Curr Psychiatry Rep (2012) 14:101–110
DOI 10.1007/s11920-012-0258-y

CHILD AND ADOLESCENT DISORDERS (TD BENTON, SECTION EDITOR)

Evaluation and Treatment of Children and Adolescents With Psychotic Symptoms

Sibel Algon · James Yi · Monica E. Calkins · Christian Kohler · Karin E. Borgmann-Winter

Published online: 16 February 2012

Abstract In recent years, there have been increasing efforts to develop early detection and prevention strategies for patients at risk of the development of psychotic disorders. These efforts have led to improved recognition and characterization of psychotic symptoms in youth. This review focuses on the evaluation of children and adolescents with psychotic symptoms who are experiencing functional impairment but who do not meet current criteria for schizophrenia. For this article, emphasis is placed on the evaluation of symptoms, differential diagnosis, and consideration of potential interventions.

K. E. Borgmann-Winter (✉)
Center for Neurobiology and Behavior, Department of Psychiatry,
University of Pennsylvania,
2216 TRL, 25 South 31st Street,
Philadelphia, PA 19104-3403, USA
e-mail: kbwinter@upenn.edu

S. Algon · J. Yi · K. E. Borgmann-Winter
Department of Child and Adolescent Psychiatry,
Children's Hospital of Philadelphia,
Philadelphia, PA 19104, USA

S. Algon
e-mail: algons@email.chop.edu

J. Yi
e-mail: yij@email.chop.edu

M. E. Calkins · C. Kohler
Neuropsychiatry Section Schizophrenia Research Center,
University of Pennsylvania,
10 Gates, HUP 3400 Spruce,
Philadelphia, PA 19104, USA

M. E. Calkins
e-mail: mcalkins@upenn.edu

C. Kohler
e-mail: kohler@upenn.edu

Keywords Ultra high risk (UHR) · Prodrome · At-risk · Psychosis · Psychotic symptoms · Children · Adolescents · Schizophrenia · Youth

Introduction

The evaluation and treatment of children with psychotic symptoms presents a formidable challenge for clinicians. Psychotic symptoms may present in the context of medical illnesses, substance use, congenital disorders, a variety of psychiatric conditions (e.g., affective disorders), as well as primary psychotic diagnoses such as schizophrenia or schizoaffective disorder. Because the duration of untreated illness has been correlated with poorer functional outcomes, it has been suggested that early identification and intervention in youth at risk of schizophrenia has the potential to prevent some of the very significant morbidities associated with schizophrenia spectrum disorders. At the same time, given the low prevalence of schizophrenia in the very young (<1 per 10,000–50,000 in early-adolescents and children and 1 per 500–10,000 in mid-adolescents [1, 2•]), identification of other treatable conditions that present with psychotic symptoms is equally important.

Characterization of Symptoms and Differential Diagnosis

Children and adolescents can present with a variety of psychotic and subthreshold psychotic symptoms. When psychotic symptoms are suspected, the clinician's primary tasks are to characterize the symptoms and their context:

- Do the unusual beliefs or perceptions exceed a psychotic threshold?
- When was the onset and what is the frequency?

- Do they affect behavior?
- Are there known or suspected medical or substance contributors?
- If other psychiatric conditions are present, what is the temporal relationship between the onset of psychotic symptoms and the other psychiatric symptoms?

Characterization of Symptoms

Over the past 15 years, research approaches to symptom assessment have contributed to our operational definitions of boundaries on the psychosis continuum [3]. Although these research instruments are not typically used in clinical practice, these approaches provide a helpful framework for the characterization of symptoms, in particular regarding the content and severity of symptoms. The widely used "attenuated symptom approach" (most commonly used in the United States [4]) examines the domains of positive symptoms (unusual thought content, suspiciousness/persecutory ideas, grandiose ideas, perceptual abnormalities, disorganized communication), negative symptoms (social anhedonia, avolition, expression of emotion, experience of emotions and self, ideational richness, occupational functioning), disorganization symptoms (odd behavior or appearance, bizarre thinking, trouble with focus and attention, impairments in personal hygiene), and general symptoms such as impaired tolerance to normal stress. However, within this model, determination of a psychotic syndrome relies primarily on the presence of positive symptoms. Other models, such as the "basic symptom" approach, include additional features such as thought interference and disturbances of receptive language [5].

The boundary between psychotic and subpsychotic unusual, suspicious, or grandiose beliefs is the degree of conviction. For example, severe but nonpsychotic beliefs are thoughts that may be compelling but in which doubt or skepticism can be induced, whereas psychotic beliefs are at least intermittently held with a delusional conviction such that doubt cannot be induced. In addition, the impact of psychotic symptoms on functioning is considered: while subpsychotic beliefs may affect functioning, psychotic delusions usually do interfere. For example, a hallucination would be rated as moderately severe, but not psychotic, if the experience was recognized as not real but was nevertheless experienced as frightening, possibly affecting behavior slightly. Disorganized communication is considered to have reached psychotic threshold when speech is incoherent or unintelligible and is unresponsive to attempts to structure the conversation. In contrast, subthreshold disorganized speech may be tangential or loose but is responsive to brief questions. Functional impacts of symptoms in younger individuals may be manifested as a decline in academic functioning or social functioning at home or in school [6].

Once psychotic symptoms are characterized, of key importance for differential diagnosis is the evaluation of concurrent medical conditions, substance use, affective symptoms, and history of trauma [7]. In children, it is particularly important to gather information from multiple sources of information, including parents or guardians and teachers/school records.

