

# AMERICAN ACADEMY OF CHILD AND ADOLESCENT PSYCHIATRY

## PRACTICE PARAMETER FOR THE ASSESSMENT AND TREATMENT OF CHILDREN AND ADOLESCENTS WITH SCHIZOPHRENIA

This parameter was developed by Jon McClellan, M.D., and John Werry, M.D. and the Work Group on Quality Issues: William Bernet, M.D., Chair, Valerie Arnold, M.D., Joseph Beitchman, M.D., R. Scott Benson, M.D., Oscar Bukstein, M.D., Joan Kinlan, M.D., Jon McClellan, M.D., David Rue, M.D., and Jon A. Shaw, M.D. AACAP Staff: Kristin Kroeger.

The summary and full text of the Practice Parameter for the Assessment and Treatment of Children and Adolescents with is available to Academy members on the World Wide Web ([www.aacap.org](http://www.aacap.org)) and appears in the December 2000 supplement to the JAACAP. The full text of these parameters was reviewed at the 1999 Annual Meeting of the American Academy of Child and Adolescent Psychiatry. Both the full text and this Summary were approved by AACAP Council on June 6, 2000.

Reprints requested by the AACAP Communications Department, 315 Wisconsin Ave., NW, Washington, D.C. 20016.

© 2000 by the American Academy of Child and Adolescent Psychiatry.

### ABSTRACT

This practice parameter reviews the literature on the assessment and treatment of children and adolescents with schizophrenia. Recommendations are based on the limited research available, the adult literature, and clinical experience. Early-onset schizophrenia is diagnosed using the same criteria as in adults, and appears to be continuous with the adult form of the disorder. Noted characteristics of youth with schizophrenia include predominance in males, high rates of premorbid abnormalities, and often poor outcome. Differential diagnosis includes psychotic mood disorders, developmental disorders, organic conditions, and nonpsychotic emotional/behavioral disorders. Treatment strategies incorporate antipsychotic medications with psychoeducational, psychotherapeutic, and social and educational support programs. The advent of atypical antipsychotic agents has enhanced the potential for effective treatment. **Key Words:** schizophrenia, children, adolescents, psychosis.

# **AMERICAN ACADEMY OF CHILD AND ADOLESCENT PSYCHIATRY**

## **INTRODUCTION**

Schizophrenia is a neurodevelopmental disorder that is associated with deficits in cognition, affect and social functioning. Onset of the illness occurs rarely before the age of 13 years, but then increases steadily during adolescence. Accurate diagnosis and treatment requires familiarity with the clinical presentation, phenomenology and course of the disorder. Diagnostic assessment must also incorporate an understanding of the youth's developmental, social, educational, and psychological needs. Treatment strategies should focus on alleviating symptoms, reducing long-term morbidity, and relapse prevention. Associated comorbid disorders and/or biopsychosocial stressors may also need to be addressed. Intervention strategies also must be consistent with the developmental, social, and cultural aspects of the youth and his or her family.

## **EXECUTIVE SUMMARY**

This summary provides an overview of the assessment and treatment recommendations contained in the Practice Parameters for the Assessment and Treatment of Children and Adolescents with Schizophrenia. This summary includes many of the most important points and recommendations that are in these practice guidelines. However, the treatment and assessment of children and adolescents with schizophrenia requires the consideration of many important factors that cannot be conveyed fully in a summary, and the reader is encouraged to review the entire document. Each recommendation in the executive summary is identified as falling into one of the following categories of endorsement, indicated by an abbreviation in brackets following the statement. These categories indicate the degree of importance or certainty of each recommendation.

[MS] “Minimal Standards” are recommendations that are based on substantial empirical evidence (such as well controlled, double-blind trials) or overwhelming clinical consensus or legal and regulatory requirements. Minimal standards are expected to apply more than 95 percent of the time, i.e., in almost all cases. When the practitioner does not follow this standard in a particular case, the medical record should indicate the reason.

[CG] “Clinical Guidelines” are recommendations that are based on empirical evidence (such as open trials, case studies) and/or strong clinical consensus. Clinical guidelines apply approximately 75 percent of the time. These practices should always be considered by the clinician, but there are exceptions to their application.

[OP] “Options” are practices that are acceptable, but not required. There may be insufficient empirical evidence to support recommending these practices as minimal standards or clinical guidelines. In some cases they may be indicated, but in other cases should be avoided. If possible, the practice parameter will explain the pros and cons of these options.

[NE] “Not Endorsed” refers to practices that are known to be ineffective or contraindicated.

The following recommendations should be considered in the assessment and treatment of schizophrenia in children and adolescents.

# AMERICAN ACADEMY OF CHILD AND ADOLESCENT PSYCHIATRY

## ASSESSMENT

### Psychiatric Assessment

A comprehensive diagnostic assessment is needed [MS]. This should include, when possible, interviews with the both the child or adolescent and the family, plus a review of past records and any other available ancillary information. The assessment should include a detailed evaluation of the psychotic symptoms that are required for the diagnosis. Issues to address include:

1. Symptom presentation;
2. Course of Illness;
3. Other pertinent symptoms and/or confounding factors, including any history of significant developmental problems, mood disorders or substance abuse;
4. Family psychiatric history, with a focus on psychotic illnesses; and
5. Mental Status Examination, including clinical evidence of psychotic symptoms and thought disorder.

### Physical Assessment

General medical causes of psychotic symptoms should be ruled out [MS]. Potential organic conditions that need to be considered include acute intoxication, delirium, central nervous system lesions, tumors or infections, metabolic disorders, and seizure disorders. A thorough physical examination is needed. Other tests and procedures, such as neuroimaging, electroencephalographs, laboratory tests, and toxicology screens, should be ordered as indicated based on the history and physical examination. In addition, some laboratory testing, such as assessing renal or hepatic functioning, may also be indicated for monitoring potential adverse-effects of psychopharmacologic agents. Finally, some cases may require consultation with other medical specialties.

### Psychological Assessment

Psychological testing, including personality and projective tests, is not indicated as a method of diagnosing schizophrenia. An intellectual assessment may be indicated when there is clinical evidence of developmental delays, since these deficits may influence the presentation and/or interpretation of symptoms [CG]. Cognitive testing also may be useful for assessing the degree of impairment associated with the illness, and to help guide treatment planning [OP].

