Early onset schizophrenia: diagnostic dilemmas and treatment challenges

Jennifer Cheng Shannon†1 and Jon McClellan2

†Author for correspondence
1University of Washington, Department of Psychiatry, Box 356560, Seattle, WA 98195, USA
Tel.: +1 206 543 6577
jkcheng@u.washington.edu

2Children's Hospital and Regional Medical Center PO Box 5371/M1-1 Seattle, WA 98105, USA
Tel.: +1 206-987-2760
drjack@u.washington.edu

Early onset schizophrenia (EOS), which is defined as onset prior to 18 years of age, is associated with significant morbidity, chronicity and psychosocial impairment. EOS appears to be both clinically and neurobiologically continuous with the adult-onset form, although there are some important differences. Although the treatment literature specifically addressing juveniles with schizophrenia is sparse, the adult literature appears to apply, given appropriate developmental considerations. Given the significant morbidity, chronicity and psychosocial impairment associated with EOS, it is imperative that clinicians are familiar with the phenomenology, diagnosis, clinical course and treatment of this disorder. This article provides a brief description of EOS with a focus on treatment modalities, including a detailed review of psychopharmacologic and psychotherapeutic interventions.

Keywords:
atypical antipsychotics, early onset schizophrenia, psychosis

Early onset schizophrenia (EOS) (defined as onset prior to age 18 years) is diagnosed using the same criteria as for adults and appears to be both clinically and neurobiologically continuous with the adult-onset form. Unfortunately, it is often a more severe form of the disease and is associated with significant morbidity, chronicity and psychosocial impairment. There are also considerable differences between demographic factors, clinical presentation and long-term outcome of EOS as compared with adults.

The study of EOS is important for several reasons. This subgroup of patients may share a higher degree of homogeneity and in as much are an important population in which to study suspected etiologic factors. Since the illness disrupts neurodevelopmental processes in the growing child, important information may be gleaned by examining the onset and progression of the illness against the backdrop of normal development. Moreover, EOS is often a debilitating disorder that can have a particularly deleterious effect upon cognitive and social functioning. Therefore, efforts to improve the impact of therapeutic interventions are critical. It is imperative that clinicians working with the young are familiar with the phenomenology, diagnosis, clinical course and treatment of this disorder. This article will give a brief description of EOS with an emphasis on treatment modalities.

Background

Historically, EOS was originally characterized as being similar to schizophrenia in adults, dating back to Kraeplin's initial descriptions of psychotic disorders. However, other psychopathologists, such as Bender and Kanner, placed it within broader categories defined by developmental deficits in language, social relations, perception and movement. Therefore, childhood psychoses often included a broader category of neurodevelopmental disorders, including autism. It was the work of Kolvin [1] and Rutter [2] who demonstrated that EOS was a specific entity, similar to adult schizophrenia. In the 1970s, DSM-III revised the criteria so that EOS was diagnosed using the same criteria as those used for adults.

Epidemiology

Given the rarity of EOS, few studies have examined the incidence rates in the population. However, available evidence suggests the prevalence of schizophrenia in children is significantly lower than in adults, which is estimated at approximately 1% [3]. The onset rate rises precipitously during the age range of 15 to 30 years [3]. Onset prior to the age of 12 years is very rare. In early onset samples, males tend to predominate [4]. Thomsen found that, in a study of all youths hospitalized for schizophrenia in Denmark over a 13-year period (n = 312), only four were under the age of 13 years and only 28 were younger than 15 years of age [5]. EOS, especially in those under the age of 13 years, occurs predominantly in males, with ratios of approximately 2:1 [1,6–10]. The validity of the diagnosis in preschoolers is questionable given developmental challenges in discerning true psychotic symptoms.

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Etiology & pathogenesis

Schizophrenia is currently thought to be a complex disorder with polygenic, multifactorial etiologies. Three primary areas of focus have been identified in the adult literature thus far: genetics; viral exposure; and neurodevelopmental insults.

It is important to remember however, that mechanisms may not necessarily have a causal relationship and that schizophrenia continues to be viewed as a complex syndrome without a single etiology. Given the lack of research specifically focusing on the etiologies of EOS, the data presented is what is currently known about schizophrenia in the general population. When available, studies specifically examining EOS will be noted.

Genetics

There is substantial evidence that genetics play an important role as a risk factor for the development of schizophrenia with a heritability rate of approximately 80% [11]. The lifetime risk of developing schizophrenia is 5–20 times higher in first-degree relatives of affective probands when compared with the general population [12]. Positive family histories of schizophrenia are noted in youths with EOS, although whether the relative risk is the same as adults has not been well studied [4]. Despite this evidence, no single model of genetic inheritance has yet been identified. The phenotype of schizophrenia is heterogeneous and it is likely that multiple genes are involved. Moreover, the risk conferred may not always be expressed as schizophrenia but rather as related traits, such as a schizoid personality. Finally, many cases are assumed to be sporadic and perhaps due to complicated gene–environment interactions. Numerous linkage and candidate genes studies have been completed to date. There are several chromosomal regions that at least one study has associated with schizophrenia, including 1q, 5p, 5q, 6p, 6q, 8p, 10p, 13q, 15q and 22q [13]. Another study identified these genes as well as 18p, although the precise linkage in schizophrenia has yet to be established [14]. Genes of interest include dybindin (6p22), neuregulin (8p22) and catechol-*O*-methyltransferase (COMT) (22q11) [15]. COMT is of particular interest because it is found in the commonly deleted region of chromosome 22 that is associated with velo-cardio-facial syndrome (VCFS), although there are other genes of interest in this region as well. VCFS is a genetic disorder characterized by palatal, facial, cardiac, congenital abnormalities and psychiatric conditions. Approximately 30% of people with this deletion develop symptoms of psychosis [16,17]. Although cases of 22q11 deletion are over-represented in a study of childhood-onset schizophrenia (COS) [18], an earlier age of onset was not associated with the deletion in a large screening study [19].