Medical and Congenital Conditions

In young people with psychosis, particularly at first onset, neurological and medical conditions that may cause or contribute to the clinical presentation must be considered. Common medical contributors to psychotic symptoms are described below. Table 1 provides a summary of medical causes and genetic disorders that have been associated with psychosis. In general, medical conditions include central nervous system processes; autoimmune and infectious diseases; genetic, endocrine, and metabolic disorders; electrolyte imbalances; and prescription medications and drugs of abuse (Table 1).

Epilepsy may present with psychosis (10%–15% lifetime prevalence), most commonly in temporal lobe epilepsy [8]. In children, however, multiple seizure types may be associated with psychosis [9]. Specifically, mixtures of partial and generalized seizures or either type alone, including complex and simple partial, tonic-clonic, absence, and myoclonic seizures, were found in children with epilepsy and psychosis [9]. In adults, psychotic events are described in terms of their temporal relationship with seizures: ictal, postictal, or interictal [9]. However, this temporal delineation may not be as easily applied to children, as young patients may have difficulty reliably determining the timing and description of symptoms due to developmental limitations [9].

Undiagnosed brain tumors, while uncommon, must also be considered, in particular slow-growing tumors with localization in the limbic system or posterior fossa regions, where tumor growth more likely affects dopaminergic transmission. Common tumor types in this age group include astrocytomas and ependymomas.

Autoimmune disorders such as systemic lupus erythematosus and multiple sclerosis can also present with neuropsychiatric syndromes, including psychotic symptoms, along with cognitive dysfunction, psychosis, disordered mood and anxiety, and delirium. A longitudinal 20-year study found neuropsychiatric symptoms in nearly 35% of lupus patients with a young age at onset [10]. Thyroid disorders show association with psychosis, including both hypo- and hyperthyroidism and Hashimoto's thyroiditis [11–13]. B12 deficiency can also precipitate psychotic symptoms in adults.

Table 1 Common medical conditions associated with possible psychosis in children and adolescents

Autoimmune diseases
•Systemic lupus erythematosus
•Poststreptococcal acute disseminated encephalomyelitis
•Mixed collagen vascular diseases
•Paraneoplastic syndromes (e.g., NMDA receptor encephalitis)
•Multiple sclerosis in childhood
Chromosomal disorders and congenital disorders[a]
•Velocardiofacial syndrome (22q11.2 deletion syndrome)
•Turner syndrome (XO)
•Fragile X syndrome
Drugs of abuse
•Amphetamines
•Hallucinogens (e.g., cannabis, PCP, MDMA, ketamine)
•Inhalant abuse
•Opiates
Endocrinopathies + electrolyte anomalies
•Hyper- and hypoparathyroidism
•Hyper- and hypothyroidism
•Hypocalcemia/hypoglycemia
•Hypomagnesemia/hypophosphatemia
Infections
•Brain abscesses and cysts
•Central nervous system–invasive parasitic infection
•HIV/AIDS
•Syphilis
•Neuroborreliosis (lyme disease)
•Viral encephalitis
Medications
•Stimulants (including modafinil)
•Antidepressants: selective serotonin reuptake inhibitors, bupropion
•Hypnotics: barbiturates, benzodiazepines
•Opiates
•Guanfacine
•Herbal therapies (e.g., St. John's wort, ginseng, ma-huang)
Metabolic diseases[a]
Neurologic disorders
•Epilepsy
•Head trauma
•Hydrocephalus
•Brain neoplasms
•Arteriovenous malformations
•Hamartoma (e.g., as in tuberous sclerosis)
Neuropsychiatric disorders[a]
•Friedreich's ataxia
•Huntington's disease
•Tuberous sclerosis
•Wilson's disease
Nutritional anomalies
•Magnesium deficiency
•Vitamin A, vitamin D, or vitamin B12 deficiency

NMDA *N*-methyl-*D*-aspartate, PCP phencyclidine

(*Data from* Lauterbach et al. [27], Young and Findling [33], and Freudenreich et al. [37].)

[a] See Lauterbach et al. [27] for further examples

Anti–*N*-methyl-*D*-aspartate receptor (NMDA) encephalitis was first reported in 2005 [14] in young women with ovarian teratomas, commonly presenting with psychiatric symptoms, including auditory and visual hallucinations, paranoia, and bizarre behavior progressing to seizures and encephalopathy. NMDA receptors are ligand-gated cation channels with subunits that bind glycine and glutamate. The receptors have important functions in synaptic transmission and plasticity [14]. Pediatric patients as young as 5 years of age represent 40% of cases and are less likely than adults to have underlying tumors [15].

HIV infection can be associated with psychosis and is typically associated with advanced cases of delirium or with immunosuppressant treatment [16]. In a study of an adult inpatient psychiatric population 18 years of age and older in Uganda, HIV-1 seropositivity was correlated with first-episode mental illness [17]. Nearly 15% of HIV-seropositive inpatients had primary psychotic disorders. A recent review of the literature found the most common psychiatric disorders in children and adolescents with HIV infection were attention-deficit/hyperactivity disorder and anxiety disorders [18]. An uncontrolled clinical study of 17 children and adolescents with HIV-1 found 2 patients had brief psychotic syndromes and 1 patient had depression with psychotic features [19]. Taken together, this suggests that the rise in cases of adolescent HIV may lead to an increase in new-episode psychiatric disorders and psychosis.