### Phases of Schizophrenia

In order to adequately diagnosis and treat individuals with schizophrenia, clinicians must be able to recognize the various phases of the disorder [MS]. These phases include:

*Prodrome.* Prior to developing overt psychotic symptoms, most individuals will experience some period of deteriorating function, which may include social isolation, idiosyncratic or bizarre preoccupations, unusual behaviors, academic problems and/or deteriorating self-care skills. However, while the presence of these problems should raise concerns, psychotic symptoms must be present before a diagnosis of schizophrenia can be made.

*Acute Phase.* This is the phase in which patients often present, and is dominated by positive

## AMERICAN ACADEMY OF CHILD AND ADOLESCENT PSYCHIATRY

psychotic symptoms (i.e., hallucinations, delusions, formal thought disorder, bizarre psychotic behavior) and functional deterioration.

*Recovery Phase.* This follows the acute phase, as the active psychosis begins to remit. This phase often has some ongoing psychotic symptoms, and may also be associated with confusion, disorganization and/or dysphoria.

*Residual Phase.* During this phase, positive psychotic symptoms are minimal. However, patients will still generally have ongoing problems with “negative symptoms”, i.e., social withdrawal, apathy, amotivation, and/or flat affect.

*Chronic Impairment.* Some patients remain chronically impaired by persistent symptoms that have not responded adequately to treatment.

### Psychiatric Formulation

A diagnosis of schizophrenia is made when the prerequisite DSM-IV (or ICD-10) symptoms are present for the required duration, and other disorders have been adequately ruled out [MS]. The differential diagnosis includes mood disorders (especially psychotic symptoms associated with mania or mixed episodes of bipolar disorder), pervasive developmental disorders, non-psychotic emotional and behavioral disturbances (including posttraumatic stress disorder), and organic conditions (including substance abuse). The formulation must also incorporate other clinically significant issues, such as developmental delays and child maltreatment. Once the diagnosis is established, it needs to be reassessed longitudinally as misdiagnosis at the time of onset is a common problem.

## TREATMENT

Adequate treatment requires the combination of psychopharmacologic agents plus psychosocial interventions [MS]. Treatment strategies may vary depending on the phase of illness. Therapeutic recommendations are primarily based on the adult literature, since there is a lack of treatment research for youth with schizophrenia.

### Psychopharmacology

Antipsychotic agents are recommended for the treatment of the psychotic symptoms associated with schizophrenia [MS]. First-line agents include traditional neuroleptic medications (block dopamine receptors), or the atypical antipsychotic agents (that have a variety of effects, including antagonism of serotonergic receptors). Compared to traditional agents, the atypical antipsychotics are at least as effective for positive symptoms, and may be more helpful for negative symptoms. Clozapine has documented efficacy for treatment-resistant schizophrenia in adults. However, clozapine is usually not considered a first-line agent due to its significant potential adverse effects, and is generally only used after therapeutic trials of at least two other antipsychotic medications (one or both of which should be an atypical agent) [MS].

The use of antipsychotic agents requires the following [MS]:

1. Adequate informed consent from the parent/youth (depending on the legal age requirements and/or legal status of the patient).
2. Documentation of target symptoms.
3. Documentation of any required baseline and follow-up laboratory monitoring, dependent on

## AMERICAN ACADEMY OF CHILD AND ADOLESCENT PSYCHIATRY

the agent being used.

4. Documentation of treatment response.
5. Documentation of suspected side-effects, including monitoring for known side-effects (e.g., extrapyramidal side-effects, weight gain, agranulocytosis and seizures with clozapine).
6. Adequate therapeutic trials, which generally require the use of sufficient dosages over 4 – 6 weeks.
7. Long-term monitoring to reassess dosage needs, dependent on the stage of illness. Higher dosages may be required during the acute phases, with smaller dosages during residual phases. The decision to lower dosages (which minimizes the side-effect risks), or undergo medication-free trials, must be balanced by the potential increased risk for relapse. In general, first-episode patients should receive some maintenance psychopharmacological treatment for one to two years after the initial episode, given the risk for relapse.

Some patients may benefit from the use of adjunctive agents, including antiparkinsonian agents, mood stabilizers, antidepressants or benzodiazepines [CG]. These medications are either used to address side-effects of the antipsychotic agent or to alleviate associated symptomatology (e.g., agitation, mood instability, dysphoria, explosive outbursts). Although commonly used, there are no studies that systematically address the use of adjunctive agents in juveniles.

### Psychosocial Interventions

Psychosocial interventions are recommended [MS]:

- 1) Psychoeducational therapy for the patient, including ongoing education about the illness, treatment options, social skills training, relapse prevention, basic life skills training and problem solving skills strategies.
- 2) Psychoeducational therapy for the family to increase the understanding of the illness, treatment options, prognosis and developing strategies to cope with the symptoms of the patient.

Specialized educational programs and/or vocational training programs may be indicated for some child or adolescents to address the cognitive and functional deficits associated with the illness [CG]. Some individuals will require more intensive community support services, including day programs. Furthermore, there are some cases where the severity and chronicity of symptoms warrants long-term placement in a residential facility. However, efforts should always be made to maintain the child or adolescent in the least restrictive setting possible.

### Other Treatments

In addition to those treatments provided specifically for schizophrenia, other interventions and services may be needed to address either comorbid conditions, or associated sequelae of the disorder, such as substance abuse, depression and suicidality [CG].

There are case-reports of electroconvulsive therapy (ECT) being used for youth with treatment refractory schizophrenia. However, ECT does not appear to be as effective for schizophrenia as it is for mood disorders. The use of ECT should be reserved for those cases where several trials of medication therapy (including a trial of clozapine) have failed. ECT may also be considered for catatonic states [OP].

# AMERICAN ACADEMY OF CHILD AND ADOLESCENT PSYCHIATRY

## LITERATURE REVIEW

This parameter was originally published in July, 1994. The literature review process was performed using the National Library of Medicine database. Key words included: adolescents, children and schizophrenia, with other topics (e.g., specific medications) also examined over time. The initial Medline search covered a 5-year period dating back to 1988, and has been periodically updated, most recently in December 1999. Relevant papers identified through this process were reviewed in detail. Pertinent papers published prior to the period covered in the literature search were also reviewed, as were review articles regarding adult-onset schizophrenia. Finally, the authors drew from their own work in this area. An asterisk in the reference section notes key articles from which recommendations were primarily based.

