prodromal presentation. See Appendix 2 for example questions.

Patients presenting with psychotic symptoms are at greater risk for suicide; therefore, it is critical to inquire about thoughts of self-harm or suicidal ideation, passive or active, with or without plan or intent. The Ask Suicide Screening Questions screening tool is helpful in determining the presence of suicidal thinking, and the Columbia-Suicide Severity Rating Scale can be used to determine the level of risk.107,108 Patients may report command hallucinations telling them to hurt or kill themselves or others; derogatory hallucinations, such as voices that say negative things about them or put them down; or persecutory or religious delusions in which they could report feeling threatened by others or “the devil.” If there are concerns for safety to self or others, it is important for providers to refer immediately to the ED for evaluation and to ensure safe transportation. Other concerning symptoms that warrant referral to the ED include severe impairment in functioning, such as lack of self-care (eg, severe weight loss because of worry that the food is being poisoned) or complete isolation (eg, refusal to leave the room or home because of a belief that others will place thoughts in their...
heads). If there are no acute safety concerns but symptoms seem to be fully psychotic rather than attenuated, the patient is unable to come up with alternative explanations to delusions, the patient appears to be in distress, and/or functioning is affected, the pediatrician should refer the patient to a child and adolescent psychiatrist.

**Physical Examination**

When a patient presents with psychotic-like symptoms, providers should perform a thorough physical examination with a detailed neurologic examination to exclude medical etiologies. Focal neurologic findings may warrant urgent consultation with neurology and may require additional evaluation such as EEG and brain imaging. Hallucinations that are primarily gustatory or olfactory can be suggestive of organic causes, such as seizure disorder or tumor, although a more recent study suggests tactile, olfactory, and gustatory hallucinations are actually common in primary psychotic disorders and not necessarily indicative of organic brain disease. Authors also found an association of tactile, olfactory, and gustatory hallucinations with earlier age of onset with psychosis. Hallucinations associated with headaches warrant referral to a neurologist as well.

**Laboratory and Imaging Studies**

Pediatricians may consider the following laboratory tests: complete blood cell count, comprehensive metabolic panel (including glucose, serum urea nitrogen/creatinine, liver function tests), thyroid-stimulating hormone, calcium and phosphorus, ceruloplasmin (to evaluate for Wilson disease), antinuclear antibodies, erythrocyte sedimentation rate, syphilis screening, HIV screening, vitamin B₁₂ and folate concentrations, and urinalysis and urine toxicology. Testing levels of heavy metals may also be considered if clinically indicated. Testing for copy number variants in patients with psychosis may be considered when there is suspicion for a genetic syndrome. See Table 2 for a list of medical illnesses, the symptoms of which can include psychosis, and recommended testing.

There is limited evidence supporting imaging studies for patients who do not present with associated focal neurologic signs, although it may be helpful in those with a history of head trauma. Patients with positive antinuclear antibody titers should be referred to pediatric rheumatology, and neuroimaging studies should be performed for evaluation of possible lupus cerebritis. The American College of Radiology appropriateness criteria of evidence-based imaging guidelines for specific clinical presentations suggest that MRI or a computed tomographic scan may be appropriate initially in new-onset psychosis but that the yield of brain imaging for psychosis onset was low unless there was an evident neurologic deficit.

There is also insufficient evidence to routinely perform EEG. However, in a patient presenting with FEP who has a history of a seizure disorder, EEG may rule out the possibility of ictal or interictal psychosis. Some studies support prognostic, rather than diagnostic, implications of EEG, with abnormal EEG findings reflecting poorer prognosis.