Nicolson and colleagues found that parents of patients with COS had a significantly higher morbid risk of schizophrenia spectrum disorders than parents of patients with adult-onset schizophrenia (AOS) (24.74 vs. 11.35%) [20]. This is consistent with findings by the UCLA-NPI group [21], which continue to provide convincing evidence for the hypothesis that there is a continuous etiology between COS and AOS.

Despite these promising findings, there is not one single specific gene or chromosomal region that has been consistently found across studies to be definitively associated with schizophrenia. Given schizophrenia's heterogeneity, it is likely that the genetic component of the disorder is much more complex than identifying a single gene. Moreover, there may be other types of mechanisms, such as epigenetic influences, yet to be identified that relate to the development of the disorder.

Neurodevelopmental theory

The neurodevelopmental hypothesis of schizophrenia is based on the idea that early central nervous lesions affect normal maturational processes. Evidence supporting this theory is partly based on premorbid impairments seen in childhood and adolescence of those who later develop schizophrenia and may represent the neuropathologic manifestations of the disorder. Kolvin's work in the 1970s showed that 87% of 33 children with the equivalent of EOS were premorbidly odd and had developmental delays, mostly in speech [1]. Multiple recent studies have also replicated delayed motor milestones, speech problems, lower educational test scores and/or poor social adjustment before the onset of the disorder [22–25]. A recent study suggests that these deficits may be more relevant to those with adolescent onset of the disorder [26]. In the adult literature, perinatal complications, alterations in brain structure and size, minor physical anomalies and disruption of fetal neural development, particularly during the second trimester of pregnancy, have been correlated with the illness [27–29].

Infectious processes

Viral exposure has been implicated as a risk factor for schizophrenia. Individuals with schizophrenia

are more likely to have been born during the winter months [30] or soon after an influenza epidemic more often than expected by chance [31]. These findings suggest that viral exposure during gestation may be a risk factor for the later development of schizophrenia. Some research studies have found that birth cohorts who were in the second trimester of pregnancy during an influenza epidemic were shown to have an increased risk of schizophrenia, although this result has not been consistently noted [32]. However, efforts attempting to directly link viral infections to the development of schizophrenia have been inconclusive. Further research is needed to clarify what role, if any, exposure to viral infections have in the development of schizophrenia.

Psychological factors

Psychological factors have also been a focus of research and to date have not been directly linked to the development of the illness. Chronic interpersonal stress within the family such as expressed emotion, has been found to influence the onset and exacerbation of acute psychotic episodes as well as relapse/rehospitalization rates [33]. However, this should not be interpreted as a causal mechanism, since in fact having a family member with schizophrenia often directly increases stress and difficulties with communication.

Substance abuse

The relationship between schizophrenia and cannabis use has been known for some time but the actual nature of the relationship has remained somewhat unclear. Differing theories include self-medication, other drug effects, confounding factors, predisposed population and the etiological hypothesis [34]. Results from five recent longitudinal studies imply that cannabis use increases the risk of later schizophrenia [35–39]. In the largest study from Sweden, an odds ratio of 2.1–2.5 was found in a sample size of over 50,000 subjects [35]. Controversy still exists regarding whether there is a direct causal link between cannabis abuse and schizophrenia. Nevertheless, the strong association between the two is an important clinical concern.

Neuroimaging findings

Numerous neurobiologic abnormalities have been discovered in EOS, including deficits in smooth pursuit eye movements, autonomic responsivity and neuroimaging findings [40–43]. These findings are mostly consistent with the adult literature. In a series of reports examining subjects in the ongoing National Institute of Mental Health (NIMH) study of COS, progressive cortical deficits in temporal, frontal and parietal regions have been noted [44–46]. Compared with controls, subjects with COS had a significantly accelerated loss of gray matter involving the frontal eye fields and motor, sensorimotor, parietal and temporal cortices bilaterally over a 5 year span. Progressive deficits in the lateral temporal and dorsolateral prefrontal cortex were noted on average 3 years after the onset of psychotic symptoms, suggesting the possibility that loss of gray matter may in fact occur later in the disease course [46]. Progressive cerebellar volume loss were also noted in this sample [47], consistent with reports of abnormal cerebellar function in adult schizophrenia [48]. None of the findings are consistent across all subjects and cannot be considered diagnostic. Although studies tried to control for confounding factors, some of the noted findings may have been influenced by medication exposure or other environmental factors.

Diagnosis & clinical features

The same criteria are used to diagnosis schizophrenia in children as in adults. According to the DSM-IV-TR [49] at least two of the following are needed for a diagnosis of schizophrenia, each present for a significant period of time during a 1-month period:

- Delusions
- Hallucinations
- Disorganized speech
- Grossly disorganized or catatonic behavior and/or
- Negative symptoms, such as affective flattening, alogia, or avolition

The diagnosis can also be made if only one of the following is present: bizarre delusions; hallucinations that consist of a voice keeping a running commentary on the child's behavior or thoughts; or two or more voices conversing with each other. Active psychotic symptoms need to persist for at least 1 month. Social and functional impairment are also required, although at times this can be difficult to establish since most youth have significant premorbid problems. The total duration of illness must be at least 6 months; otherwise a diagnosis of schizophreniform disorder is made.

Although the diagnostic criteria appear straightforward, assessing youth for EOS is often a challenge in clinical settings. Symptoms of EOS overlap with several other psychiatric illnesses, including mood disorders, organic brain

syndromes and post-traumatic reactions [4]. Therefore, it is important to perform a complete psychiatric assessment when evaluating a child for psychotic symptom. Psychotic symptoms must be assessed within the developmental context of the child. In general, hallucinations and negative symptoms are the most common presentations in EOS, whereas systematic delusions and catatonia are rare. In school-aged children with psychosis, the delusional content often revolves around ideas of reference, somatic preoccupations, or delusions of persecution [8]. Compared with psychotic adults, delusions are less likely to be richly detailed or elaborate. Though it may be counterintuitive, more elaborate descriptions of suspected psychotic phenomena should raise questions as to the validity of the report.