The literature review was then incorporated into the initial drafts of this manuscript, which was distributed to a panel of experts. Their comments were incorporated into the manuscript, including additions and clarifications of the literature review.

## BRIEF HISTORY

Historically, rare cases of schizophrenia in children were noted, dating back to the observations of Kraepelin. The patterns of symptoms described were similar to the adult form of the disorder, and distinct from autism and pervasive developmental disorders (Werry, 1979). However, beginning with the works of Bender, Kanner, and others (Fish and Ritvo, 1979), childhood schizophrenia was equated with the broader construct of childhood psychoses. This cluster of syndromes (which also included infantile autism) was defined by developmental lags in the maturation of language, perception, and motility (Fish and Ritvo, 1979). While psychotic speech and thought were considered inherent components of childhood schizophrenia, hallucinations and delusions were not required criteria (Fish and Ritvo, 1979). *DSM-II* adopted this nosology by grouping all childhood psychoses under childhood schizophrenia. As a result, the literature from this period regarding childhood schizophrenia overlaps with that of autism and other psychotic disorders.

The work of Kolvin (1971) and Rutter (1972) demonstrated the distinctiveness of the various childhood psychoses and the similarity between child and adult schizophrenia. Therefore, beginning with *DSM-III* (American Psychiatric Association, 1980), the diagnosis of schizophrenia in childhood has been made using the same criteria as for adults, regardless of age of onset. Research since the advent of *DSM-III* has generally validated this decision (Beitchman, 1985; Werry, 1992).

The available literature examining schizophrenia in youth is sparse, and confounded by several methodological limitations. Early studies did not distinguish childhood schizophrenia from autism and thus are confounded by the diagnostic overlap. In studies using current diagnostic standards, most have focused on childhood onset, even though onset during adolescence is more common. Other methodological difficulties include the use of retrospective designs, a lack of standardized assessment tools such as diagnostic interviews, small subject pools, and lack of comparison groups (Werry, 1992). Treatment studies are particularly lacking. However, despite these limitations, there are enough data to draw some reasonable conclusions regarding the diagnosis and treatment of schizophrenia in children and adolescents. The available data also suggest that the research on adults can be reasonably extrapolated to children

## AMERICAN ACADEMY OF CHILD AND ADOLESCENT PSYCHIATRY

and adolescents with appropriate developmental adjustments.

### DEFINITIONS

Schizophrenia in children younger than 13 years of age has often been referred to as “prepubertal.” However, this term may not be accurate when puberty is defined by age rather than physical development. To avoid ambiguity, we will use the convention of defining early-onset schizophrenia (EOS) as onset before age 18 years, with very-early-onset schizophrenia (VEOS) developing before age 13 years.

The diagnosis in children and adolescents is made using the same criteria as in adults. The DSM-IV (APA, 1994) diagnostic criteria include:

*Psychotic Symptoms.* These are the hallmark symptoms of the disorder. At least two of the following are needed, each present for a significant period of time during a 1-month period: (1) delusions, (2) hallucinations, (3) disorganized speech, (4) grossly disorganized or catatonic behavior, and/or (5) negative symptoms (e.g., affective flattening, paucity of thought or speech). Only one symptom is needed if (1) the delusions are bizarre, (2) the hallucinations include a voice providing a running commentary on the person’s behavior or thinking, or (3) two or more voices are conversing with each other. Finally, the duration of symptoms may be less if the symptoms resolved with treatment.

*Social/Occupational Dysfunction.* For a significant portion of the time since onset of the disorder, the level of social, occupational, and self-care functioning has markedly deteriorated below the level achieved before onset. In children and adolescents, this may include the failure to achieve age-appropriate levels of interpersonal, academic, or occupational development.

*Duration.* The disturbances must be present for a period of at least 6 months. If the duration criterion of 6 months is not met, a diagnosis of schizophreniform disorder is made. The period of illness includes an active phase of overt psychotic symptoms (criterion A) with or without a prodromal or residual phase. A prodromal phase involves deterioration in functioning before the onset of psychotic symptoms, and the residual phase follows the active phase. Symptoms characteristic of both prodromal and residual phases include marked social isolation; deterioration in occupational functioning; peculiar behavior such as food hoarding, poor hygiene, blunted or inappropriate affect; disordered thought processes (tangentiality, circumferentiality); poverty of speech or speech content; odd beliefs or perceptions; and anergia.

*Schizoaffective and Mood Disorder Exclusion.* Schizoaffective disorder and mood disorders with psychotic features should be ruled out. This is especially pertinent for adolescents with bipolar disorder, inasmuch as manic episodes in this age group frequently include schizophrenic-like symptoms at onset (Carlson, 1990; McClellan et al., 1993; McGlashan, 1988; Werry et al., 1991). This criterion needs to be systematically reassessed in patients, because continued follow-up may be the only accurate method for distinguishing the two disorders.

*Substance Abuse/General Medical Condition Exclusion.* Other medical conditions, including drug abuse or medications, should be ruled out.

The ICD-10 diagnostic criteria are similar to DSM-IV except that the diagnosis can be made once sufficient symptoms have been present for a period of 1 month or more, rather than 6 months (World Health Organization, 1992). Armenteros et al., (1995) found a high rate of diagnostic agreement between DSM-III-R, DSM-IV and ICD-10 in hospitalized psychotic adolescents.

## **AMERICAN ACADEMY OF CHILD AND ADOLESCENT PSYCHIATRY**

### **EPIDEMIOLOGY**

Although the prevalence of EOS has not been adequately studied, the few studies available, plus clinical experience, suggest that onset prior to age 13 years is quite rare. The rate of onset then increases sharply during adolescence, with the peak ages of onset for the disorder ranging from 15 to 30 years (APA, 1997). Although the onset of puberty has been theorized to play some type of neurobiologic role, pubertal status was not associated with the onset of psychosis in a study of youth with childhood schizophrenia (Frazier et al., 1997). Thomsen (1996) found that, in a study of all youth hospitalized for schizophrenia in Denmark over a 13 year period (n = 312), only 4 were under the age of 13 years, and only 28 were younger than 15 years. In the literature, the youngest reported cases had onset at 3 years (Russell et al., 1989) and 5.7 years of age (Green and Padron-Gayol, 1986). However, a diagnosis of schizophrenia in children of this age group must be carefully scrutinized.