Electrolyte imbalances have long been associated with emergence of psychosis, commonly occurring in the setting of delirium. For example, calcium, phosphate, sodium, and magnesium derangements are all associated with psychotic symptoms [20, 21]. Similarly, heavy metals such as intoxication with lead and copper should be considered. Case reports of psychosis in the setting of elevated lead levels in young children and adolescents have been reported [22, 23]. Approximately 40% of individuals with childhood onset of Wilson's disease, which is linked to abnormalities in copper metabolism, present with neuropsychiatric symptoms [24], including psychosis [25]. Literature exists correlating levels of alterations in zinc, calcium, copper, and cadmium in hair samples of adults with schizophrenia versus healthy controls, and some researchers speculate that

these alterations may contribute to the pathogenesis of schizophrenia [26]. However, no case reports or studies of heavy metals in pediatric patients with psychosis were found.

In addition, more than 60 congenital disorders, including genetic and metabolic disorders and lysosomal storage diseases, may present with psychosis from childhood through middle age [27]. Of these, 70% have neurological features and nearly 30% have unique phenotypes that facilitate early recognition (see Lauterbach et al. [27] for a comprehensive review).

The prevalence of recreational drug consumption rises rapidly during the teenage years and in the United States: 15% for alcohol and 10% for illicit substances [28, 29]. The potential effects of illicit substances on psychotic symptoms may be causally related or coincidental, and the potential distinction is based on frequency of use, persistence of symptoms during abstinence, and type of drug. Commonly used substances such as cannabis, stimulants, and hallucinogens can be associated with psychotic symptoms, and large-scale studies have reported the correlation between schizophrenia and cannabis use, particularly at younger ages [30]. The list of prescription drugs that may cause psychosis is extensive and ranges from psychostimulants [31], dopamine agonists, anticholinergics, and morphine derivatives to chemotherapeutic agents, HIV medication, and antibiotics such as quinolones [32]. Over-the-counter preparations used at high doses may also be associated with psychosis. However, evidence for such associations is based on case reports, and direct causality can be difficult to establish.

Recommended Work-Up

At initial onset of psychotic symptoms, a general evaluation for medical disorders is warranted, including toxicology for recreational drugs, complete blood count, basic metabolic panel, and thyroid function tests. Where history or signs upon physical or neurological examination suggest a medical disorder, further testing should be considered (e.g., comprehensive metabolic panel, antinuclear antibody, HIV, B12, RPR, serum calcium/phosphorus, copper/ceruloplasmin and heavy metal levels, and genetic testing) [33, 34]. Screening for metabolic disorders, storage diseases, infectious diseases, and autoimmune encephalopathies may also be considered under consultation with health care providers with specific expertise in these areas. In cases of persistent psychosis or cases with suspected neurological conditions, evaluation with MRI is recommended. Although of low yield in larger cohorts of individuals with first-onset psychosis [35, 36], brain imaging should be considered before rendering the diagnosis of severe mental illness [37]. The diagnostic utility of obtaining electroencephalograms in patients with psychosis is limited and should be guided by index of suspicion for seizures [37].

Psychiatric Disorders with Psychosis

Differential diagnosis of psychiatric disorders with psychosis in youth can be challenging, as a number of disorders can present with psychotic spectrum symptoms, including mood disorders, substance use disorders, anxiety disorders, and pervasive developmental disorders. A history of early- or late-childhood trauma without a post-traumatic stress disorder diagnosis is also associated with self-report of psychotic symptoms [38].

Comorbidities of Subpsychotic Symptoms

The earliest studies of prodromal individuals focused on the characterization of the putative prodromal symptomatology. More recent studies have also assessed the presence of Axis I disorders at the time of study entry utilizing clinical interviews and structured clinical interviews such as the Structured Clinical Interview for the *DSM-IV* (SCID) and the Schedule for Affective Disorders and Schizophrenia for School-Age Children (K-SADS) [7]. These studies have helped to identify commonly occurring psychiatric disorders in this population in which considerable diagnostic uncertainty remains. Mood disorders have been most commonly identified in populations presenting with presumed prodromal symptoms, with rates of affective disorders of 40% to 61% [3, 39–42]. Anxiety disorders are also commonly identified, at rates ranging from 16% to 46% [40–42]. Although substance use disorders are common among patients with schizophrenia, rates reported in prodromal and high-risk populations have ranged from 4% [40] to 25% [42]. A variety of disorders of childhood have also been reported among prodromal/clinical risk populations, including ADHD (14%–56%) [39, 40, 42], externalizing disorders (28%–56%) [39, 42], developmental disorders, tic disorders, and learning disorders [39, 42].

Comorbidities of Psychotic Symptoms

Investigations of children and adolescents diagnosed with mood disorders suggest that psychotic symptoms are common. In youth with bipolar disorder, rates of psychotic features are reported as ranging from 16% to 87.5%, with higher rates in adolescent-onset than in childhood-onset cases, and mood-congruent delusions (especially grandiose delusions) most commonly reported [43]. In contrast, major depressive disorder appears to be associated with lower rates of psychotic symptoms (~4%), which are most often hallucinations [44]. Studies of children and adolescents presenting with psychosis also suggest a high comorbidity of mood and psychosis. Of 215 children with psychosis referred for a National Institute of Mental Health study of childhood-onset schizophrenia, 30% met criteria for schizophrenia, 4.6% for

schizoaffective disorder, 12% for major depressive disorder with psychotic features, and 15.2% for bipolar disorder [45]. Similar results were reported in another large-scale investigation of youth with psychosis [46]. Thus, psychotic symptoms are not specific to psychotic disorders and may occur in the context of other domains of psychopathology.