**WHEN TO REFER TO SPECIALTY CARE OR ED**

As noted previously, if attenuated symptoms worsen or become fully psychotic, pediatricians should refer patients for psychiatric care. If there are any concerns for safety, such as suicidal thoughts, self-harming thoughts or behaviors, or homicidal ideations because of suspicion of others, the pediatrician should immediately refer the patient to the ED or other mental health facility with means to evaluate and stabilize the patient or summon an ambulance for emergency transport to the ED depending on acuity of safety concerns. Although providers should maintain confidentiality for many mental health care concerns, in the event of concerns for danger; such as suicidal or homicidal ideation, abuse, or disorganization that is so severe that basic functioning is lost (such as not eating, drinking, or sleeping), providers must breach confidentiality to protect the minor patient and others from harm and document that they are doing so. If a patient reports symptoms that are not potentially dangerous and do not seem to affect functioning, these can be kept confidential between the patient and the treating physician and documented in a confidential section of the electronic medical record if available. The physician is advised to use his or her clinical judgment with regard to confidentiality and may encourage the patient to discuss these issues with the parent or guardian (even offering to be present during the discussion to lend support). In the case of a young adult, over 18 years, who has capacity and who presents with a parent or guardian, the clinician is able and encouraged to gather collateral information; however, the clinician cannot share confidential information with the family unless the patient asks him or her to do so. If a patient is considered a danger to self or others or is not able to conduct basic activities of daily living because of the severity of symptoms and needs to be psychiatrically hospitalized, the parent or guardian cannot be told unless the patient asks specifically that this be done or the parent has guardianship.

If a patient is at imminent risk to the safety of himself or herself or others or deemed unsafe or unwilling to engage in care, emergency medical services or police transport is
advised, and referral communication to the ED is recommended. Some states have special procedures to mandate transfer, as well as documents that may accompany patients to indicate the pediatrician’s assessment that the patient needs emergency evaluation. Providing this documentation to the guardian who takes the patient to the ED may improve the likelihood of psychiatric hospitalization. States have varying legal requirements for involuntary evaluation and/or treatment of patients, and pediatricians are advised to consult their state department of health Web sites to determine the relevant mental health laws of their state. Although collaboration with a psychiatrist on appropriateness of transfer would be ideal, this is not always possible given the shortage of child psychiatrists. Therefore, in acute situations in which safety is a concern, a pediatrician should feel justified in sending a patient directly to the ED with the guardian if guardian is cognizant of the urgency of the situation and will take the patient to the ED or call 911 to transport the patient. See Fig 1 for consideration of monitoring, breaking confidentiality, and transport to ED for emergency evaluation.

**TREATMENT**

Pediatricians may be the first providers to assess and identify psychotic-like symptoms. Because visits to the pediatrician may decrease in adolescence, pediatricians should be vigilant in assessing for mental health concerns and changes in functioning or unusual beliefs. Because adolescence can be a difficult time for youth and parents alike, addressing stressors at home and in the environment can be beneficial for all adolescents, including those manifesting psychotic-like symptoms. Recommendations to spend more time in familiar settings among family members and/or close friends can be helpful. Helping the patient to obtain educational or career supports and appropriate psychiatric care earlier may decrease DUP and improve outcomes. In a study of patients presenting with psychotic symptoms associated with a nonpsychotic primary disorder, enhancement of coping skills was associated with improved outcomes.

NAPLS provides a relatively new concept of “clinical staging” for psychotic disorders that may help determine treatment at different levels of presentation and symptom manifestation. Patients presenting with less severe symptoms and/or risk factors receive psychosocial treatments initially, and individuals with increased severity of symptoms and/or more risk factors receive pharmacotherapy in addition to psychosocial treatments. Once a pediatrician identifies psychotic symptoms in an adolescent, it is likely that a referral to a mental health provider will result. Below are the
current treatment modalities for psychotic disorders.

**CBT**

CBT is an evidence-based treatment of patients presenting with psychotic-like symptoms. CBT aims to lower distress and disability through working with delusions, hallucinations, and negative symptoms, using the "ABC method" (activating event leading to an automatic thought, which in turn affects affect and behavior). CBT aims to derive alternative explanations for the patient’s psychotic symptoms that are acceptable to the patient and the therapist and to decrease the patient’s distress from the symptom(s).119,120 In a systematic review and meta-analysis, researchers found CBT lowered the risk of progression to psychosis at 6, 12, and 18 to 24 months and decreased symptoms at 12 months.121 Authors of a more recent meta-analysis found that CBT resulted in a trend toward significant reduction of attenuated psychotic symptoms at 12 months.122 In the Dutch Early Detection Intervention Evaluation Trial, authors studied people at “ultrahigh risk” of psychosis who received CBT in addition to routine care compared with a control group with routine care only. CBT plus routine care demonstrated averted transition to psychosis and reduced costs.123 In addition, the National Institute for Health and Care Excellence recommends CBT with or without family therapy for patients presenting with attenuated psychotic symptoms.124