Children and adolescents may respond positively to questions about hallucinations and delusions for a variety of reasons, including developmental delays, misunderstanding the concept being described, overactive imaginations and/or attention seeking [4]. Furthermore, youths with histories of child maltreatment are more likely to report hallucinations [50]. These issues add to the diagnostic complexity since the symptoms are generally being reported against a backdrop of emotional and behavioral difficulties. Thought disorder may not even be specific, since disorganized or loose thinking may be simply due to inattention or impulsiveness [51]. Misdiagnosis of schizophrenia in youth is a significant problem. A substantial number of youths first diagnosed with schizophrenia have other disorders at outcome, including bipolar [9] and personality disorders [5]. Moreover, the majority of youths referred to a national study of childhood schizophrenia did not have the disorder but instead displayed a mixture of developmental delays, mood lability and subclinical psychotic symptoms [52].

Atypical reports of psychotic symptoms that suggest a child may not truly have a psychotic illness include:

- The reports are inconsistent and there is no other documented evidence of a psychotic process such as thought disorder or bizarre disorganized behavior
- The qualitative nature of the reports were not typical of psychotic symptoms, such as, greatly detailed descriptions or reports more suggestive of fantasy or imagination
- The reported symptoms only occurred at specific times, such as, only hearing voices after an aggressive outburst [53]

Differential diagnoses

The full discussion of the differential diagnoses of EOS is beyond the scope of this article, however, important highlights will be discussed. EOS is considered a relatively rare disease, especially in children less than 13 years of age. Despite this, it is easily misdiagnosed given an extensive differential diagnosis as well as the lack of trained professionals able to assess psychotic symptoms in the correct context [52]. Given extensive overlap of symptomatology with a wide variety of other psychiatric disorders, a thorough review of presenting symptoms, course and premorbid functioning, adherence to DSM-IV-TR criteria, familiarity with how psychotic symptoms present in this age group and determination of family psychiatric history all will help improve the accuracy of diagnosis. Periodic reassessment of the accuracy of this diagnosis is crucial given the phasic course of this illness.

All organic causes of psychosis must be ruled out including drug or alcohol intoxication, delirium, CNS lesions, tumors, bacterial or viral infections, metabolic disorders and seizure disorders. Certain tests, such as neuroimaging, electroencephalographs and laboratory tests may be helpful in narrowing the diagnosis although are not essential in making a diagnosis of a psychotic disorder.

The psychiatric history should focus on the presenting symptomatology, the longitudinal timeline of symptom development and associated features and/or confounding factors (e.g., mood disorders, developmental problems and substance abuse). One of the most important aspects of obtaining a psychiatric history should be to obtain an understanding of the longitudinal course of the illness given that psychotic disorders have several phases. In collecting this history, it is important to collect as much collateral information from outside sources including the child's parents, other caregivers, teachers, treatment providers and community support persons such as case workers, probation officers and peers.

Developmental characteristics must be taken into account. For children, it is often difficult to distinguish true psychotic symptoms from other factors, such as an overactive imagination, developmental delay, language problem, posttraumatic phenomenon and/or misperception of the questions. Furthermore, very young children's inability to apply logical reasoning to their perceptions can make it difficult to identify delusions in children

younger than 5 years of age. However, language problems may be greater in childhood onset cases, therefore the presence of a language disorder does not rule out the possibility of schizophrenia [54]. Adolescents have mental status features more like adults. Confounding factors, such as substance abuse, may confuse the clinical picture. In general, children and adolescents may not report hallucinations since they are frightened or confused and/or they recognize the implications of acknowledging 'being crazy'.

Another factor that often complicates the diagnostic picture is that 10–20% of youths with EOS having IQ's in the borderline to mentally retarded range [4]. Learning and language disorders are also common. Although youths with schizophrenia are at risk for cognitive deficits, the presence of developmental delays also creates diagnostic difficulties. In these cases, reported psychotic symptoms may simply represent misunderstanding of the concepts and/or misinterpreted normal sensory phenomena. Furthermore, it is also common for youths with EOS to have either other comorbid or premorbid psychiatric disturbances, such as attention deficit hyperactivity disorder (ADHD), conduct problems, anxiety and/or substance abuse, all of which may complicate diagnosis and/or treatment.

The first step in the differential is deciding whether the child or adolescent is truly psychotic. Once psychotic symptoms are documented and other medical causes are ruled out, the differential includes schizophrenia, psychotic mood disorders or schizo-affective disorder. Both schizophrenia and psychotic mood disorders (especially bipolar disorder) present with a variety of affective and psychotic symptoms [9,55–57].

In children and adolescents with schizophrenia, negative symptoms may be mistaken for depression. Alternatively, mania in teenagers often presents with florid psychosis, including hallucinations, delusions and thought disorder [58]. The overlap between mood and psychotic symptoms increases the likelihood of misdiagnosis at the time of onset. Longitudinal reassessment is needed to ensure accuracy of diagnosis. Family psychiatric history may also be a helpful differentiating factor.

There are children with complex developmental problems, including disturbances in affect modulation, social relatedness and thinking, whose symptoms do not fit well within the current criteria for schizophrenia. Kumra and colleagues, have characterized a group of children with deficits in attention, impulse control, affect regulation and transient or subclinical psychotic symptoms as multidimensionally impaired [59]. Others have noted that many youth with atypical presentations, or psychosis not otherwise specified (NOS) have traumatic histories, including physical, sexual and/or emotional abuse [60]. These youths may describe symptoms suggestive of auditory or visual hallucinations and/or paranoid delusions, yet the reports are generally either brief or atypical in nature and the child does not demonstrate the other hallmark symptoms of schizophrenia. Further, some children with abuse histories may report psychotic symptoms in the context of reinforcement that occurs in a chaotic environment. Therefore, potential environmental reinforcers of psychotic behaviors should be assessed. Although some youth characterized with psychosis nos eventually develop definable psychotic disorders, many do not [60,61].

