MASTER CLINICIAN REVIEW

Psychosis in Children and Adolescents

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Psychosis is characterized by overt disruptions in thought, perceptions, and behavior. Complex syndromes presenting with psychosis, including schizophrenia spectrum disorders, mood disorders, and medical illnesses, are differentiated by characteristic patterns of symptom presentation and course of illness. Accurate diagnosis is important to guide treatment and to avoid inaccurate labeling, because most youth reporting psychotic-like experiences do not have a true psychotic disorder.

Key words: psychosis, schizophrenia, hallucinations, delusions, antipsychotic medications

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The focus of this review is on early-onset schizophrenia (EOS), defined as onset before 18 years of age. Schizophrenia typically first presents during adolescence and young adulthood. Onset before 12 years of age is rare. Early onset is often associated with chronic morbidity and functional impairment. Effective treatment includes antipsychotic medication plus educational, supportive, and psychotherapeutic interventions. Innovative models of community-based coordinated specialty care focus on early identification, evidence-based psychopharmacology, and the provision of intensive psychosocial, family, and occupational/education support. Although the efficacy of antipsychotic medication for treating schizophrenia is well established, many affected persons do not adequately respond. More effective treatments are needed, the development of which depends in part on the identification of specific underlying neurodevelopmental and genetic causal factors.

> Tommy is a 15-year-old adolescent boy brought to the emergency room by the police after found walking the streets at 2:30 in the morning. Tommy told the police that he was searching for the Illuminati. He hears them whispering, telling him that they are coming to get him. Tommy's parents report that he stopped going to school 2 weeks previously and spends most of the time in his room. They hear him yelling and talking to himself and describe odd changes in behavior, such as taking apart his laptop to remove the camera. He has always been shy, with only a few friends during elementary and middle school, and was diagnosed with a reading disorder in the third grade. In the months preceding the evaluation, he has become increasingly withdrawn and isolated. His parents worry that he is depressed or using drugs. They tried taking him to the family doctor, but he refused to go. They called the local crisis line, but were told that nothing could be done unless he was dangerous to himself or others.

Psychosis, characterized by aberrant thinking, perceptions, and behavior, presents with many different conditions, including schizophrenia spectrum disorders, mood disorders, and medical conditions. These clinical syndromes are defined by overt changes in mental status, functioning, and behavior and by characteristic patterns of symptom presentation and course of illness. Accurate diagnosis is key to effective treatment.

This review focuses on the diagnosis and treatment of EOS. Schizophrenia is defined by positive (e.g., hallucinations, delusions), negative (e.g., social withdrawal, apathy), and disorganized (e.g., disordered thinking, bizarre behaviors) psychotic symptoms.[1] EOS is often associated with negative symptoms, cognitive deficits, and premorbid problems, all of which predict greater long-term morbidity and impairment.[2] With early effective treatment, most individuals show improvement, and in some cases the symptoms remit, but most affected persons need long-term treatment.[2]

In the case example, Tommy presents with paranoia, hallucinations, and bizarre behaviors consistent with schizophrenia. He had significant premorbid difficulties, including social deficits, cognitive delays, and behavioral problems, and a sharp decline in functioning in the months before the onset of acute psychosis (prodromal symptoms). Such clinical histories are common in youth who develop schizophrenia and potentially represent early manifestations of the disruptions in neurodevelopment that ultimately lead to the disorder.[3]

Some affected youth have extended periods of unrecognized psychosis. Delays in diagnosis can reflect the presence of overlapping nonspecific symptoms (e.g., dysphoria, avoidance, anger, anxiety); difficulties assessing the patient's internal thought processes and experiences (especially in persons with paranoia); and/or the hesitancy to diagnosis schizophrenia in a young person given prognostic implications. Although care must be taken in applying the diagnosis, it is important to recognize and acknowledge psychotic symptoms to initiate necessary treatment.