CBT in early psychosis has also revealed some benefit as a stand-alone treatment of psychosis, although most studies have been conducted with CBT in combination with antipsychotic medication treatment. CBT may be more acceptable to patients because of its lower side effect profile and decreased stigma; in addition, discontinuation of CBT is less common than discontinuation of treatment with antipsychotic medications.125–127

**Other Psychosocial Interventions**

Aside from CBT, family-focused interventions, social skills training, supported education and employment, and healthy lifestyle training are early interventions that can be helpful for CHR patients.128 Family interventions include family psychoeducation and improving communication between family members. In a meta-analysis, family therapy was found to show a nonsignificant trend toward decreasing attenuated psychotic symptoms at 6 months.122 Because impairment in social skills can be associated with difficulty making friends, bullying, and poor occupational functioning, social skills training can involve role playing as well as practicing specific social skills to improve interpersonal skills.128 CHR youth may be at higher risk for academic difficulties, so they may benefit from special education services, such as a 504 or individualized education program. Increased resources and appropriate accommodations can help these youth feel successful. In addition, supported employment can be helpful for patients at CHR, who may have trouble finding and maintaining jobs. Healthy lifestyle interventions include emphasis on proper nutrition, physical activity, getting enough sleep, managing stress, and not engaging in behaviors like smoking, substance use, and risky sexual practices.128

The Schizophrenia Patient Outcomes Research Team psychosocial treatment recommendations, which report evidence-based psychosocial treatments for people with schizophrenia, include assertive community treatment, supported employment, skills training, CBT, token economy interventions (positive reinforcement for target behaviors), family-based services, psychosocial interventions for alcohol and substance use disorders, and psychosocial intervention for weight management.129 Correll et al130 reported that early intervention services were superior to treatment as usual in FEP.

**Medications**

Initiating medication for the treatment of psychotic symptoms is generally out of the scope of pediatricians. However, limited access to mental health specialists may necessitate prescribing in some circumstances, ideally with consultation from a child and adolescent psychiatrist or developmental-behavioral pediatrician.

Several antipsychotic medications may alleviate psychotic symptoms if the symptoms are caused by a primary psychotic disorder (see Tables 4 and 5), although it is important to mention that ziprasidone and asenapine failed to separate from placebo in treatment of adolescents with schizophrenia.131,132 When selecting an antipsychotic medication, those with FDA approval should be considered first. Other factors that may help guide the choice of treatment include side effect profile, patient and family preference, cost, insurance coverage, and availability of the medication.133

If psychotic symptoms are caused by another psychiatric disorder, the primary disorder (such as depression, bipolar disorder, or anxiety) should be treated first, unless the psychotic symptoms are so severe that brief treatment with an antipsychotic medication concurrently with a medication to treat the primary disorder should be considered. Given the adverse effects associated with antipsychotic medications, great care and consideration are advised before prescribing these medications.
With regard to dosing, the mantra is to “start low, and go slow,” always monitoring for adverse effects. Generally, lower doses should be effective in patients with FEP. A meta-analysis and pooled data from 7 randomized controlled trials indicate an observable response usually within 2 weeks and that the initial improvement (in 2 weeks) is greater than in the subsequent 2 weeks. See Table 4 for a list of antipsychotic medications and side effects and Table 5 for dose ranges and FDA approval for children and adolescents.

There have been trials comparing efficacy of first-generation and second-generation antipsychotic medications, including the Clinical Antipsychotic Trials of Intervention Effectiveness and European First Episode Schizophrenia Trial. Researchers in these studies did not find significant differences among efficacy of these antipsychotics but did find different side effect profiles, which influenced time to discontinuation.

There are 2 main treatment studies of adolescents and young adults with schizophrenia. Researchers in the Treatment of Early-Onset Schizophrenia Symptoms (TEOSS) study compared the efficacy of first-generation or atypical (second generation) antipsychotic medications on early-onset schizophrenia and schizoaffective disorder because providers were prescribing more atypical antipsychotics because of better efficacy and tolerability, although there was no clear evidence of this. The study included patients between 8 and 19 years of age receiving risperidone, olanzapine (both atypical antipsychotics), or molindone (first-generation antipsychotic). The 3 medications had similar efficacy (50% treatment response), but adverse effect profiles differed.