Children with pervasive development disorders (PDDs) may be suspected as having schizophrenia based on their potentially odd behaviors. By definition, youths with PDD will have problems with social relatedness, language difficulties and idiosyncratic behaviors, thus raising the question of negative symptoms or disorganized behaviors. However, unless they develop overt hallucinations or delusions the diagnosis of schizophrenia should not be used [4]. Conversely, the prodromal phase of schizophrenia may resemble Aspergers Disorder and cannot be differentiated until the psychotic symptoms fully present.

Differential diagnosis.

Psychiatric
– Psychotic disorder due to a general medical condition
– Bipolar disorder
– Major depressive episode with psychotic features
– Schizoaffective disorder
– Psychotic disorder NOS
– Delusional disorder
– Posttraumatic stress disorder
– Obsessive compulsive disorder
– Pervasive developmental disorder
– Conduct disorder
– Evolving borderline personality disorder

Psychosocial
– Abuse
– Traumatic stress
– Chaotic family environment

Medical
– Substance intoxication
– Delirium
– Brain tumor
– Head injury
– Seizure disorder
– Meningitis

Longitudinal course

EOS is a phasic disorder, consisting of a prodromal, acute, recuperative/recovery and residual phase. The prodromal phase varies in time from an acute change lasting days to weeks to a chronic impairment lasting months to years. Prodromal features may include deteriorating function, social isolation and increasingly odd or bizarre behavior. Cornblatt and colleagues have identified three clinical high-risk groups including:

- Negative and nonspecific symptoms, such as social isolation which is the earliest prodrome
- Moderate intensity positive symptoms (attenuated)
- Severe-attenuated positive symptoms which are considered the closest to psychosis

With regards to EOS, children in the prodromal phase of illness may also exhibit increased behavioral problems, such as aggression, deceitfulness and/or substance abuse that may represent a significant change from baseline functioning or a worsening of premorbid personality characteristics. Children with EOS tend to have more insidious onsets [62].

The acute phase usually lasts 1–6 months and is one in which positive symptoms predominate and cause significant deterioration of function. A gradual shift from positive to negative symptoms may occur during the course of treatment. Treatment response often determines the length of this phase. The recuperative/recovery phase occurs as the acute psychosis resolves and is most often characterized by ongoing negative symptoms that cause a significant degree of impairment. The residual phase can last prolonged periods of time (several months or more) and is a period during which youths with EOS do not have active positive symptoms. A small proportion of patients may go into remission. Few studies have examined long-term outcome in EOS and most are retrospective. Generally, these studies have found that 75–90% of subjects with EOS are moderately to severely impaired at follow-up (ranging from 2–42 years) [63–65], although not all studies have found such a poor prognosis [66]. The outcome for patients with EOS is generally thought to be poor and has been reported to possibly be worse than that of AOS with regards to multiple domains of function including educational achievement, employment, and social relationships. A mortality rate of approximately 5% for EOS due to suicide, or accidental death related to psychosis has been reported [9,67,68]. This reported risk for completed suicide in adults with schizophrenia is approximately 10% [4].

In comparison with other early onset psychotic illnesses, those with schizophrenia generally fare worse than those with psychotic mood disorders [60,69]. Predictors of outcome are less well studied in EOS as compared with adult-onset but onset below the age of 10 years, negative symptoms, low IQ and level of premorbid functioning have been associated with a worse prognosis [65].

Treatment

A multimodal approach should be utilized in the treatment of EOS incorporating psychopharmacology and psychosocial interventions. The treatment plan should be tailored to each patient based on the developmental characteristics of the patient, the phase of the disorder and needs of the family. Given the lack of both psychopharmacologic and psychosocial research in the area of EOS, treatment recommendations are generally based on the adult literature. Since EOS appears to be continuous with the adult-onset form, this practice seems justified as long as developmental considerations are taken into consideration.

Psychopharmacology

Antipsychotic agents are the cornerstones of treatment for psychotic disorders in the adult population. The atypical antipsychotics are a major advance and add to the therapeutic armamentarium of drugs available for the treatment of schizophrenia. However, at this time there are only five randomized controlled trials examining the efficacy and safety of antipsychotics in youths with EOS, only two of which examined an atypical agent. Controlled trials using traditional agents in children and adolescents with schizophrenia: thiothixene and thioridazine (Mellaril®, Novartis Pharma) [70], haloperidol (Haldol®, Janssen Cilag) [71] and loxitane® (loxapine, Apotex) [72] suggested a similar response rate and side effect profile to that found in adults. However, in clinical practice, traditional agents are usually relegated to second-line treatments. The atypical antipsychotic agents have become the agents of first choice based upon a more favorable side effect profile, greater efficacy for negative symptoms and mood stabilization properties in adults. **Table 1** summarizes the published data to date with these agents for EOS. We will discuss each of the atypical antipsychotics in greater detail below.

Table 1. Atypical antipsychotic trials in early onset schizophrenia .