DIFFERENTIAL DIAGNOSIS

Schizophrenia and psychotic mood disorders are the most common psychiatric conditions associated with psychosis. Schizophrenia and bipolar I disorder collectively affect approximately 2% of the general population, with peak ages of onset in late adolescence and early adulthood.[1] Psychotic depression has an estimated lifetime prevalence of 0.35% to 1%, with higher rates in older populations.[4]

The differential diagnosis of psychosis can be a challenge. During acute episodes, it is difficult to distinguish between schizophrenia and psychotic mania,[5] both of which can present with hallucinations,

delusions, and disorganized thinking and behavior. The ultimate illness presentation can take months (or years) to manifest. Long-term monitoring with ongoing reassessment is necessary to clarify and confirm the diagnosis.[6]

There are potential clues that help distinguish schizophrenia from mania. Mania is not typically associated with negative symptoms (although differentiating depression from negative symptoms can be a challenge). Psychotic symptoms in mania often involve florid delusions and elaborate thought versus the paucity of speech and thought characteristic of schizophrenia. Markedly decreased sleep is a hallmark of mania, but disrupted sleep also occurs with schizophrenia. Family psychiatric history can be informative.

Distinguishing psychotic symptoms in youth with autism spectrum disorder also can be a challenge. Symptoms characteristic of autism and other developmental disorders, including perseverative thinking, cognitive and language delays, idiosyncratic beliefs, and lack of social reciprocity, resemble negative symptoms and thought problems characteristic of schizophrenia. Many individuals with schizophrenia had symptoms suggestive of autism before the onset of psychosis. The 2 disorders stem from disruptions in early brain development and share genetic and neuropathologic risk factors.[7] To distinguish, perseverative idiosyncratic beliefs and longstanding cognitive impairments characteristic of autism represent baseline patterns of functioning, whereas the development of psychotic symptoms with schizophrenia represents a marked change in baseline mental status and functioning. If a person with autism spectrum disorder develops prominent hallucinations and delusions lasting at least 1 month, then the diagnosis of schizophrenia is made.[1]

Psychosis also can develop secondary to medical conditions, including intoxication, seizure disorders, central nervous system infections, autoimmune disorders (e.g., anti–N-methyl-D-aspartate receptor encephalitis, cerebral lupus), genetic syndromes (e.g., velocardiofacial syndrome), medication side effects (e.g., steroids), and neoplasms. Signs and symptoms that warrant a more extensive medical evaluation include delirium, fluctuating mental status, neurologic focal findings, co-occurring physical symptoms (e.g., rash, fever, abnormal movements), and potential exposure to toxins or substances of abuse. Most medical conditions associated with psychosis, with the exception of substance abuse, are rare. The medical evaluation for potential medical causes should be dictated by the clinical presentation and history,[2] rather than broadly screening every patient for every possible condition.

WHAT IF IT IS NOT PSYCHOSIS?

The assessment of psychosis in youth presents unique developmental challenges. Reports of suspected psychosis must be gauged in the context of the youngster's age, culture, and cognitive development. The failure to account for developmental or cultural factors can result in the mischaracterization of childhood beliefs and experiences as psychotic symptoms.

> DJ is an 8-year-old boy brought to your office for hearing voices. He has a history of poor impulse-control and anger problems. After an aggressive outburst, he told his mother that he heard a voice telling him to hurt her. In your evaluation, DJ said the voice has a name, "Desparado." He drew a picture of Desparado, a devilish demon with fiery eyes. DJ reports that anytime someone says something that he does not like, Desparado tells him not to listen or to act out. Otherwise, DJ's thinking and behavior are typical for an 8-year-old boy with behavioral difficulties. He does not appear to be overly concerned or confused about the voice. The more questions you ask, the more elaborate details he provides, much of which serves to justify his behavior. In taking the family history, you discover that his mother's brother has schizophrenia, and that his mother is quite concerned that DJ will develop the illness.

Approximately 8% of adolescents (13–18 years old) and 17% of children (9–12 years old) describe psychotic-like experiences.[8] Normative childhood experiences, including overactive imaginations and vivid fantasies, can be misinterpreted as psychosis. Well-meaning anxious parents sometimes inadvertently reinforce symptom reports by avoiding setting limits or by explaining away egregious behavior, thereby introducing an element of secondary gain.