### Table 4: Commonly Used Antipsychotic Medications and Adverse Effects

<table>
<thead>
<tr>
<th>Antipsychotic Medication</th>
<th>Akathisia</th>
<th>TD</th>
<th>Sedation</th>
<th>Anticholinergic Side Effects</th>
<th>Orthostatic Hypotension</th>
<th>Wt Gain</th>
<th>Dyslipidemia</th>
<th>Hyperglycemia</th>
<th>Prolactin Elevation</th>
<th>QTc Prolongation</th>
</tr>
</thead>
<tbody>
<tr>
<td>First generation</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chlorpromazine</td>
<td>Minimal</td>
<td>Minimal</td>
<td>Moderate</td>
<td>Moderate</td>
<td>Severe</td>
<td>Severe</td>
<td>Severe</td>
<td>Severe</td>
<td>Minimal</td>
<td></td>
</tr>
<tr>
<td>Haloperidol</td>
<td>Severe</td>
<td>Moderate</td>
<td>Mild</td>
<td>None</td>
<td>Minimal</td>
<td>Minimal</td>
<td>Moderate</td>
<td>Moderate</td>
<td>Minimal</td>
<td>Minimal</td>
</tr>
<tr>
<td>Second generation (atypical)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aripiprazole</td>
<td>Moderate</td>
<td>Minimal</td>
<td>Minimal</td>
<td>None</td>
<td>Minimal</td>
<td>Minimal</td>
<td>Minimal</td>
<td>Minimal</td>
<td>Minimal</td>
<td></td>
</tr>
<tr>
<td>Clozapine</td>
<td>Mild</td>
<td>None</td>
<td>Severe</td>
<td>Severe</td>
<td>Moderate</td>
<td>Severe</td>
<td>Severe</td>
<td>Severe</td>
<td>Mild</td>
<td></td>
</tr>
<tr>
<td>Lurasidone</td>
<td>Mild to moderate</td>
<td>Minimal</td>
<td>Mild to moderate</td>
<td>Minimal</td>
<td>Minimal</td>
<td>Minimal</td>
<td>Minimal</td>
<td>Minimal</td>
<td>Mild</td>
<td>Minimal</td>
</tr>
<tr>
<td>Paliperidone</td>
<td>Mild</td>
<td>None</td>
<td>Minimal</td>
<td>None</td>
<td>Moderate</td>
<td>Mild</td>
<td>Moderate</td>
<td>Mild</td>
<td>Mild</td>
<td></td>
</tr>
<tr>
<td>Quetiapine</td>
<td>Mild to moderate</td>
<td>Minimal</td>
<td>Moderate</td>
<td>Mild to moderate</td>
<td>Moderate</td>
<td>Moderate</td>
<td>Moderate</td>
<td>Moderate</td>
<td>None</td>
<td>Minimal</td>
</tr>
<tr>
<td>Risperidone</td>
<td>Mild</td>
<td>Minimal</td>
<td>Mild</td>
<td>None</td>
<td>Moderate</td>
<td>Mild</td>
<td>Mild</td>
<td>Mild</td>
<td>Severe</td>
<td></td>
</tr>
<tr>
<td>Ziprasidone</td>
<td>Mild to moderate</td>
<td>Minimal</td>
<td>Mild to moderate</td>
<td>Minimal</td>
<td>Minimal</td>
<td>Minimal</td>
<td>Minimal</td>
<td>Minimal</td>
<td>Mild</td>
<td>Moderate</td>
</tr>
</tbody>
</table>

Sources: 151 and 152. TD, tardive dyskinesia.
akathisia, an inner feeling of restlessness that compels people to be in motion; olanzapine and risperidone were associated with weight gain and metabolic changes. Risperidone also caused increase of prolactin levels.138

The National Institute of Mental Health Recovery After Initial Schizophrenia Episode (RAISE) study of participants 15 to 25 or 30 years of age aimed to develop and implement integrated treatment protocols in FEP. The treatment program is NAVIGATE, named as such to support and guide patients and their families through the experience of FEP toward recovery.140 NAVIGATE is a team-based, multidisciplinary treatment program designed for implementation in community mental health facilities. Treatment interventions include individualized medication treatment (shared decision-making), family education program, individual resiliency training, and supported education and employment.141,142

Coordinated specialty care with these components is now considered evidence-based care in treatment of early-onset psychosis and is tightly coordinated with primary medical care to optimize both mental and physical health. In a comparison of NAVIGATE and usual community care, NAVIGATE participants continued treatment of longer periods of time, had more improvement in symptoms and quality of life, and were more involved in school and work over a period of 2 years.141 Patients also had fewer adverse effects and were less depressed.143 Patients with shorter DUP seemed to benefit more from NAVIGATE than those with longer DUP.141