Trial	Subjects (age)	Study type	Dosage	Outcome	Efficacy measures	Ref.
Clozapine						
Siefen *et al.* (1986)	n = 21 (18.1)	Open	352	17/21 positive response	NA	[74]
Schmidt *et al.* (1989) >50% schizophrenia	n = 57 (9–21)	Retrospective review	285	67% significantly improved	NA	[111]
Birmaher *et al.* (1992)	n = 3 (17–18)	Case series	300	3/3 positive response	NA	[112]
Blanz *et al.* (1993) Majority TR schizophrenia	n = 57 (10–21)	Open	285	50/57 positive response (67% significant improvement, 21% partially improved)	NA	[76]
Frazier *et al.* (1994)	n = 11 (12–17)	Open	370	> 50% positive response in Brief Psychiatric Rating Scale	Brief Psychiatric Rating Scale, Children's Global Scale for Assessment of Positive and Negative Symptoms	[75]
Remschmidt *et al.* (1994)	n = 36 (18)	Chart review	330	27/36 with some degree of clinical improvement, less effective in negative symptoms	Scale for Assessment of Positive and Negative Symptoms	[113]
Levkovitch *et al.* (1994)	n = 13 (14–17)	Open	240	10/13 more than 50% decline of Brief Psychiatric Rating Scale	Brief Psychiatric Rating Scale	[114]
Mozes *et al.* (1994)	n = 4 (10–12)	Case series	150–300	4/4 substantial improvement, remission of symptoms in daily functioning, social interaction, academics	Brief Psychiatric Rating Scale, Clinical Global Impression	[115]
Piscitelli *et al* (1994)	n = 11 (14.1)	Clozapine vs. haloperidol plasma levels and efficacy	5.99 mg/kg/d vs. 0.24 mg/kg/d	Linear relationship between clozapine concentration and efficacy, not observed with haloperidol	NA	[116]
Levkovitch *et al.* (1995) TD	n = 2	Case series	450–500	2/2 significant improvement of tardive dyskinesia, 30% reduction in Brief Psychiatric Rating Scale	Brief Psychiatric Rating Scale, Tardive dyskinetic rating scale	[117]
Kowatch *et al.*(1995) (TR schizophrenia and bipolar disorder)	n = 5 (6–15)	Case series	75–225	5/5 had 42% decrease in Clinical Global Impression-severity of illness	Clinical Global Impression, Children's Global Assessment	[118]
Kumra *et al.* (1996) TR schizophrenia	n = 21 (14.4)	Double-blind/ haloperidol	176	Clozapine > haloperidol on all measures of psychosis	Brief Psychiatric Rating Scale, Clinical Global Impression, Bunney-Hamburg Psychosis Scale, Positive and Negative Symptom Scale	[77]

Table 1. Atypical antipsychotic trials in early onset schizophrenia (Continued).						
Schulz *et al.* (1996)	n = 40 (14–22)	Open: clozapine vs. typical neuroleptic	324/465	Higher serotonin levels associated with fewer negative symptoms, higher MHPG with less depression	NA	[119]
Turetz *et al*. (1997) TR schizophrenia	n = 11 (9–13)	Open	220	11/11 had > 50% reduction in all scales	Brief Psychiatric Rating Scale, Positive and Negative Symptom Scale, Clinical Global Impression	[120]
Chalasani *et al.* (2001) schizophrenia or schizoaffective	n = 6	Chart review	NA	Improved social interaction, decrease in violence, SI/HI	NA	[121]
Zan *et al.* (2001)	n = 43 (12–18)	Open	100–450	50% reduction in Clinical Global Impression	Clinical Global Impression, Global Assessment Functioning Scale	[122]
Frazier *et al*. (2003) (pharmacokinetics)	n = 6 (9–16)	Open	3.4 mg/kg	NA	NA	[78]
Risperidone						
Cozza *et al.* (1994)	n = 2 (15)	Case series	2	2/2 had significant improvement in positive and negative symptoms	NA	[123]
Quintana *et al.* (1995)	n=4 (12-17)	Case series	4–5	3/4 marked improvement in negative symptoms	Clinical Global Impression, Brief Psychiatric Rating Scale, Positive and Negative Symptom Scale	[124]
Lykes *et al.* (1996)	n = 2 (7, 11)	Case series	2.5/5.5	1 moderately and 1 markedly improved	Global Clinical Judgment Scale	[125]
Grcevich *et al.* (1996)	n = 16	Chart review	2–10	15/16	Brief Psychiatric Rating Scale, Clinical Global Impression	[126]
Armenteros *et al* (1997)	n = 10 (15.1)	Open	6.6	6/10 significant reduction in Positive and Negative Symptom Scale	Positive and Negative Symptom Scale, Clinical Global Impression, Brief Psychiatric Rating Scale	[127]
Calhoun *et al.* (1999) Psychotic symptoms	n = 191 (13–17)	Chart review	1.8	164/191 had target symptom improvement	NA	[128]
Zalsman *et al.* (2003)	n = 11 (15–20)	Open	3.14	10/11 had 20% reduction in Positive and Negative Syndrome Scale, not effective for negative signs and symptoms	Positive and Negative Syndrome Scale, Clinical Global Impression, Brief Psychiatric Rating Scale	[129]

Table 1. Atypical antipsychotic trials in early onset schizophrenia (Continued).