> Gloria is a 17-year-old girl in residential treatment with a history of self-harm and suicidal behaviors. She describes seeing a tall man, with curly brown hair, wearing Wranglers and sunglasses. The man sometimes talks to her. Gloria says the man used to say supportive things, but now he is mean and tells her that she is ugly or that she should cut herself. Gloria usually experiences seeing the man when she is upset, angry, or alone, particularly at night before she falls asleep. Otherwise her thinking is organized, and there are no overt signs of responding to internal stimuli or thought disorder on mental status examination. In therapy, she eventually tells her therapist that she first started seeing the man when her stepfather was sexually abusing her. She imagined that the man might come and rescue her, and found the perception hopeful at first, but later the image become upsetting as she was reminded of the abuse.

Children with other forms of psychopathology, including anxiety, demoralization, and histories of trauma, sometimes express distressful internal experiences as hearing or seeing things or unusual beliefs. Symptom reports that are situationally specific (e.g., only hearing voices when angry or at bedtime), overly elaborate and detailed, and/or occur absent of more overt evidence of thought disorder and disorganized behaviors are atypical for true psychosis.[9] Expertise in developmental psychopathology is important when assessing the veracity of psychotic-like symptoms in youth.

Youth reporting psychotic-like experiences are at risk for general psychopathology, including anxiety, depression, behavioral problems, substance abuse, and self-harm.[8] However, most do not have (nor will ever develop) a psychotic illness. Some literature suggests that psychosis exists on a continuum, based on population survey data. Questionnaire data are not sufficient to characterize biological continuums. Labeling everyone who reports an usual experience or hearing a voice as "psychotic" greatly expands the diagnosis, creates the risk for exposure to unnecessary treatment (antipsychotic medications), and confounds efforts to identify underlying biological causes.[10] The art of medicine is to distinguish unique clinical syndromes and not to lump everything together into a one-size-fits-all category.

TREATMENT

The effective management of schizophrenia spectrum disorders combines psychosocial interventions and psychopharmacology. Antipsychotic medications target active psychotic symptoms, whereas psychosocial interventions address the associated morbidity and functional deficits of the disorder and help improve social interactions, self-care, scholastic and occupational performance, and relapse prevention.

Psychopharmacology

The efficacy of antipsychotic medications for treating symptoms of schizophrenia in youth and adults is well established.[11,12] However, although this class of agents is clearly superior to placebo, patients often remain symptomatic and there is a high rate of treatment discontinuation due to lack of efficacy, side effects, or noncompliance. There is insufficient evidence to guide practitioners as to which medication will work best for which patient.[2] Although pharmacogenomics holds great promise for personalized prescribing, current evidence does not support the utility of available pharmacogenomics test batteries for routine care.[13] Therefore, the choice of which agent to use first is generally based on side effect profile, patient and family preference, clinician familiarity, and cost. In the United States, risperidone, aripiprazole, quetiapine, and olanzapine are the mostly commonly prescribed second-generation antipsychotic agents for youth with schizophrenia spectrum disorders according to Medicaid claims data.[14]

Most available randomized controlled trials for EOS compare a single agent with placebo, with only a few studies directly comparing the efficacy and safety of different agents. The Treatment of Early Onset Schizophrenia Spectrum Disorders Study (TEOSS) compared olanzapine, risperidone, and molindone for youth with EOS spectrum disorders ($N = 119$) using a randomized double-blinded design. Fewer than 50% of participants responded to 8 weeks of acute treatment.[15] No significant differences were found among treatment groups in response rates or the magnitude of symptom reduction. Olanzapine and risperidone were associated with greater weight gain, whereas molindone was associated with more self-reports of akathisia. Given marked weight gain and metabolic changes, enrollment in the olanzapine arm was stopped by the study's data safety and monitoring board.

Subjects in the TEOSS who responded to 8 weeks of therapy were allowed to continue on the same medication for up to an additional 44 weeks of treatment.[16] Overall, only 12% of subjects completed 12 months of therapy on their first randomized medication. There were no significant differences among molindone, risperidone, and olanzapine in long-term outcomes. Symptomatic improvements noted after 8 weeks of therapy tended to plateau. The findings of TEOSS are similar to those of large multiagent comparative trials in adults, all of which challenge the assumption that second-generation antipsychotic agents are more effective than traditional neuroleptics for treating schizophrenia.[17-19]

Other comparative multiagent pediatric trials for EOS and related conditions failed to find differences in efficacy between aripiprazole and paliperidone,[20] olanzapine, risperidone, and haloperidol,[21] risperidone and quetiapine,[22] or olanzapine, risperidone, and quetiapine.[23] For treatment-refractory EOS, clozapine provided greater benefit than haloperidol[24] and olanzapine.[25,26] Clozapine is generally considered the only agent with established superiority for treatment-resistant schizophrenia,[27] although not all studies in the adult literature support this finding.[28] Given its side effect profile, clozapine is not used as a first-line agent.