EOS, especially VEOS, occurs predominantly in males, with ratios of approximately 2:1 (Bettes and Walker, 1987; Green et al., 1992; Green and Padron-Gayol, 1986; Kolvin, 1971; McClellan and McCurry, 1998; Russell et al., 1989; Werry et al., 1991). As age increases, this ratio tends to even out. Since the adult literature suggests that the average age of onset in males is 5 years earlier than that in females (Loranger, 1984), the male predominance in EOS may be a cross-sectional effect.

### **CLINICAL PRESENTATION**

The available research is limited, but it does suggest that, as in adult schizophrenia, there are a wide variety of associated symptoms and phenomena seen in EOS.

#### **Rapidity of Onset**

VEOS generally has an insidious onset (Asarnow and Ben-Meir, 1988; Green and Padron-Gayol, 1986; Kolvin, 1971). In young adolescents, both acute onset (less than 1 year) and insidious onset are noted (Kolvin, 1971; McClellan et al., 1993; McClellan and McCurry, 1998; Werry et al., 1991).

#### **Premorbid Functioning**

Schizophrenia is considered to be a neurodevelopmental disorder with early central nervous system lesions affecting normal maturational processes (Akbarian et al., 1993; Fish et al., 1992; McClellan and McCurry, 1998; Weinberger, 1987). Perinatal complications, alterations in brain structure and size, minor physical anomalies, and disruption of fetal neural development, especially during the second trimester of pregnancy, have been correlated with the incidence of adult schizophrenia (McClellan and McCurry, 1998). Infants genetically at risk for schizophrenia may display a neurointegrative defect described as pandysmaturation (Fish et al., 1992). Thus the occurrence of premorbid abnormalities and developmental delays may represent the early neuropathological manifestations of the disorder.

The majority of patients with EOS (with some reports as high as 90 percent) have premorbid abnormalities, especially those with VEOS (Alaghband-Rad et al., 1995; Asarnow and Ben-Meir, 1988; Eggers, 1978; Green and Padron-Gayol, 1986; Hollis, 1995; Kolvin, 1971; McClellan and McCurry, 1998; Watkins et al., 1988; Werry et al., 1991). Most studies have



## AMERICAN ACADEMY OF CHILD AND ADOLESCENT PSYCHIATRY

found a wide range of premorbid difficulties, including social withdrawal and isolation, disruptive behavior disorders, academic difficulties, speech and language problems, and developmental delays. Autism and pervasive developmental disorders also have been reported, although these conditions should be considered distinct and separate from schizophrenia (Cantor et al., 1982; Watkins et al., 1988; AACAP, in press). Hollis (1995) found that youth with EOS had significantly higher rates of premorbid social, motor and language impairments than matched psychiatric controls. Within the schizophrenic group, onset before age 14 years was associated with higher rates of language problems. McClellan and McCurry (1998) found that social withdrawal and aberrant peer relationships, characteristics that equate to negative symptoms, differentiated the premorbid histories of youth with EOS from those with bipolar disorder.

### Symptomatology in Early Onset Schizophrenia

Schizophrenia has generally been characterized as having two broad sets of symptom clusters, positive and negative. Positive symptoms of schizophrenia refer to the more florid hallucinations, delusions, and thought disorder, whereas negative symptoms are those of deficits, i.e., flat affect, anergy, and paucity of speech and thought (APA, 1997). Recent research has suggested that disorganized behavior may represent an independent third dimension, which would include disorganized speech (thought disorder), bizarre behavior and poor attention (APA, 1997). Hallucinations, thought disorder, and flattened affect all have been consistently found in EOS, while systematic delusions and catatonic symptoms may be less frequent (Green et al., 1992; Russell et al., 1989; Werry et al., 1991). Developmental differences in language and cognition may affect the range and quality of symptom presentation (Caplan et al., 1989; Volkmar et al., 1988; Watkins et al., 1988; Werry, 1992). One study found that, in children with schizophrenia and other psychiatric disturbances children, positive symptoms increased linearly with age and were associated with IQs greater than 85, whereas negative symptoms were associated with brain damage (Bettes and Walker, 1987).

Children with schizophrenia also display evidence of formal thought disorder. In comparison to normal children, those with schizophrenia have three characteristic communication deficits, loose associations, illogical thinking, and impaired discourse skills (Caplan et al., 1989; 1994). Rates of incoherence and poverty of speech content are low (Caplan et al., 1989). When assessing a child's thinking, it is important to differentiate the thought disorder of psychosis from developmental delays or language disorders.

### Schizophrenic Subtypes

Different subtypes of schizophrenia are found in both DSM-IV and ICD-10, including paranoid, disorganized (hebephrenic), catatonic, undifferentiated, and residual. In addition, the subtypes simple and postschizophrenic depression are found in the ICD-10, but not in DSM-IV. Reports vary as to whether the paranoid subtype (Eggers, 1978) or the undifferentiated subtype (McClellan et al., 1993; Werry et al., 1991) is more common in EOS. There is not sufficient evidence currently to justify categorizing EOS as a separate diagnostic subcategory (Werry, 1992).

*Cognitive Delays.* At least 10% to 20% of children with EOS have IQ's in the borderline to mentally retarded range (Asarnow and Ben-Meir, 1988; Eggers, 1978; Goldberg et al., 1988;

## AMERICAN ACADEMY OF CHILD AND ADOLESCENT PSYCHIATRY

Green et al., 1992; Kenny et al., 1997; Kolvin, 1971; McClellan et al., 1993; McClellan and McCurry, 1998; Werry et al., 1991). The estimated rates may be low since some studies have excluded patients with mental retardation (Bettes and Walker, 1987; Russell et al., 1989). It is difficult to determine whether intellectual delays are due to the impact of the illness on cognitive testing, since premorbid testing is generally not available. Furthermore, the finding of low IQ may not be specific to EOS, but instead may represent a general risk for psychopathology and psychosis (McClellan and McCurry, 1998). Nevertheless, it is clear that schizophrenia is associated with cognitive deficits that produce functional impairment. Language and communication deficits are common (Baltaxe and Simmons III, 1995; Caplan et al., 1996). Neuropsychological studies suggest that children with schizophrenia have difficulties across tasks that require greater capacity for information-processing, rather than deficits isolated to specific functions or areas of the brain locations (Asarnow et al., 1994). These findings are consistent with those in the adult literature.