Olanzapine						
Kumra *et al.* (1998)	n = 8 (olanzapine) n = 15 (clozapine)	Open comparison to clozapine	Olanzapine: 17.5 mg Clozapine: 317 mg +/- 147 mg	53% of clozapine treated met responder criteria vs. 0% of 8 treated with olanzapine at week 6, at week 8, 5/8 olanzapine treated had minimal to much improvement on the Clinical Global Impression	Brief Psychiatric Rating Scale, Scale for Assessment of Positive and Negative Symptoms, Clinical Global Impression	[89]
Dittman *et al.* (1999)	n = 24 (13–19.5)	Chart review	16.8	18/24 moderate significant improvement	Similar to Clinical Global Improvement Scale	[130]
Junghanss *et al.* (1999)	n = 24 (17.2)	Chart review	16.8	2 very much improved, 18 much improved	Similar to Clinical Global Improvement Scale	[131]
Sholevar *et al.* (2000)	n = 15 (6–13)	Open	2.5–5	5/15 moderate improvement	NA	[132]
Grothe *et al.* (2000) (pharmacokinetics)	n = 8 (10–18)	Open	20	NA	NA	[133]
Findling *et al.* (2003b)	n = 16	Open	12.4	11/16 much improved	Positive and Negative Symptom Scale, Clinical Global Impression, Children's Global Assessment Scale	[134]
Dittman *et al.* (2003)	N = 96 (12–21)	Open	16.7	60/96 responders at 6 weeks	Brief Psychiatric Rating Scale, Clinical Global Impression	[135]
Ross *et al.* (2003)	N = 20 (6–15)	Open	10.4	74% responders at 1 year	Brief Psychiatric Rating Scale-child version, Scale for Assessment of Positive and Negative Symptoms	[136]
Mozes *et al.* (2003) (population treatment refractory to 2 or more prior antipsychotics)	n = 9	Open		8/9 sustained improvement at 1 year		[90]
Quetiapine						
McConville *et al.* (2000)	n = 10 (12.3–15.9)	Open	400 bid	10/10 significant decreases in all measures	Brief Psychiatric Rating Scale, Clinical Global Impression	[92]
Shaw *et al.* (2001)	n = 15 (13–17)	Open	467	13/15 moderate to significant improvement	Brief Psychiatric Rating Scale, Clinical Global Impression, Positive and Negative Symptom Scale, Young Mania Rating Scale	[91]

Table 1. Atypical antipsychotic trials in early onset schizophrenia (Continued).

Grcevich *et al.* (2001)	n = 14 (11.6)	Open	308.9	11/14 positive response	Brief Psychiatric Rating Scale, Clinical Global Impression, Global Assessment of Functioning	[137]
McConville *et al.* (2003)	n = 10 (12.3–15.9)	Open	300–800	Significant improvement in positive and negative symptoms	Brief Psychiatric Rating Scale, Clinical Global Impression, Scale for Assessment of Negative Symptoms	[138]
Ziprasidone						
NA						
Aripiprazole						
NA						
Combined						
Sikich *et al.* (2004) (schizophrenia spectrum disorders, MDD with psychotic features)	n = 50 (8–19)	DB/flexible dose of haloperidol vs. risperdal vs. olanzapine	5 mg vs. 4 mg vs. 12.3 mg (mean dosage at end of study)	53% met response criteria with haloperidol, 74% with risperidone, 88% with olanzapine		[79]

Case reports included. Positive response based on study's primary and secondary efficacy measures.
MDD: Major depressive disorder; MHPG: Methoxyhydroxyphenylglycol.

Clozapine

Kane and colleagues [73] noted that schizophrenic adolescents and adults with chronicity and poor response to standard neuroleptics had positive responses to clozapine. This marked the beginning of several studies examining the use of clozapine in this population. Open trials supported its efficacy in this age group. Siefen and Remschmidt completed an open-label trial of clozapine in 21 in-patients (average age 18 years) who had either been treatment resistant or had not tolerated a typical neuroleptic [74]. Overall clozapine was well tolerated (mean dose of 352 mg). Marked improvement or complete remission of psychotic symptoms was seen in 52% of subjects. Frazier and colleagues found clozapine to be helpful in a sample of subjects with treatment-resistant childhood schizophrenia [75]. Blanz and Schmidt reviewed the records of 57 in-patients (9–21 years of age) treated with mean dosage of 285 mg of clozapine [76]. Significant improvement was seen in 67% of patients.

There has only been one randomized, controlled study examining the use of clozapine in EOS [77]. In the NIMH study, clozapine (mean dose 176 ± 149 mg/day) was superior to haloperidol (16 ± 8 mg/day) for treating both positive and negative symptoms in 21 youth (mean age 14.0 ± 2.3 years) with COS. However, while on clozapine, five youths developed significant neutropenia (this resolved spontaneously in three of subjects) and two had seizures. Such high rates of neutropenia have not been observed in other large case studies and it is difficult to infer the overall risk based on a small sample size. Nevertheless, although potentially more efficacious, clozapine's apparent increased risk for adverse reactions in youth raises caution. At this time, although clozapine may be effective for treatment resistant cases, it is not recommended as a first line agent based on its side effect profile.

Clozapine pharmacokinetics was studied completed in 6 youths (aged 9–16 years) with schizophrenia [78]. Serum was collected after 6 weeks treatment prior to and 30 mins* following a morning dose of 3.4 mg/kg. The metabolite norclozapine was found to exceed clozapine in its concentration in contrast to adults in whom the opposite is true. Dose-normalized concentrations of clozapine did not vary with age and were similar to adults.

Risperidone

There are no placebo-controlled studies of risperidone in EOS, although several open studies and case reports suggest that many patients

demonstrate measurable improvement. Sikich and colleagues compared responses with risperidone (1–6 mg/d), haloperidol (2–8 mg/d) and olanzapine (Zyprexa®, Eli Lilly & Co.) (5–20 mg/d) in 50 children (aged 8–19 years) with more broadly defined psychosis. Subjects maintained treatment on olanzapine significantly longer than the other two agents, with a positive response noted in 74% of those treated with risperidone, 88% with olanzapine and 53% with haloperidol. In this pilot study, improvement was noted for all agents, without significant differences between the individual medications. The rates of extrapyramidal side effects (EPS) and weight gain for children treated with atypical antipsychotics were higher than typically reported in adults [79].

Reports vary as to whether children and adolescents are at a higher risk for EPS with risperidone [80–83]. Case reports describe the development of withdrawal dyskinesias and tardive dyskinesia [84–86] and risperidone-related neuroleptic malignant syndrome (NMS) [87]. Comparative risks for these untoward effects with adult patients are unknown. Compared with other atypicals, risperidone has been more often associated with elevated prolactin levels. Prolactin levels in children treated with risperidone were reviewed examining data from five studies [88]. There was a modest early increase in mean serum prolactin levels that decreased after eight weeks of risperidone therapy. Levels were above baseline but within normal limits by the end of 1 year.