<p>| TABLE 5 Second-Generation Antipsychotic Medications: FDA Approval and Dose Ranges for Adolescents With Schizophrenia |
| ---------------------------------- | ---------------------------------- | ---------------------------------- | ---------------------------------- |</p>
<table>
<thead>
<tr>
<th>FDA Approval</th>
<th>Recommended Dose</th>
<th>Starting Dose</th>
<th>Maximum Dose, mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aripiprazole</td>
<td>Schizophrenia: ≥13 y</td>
<td>10 mg</td>
<td>2 mg</td>
</tr>
<tr>
<td>Lurasidone</td>
<td>Schizophrenia: ≥13 y</td>
<td>40–80 mg</td>
<td>20 mg</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>Schizophrenia: ≥13 y</td>
<td>10 mg</td>
<td>2.5 mg</td>
</tr>
<tr>
<td>Paliperidone</td>
<td>Schizophrenia: ≥12 y</td>
<td>Wt &lt;51 kg: 3–6 mg</td>
<td>3 mg</td>
</tr>
<tr>
<td></td>
<td>Schizophrenia: ≥12 y</td>
<td>Wt ≥51 kg: 3–12 mg</td>
<td>3 mg</td>
</tr>
<tr>
<td>Quetiapine</td>
<td>Schizophrenia: ≥13 y</td>
<td>400–800 mg/d</td>
<td>25 mg to 25 mg BID</td>
</tr>
<tr>
<td>Risperidone</td>
<td>Schizophrenia: ≥13 y</td>
<td>0.5–6 mg/d</td>
<td>0.25–0.5 mg</td>
</tr>
</tbody>
</table>

Sources: 153 and 154. BID, twice a day.

Adverse Effects of Antipsychotic Medications and Recommended Monitoring

The pediatrician may be asked to evaluate a patient with medical symptoms that could be related to antipsychotic medication. Moreover, because of geographic limitations and cost concerns, families may rely on the pediatrician in the medical home to work collaboratively with the psychiatrist to monitor for certain side effects of antipsychotic medications. Adverse effects of antipsychotic medications include extrapyramidal symptoms, weight gain, impaired glucose metabolism, increased lipid concentrations, increased prolactin concentrations (leading to menstruation irregularities and galactorrhea), increased QTc interval, and sedation. Extrapyramidal symptoms include bradykinesia (decreased movement), akathisia, tremor, muscle rigidity, dystonia (intermittent or sustained muscle contractions), and tardive dyskinesia (involuntary and repetitive athetoid or choreiform movements of the body, lasting at least a few weeks).144,145 Tardive dyskinesia can develop in association with the use of a neuroleptic medication for at least a few months and can persist beyond 4 to 8 weeks1 (see Table 4).

The American Academy of Child and Adolescent Psychiatry practice parameter provides guidelines on metabolic monitoring for pediatric patients receiving antipsychotics, as second-generation antipsychotics are more likely to increase risk of metabolic syndrome, with increased waist circumference and blood pressure as well as hypertriglyceridemia, hyperglycemia, and low high-density lipoprotein ("good cholesterol") concentration.144,146,147 The guideline recommends baseline measurement of BMI, waist circumference, fasting blood glucose concentration, hemoglobin A1c, and fasting lipid concentrations. Additionally, monitoring includes BMI and waist circumference monthly for the first 3 months, at 6 months, and then yearly, unless there is a change in medication dose (in which case more frequent measurements should be made until dose stabilization). The guidance recommends measuring fasting glucose concentration, lipid concentrations, and hemoglobin A1c at 3 months and then yearly.146,147 Providers may consider more frequent monitoring of children and adolescents.

Neuroleptic malignant syndrome (NMS) is a rare but life-threatening adverse effect of treatment with antipsychotic medications caused by excessive dopamine blockade. Symptoms include “lead-pipe” muscle rigidity, fever, autonomic dysfunction, and altered mental status. NMS is mostly likely to occur within hours to days of taking the medication, with the most common laboratory finding of elevated creatine concentrations of 1000 μg/L.148 Initial management of NMS includes cessation of the causative drug and supportive medical care. Severe NMS may require treatment with bromocriptine.
A dartaglye, which is a dopamine agonist, and dandrene sodium, a muscle relaxant. If pediatricians detect potential NMS symptoms, it is important that the patient receive immediate assessment and treatment, because it is a potentially fatal emergency.