### Neurobiologic Deficits

Neurobiologic abnormalities in youth (primarily adolescents) with VEOS are being examined in an ongoing study at the National Institutes of Mental Health (NIMH). Similar to the adult literature, noted findings include deficits in smooth pursuit eye movements, autonomic responsivity, and neuroimaging findings (Frazier et al., 1996; Gordon et al., 1994; Jacobsen et al., 1997; Jacobsen and Rapoport, 1998; Zahn et al., 1997). A progressive increase in ventricular size was seen in these subjects over a two-year period (Rapoport et al., 1997). In comparison to normal controls, youth with VEOS had a four-fold greater decrease in cortical gray matter volume during adolescence, with the greatest differences occurring in the frontal and temporal regions (Rapoport et al., 1999). Smaller total cerebral volumes were correlated with negative symptoms (Alaghband-Rad et al., 1997). Others have also reported frontal lobe dysfunction (Thomas et al., 1998), consistent with the adult literature. These findings are important for understanding the underlying neurobiologic mechanisms of the disorder. However, none are diagnostic. The primary role for laboratory evaluations and neuroimaging techniques in the standard assessment of EOS is for ruling out other medical disorders.

### Psychological and Social Factors

There is no evidence that psychological or social factors cause schizophrenia. Rather, environmental factors may potentially interact with biologic risk factors to mediate the timing of onset, course and severity of the disorder. Psychosocial stressors, including expressed emotion within the family setting, influence the onset and/or exacerbation of acute episodes, and relapse rates (APA, 1997). Communication deficits are often found in families of children with VEOS, although these are probably genetic traits rather than etiological agents (Asarnow et al., 1988). The interactions between psychological, social and illness related factors are complex and bi-directional. For example, the presence of difficult family interactions may not be “causal”, but rather a reaction to the collection of difficulties the patient brings to the family setting.

It is not possible to say whether there is any relationship to socioeconomic status. The available studies have a selection bias toward inpatient samples, with higher rates of low socioeconomic status found in some studies (Green et al., 1992; Kolvin, 1971; McClellan et al., 1993), but not in others (Russell et al., 1989; Werry et al., 1991).

## AMERICAN ACADEMY OF CHILD AND ADOLESCENT PSYCHIATRY

### Familial Patterns

An increased family history of schizophrenia and schizophrenia spectrum disorders (e.g., schizotypal or paranoid personality disorders) has been found in patients with EOS (Eggers, 1978; Green et al., 1992; Kolvin, 1971; McClellan et al., 1993; McClellan and McCurry, 1998; Nicholson and Rapoport, 1999; Werry et al., 1991). However, these findings are limited by small sample size and by methodological limitations in the ascertainment and assignment of diagnoses in relatives (Werry, 1992). An increased family history of affective disorders, primarily depression, also has been reported (Eggers, 1978; Werry et al., 1991). While this may represent a true familial association, it also highlights the potential diagnostic confusion between EOS and bipolar disorder.

### Course and Outcome

Schizophrenia is a phasic disorder, with a great deal of individual variability (Werry and Taylor, 1994). It is important that clinicians recognize the various phases of the illness when making diagnostic and therapeutic decisions. The phases include:

*Prodrome.* Most patients experience some degree of functional deterioration prior to the onset of psychotic symptoms, including: social withdrawal and isolation; idiosyncratic or bizarre preoccupations, unusual behaviors; academic failure; deteriorating self-care skills, dysphoria, anxiety symptoms or physical complaints such as alterations in sleep or appetite. These changes may be associated with aggressive behaviors or other conduct problems, including substance abuse, which often confuse the diagnostic picture.

The prodromal phase may vary from an acute change (days to weeks) to chronic impairment (months to years) (Werry and Taylor, 1994). The symptoms may represent a marked change from baseline functioning, or alternatively, a worsening of premorbid personality/behavioral characteristics. Since many youth with EOS have an insidious onset, it is often difficult to distinguish between premorbid personality/cognitive abnormalities and the onset of the disorder.

*Acute Phase.* The acute phase is marked by a predominance of positive symptoms (i.e., hallucinations, delusions, disorganized speech and behavior), as well as a significant deterioration in functioning. This phase generally lasts one to six months, or longer depending in part on the response to treatment (Werry and Taylor, 1994). Remschmidt et al., (1991) found that symptoms tended to shift from positive to negative over time.

*Recuperative/Recovery Phase.* There is generally a several month period following the acute phase where the patient continues to experience a significant degree of impairment (Werry and Taylor, 1994). This is primarily due to negative symptoms (flat affect, anergia, social withdrawal), although some positive symptoms may persist (Remschmidt et al., 1991). In addition, some patients will develop a post-schizophrenic depression characterized by dysphoria and flat affect.

*Residual Phase.* Youth with EOS may have prolonged periods (several months or more) between acute phases where they do not experience significant positive symptoms. However, most patients will continue to be at least somewhat impaired due to negative symptoms.

*Chronically Ill Patients.* Some patients will remain chronically symptomatic, despite adequate treatment, over many years (Asarnow et al., 1994; Eggers, 1997; Maziade et al., 1996b;

## AMERICAN ACADEMY OF CHILD AND ADOLESCENT PSYCHIATRY

McClellan et al., 1993; Werry et al., 1991). These patients are generally the most severely impaired and require the most comprehensive treatment resources. The advent of the atypical antipsychotic agents offers some promise for these individuals, since clozapine has been effective for treatment refractory schizophrenia (Meltzer et al., 1994).

Schizophrenia classically follows a pattern characterized by cycles of the above phases, with increasing deterioration after each cycle. However, after approximately ten years, the acute phases of the disorder tend to remit, leaving a residual state (predominately negative symptoms) with varying disability (Werry and Taylor, 1994). Further research is needed to clarify whether this long-term pattern holds for EOS. Some youth with schizophrenia may only have one cycle, although most have more (Asarnow et al., 1994; Eggers, 1978; McClellan et al., 1993; Werry et al., 1991). Recovery is incomplete in approximately 80 percent of cases where youth have had more than one episode (Werry and Taylor, 1994).