Differential Diagnosis

Accumulating studies of young people with subthreshold symptoms have provided a foundation for characterizing symptoms and assessing comorbid conditions. Consequently, it has become clear that it is essential to tolerate uncertainty in differential diagnosis in this population, as symptoms are occurring in an evolving developmental context. Diagnoses in children and adolescents are frequently based on newly emergent symptoms, and it is impossible to predict the future course of illness; thus, by necessity, diagnoses are cross-sectional, in contrast to many *DSM-IV* diagnoses that are based on longitudinal information. Indeed, reassessment over time provides the longitudinal framework necessary for clarity of diagnosis. Moreover, as illustrated by the comorbidities described, disorders in children may not "resolve" into a unitary disorder. Although there is a proposal for the inclusion of an "attenuated psychosis syndrome" in the *DSM-5*, which specifies criteria for a disorder in which subsyndromal psychotic symptoms are present and distressing or disabling but do not reach threshold for a psychotic disorder (http://www.dsm5.org), there is presently no formal diagnosis associated with subpsychotic symptoms in children. Thus, consideration of the *DSM-IV* diagnosis with a psychotic component should only occur if a psychotic threshold has been exceeded. Similar to adults, the differential diagnosis between mood and psychotic disorders is based on the temporal relationship between mood episodes and psychotic episodes. If both are present, an attempt should be made to determine if the psychotic symptoms occur in the absence of a mood disturbance. Anxiety disorders and psychotic disorders may co-occur, but the focus of anxiety or worry cannot be attributed to psychotic symptoms.

Psychosocial Treatments in the "At-Risk" Population

While on the one hand, diagnostic uncertainty is common in this population, the risk period prior to and after the onset of first-episode psychosis may also be a critical period for intervention with the potential to modify the disease process and prognosis. Several studies suggest that the duration of untreated psychosis can lead to increased risk of treatment unresponsiveness, poor functional/social outcome [47], poor neurocognitive function [48], and relapse of psychosis (reviewed in Perkins et al. [49]). A longer duration of untreated psychosis has also been associated with reduction in overall gray matter volume, suggesting that prolonged untreated psychosis may have a neurotoxic effect [50]. As it remains difficult to predict which patients with subthreshold symptoms will go on to develop schizophrenia or another psychotic disorder, pharmacologic strategies in early-intervention remain controversial (reviewed in McGorry et al. [51]). Accumulating evidence indicates that on average, 76% of ultra high-risk (UHR) individuals do not transition to psychosis during follow-up periods of 6 to 40 months (reviewed in Simon et al. [52•]). Given the lack of a precise method for identifying those who will transition to psychosis, the risks of treating those with transient psychosis or subthreshold symptoms such as medication side effects and stigma require careful consideration. [53, 54]. In addition, nonadherence early in the course of illness generates potential barriers to treatment in patients who ultimately develop schizophrenia [1, 55]. As such, psychosocial interventions that appear to be correlated with the fewest potential adverse effects should receive first consideration as part of a treatment plan in this population pending further clarification of the effectiveness of pharmacologic interventions (see also de Koning et al. [56••] for a review of interventions, including antipsychotics for symptom treatment).

Psychosocial Treatments

To date, studies of psychosocial treatments in the high-risk population have focused largely on cognitive therapies (CTs), although therapies targeting several domains of functioning may be helpful. These include social problem solving, cognitive rehabilitation, and family interventions, as well as school interventions and occupational therapy for vocational development [57–61, 62•].

Cognitive Therapies

CTs have been examined in uncontrolled trials in the high-risk population and in comparison to low-dose pharmacologic interventions. Results from these studies suggest possible benefits in this population.

In the EDIE (Early Detection and Intervention Evaluation) trial, 58 antipsychotic-naïve UHR patients 16 to 36 years of age were treated for 6 months with CT versus routine monitoring [63]. Patients receiving routine, semi-structured interviews were more likely to transition to PACE-defined psychosis or be prescribed an antipsychotic by an independent physician than those receiving CT at 1-year follow-up. Positive symptoms and emotional dysfunction (depression or anxiety) declined in both groups. CT specifically reduced positive symptoms without additional benefit on emotional distress [59].

In a multicenter parallel group trial, the German Research Network of Schizophrenia trial compared cognitive-behavioral therapy (CBT) and supportive counseling in 113 patients with a mean age of 25 in the early prodromal phase of psychosis (basic symptom approach). CBT and supportive counseling both improved social adjustment at 12 months, and patients in the CBT group were less likely to convert to psychosis or transition to the late prodrome than those in supportive counseling. The authors concluded that a CBT treatment with a stronger focus on social functioning could have more beneficial effects [58].

Similarly, Addington et al. [57] conducted a single-blind, randomized controlled trial of CBT versus supportive therapy in youth 14 to 30 years of age meeting prodromal criteria with a 6-month treatment phase and 12-month follow-up phase. There were no conversions to psychosis in the CBT group and three conversions in the supportive therapy group. Conversion rates were lower than expected, and differences were not statistically significant. Importantly, both treatment groups had significant and comparable improvements in depression, anxiety, and positive symptoms, while neither group had benefits in negative symptoms or global functioning. The authors suggest that a supportive therapy that is less costly than CBT may be offered earlier to high-risk youth and that CBT may be needed to target positive symptoms.

In a randomized controlled trial, Yung et al. [62•] compared CT plus low-dose risperidone to CT, supportive therapy, and a monitoring control condition in 115 UHR patients 14 to 30 years of age. No significant differences between treatment groups were found in transition to psychosis following the 6-month interventions. However, all treatment groups had improvements in measures of psychosis and depression [62•].

Substance Use Interventions

No specific intervention trials have been reported for substance use in this population. However, rates of substance abuse among patients with first-episode psychosis range from nearly 25% to greater than 60%, with cannabis and alcohol most commonly abused [64, 65]. Psychotic symptoms are twice as common in young people using cannabis than in nonusers [64], suggesting pre-illness cannabis use may be a risk factor for psychosis and for earlier onset of symptoms [65, 66]. Substance-abusing psychotic youth may benefit from motivational therapy, psychoeducation, skills training, and support [64].