AVOIDING MISDIAGNOSIS AND UNNECESSARY TREATMENT

Encountering a patient with psychotic-like or frank psychotic symptoms may be unsettling to pediatricians, who may have limited experience with mental health disorders. Psychotic-like symptoms can be frightening and debilitating, often fueling the pressure to treat with medication. Although data have shown an improved prognosis for shorter DUP, these data do not suggest that all psychotic symptoms should be treated with antipsychotic medication.

Pediatricians should proceed cautiously and thoughtfully with their evaluation, keeping a broad differential diagnosis in mind and attending to possible safety concerns. Because presentation of psychotic-like or frank psychotic symptoms can be complex, consultation with a child psychiatrist is generally warranted to avoid misdiagnosis and unnecessary treatment with antipsychotic medications. Additionally, we advise caution before making a diagnosis of unspecified psychotic disorder or any other psychotic disorder because these diagnoses often persist and may unnecessarily stigmatize patients.

RESOURCES FOR PEDIATRICIANS

Because of the shortage of child psychiatrists, there are resources within states that allow “live, real-time” consultations with child and adolescent psychiatrists in the area. Programs across the nation consisting of telephone or video consultations with a range of mental health providers are excellent resources that can guide diagnosis and treatment. These programs are free to primary care physicians, sometimes only within a certain geographic area, and are often funded by the state department of health. Pediatricians can generally call the number for the program and undergo an orientation before beginning use of the telephone consult and, in some cases, telepsychiatry or physical consultation services. Some programs are open only to patients with medical assistance (Medicaid). Other programs not only offer consultation services but also offer training programs or continuing medical education opportunities to primary care physicians on the assessment and management of mental health issues. In some programs, if phone consultations are insufficient, pediatricians can schedule in-person evaluations within a few days of the phone consultation, which may be especially helpful to those practicing in remote or more rural areas where there are few to no child psychiatric providers. Other helpful resources for pediatricians are listed in Appendix 3. The resources include a link for coding recommendations, including new collaborative care codes used in the Psychiatric Collaborative Care Model, with a primary treating practitioner collaborating with a behavioral health care manager and a psychiatric consultant.

CONCLUSIONS

Psychotic symptoms can be frightening and confusing for patients, caregivers, and providers. Pediatric providers are unique in that they may be the first providers to observe attenuated psychotic symptoms or the first providers parents and guardians turn to if they observe such symptoms in their children. Understanding risk factors and symptoms to evaluate in patients who present with attenuated or psychotic symptoms is helpful in the evaluation of these youth and direct intervention, treatment, and referral, as early intervention can improve prognosis and level of functioning.

ADVICE FOR PEDIATRICIANS

1. In patients who present with psychotic-like or full psychotic symptoms, follow-up questions to better characterize the patient’s presentation and disposition are helpful.
2. In patients presenting with psychotic-like experiences, pediatricians should evaluate for history of trauma, including sexual, physical, or emotional abuse, neglect, and bullying; substance use; and developmental delays.
3. Clinical interview, comprehensive physical examination including neurologic examination, laboratory studies, and imaging (when clinically indicated) may be helpful in determining an underlying cause of psychotic symptoms.
4. Pediatricians should facilitate referrals to specialists (therapist, psychologist, or child and adolescent psychiatrist or general psychiatrist) according to severity of symptoms. Consultation with psychiatry, if available, can be helpful in ensuring that the appropriate referrals are made. For those with ID or ASD, referral to a developmental-behavioral pediatrician should be considered as well. The medical home model can be helpful in coordinating care and supporting the patient and family as they navigate the mental health system.
5. Screening for suicidal thoughts is an essential component of the evaluation process because psychosis is associated with increased suicidal ideation; if there are suicidal thoughts or thoughts to hurt others, the patient should be transported immediately to the ED for evaluation. Severe decrease in functioning, such as inability to
When starting antipsychotic medication, "start low and go slow" and provide regular monitoring for adverse effects. Pediatricians would generally not be expected to initiate antipsychotic medications. However, in some circumstances (e.g., severe symptoms that do not meet inpatient criteria in the setting of limited access to mental health care), it may be appropriate for the pediatrician to start or manage a medication while awaiting subspecialty care, ideally with ongoing consultation with a child psychiatrist.