As a general guideline, it is best to start with an agent approved by the Food and Drug Administration (FDA) to treat schizophrenia in adolescents, including risperidone, aripiprazole, and quetiapine (all approved for treating schizophrenia in youth $\geq$13 years old) and paliperidone (approved for youth $\geq$12 years old). Olanzapine is approved for youth with schizophrenia ($\geq$13 years old) but is generally reserved as a second choice given the risk of weight gain and metabolic side effects. Ziprasidone[29] and asenapine[30] were not found to be statistically superior to placebo for treating adolescents with schizophrenia and therefore are not recommended for this indication. Some traditional neuroleptics (e.g., haloperidol, perphenazine, chlorpromazine, and thiothixene) are approved by the FDA for use in children and adolescents but have not been as well studied as second-generation agents in the pediatric population.

Antipsychotic medications approved for use in adults with schizophrenia can be considered for EOS as secondary options. However, newer agents that have not been systemically studied in EOS (e.g., iloperidone, brexpiprazole, cariprazine) are best avoided until pediatric data are available. Furthermore, drugs that are pharmacologic "knockoffs" (e.g., paliperidone is a metabolite of risperidone) are typically more expensive and do not offer any proven advantage over the parent compound. Newer and more expensive does not equal safer and more effective.

For all antipsychotic trials, treatment response and potential side effects need to be systematically monitored. Incorporating standardized measures into clinical practice helps improve the quality of care and documentation. Questionnaires useful for assessing psychotic symptoms include the Positive and Negative Syndrome Scale (PANSS),[31] Scales for the Assessment of Positive and Negative Symptoms,[32] and the Brief Psychiatric Rating Scale for Children (BPRS-C).[33] The Abnormal Involuntary Movement Scale (AIMS)[34] and the Neurological Rating Scale[35] are useful for monitoring abnormal movements and neurologic side effects. Standard guidelines for monitoring metabolic parameters have been widely disseminated, with recommendations for baseline and follow-up assessment of weight, blood pressure, fasting glucose, lipids, and hemoglobin A_{1c}, by the prescribing physician or in collaboration with primary care. However, although most prescribers are aware of these guidelines, many patients do not receive adequate monitoring.[36]

A therapeutic trial is generally defined as 4 to 6 weeks with doses up to FDA-approved dosages in adults (with allowances for children $<$13 years of age) as tolerated. If there is no response after 2 weeks on a therapeutic dose, then changing to a different agent should be considered. Long-term maintenance treatment is indicated for patients who have persistent symptoms and impairment. For patients with first-episode psychosis that achieve complete remission, clinical guidelines generally recommend 1 to 2 years of maintenance therapy after the cessation of symptoms.[37] The decision to maintain or taper medications depends on the degree of symptomatic improvement and overall functioning, patient and family preference, and the balance between the risks of medication side effects and the risks of relapse. When undertaking a medication-free trial, a gradual stepwise decrease in dose is recommended, with careful monitoring for relapse.

Patients who do not respond to at least 2 adequate trials of antipsychotic medications warrant a trial of clozapine. Because of the risk of agranulocytosis, clozapine requires systematic blood count monitoring,[38] with coordination among the physician, laboratory, and pharmacy. Although these requirements can be intimidating to clinicians, once established, the monitoring protocols are straightforward. Although none of the currently available long-acting injectable agents are approved by the FDA for use in children and adolescents, these preparations can be considered for patients who struggle with treatment compliance and have ongoing impairment.