Other Psychosocial Interventions

Other modes of treatment, such as family interventions and occupational therapy, have been used in patients with early psychotic disorders but not tested in the at-risk population and deserve further study.

Family psychoeducational programs such as psychoeducational multiple-family group therapy decrease relapse requiring hospitalization by 20% to 50% [1] and improve social adjustment, quality of life, family burden, and treatment adherence in schizophrenics [66]. Psychoeducational multiple-family group therapy in families of children and adolescents with mood and disruptive behavior disorders has yielded mixed results [1]. A similar treatment, family-focused treatment for adolescents, significantly decreases depression, mania, and problem behaviors in adolescents with mood disorders [1] but has not been studied in psychotic youth.

In a retrospective chart review, Poon et al. [60] examined the efficacy of occupational therapy in youth 15 to 25 years of age diagnosed with schizophrenia (32%) and psychotic disorders (57.1%) who had been referred from the Early Assessment Service for Young People with Psychosis (EASY) program. Occupational therapists worked with patients for an average of 3.5 months toward a goal of rehabilitation and assisting patients in developing independent occupations, structured routines, and support networks. Upon program discharge, approximately half of the patients were productive in their work, study, or vocational training programs for a period of greater than 3 months [60]. This study calls attention to the understudied area of methods of maximizing vocational functioning in young patients with psychotic disorders.

At-Risk Studies in Progress

Studies currently under way to examine psychosocial treatments in at-risk populations include the following:

- The National Institute of Mental Health's Recovery after an Initial Schizophrenia Episode study (RAISE), which is examining the efficacy of integrating medication, psychosocial therapies, family involvement, rehabilitation services, and supported employment in early intervention (http://www.clinicaltrials.gov/ct2/show/NCT01321177)
- The Portland Identification and Early Referral (PIER) program examining psychosocial supports, regular follow-up, and proficient pharmacologic management versus medication, regular follow-up visits, and crisis visits (http://www.preventmentalillness.org/) [61]
- The Dutch Early Detection and Intervention Evaluation (EDIE-NL) trial examining 6 months of CBT versus treatment as usual in help-seeking prodromal patients
- The PACE clinic in Melbourne, Australia, a 12-month follow-up study examining the role of CT with low-dose antipsychotic treatment versus CT alone, supportive

therapy alone, and a monitoring-only control condition for which 6-month data are presented above [62•].

Pharmacologic Intervention

The literature on pharmacologic intervention in high-risk populations is very limited and consists of studies of groups with varying levels of psychotic symptoms. The majority of studies examine strategies targeted at the prevention of progression of illness. Aside from a few controlled trials of typical and atypical antipsychotics, few trials of alternative medications exist in children and adolescents in the premorbid or prodromal phase [67••].

Pharmacologic Interventions Aimed at Preventing Conversion to Psychosis

Antipsychotics

Two randomized clinical trials have examined pharmacologic interventions in a UHR population. McGlashan and colleagues [68] conducted a study of UHR patients randomly assigned to receive either 5 to 15 mg/d of olanzapine or placebo over a 1-year treatment period. About 16.1% of olanzapine patients converted to psychosis, while 37.9% of placebo patients converted. These differences were not statistically significant, highlighting the need for a larger study. Notably, the olanzapine group gained on average 8.79 kg of weight, compared with 0.3 kg in the placebo group [68]. McGorry et al. [69] compared the rate of conversion between the low-dose risperidone with CBT group and the need-based treatment group. Although both groups had symptomatic improvements, the conversion rates were about threefold higher in the need-based group compared with the risperidone with CBT group after 6 months of treatment. At the end of the 12-month follow-up period, this difference was only seen in the subset of specific treatment group patients who were fully adherent to risperidone [69].

Selective Serotonin Reuptake Inhibitors

Two naturalistic studies of UHR patients have reported reduced conversion rates in those prescribed antidepressants. McGorry et al. [51] and Larson et al. [66] reported reduced conversion in those prescribed selective serotonin reuptake inhibitors compared with those prescribed antipsychotics [51, 66]. Cornblatt et al. [70] reported a similar observation, suggesting that differences in the conversion rates could be due to a high nonadherence rate among those prescribed antipsychotics versus antidepressants. However, the evidence for efficacy of selective serotonin reuptake inhibitors remains unclear.

Omega-3 Fatty Acids

A recent double-blind, placebo-controlled study found that UHR individuals 13 to 25 years of age supplemented with 1.5 g of omega-3 polyunsaturated fatty acid (PUFA) compared with those receiving placebo had a nearly 10-fold decrease in the conversion rate at 12-week follow-up and a nearly 6-fold decrease at the 12-month follow-up [71•]. Additionally, the omega-3 PUFA group showed improvements in attenuated symptoms of psychosis and function. Treatment groups were found to have significant increases in omega-3 to omega-6 fatty acid ratios compared with control groups, and the change in the ratio from baseline to post-treatment correlated with functional improvement [71•]. Reported side effects were primarily gastrointestinal (e.g., loose stool, nausea) [71•].

Other Pharmacologic Interventions

Glutamatergic agents such as glycine and cycloserine have been examined for treatment of negative symptoms in randomized controlled trials of adults with schizophrenia, with mixed results [2•]. Studies of these agents have been initiated in UHR groups. The results of an open-label pilot study have been reported in abstract form, and another study is currently under way. In the open-label trial, glycine titrated to a dose of 0.4 g/kg given twice daily for 8 weeks in 10 UHR patients (mean age, 17 years) led to significant improvements in prodromal symptoms in 70% of patients [72].