In some states, free, state-funded services with telephone, and sometimes in-person, consultations with child and adolescent psychiatrists are available. These programs can be helpful in supporting pediatricians to extend their mental health expertise and should be used where available. Expansion of these programs and continued funding support for them are encouraged.

### APPENDIX 1: CASE VIGNETTES

#### Primary Psychotic Disorder

A 14-year-old patient presented with derogatory auditory hallucinations as well as visual hallucinations of eyes watching him. He had a history of declining grades, social relationships, and self-care. He described a recent visit to the ED after smoking cannabis that he believed may have been laced with something. He believed that he died or fell into a coma after that experience and that nothing is real now. When asked if there could be any other possible explanation, the patient replied that it could be aliens. The patient admitted that he was terrified by these thoughts and contemplated suicide, although part of him believed that he would not actually die if he tried to kill himself, because nothing was real. Because of the patient's level of distress, delusions, and loss of reality testing, he was believed to be in real danger of harm to himself and/or others. He was transported to the ED for further evaluation and safety assessment.

#### Mood Disorder With Psychotic Features

A 15-year-old, high-achieving patient presented with delusions and auditory hallucinations that peers were talking about her. She believed that her parents were poisoning her food and telling peers about her weaknesses and vulnerabilities to use them against her. Her parents reported that she had been staying up late doing homework and sleeping only 1 to 2 hours a night, with associated racing thoughts, pressured speech, poor concentration, and inability to complete many tasks she started. Because of the paranoid delusions and effect on her functioning, the patient was transferred to the ED. As part of the evaluation, no suicidal or homicidal ideations were noted, and the parents believed that they could ensure her safety. The patient was discharged from the hospital and referred to a child and adolescent psychiatrist, who ultimately diagnosed the patient with bipolar disorder, type I, severe with psychotic features, most recent episode manic. She was started on an atypical antipsychotic medication initially because of the severity of psychotic symptoms, as a mood stabilizer was slowly titrated to therapeutic level. She also began therapy. When the psychotic symptoms resolved, she returned to school and did well. At that time, her provider slowly discontinued the antipsychotic medication, and she remained on a mood stabilizer. She graduated from high school and went on to college.

#### Anxiety

A 16-year-old presented with hallucinations of people talking about her and making derogatory comments. She had previously done well but was now unwilling to leave her home because of severe anxiety attacks. The patient was referred to a child and adolescent psychiatrist as well as a psychotherapist. She eventually received a diagnosis of social anxiety disorder and was treated with a selective serotonin reuptake inhibitor (SSRI). She was able to return to school, and social relationships gradually resumed. After a period of stability, the patient returned to her pediatrician to manage her medication but continued to see a therapist.

#### Obsessive-Compulsive Disorder

A 17-year-old patient presented with intrusive sexual thoughts about her father and friends and worried that people and objects were dirty if they accidentally rubbed against her genitalia. She also expressed fears...
that she was homosexual when she thought another girl was attractive and would perseverate on this belief for hours to anyone who would listen at home. The patient was devoutly Catholic and feared that having these thoughts meant she was evil and deserved to die, although the thought of doing harm to herself was frightening to her. She began to pray multiple times a day to rid herself of these thoughts. Her pediatrician referred her to a psychologist, who referred her to a psychiatrist while continuing to work with her in therapy. With a combination of intensive CBT and an SSRI, the patient was able to overcome the obsessive thoughts and compulsions. Although she would sometimes still have them, she was able to tell herself that her mind was playing “tricks” on her and challenge these thoughts. She ultimately returned to her pediatrician for management of the SSRI and continued to have “booster” CBT sessions with the psychologist as needed.