Olanzapine

There are no pediatric double-blind/controlled studies of olanzapine in EOS. In an open label study, olanzapine was efficacious (defined as more than 28% improvement in Brief Psychiatric Rating Scale [BPRS] scores) in two out of eight children with treatment refractory COS. In this sample, olanzapine was inferior to clozapine given 53% of clozapine versus 0% of olanzapine subjects had responded at 6 weeks. Increased appetite, constipation, somnolence, insomnia, tachycardia and transient increases in liver function tests were the main side effects observed in the olanzapine-treated group [89]. Mozes and colleagues used olanzapine in nine children hospitalized for schizophrenia who had been treatment resistant to two previous antipsychotics [90]. At 12 weeks, a reduction in all psychopathology scores was observed compared with baseline. Overall, olanzapine was well-tolerated with weight gain being the most common side effect. Average weight gain of 6.10 ± 3.25 kg was observed. At 1-year follow-up, improvement in psychiatric symptoms continued in eight children.

Quetiapine

There are no pediatric double-blind/controlled studies of quetiapine monotherapy. Multiple case reports and open-label studies have described quetiapine's efficacy in the treatment of EOS. In one open-label study, Shaw and colleagues studied the efficacy and tolerability of quetiapine in 15 psychotic adolescents with a mean dosage of 467 mg/day. Quetiapine was found to have a positive effect with improvement in psychotic and manic symptoms. Most common side effects included somnolence, agitation and drowsiness [91]. Decreased thyroxine (T4) levels have been reported with quetiapine use suggesting that clinical monitoring to signs of hypothyroidism is warranted [92].

Ziprasidone & aripiprazole

To our knowledge, no studies have yet been published examining the use of ziprasidone in EOS. It is being used in clinical settings and offers promise given the advantage of not being associated with significant weight gain. Cardiac monitoring is needed since the agent may cause prolongation of QT intervals. In addition, there is one report of an adolescent with schizophrenia developing mania associated with ziprasidone therapy [93].

The newest agent on the market, aripiprazole (Abilify®, Bristol Myers Squibb) has been shown to be more efficacious than placebo and as efficacious as conventional antipsychotics in the treatment of adult schizophrenia [94–96]. To our knowledge, no studies have yet been published regarding the use of aripiprazole in EOS. An early report described short-term safety and tolerability of aripiprazole in which initial doses of 1 mg/kg/day were titrated to a maximum of 15 mg/day and well-tolerated [97]. Nausea and vomiting were the most common side effects and no other adverse events, including negative cardiovascular outcomes, were reported.

Given the dearth of data regarding use of atypical antipsychotics in this population, further trials need to focus on safety and effectiveness of these agents for EOS using randomized controlled designs and adequate sample sizes. There are such studies underway nationally at this time.

Safety monitoring

Youths appear to have the same spectrum of side effects with typical antipsychotics as those described in adults, including: extrapyramidal symptoms, sedation, tardive dyskinesia and neuroleptic malignant syndrome [84,86,98,99]. Although they are often viewed as more benign, atypical antipsychotics are associated with significant adverse events, including weight gain and endocrine abnormalities, cardiovascular changes and sedation. There have been concerns that these occur at even higher rates than those reported in adults, with weight gain being a particular concern [79,100]. A 12-week naturalistic study of olanzapine, risperidone and quetiapine in juveniles demonstrated significant weight gain, increased triglycerides and insulin resistance for all compounds (n = 134) [101]. EPS is also a concern for this age group. In a report of 34 patients with EOS being treated with either clozapine, haloperidol, or olanzapine, 50% of patients were noted to have either withdrawal dyskinesias or tardive dyskinesia at some point during the trial [102]. Finally, there may be the potential for long-term risks for which there are currently no studies. For example, decreased mineral bone density has been observed with risperidone use in adults [103]. The relationship between hyperprolactinemia and osteoporosis is a theoretical risk but to date has not been examined in the pediatric population.

It is recommended that youths are monitored for side effects in a systematic fashion. Baseline assessments should include a full physical examination and review of systems, with special attention to seizures, pre-treatment extrapyramidal signs, cardiac symptoms and prolactin-associated phenomena, such as galactorrhea or amenorrhea. Once on the agent, routing monitoring of weight, metabolic functioning and examininations for the presence of abnormal movements is needed. The US Food and Drug Administration (FDA) recently asked manufacturers of all six atypical antipsychotic drugs to include a warning statement in their inserts regarding the increased risk of developing high blood sugar levels and diabetes associated with these drugs. Consistent with recent FDA guidelines, weight, fasting glucose and lipid levels should be assessed every 3 to 6 months for all atypical antipsychotics. Specific agents may need other additional tests, for example, cardiac monitoring with ziprasidone [104]. It is important to remember that almost all uses of atypical antipsychotics in children are off-label and that the effects of long-term treatment are unknown.

Treatment guidelines

Treatment varies depending on the phase of the illness and the patient's history of medication response and side effects. The American Academy of Child and Adolescent Psychiatry provides the following general guidelines for the psychopharmacological management of schizophrenia [4].

Antipsychotics are the front-line treatment for EOS with atypical antipsychotics generally being the first choice (**Table 2**). With regards to choice of antipsychotic, this should be made based on the agent's relative potency, potential side effects and the patient's history of medication response.

Acute phase

In the acute phase, a trial of an adequate dosage of antipsychotic should last no less than 4 to 6 weeks before any conclusions regarding efficacy are made. Although children usually require lower dosages of drugs, it should be kept in mind that the drug metabolism of antipsychotics in children tends to be higher and therefore children usually require approximately adult dosages. If no improvement is seen at 4 to 6 weeks, then a change in antipsychotic should be made.