Antipsychotics as Symptom Treatment

The evidence base for the use of antipsychotics as symptom treatment of subsyndromal psychotic symptoms is very limited (most recently reviewed by de Koning et al. [56••]). In an open-label and case series report of short-term treatment with low-dose aripiprazole in UHR individuals, Liu et al. [73] reported nine cases of rapid improvement in psychotic-like symptoms. Woods et al. [74] reported 15 UHR individuals with significant improvement in symptoms after the first week of treatment. However, there were no consistent neurocognitive improvements, and significant side effects such as weight gain and akathisia were observed [74]. To date, clear benefits over risk have not been demonstrated.

Conclusions

Regular follow-up treatment of specific symptoms/syndromes such as mood disorders, anxiety, and substance

use, and the employment of available psychosocial supports present the best risk/benefit ratio in this population. Available resources in the community may include family-based services, case management, and therapeutic support in school or at home. Another important component of treatment is family education regarding the effectiveness of treatments in reducing risk of transition to a primary psychotic disorder along with the known risks of specific interventions such as antipsychotics. Clearly, additional study of psychosocial interventions and alternate pharmacologic agents is needed.

Acknowledgments Dr. Calkins has received research grant support from the National Institute of Mental Health (K08 Award). Drs. Algon and Yi contributed equally to this manuscript.

Disclosure No potential conflicts of interest relevant to this article were reported.

References

Papers of particular interest, published recently, have been highlighted as:
- • Of importance
- •• Of major importance

1. Gearing, R. E. Evidence-based family psychoeducational interventions for children and adolescents with psychotic disorders. J Can Acad Child Adolesc Psychiatry. 2008;17(1).
2. • Masi G, Liboni F. Management of schizophrenia in children and adolescents: focus on pharmacotherapy. Drugs. 2011;71(2):179–208. *In this systematic review, the authors offer a comprehensive overview of available literature on pharmacologic interventions for childhood-onset schizophrenia. The authors summarize limitations in several aspects of current pharmacotherapy, including low effect size, high rates of adverse effects, and low rates of remission. They highlight the need for further research with both randomized, placebo-controlled studies and long-term, naturalistic follow-up of large samples of patients with different age ranges.*
3. Simon AE, et al. Defining subjects at risk for psychosis: a comparison of two approaches. Schizophr Res. 2006;81(1):83–90.
4. Miller TJ, et al. Prospective diagnosis of the initial prodrome for schizophrenia based on the Structured Interview for Prodromal Syndromes: preliminary evidence of interrater reliability and predictive validity. Am J Psychiatry. 2002;159(5):863–5.
5. Klosterkotter J, et al. Diagnosing schizophrenia in the initial prodromal phase. Arch Gen Psychiatry. 2001;58(2):158–64.
6. Miller TJ, et al. Prodromal assessment with the structured interview for prodromal syndromes and the scale of prodromal symptoms: predictive validity, interrater reliability, and training to reliability. Schizophr Bull. 2003;29(4):703–15.
7. Borgmann-Winter K, et al. Assessment of adolescents at risk for psychosis. Curr Psychiatry Rep. 2006;8(4):313–21.
8. Sachdev P. Schizophrenia-like psychosis and epilepsy: the status of the association. Am J Psychiatry. 1998;155(3):325–36.
9. Lax Pericall MT, Taylor E. Psychosis and epilepsy in young people. Epilepsy Behav. 2010;18(4):450–4.
10. Yu HH, et al. Neuropsychiatric manifestations in pediatric systemic lupus erythematosus: a 20-year study. Lupus. 2006;15(10):651–7.
11. Bismilla Z, Sell E, Donner E. Hashimoto encephalopathy responding to risperidone. J Child Neurol. 2007;22(7):855–7.
12. Arrojo M, et al. Psychiatric presentation of Hashimoto's encephalopathy. Psychosom Med. 2007;69(2):200–1.
13. Benvenga S, Lapa D, Trimarchi F. Don't forget the thyroid in the etiology of psychoses. Am J Med. 2003;115(2):159–60.
14. Dalmau J, et al. Anti-NMDA-receptor encephalitis: case series and analysis of the effects of antibodies. Lancet Neurol. 2008;7(12):1091.
15. Florance NR, et al. Anti-N-methyl-D-aspartate receptor (NMDAR) encephalitis in children and adolescents. Ann Neurol. 2009;66:11.
16. Fenton KA. Changing epidemiology of HIV/AIDS in the United States: implications for enhancing and promoting HIV testing strategies. Clin Infect Dis. 2007;45:S213.
17. Maling S, et al. HIV-1 seroprevalence and risk factors for HIV infection among first-time psychiatric admissions in Uganda. AIDS Care. 2011;23(2):171–8.
18. Scharko AM. DSM psychiatric disorders in the context of pediatric HIV/AIDS. AIDS Care. 2006;18(5):441–5.
19. Misdrahi D, et al. DSM-IV mental disorders and neurological complications in children and adolescents with human immunodeficiency virus type 1 infection (HIV-1). Eur Psychiatry. 2004;19(3):182–4.
20. Carman JS, Wyatt RJ. Calcium: pacesetting the periodic psychoses. Am J Psychiatry. 1979;136(8):1035–9.
21. Ang AW, Ko SM, Tan CH. Calcium, magnesium, and psychotic symptoms in a girl with idiopathic hypoparathyroidism. Psychosom Med. 1995;57(3):299–302.
22. Hershko C, et al. Lead poisoning in a West Bank Arab Village. Arch Intern Med. 1984;144(10):1969–73.
23. McCracken JT. Lead intoxication psychosis in an adolescent. J Am Acad Child Adolesc Psychiatry. 1987;26(2):274–6.
24. Hancu A, Mihai MC, Axelerad AD. Wilson's disease: a challenging diagnosis. Clinical manifestations and diagnostic procedures in 12 patients. Rev Med Chir Soc Med Nat Iasi. 2011;115(1):58–63.
25. Dening TR, Berrios GE. Wilson's disease. Psychiatric symptoms in 195 cases. Arch Gen Psychiatry. 1989;46(12):1126–34.
26. Rahman A, et al. Zinc, manganese, calcium, copper, and cadmium level in scalp hair samples of schizophrenic patients. Biol Trace Elem Res. 2009;127(2):102–8.
27. Lauterbach MD, Stanislawski-Zygaj AL, Benjamin S. The differential diagnosis of childhood- and young adult-onset disorders that include psychosis. J Neuropsychiatry Clin Neurosci. 2008;20(4):409.
28. Results from the 2010 National Survey on Drug Use and Health: Summary of National Findings, in NSDUH Series H-41, HHS Publication No. (SMA) 11-4658, S.A.a.M.H.S. Administration, Editor. 2011: Rockville, MD.
29. Veen ND, et al. Cannabis use and age at onset of schizophrenia. Am J Psychiatry. 2004;161(3):501–6.
30. Dragt S, et al. Cannabis use and age at onset of symptoms in subjects at clinical high risk for psychosis. Acta Psychiatr Scand. 2012;125(1):45–53.
31. Curran C, Byrappa N, McBride A. Stimulant psychosis: systematic review. Br J Psychiatry. 2004;185:196–204.
32. Tome AM, Filipe A. Quinolones: review of psychiatric and neurological adverse reactions. Drug Saf. 2011;34(6):465–88.
33. Young CM, Findling RL. Pharmacologic treatment of adolescent and child schizophrenia. Expert Rev Neurother. 2004;4(1):53–60.
34. AACAP official action. Summary of the practice parameters for the assessment and treatment of children and adolescents with schizophrenia. American Academy of Child and Adolescent Psychiatry. J Am Acad Child Adolesc Psychiatry. 2000;39(12):1580–2.
35. Lubman DI, et al. Incidental radiological findings on brain magnetic resonance imaging in first-episode psychosis and chronic schizophrenia. Acta Psychiatr Scand. 2002;106:331.