There are few studies examining the longitudinal course and outcome of EOS. Most are retrospective, and none factor out the influence of treatment. Furthermore, outcome studies may be influenced by diagnostic errors, since bipolar disorder historically was frequently misdiagnosed as schizophrenia (Werry et al., 1991). Finally, ratings of outcome will vary dependent on the phase of the illness during which the assessment occurs.

Premorbid characteristics, treatment response, and adequacy of therapeutic resources invariably influence short-term outcome. Renschmidt et al., (1991) found that only 14 percent of 113 adolescents and young adults with schizophrenia (mean age  $18.3 \pm 3$  years) had a complete remission of symptoms during the index hospitalization. In the same report, the authors described the one year course of 64 individuals with schizophrenia (ages 12 - 22 years) that were enrolled in a special rehabilitation program. Over the follow-up period, significant improvement was noted in symptomatology and cognitive functioning, with higher levels of cognitive abilities and premorbid functioning predicting a better outcome.

Studies that examine outcome over approximately a five year period have varied somewhat in their findings. In two retrospective studies of youth with primarily adolescent onset schizophrenia (McClellan et al., 1993; Werry et al., 1991) the majority of subjects displayed moderate to severe impairment at outcome. Eighty to ninety percent had two or more episodes during the follow-up period, while only a few had a complete remission. Outcome was best predicted by premorbid and intellectual functioning (Werry et al., 1992). In contrast, Asarnow et al., (1994) followed 18 children with EOS over a two to seven year period. In their sample, 10 subjects showed substantial improvement over the follow-up period, including 4 children that had a complete remission of symptoms. The children in this study received extensive treatment, which may have influenced the findings.

Two studies have examined the long-term outcome of EOS. Maziade et al., (1996a, 1996b) followed up on 40 subjects (mean follow-up period 14.8 years, mean age of onset 14.0 years). Only two subjects had a complete recovery, while the majority (74%) were moderately to severely impaired. Outcome was best predicted by premorbid functioning, and the severity of positive and negative symptoms during acute episodes (Maziade et al., 1996a).

Eggers (1978; 1989) followed 57 patients with childhood schizophrenia (onset between 7 and 13 years of age) over a mean follow-up period of 16 years. At outcome, 28 percent had schizo affective disorder (ICD-9 diagnosis) (Eggers, 1989). Overall, 50 percent of the sample were significantly impaired at outcome, 30% had good to satisfying social adaptation, and 20%

## AMERICAN ACADEMY OF CHILD AND ADOLESCENT PSYCHIATRY

had a complete remission (Eggers, 1979). Those with schizo affective disorder (which may include the DSM-IV diagnosis of bipolar disorder) had a more favorable course (Eggers, 1989). They also tended to have less premorbid difficulties, which was also a significant prognostic factor. Onset before age 10 ( $n = 11$ ) was uniformly associated with a poor outcome. The investigators then followed up on a subset of this cohort (44 subjects) after a mean period of 42 years (Eggers and Bunk, 1997). The outcome ratings were similar: 25% had complete remission; 25% partial remission, and 50 % had chronic impairment. An insidious onset (over more than a four week period) and an age of onset before age 12 years were both associated with greater disability at outcome.

Overall, these findings are consistent with the adult literature. Few studies have compared early-onset to adult-onset schizophrenia. Yang et al., (1995) found that onset before 15 years of age was associated with higher ratings of negative symptoms in adulthood, while Hafner and Nowotny (1995) reported greater social impairment in patients with onset before age 21 years. These two studies support the clinical observations that EOS may have a more insidious and chronic course, with less favorable outcome.

### Mortality

The risk of suicide or accidental death directly due to behaviors caused by psychotic thinking appears to be at least 5% (Eggers, 1978; Werry et al., 1991), although the numbers studied are small and the follow-up periods short in some subjects. In adults with schizophrenia, there is an increased risk for medical illnesses and mortality, including a suicide rate of approximately 10 percent (APA, 1997).

### ASSESSMENT

A diagnosis of schizophrenia is made in youth when DSM-IV (or ICD-10) criteria are met, and other pertinent disorders have been ruled out. Standard psychiatric assessment principles and procedures should be followed (AACAP, 1997b), including an interview with the child, family and a review of past records and historical information. It is important to establish the duration, type, number, and combinations of symptoms required for diagnosis, as well as elucidate the pattern of symptom development and the course of illness. Structured interviews, symptom scales, and diagnostic decision trees (including one in the *DSM* manual) may serve as important aids to ensure reliability and veracity of diagnosis (Werry and Taylor, 1994). Other techniques, such as laboratory evaluations and neuroimaging techniques, are used mostly to rule out other disorders, such as organic psychoses. Neuropsychological tests are primarily helpful for the assessment of functioning and associated cognitive deficits, directing rehabilitative efforts and qualifying the individual for supportive services.

Some clinicians are hesitant to make a diagnosis of schizophrenia, even when there is sufficient evidence to do so, because of its ominous prognosis and social stigma. This potentially denies the child or adolescent and the family access to appropriate treatment, knowledge about the disorder, and support services. Therefore, the diagnosis should be made when the diagnostic criteria are met and other illnesses have been adequately ruled out. However, studies examining the longitudinal course of early onset psychotic disorders have noted that misdiagnosis is a common problem, especially at the time of onset (Carlson, 1990; McClellan et al., 1993; McClellan and McCurry, 1998; Werry et al., 1991). Therefore, the

## AMERICAN ACADEMY OF CHILD AND ADOLESCENT PSYCHIATRY

patient must be followed longitudinally, with periodic diagnostic reassessments, to ensure accuracy. Patients and families should be educated about these diagnostic issues.

### DIAGNOSTIC ISSUES

Although the same diagnostic criteria are used as for adults, there are certain clinical features in children and adolescents that create dilemmas (McClellan, 2000). Misdiagnosis of schizophrenia in youth is a significant problem. A substantial number of youth first diagnosed with schizophrenia have other disorders at outcome, including bipolar disorder (Werry et al., 1991) and personality disorders (Thomsen, 1996). Moreover, the majority of youth 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 (McKenna et al., 1994). Thus, while early onset schizophrenia appears to be continuous with the adult form of the disorder (Jacobsen and Rapoport, 1998; Werry, 1992), the accuracy of the diagnosis in clinical settings remains a concern.