Recuperative phase

Although improvements in positive symptoms are observed in the recuperative phase, it is important to maintain medication given additional recovery may be obtained over the next 6–12 months. If side effects were elicited with higher dosages in attempts to control the acute phase, gradual decreases in the dosage may be attempted. However, any reductions in dosage consequently increase risk for relapse, therefore close monitoring is required.

Recovery phase

During this period, a medication free trial may be attempted in those youth who have been symptom free for 6–12 months. However, statistics are grim and without maintenance therapies, approximately 65% of adult patients have been shown to relapse within 1 year [3] and a striking 80% relapse at least once over 5 years [105]. Physicians should be meeting frequently, at least monthly, to monitor symptoms, side effects and medication adherence.

Nonresponders

For the minority of patients who do not respond to a first trial of antipsychotic, the etiology may be a misdiagnosis or side effects of the medication

Table 2. Psychotropics used for psychosis in children and adolescents.

Atypical antipsychotics	Typical antipsychotics	Considered when other medications fail
Olanzapine	Haloperidol	Clozapine
Risperidone	Thiothixene	Electroconvulsive therapy (ECT)
Quetiapine	Chlorpromazine	
Aripiprazole	Trifluoperazine	
Ziprasidone	Molindone	

clouding the clinical presentation. Therefore, a medication-free trial may be attempted if diagnostic questions exist. Clozapine is a proven drug of choice for nonresponders and is reserved for those who are truly treatment resistant which is defined by failure of at least two therapeutic trials of other neuroleptics (at least one of which is an atypical agent).

Psychosocial interventions

Psychological interventions include education, family and individual therapy. Psychoeducation for the patient should include ongoing education about the illness, treatment options, social skills training, relapse prevention, basic life skills training and problem-solving strategies. Psychoeducation for the family include education about the illness, treatment options and short- and long-term prognosis. There should be a focus on helpful coping strategies to deal with their child's symptoms and behavioral manifestations of the disorder. It is important that the patient and family are told that its course is unpredictable and different for each child.

Cognitive behavioral therapy (CBT) has been gaining more attention as an important component of schizophrenia treatment. In schizophrenia, CBT focuses on challenging thoughts and beliefs that surround psychotic symptoms such as hallucinations and delusions, problem solving skills and increasing compliance. In adults, adjunctive CBT has been found to produce large clinical effects on both positive and negative symptoms of schizophrenia [106]. In children, there have been no studies examining the outcomes of CBT in EOS. McGorry and colleagues conducted a randomized controlled trial comparing risperidone and CBT against needs-based intervention (supportive psychotherapy, no antipsychotic medication) in 59 patients at risk of progression to first-episode psychosis [107]. The medication and CBT group showed lower rates of early transition to psychosis and this study suggests that it may be possible to at least delay the progression to psychosis [107].

As would be expected, psychotherapy alone has not been proven to be an effective treatment for schizophrenia. However, adjunctive psychosocial treatments including psychoeducation [108], behaviorally based family therapy [109,110] and cognitive behavioral therapy [106] have been shown to reduce relapse rates and improve positive and negative symptoms in schizophrenic patients.

Therapeutic resources, such as in-patient/partial hospitalization programs, case management, vocational and rehabilitative assistance, or special education programs may also be incorporated. Unfortunately, these resources are often unavailable or difficult to obtain secondary to lack of resources. The gross lack of mental health services for this population has fueled the impetus for legislation, such as the Child Healthcare Relief Crisis Act which aims to address the national shortage of children's mental health professionals, including child and adolescent psychiatrists.

Expert opinion

EOS, although a relatively rare disorder, has significant importance given its morbidity, chronicity and psychosocial impairment. Although the same DSM-IV criteria are used, clinicians should be aware of differences that exist between schizophrenia in youths and adults as well as the greater diagnostic challenges of truly identifying psychotic symptoms in children. Treatment should be based on the phase of illness as well as tailored to each individual child and family's characteristics and needs. Psychopharmacology is best combined with different types of psychotherapy, including psychoeducational and cognitive behavioral therapies, to optimize outcomes. Antipsychotic agents are considered front-line therapy, with atypical antipsychotics being preferred over typical neuroleptics given their reported superior side effect profile in adults. However, these agents bring their own set of concerns including weight gain and metabolic disturbances. Children and adolescents may be at even higher risk for these problems. The current treatment literature for EOS is sparse, and most treatment guidelines are based on adult literature. Further randomized controlled trials need to be conducted before firm conclusions regarding the efficacy and safety of antipsychotic agents in this population can be made.

Highlights

- Early onset schizophrenia (EOS) has significant importance given its morbidity, chronicity and psychosocial impairment.
- Although the same DSM-IV criteria are used for diagnosis, several diagnostic considerations should be made within a developmental context when evaluating psychotic symptoms in a child.
- Treatment should involve a multidimensional approach, including both psychopharmacology and psychotherapy, that is tailored to the phase of illness and individual needs of child and family.
- Antipsychotic agents are considered first line agents in the treatment of EOS, with atypical antipsychotics preferred over typical antipsychotics given their favorable side-effect profile. However, only a few randomized controlled trials have been conducted and current treatment literature is sparse in this population.

Outlook

The neurobiological underpinnings of EOS are likely to be unraveled as the understanding of neurodevelopment and genetics advance. EOS may be a more homogenous form of the disorder. Thus etiologic mechanisms underlying earlier-onset cases may be more readily identified, with discoveries paving the way for future endeavors within other realms of neuropsychiatry. Of course, neurobiological mechanisms are only one piece of the puzzle and the current biopsychosocial approach will continue to be emphasized. With the sparse treatment data available, randomized controlled trials are needed to examine the safety and efficacy of medications and psychosocial interventions in this population.

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