36. Katzman GL, Dagher AP, Patronas NJ. Incidental findings on brain magnetic resonance imaging from 1000 asymptomatic volunteers. JAMA. 1999;282(1):36–9.
37. Freudenreich O, et al. The evaluation and management of patients with first-episode schizophrenia: a selective, clinical review of diagnosis, treatment, and prognosis. Harv Rev Psychiatry. 2007;15(5):189–211.
38. Arseneault L, et al. Childhood trauma and children's emerging psychotic symptoms: a genetically sensitive longitudinal cohort study. Am J Psychiatry. 2011;168(1):65–72.
39. Mazzoni P, et al. Childhood onset diagnoses in a case series of teens at clinical high risk for psychosis. J Child Adolesc Psychopharmacol. 2009;19(6):771–6.
40. Meyer SE, et al. The psychosis prodrome in adolescent patients viewed through the lens of DSM-IV. J Child Adolesc Psychopharmacol. 2005;15(3):434–51.
41. Velthorst E, et al. Baseline differences in clinical symptomatology between ultra high risk subjects with and without a transition to psychosis. Schizophr Res. 2009;109(1–3):60–5.
42. Woods SW, et al. Validity of the prodromal risk syndrome for first psychosis: findings from the North American Prodrome Longitudinal Study.[see comment]. Schizophr Bull. 2009;35 (5):894–908.
43. Pavuluri M, Herbener E, Sweeney J. Psychotic symptoms in pediatric bipolar disorder. J Affect Disord. 2004;80:19–28.
44. Ulloa RE, et al. Psychosis in a pediatric mood and anxiety disorders clinic: phenomenology and correlates. J Am Acad Child Adolesc Psychiatry. 2000;39(3):337–45.
45. Calderoni D, et al. Differentiating childhood-onset schizophrenia from psychotic mood disorders. J Am Acad Child Adolesc Psychiatry. 2001;40(10):1190–6.
46. Biederman J, et al. Phenomenology of childhood psychosis: findings from a large sample of psychiatrically referred youth. J Nerv Ment Dis. 2004;192(9):607–14.
47. Norman RM, et al. The role of treatment delay in predicting 5-year outcomes in an early intervention program. Psychol Med. 2011; (Journal Article):1–11.
48. Lappin JM, et al. Duration of untreated psychosis and neuropsychological function in first episode psychosis. Schizophr Res. 2007;95(1–3):103–10.
49. Perkins DO, et al. Relationship between duration of untreated psychosis and outcome in first-episode schizophrenia: a critical review and meta-analysis. Am J Psychiatry. 2005;162(10):1785–804.
50. Malla AK, et al. Duration of untreated psychosis is associated with orbital-frontal grey matter volume reductions in first episode psychosis. Schizophr Res. 2011;125(1):13–20.
51. McGorry PD, et al. Intervention in individuals at ultra-high risk for psychosis: a review and future directions. J Clin Psychiatry. 2009;70(9):1206–12.
52. • Simon AE, et al. Ultra high-risk state for psychosis and non-transition: a systematic review. Schizophr Res. 2011;132(1):8–17. *This systematic review summarizes available literature on outcomes of those identified as UHR. A total of 31 studies met the inclusion criteria, and on average, 76% (range, 46%–92.6%) of UHR patients made no transition to psychosis during a follow-up period (range, 6–40 months). Characteristics of those who did not transition were poorly investigated. The authors highlight the limited specificity of current UHR criteria and the need for more studies investigating the characteristics associated with nontransition versus transition.*
53. Filakovic P, et al. Ethics of the early intervention in the treatment of schizophrenia. Psychiatr Danub. 2007;19(3):209–15.
54. McGlashan TH. Psychosis treatment prior to psychosis onset: ethical issues. Schizophr Res. 2001;51(1):47–54.
55. Rabinovitch MB-EL, et al. Early predictors of nonadherence to antipsychotic therapy in first-episode psychosis. Can J Psychiatry. 2009;54(1):28.
56. •• de Koning MB, et al. Early intervention in patients at ultra high risk of psychosis: benefits and risks. Acta Psychiatr Scand. 2009;119(6):426–42. *In this paper, early interventions in patients at UHR for psychosis are reviewed. The authors compiled preliminary publications and unpublished data from the German Research Network on Schizophrenia. Patients from the Bechdolf et al. [58] (2007) cohort who received CBT were found less likely to convert to psychosis or develop a late prodromal state at 1-year follow-up than those who received supportive counseling.*
57. Addington J, et al. A randomized controlled trial of cognitive behavioral therapy for individuals at clinical high risk of psychosis. Schizophr Res. 2011;125(1):54–61.
58. Bechdolf A, et al. Randomized controlled multicentre trial of cognitive behaviour therapy in the early initial prodromal state: effects on social adjustment post treatment. Early Interv Psychiatry. 2007;1(1):71–8.
59. French P, et al. Effects of cognitive therapy on the longitudinal development of psychotic experiences in people at high risk of developing psychosis. Br J Psychiatry Suppl. 2007;51:s82–7.
60. Poon MY, Siu AM, Ming SY. Outcome analysis of occupational therapy programme for persons with early psychosis. Work. 2010;37(1):65–70.
61. Rietdijk J, et al. A single blind randomized controlled trial of cognitive behavioural therapy in a help-seeking population with an at risk mental state for psychosis: the Dutch Early Detection and Intervention Evaluation (EDIE-NL) trial. Trials. 2010;11:30.
62. • Yung AR, et al. Randomized controlled trial of interventions for young people at ultra high risk for psychosis: 6-month analysis. J Clin Psychiatry. 2011;72(4):430–40. *The authors conducted a randomized controlled trial in youth at UHR for psychosis comparing CT plus low-dose risperidone with CT, supportive counseling, and a monitoring control condition. All treatment groups had improvements in measures of psychosis and depression, and no differences were found among groups. Declining transition rates, inadequate power, transition post-study, and a placebo effect in the monitoring control condition may explain these findings.*
63. Morrison AP, et al. Cognitive therapy for the prevention of psychosis in people at ultra-high risk: randomised controlled trial. Br J Psychiatry. 2004;185:291–7.
64. Tucker P. Substance misuse and early psychosis. Australas Psychiatry. 2009;17(4):291–4.
65. Compton MT, et al. Pre-illness cannabis use and the early course of nonaffective psychotic disorders: associations with premorbid functioning, the prodrome, and mode of onset of psychosis. Schizophr Res. 2011;126(1–3):71–6.
66. Larson MK, Walker EF, Compton MT. Early signs, diagnosis and therapeutics of the prodromal phase of schizophrenia and related psychotic disorders. Expert Rev Neurother. 2010;10(8):1347–59.
67. •• Liu P, et al. An evidence map of interventions across premorbid, ultra-high risk and first episode phases of psychosis. Schizophr Res. 2010;123(1):37–44. *The authors generated an evidence map of controlled trials, meta-analysis, and systematic reviews of biologic and psychosocial interventions in premorbid, UHR, and first-episode patients with psychosis. Most studies in this population involved first-episode patients, antipsychotic medication trials, and CBT trials. The authors concluded that trials of biologic interventions, other than antipsychotics and psychosocial treatments other than CBT, are lacking and are needed in these patients.*
68. McGlashan TH, et al. Randomized, double-blind trial of olanzapine versus placebo in patients prodromally symptomatic for psychosis. Am J Psychiatry. 2006;163(5):790–9.
69. McGorry PD, et al. Randomized controlled trial of interventions designed to reduce the risk of progression to first-episode