There are several factors that potentially lead to misdiagnosis. First, the rarity of the disorder results in a lack of familiarity with its clinical presentation. Second, there is a significant overlap between presenting symptoms of schizophrenia and psychotic mood disorders, especially at the time of onset (AACAP, 1997A). Third, most children that report hallucinations are not schizophrenic and many do not have psychotic disorders (Del Beccaro et al., 1988; Garralda, 1984a, b; Walters and McClellan, 1998). Moreover, distinguishing between the formal thought disorder of schizophrenia and that of developmental disorders (including speech and language disorders) can be difficult (Caplan and Tanguay, 1991). Although most youth with EOS have significant premorbid developmental and/or personality abnormalities, the presence of these characteristics is neither necessary nor sufficient to make the diagnosis. The vast majority of odd, developmentally delayed or language impaired children will not develop schizophrenia.

Psychotic features such as hallucinations and delusions are required to make the diagnosis. The emergence of these symptoms usually results in a marked change in both the child or adolescent's mental status and his or her level of functioning (even in a severely developmentally disabled child with absent or impaired language). True psychotic symptoms must be differentiated from children's reports of psychotic-like phenomena due to idiosyncratic thinking and perceptions caused by developmental delays, exposure to traumatic events, and/or overactive imaginations.

Clinician's biases may unwittingly influence diagnostic decision-making. For example, one study found that, in hospitalized adolescents, African-American youth were less likely to receive mood, anxiety or substance abuse diagnoses, but were more likely to be characterized as having either an organic or psychotic condition (Kilgus et al., 1995). Similarly, cultural or religious beliefs may be misinterpreted as possible psychotic symptoms when taken out of context. Cultural, developmental, and intellectual factors all need to be taken in account in the diagnostic assessment.

Another issue is that patients often first present when they are acutely psychotic, and may have not yet had symptoms that meet the 6 month duration criterion. A tentative diagnosis must then be confirmed longitudinally. Some cases remit before 6 months, making it unclear whether they will eventually turn out to have schizophrenia. Furthermore, if the symptoms resolve with

## AMERICAN ACADEMY OF CHILD AND ADOLESCENT PSYCHIATRY

antipsychotic medications, the improvement may be due to either the treatment or to spontaneous remission. However, it is unusual for recovery in schizophrenia to be complete within 6 months, as negative symptoms such as lack of social interest or amotivation usually persist.

### DIFFERENTIAL DIAGNOSIS

When assessing a child or adolescent with symptoms suggestive of schizophrenia, a thorough diagnostic evaluation is needed to rule-out other conditions that present with similar symptomatology. While a detailed discussion of all possible disorders that may mimic schizophrenia is not possible here, we will briefly elaborate on those that are most important to consider. A thorough review of presenting symptoms, course and premorbid functioning, adherence to *DSM-IV* criteria, familiarity with how psychotic symptoms present in this age group, and determination of family psychiatric history will all help improve the accuracy of diagnosis. However, discriminating among these various disorders still may be difficult, especially at the initial presentation, and periodic diagnostic reassessments are always indicated (Werry and Taylor, 1994).

### Mood Disorders

Both schizophrenia and psychotic mood disorders (especially bipolar disorder) typically present with a variety of affective and psychotic symptoms (Carlson, 1990; Joyce, 1984; McClellan et al., 1993; Werry et al., 1991). In children and adolescents with schizophrenia, negative symptoms may be mistaken for depression, especially since it is common for patients to experience dysphoria with their illness. Alternatively, mania in teenagers often presents with florid psychosis, including hallucinations, delusions and thought disorder (AACAP, 1997A). Psychotic depression may present with mood congruent or incongruent psychotic features, either hallucinations or delusions (AACAP, 1998a).

This overlap in symptoms increases the likelihood of misdiagnosis at the time of onset. Historically, approximately one-half of adolescents with bipolar disorder may be originally misdiagnosed as having schizophrenia (AACAP, 1997A). Awareness of the phenomena may now be leading to high rates of misdiagnosis in both directions (McClellan et al., 1993; McClellan and McCurry, 1999). Longitudinal reassessment is needed to ensure accuracy of diagnosis. Family psychiatric history may also be a helpful differentiating factor, although studies have found an increased family history of depression in schizophrenic youth (Werry, 1992).

### General Medical Conditions

All children and adolescents with psychotic symptoms should receive a thorough pediatric and neurological evaluation. The possibility of an organic psychosis needs to be considered when obtaining the history, completing the physical examination, and selecting initial laboratory investigations. Although the list of potential organic etiological agents, or associated neuropsychiatric conditions, is exhaustive, entities that should be considered include: (1) delirium; (2) seizure disorders; (3) central nervous system lesions (e.g., brain tumors, congenital malformations, head trauma); (4) neurodegenerative disorders (e.g., Huntington's chorea, lipid storage disorders); (5) metabolic disorders (e.g., endocrinopathies, Wilson's disease); (6) developmental disorders, such as velocardiofacial syndrome (Usiskin et al., 1999); (7) toxic

## AMERICAN ACADEMY OF CHILD AND ADOLESCENT PSYCHIATRY

encephalopathies (e.g., substances of abuse such as amphetamines, cocaine, hallucinogens, phencyclidine, alcohol, marijuana, and solvents; medications such as stimulants, corticosteroids, or anticholinergic agents; and other toxins such as heavy metals); and (8) infectious diseases (e.g., encephalitis, meningitis, and/or human immunodeficiency virus-related syndromes).

Laboratory and neuroimaging procedures are not helpful for making a diagnosis of schizophrenia, but instead are used to rule out other neurological or medical problems. Tests and procedures should be justified based on the clinical presentation, and significant findings in either the history or physical examination. As part of the basic medical evaluation, laboratory tests to be considered include: blood counts, serum chemistries, thyroid functions, urinalysis and toxicology screens. If the risk factors are present, testing for HIV should be done. Chromosomal analysis may be indicated for patients with clinical presentations/features suggestive of a developmental syndrome. Evidence of neurological dysfunction warrants a more thorough evaluation, including consideration of neuroimaging studies, electroencephalogram (EEG) and/or a neurology consultation.