The evidence supporting the use of concurrent medications to augment the effects of antipsychotic agents for schizophrenia, including the use of multiple antipsychotic medications, is at best limited in adults[39] and lacking in youth.[2] Medication trials need to be conducted systematically to avoid unnecessary polypharmacy. Common practices include the use of mood stabilizers for mood instability and aggression, antidepressants for depression, negative symptoms, or obsessive-compulsive symptoms, and benzodiazepines for anxiety, insomnia, or akathisia. Benzodiazepines also are a first-line treatment for catatonia.[40] Adjunctive treatments are important for addressing medication side

effects (e.g., antiparkinsonian agents for extrapyramidal side effects and β-blockers for akathisia).[2] Several studies in adults[41] and a recent randomized control in children and adolescents with autism spectrum disorder[42] found metformin helpful for metabolic adverse effects.

New effective treatments for schizophrenia are needed, particularly to address cognitive deficits and negative symptoms.[43] There have been a number of small trials examining agents that target hypothesized mechanisms and processes important to the illness, including glutamatergic and glycine modulators, cognitive enhancers, anti-inflammatory agents, and vitamins. Transcranial magnetic stimulation, with antipsychotic medication, potentially helps improve negative symptoms.[44] For supplements, ω-3 fatty acids as an adjunctive treatment can help during the early phases of the illness, but overall the results are mixed.[45] Melatonin can be used for insomnia.[46] Vitamin D did not significantly enhance treatment response with clozapine for chronic schizophrenia.[47]

Psychotherapies

Psychoeducational, supportive, vocational, and family interventions are important elements of treatment.[2] The goals include decreasing symptoms, improving social-occupational functioning, enhancing quality of life, and lowering the risk for relapse. Treatments also are needed to address commonly associated comorbid conditions, including substance abuse and suicidality.

In adults, family interventions are helpful for improving medication compliance, decreasing relapse, enhancing social functioning, and lowering the level of stress in the home.[48] Cognitive-behavioral therapy for psychosis can provide relief from positive symptoms and functional deficits, although not all patients respond.[49] Cognitive remediation strategies teach skills to improve cognitive deficits and enhance functioning.[50] Cognitive-behavioral and remediation strategies are often combined with rehabilitative and supportive efforts to enhance social and occupational functioning.

For youth with EOS, there is a small literature supporting the use of psychoeducational programs, family interventions, cognitive-behavioral strategies, and cognitive remediation.[51] Strategies include education regarding the illness and treatment options, social skills training, relapse prevention, basic life skills training, and problem-solving skills. Some youth need specialized educational programs and/or vocational training programs to address the cognitive and functional deficits associated with the illness.

Coordinated specialty care is an innovative model of community-wide treatment for first-episode psychosis (which is a broader diagnostic rubric than schizophrenia). Elements of coordinated specialty care include evidence-based pharmacology, individual and group psychotherapies, family support and education, assertive case management, educational and occupational support, and collaboration with primary care.[52] The NAVIGATE program, a team-based multidisciplinary treatment program implemented nationwide for individuals with first-episode psychosis, provides family education, individual resiliency training, supported employment and education, and medication therapy. During a 2-year follow-up period, recipients of NAVIGATE remained in treatment longer, demonstrated greater improvements in quality of life and psychopathology ratings, and were more involved in school and work compared with individuals randomized to community care.[53] Using similar strategies, early detection and intervention programs for youth displaying early signs of psychosis have demonstrated improvements in symptomatic and functional outcomes[54] and lower rates of hospitalization.[55] Efforts to further develop and expand such programs are underway nationally and internationally.

SUMMARY

Psychosis in children and adolescents can occur with a number of different complex clinical syndromes, each with characteristic alterations of mental status, behavior, and function. Accurate diagnosis is important because different illnesses might require different types of treatment and because most youth reporting psychotic-like symptoms do not have a psychotic illness. The hallmark psychotic illness, schizophrenia, is often a chronic severe neurodevelopmental disorder that requires long-term treatment and psychosocial support. Effective treatment includes antipsychotic medication plus educational, supportive, and psychotherapeutic interventions.

Unfortunately, none of the currently available treatments cure schizophrenia. In medicine, major therapeutic advances are often based on treatments targeting known causal mechanisms. The challenge is that schizophrenia and other complex neuropsychiatric disorders are characterized by extreme genetic heterogeneity and specific neurobiological causes remain mostly unknown. Research needs to identify unique diagnostic and treatment biomarkers, including disruptions in genetic pathways and neurocircuitry, to advance the next generation of psychiatric therapeutics.[56]

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