psychosis in a clinical sample with subthreshold symptoms. Arch Gen Psychiatry. 2002;59(10):921–8.

70. Cornblatt BA, et al. Can antidepressants be used to treat the schizophrenia prodrome? Results of a prospective, naturalistic treatment study of adolescents. J Clin Psychiatry. 2007;68(4):546–57.
71. • Amminger GP, et al. Long-chain omega-3 fatty acids for indicated prevention of psychotic disorders: a randomized, placebo-controlled trial. Arch Gen Psychiatry. 2010;67(2):146–54. *The utility of omega-3 PUFAs to diminish the progression of high-risk youth with subthreshold psychotic symptoms to first-episode psychosis was explored in the randomized, placebo-controlled trial. The authors concluded that long-chain omega-3 PUFAs reduce the risk of transition to psychotic disorders and are a safe and well-tolerated prevention strategy in youth with subthreshold psychotic symptoms.*
72. Woods SW, et al. Glycine treatment of prodromal symptoms, Abstracts of the 5th International Conference on Early Psychosis. Schizophr Res. 2006;86(WC2E):S7.
73. Liu CC, et al. Rapid response to antipsychotic treatment on psychotic prodrome: implications from a case series. Psychiatry Clin Neurosci. 2010;64(2):202–6.
74. Woods SW, et al. Aripiprazole in the treatment of the psychosis prodrome: an open-label pilot study. Br J Psychiatry Suppl. 2007;51:s96–s101.