**ASD**

A 14-year-old patient presented with auditory hallucinations consisting of multiple characters in a fantasy world he had created from a young age. He would often isolate himself to immerse himself in this fantasy world, which he preferred to “real life.” He had endured years of bullying and had no friends but was able to maintain good grades at school. The parents reported poor peer relationships and better social interactions with adults and younger children. He was obese, which correlated with multiple trials of antipsychotic medications, all of which had been stopped because of reported lack of efficacy. Because of concerns about impaired social interactions and restricted interests, the pediatrician referred the patient to a developmental-behavioral pediatrician for evaluation. After a thorough evaluation, the patient received a diagnosis of ASD. Genetic testing was completed and the result was negative. The developmental pediatrician recommended slow discontinuation of the antipsychotic medication because it became clear that the fantasy characters were a manifestation of ASD and caused no distress; in fact, they served as a coping mechanism against the challenges of real life. He began to participate in psychotherapy and a social skills group. Insight into his diagnosis and improved social interactions developed over time.

**ID**

A 13-year-old patient reported in a childlike sing-song voice that her mood was happy but that she would often see a shadow figure at night and sometimes visions of a little girl who wanted to give her flowers. She stated that her parents had been telling her she should pray whenever these figures would come, which she would always do. She had an individualized education plan, and past neuropsychological testing indicated low IQ. The pediatrician recommended follow-up in 2 weeks to determine if the visual
hallucinations or perceptions were distressing to the patient and whether the symptoms warranted a referral to a mental health specialist. At the 2-week follow-up, the patient began stating that these figures were becoming increasingly frightening, causing trouble sleeping, school refusal, and mood changes. The pediatrician referred her to a child psychiatrist for further assessment. Although the psychiatrist felt strongly that ID and possibly ASD were playing a large role in the patient’s presentation, the child’s report of distress and subsequent reports of hearing “terrifying” screaming while in school indicated need for medication initiation.

Cultural and Family Beliefs
A 15-year-old patient in treatment for ADHD for several years suddenly confessed to seeing ghosts in his room and feeling them touch him at times. He reported that these ghosts terrified him, so he had taken to wearing crosses, which he believed protected him. When the pediatrician asked if he had told anyone about these ghosts, he reported he had told his mother and father, both of whom also see ghosts. He stated that the ghosts were worse in his parents’ home, although he also felt the presence of different ghosts at his aunt’s home. Grades continued to be average, and he continued to have appropriate social interactions with peers at school. The provider routinely asked about these ghosts, as well as the patient’s functioning, at every follow-up visit but ultimately determined the patient’s reports to be associated with family beliefs or superstitions and provided no additional medications or referrals.

Trauma
A 16-year-old female adolescent confidentially told her adolescent medicine provider that she had been sexually assaulted at a party about a month ago and that since then, she was “paranoid” whenever she went out that someone was going to hurt her. If it was dark when she returned home from a school activity or work, she would constantly think that she was hearing footsteps behind her and seeing shadowy figures following her. The pediatrician asked about how she was doing at school, and the patient replied that although her concentration was decreased because of anxiety and flashbacks, she was maintaining good grades and was still managing to function at work. The pediatrician suggested seeing a therapist about the trauma that had occurred but held off on referral to a psychiatrist; he also increased frequency of follow-up visits for a few months, during which he monitored the status of the flashbacks and hyperarousal. With the help of the therapist, who used a combination of trauma-focused CBT and dialectical behavioral therapy techniques to treat the patient, these symptoms steadily decreased without need for medication.

Adverse Effect to Medication
A 7-year-old child with a history of ADHD, combined type, returned to his pediatrician’s office 2 weeks after starting a stimulant medication to help with school functioning. The parents expressed concern that the child reported seeing faces and feeling like insects were crawling on his skin. Knowing that psychotic symptoms were a rare adverse effect of stimulant treatment, the pediatrician stopped the medication. Symptoms quickly resolved.

Temporal Lobe Epilepsy
A 19-year-old young adult with no psychiatric history presented with delusions of being dirty and thinking she could not clean herself or rid herself of a foul stench. She also reported the taste of peppermint. Because of the olfactory and gustatory hallucinations, a computed tomographic scan of the head and an EEG were performed. The EEG revealed abnormal brain wave activity, and the pediatrician referred the patient to a neurologist.

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ABBREVIATIONS
ADHD: attention-deficit/hyperactivity disorder
ASD: autism spectrum disorder
CBT: cognitive behavioral therapy
CHR: clinical high risk
DSM-5: Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition
DUP: duration of untreated psychosis
ED: emergency department
FDA: US Food and Drug Administration
FEP: first-episode psychosis
ID: intellectual disability
NAPLS: North American Prodrome Longitudinal Study
NMS: neuroleptic malignant syndrome
SSRI: selective serotonin reuptake inhibitor
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