Given the significant rates of comorbid substance abuse in adolescents with schizophrenia (as high as 50% comorbidity in some studies), it is common for a history of substance abuse to be obtained at the first onset of psychotic symptoms (McClellan et al., 1993; McClellan and McCurry, 1998b). If the psychotic symptoms persist for longer than a week despite documented detoxification from the abused substance(s), the clinician must consider the diagnosis of a primary psychotic disorder, rather than an organic psychosis due to the substance(s) of abuse. In adolescents, it is not uncommon for the first psychotic break to occur with comorbid substance abuse, which acts as an exacerbating (and possibly a triggering) factor rather than a primary etiological agent (Eisner and McClellan, 1998).

### Nonpsychotic Behavioral and/or Emotional Disorders

Youth with conduct and other nonpsychotic emotional disorders may report psychotic-like symptoms, and thus be improperly diagnosed as having a primary psychotic disorder (Del Beccaro et al., 1988; Garralda, 1984a,b; Hornstein and Putnam, 1992; McClellan et al., 1993; McClellan and McCurry, 1999; Walters and McClellan, 1998). When compared to psychotic children, these youth have lower rates of negative symptoms, bizarre behavior and thought disorder (Garralda, 1985; McClellan and McCurry, 1999). At follow-up, an increase in personality dysfunction, including personality disorders, but not psychotic disorders, has been found (Garralda, 1984a,b; Lofgren et al., 1991; McClellan et al., 1993; Thomsen, 1996). Thomsen (1996) studied all youth hospitalized in Denmark from 1970 to 1993 with a diagnosis of schizophrenia, using a national registry. Of those followed over at least a 10 year period (n = 209), only 64 percent still had a diagnosis of schizophrenia. Twenty-one percent had personality disorders, primarily antisocial or borderline.

Children that report psychotic-like phenomena also may have problems with tumultuous relationships, behavioral and affective dysregulation, and are described as having borderline characteristics. At follow-up, so called "borderline" children do not seem to have an increased risk for either schizophrenia or affective disorders, when compared to other mentally ill children (Lofgren et al., 1991). Similarly, maltreated children, especially those with posttraumatic stress disorder (PTSD), report significantly higher rates of psychotic symptoms than controls (Famularo et al., 1992). In these cases, reports of psychotic-like symptoms may actually



## AMERICAN ACADEMY OF CHILD AND ADOLESCENT PSYCHIATRY

represent dissociative and/or anxiety phenomena, including intrusive thoughts/worries, derealization, or depersonalization (Altman et al., 1997; Hornstein and Putnam, 1992; McClellan and McCurry, 1999). The lack of observable psychotic phenomena, such as formal thought disorder, plus the characteristics of their relationship skills (the chaotic nature of borderline relationships versus the socially isolated and awkward relationships of the schizophrenic child) help distinguish such children from those with schizophrenia. However, since youth with schizophrenia may also have suffered child maltreatment, the diagnosis should not be ruled out based on a history of abuse (McClellan and McCurry, 1999).

### Schizoaffective Disorder

Early-onset schizoaffective disorder has not been well defined in this age group. Follow-up studies of psychotic youth have found low rates of this condition (McClellan et al., 1993; Werry et al., 1991). Using DSM-IV criteria, youth diagnosed with schizoaffective disorder may have an particularly pernicious form of illness since the diagnosis requires meeting criteria for both mood disorders and schizophrenia (McClellan et al., submitted). Alternatively, Eggers (1989) found that 28% of his EOS sample at follow-up had schizoaffective psychoses. Subjects with this diagnosis fared better at outcome. However, this is an *ICD-9* diagnosis, and may include some subjects that would be diagnosed with bipolar disorder using *DSM-IV* (APA, 1994).

### Pervasive Developmental Disorders/Autism

Autism and pervasive developmental disorders are distinguished by the absence or transitory nature of psychotic symptoms, i.e., hallucinations and delusions, and by the predominance of the characteristic deviant language patterns, aberrant social relatedness, and other key symptoms that characterize these disorders (Green et al., 1984; Kolvin, 1971; Volkmar et al., 1988; Volkmar and Cohen, 1991). The earlier age of onset and the absence of a normal period of development are also indicative, although some schizophrenic children have a lifelong history of developmental delays (Watkins et al., 1988). However, compared to pervasive developmental disorders, the premorbid abnormalities in EOS tend to be less pervasive and severe. Early central nervous system developmental abnormalities have been associated with both schizophrenia and autism (Akbarian et al., 1993; Fish et al., 1992; Kemper and Bauman, 1993; Weinberger, 1987). Therefore, it is possible that both illnesses may occasionally coexist, linked by a common defect that occurred early in brain development. However, if this occurs, the onset of schizophrenia will still be later than that of autism, generally after 5 years of age.

Childhood disintegrative disorder resembles autism except that the onset occurs after two or more years of normal development. Children with Asperger's Disorder lack the marked language disturbances associated with autism, but present with deficits in social relatedness and contextual communication (especially with social cues) and a restricted (and possibly bizarre) range of interests. The lack of overt hallucinations and delusions distinguishes both of these conditions from schizophrenia (Volkmar, 1999).

### Obsessive-Compulsive Disorder

Children with obsessive-compulsive disorder suffer from intrusive thoughts and repetitive ritualistic behaviors, symptoms that may be difficult to differentiate from psychosis

## AMERICAN ACADEMY OF CHILD AND ADOLESCENT PSYCHIATRY

(e.g., the fear of being contaminated may be either an obsessive symptom or a paranoid delusion). Patients with obsessive-compulsive disorder generally recognize their symptoms as being unreasonable and excessive products of their own thinking (although this may not be the case for young children) (AACAP, 1998b). Conversely, psychotic symptoms are usually experienced as phenomena occurring independently of the patient's own cognitive processes. However, some obsessive-compulsive disorder symptoms are so severe that distinguishing them from delusions is difficult. Conversely, patients with schizophrenia may have significant obsessive-compulsive features.

### Developmental Language Disorders

Children with developmental speech and language disorders may be mistakenly diagnosed as being thought disordered. Such children do not, however, have other prerequisite schizophrenic symptoms, such as hallucinations, delusions, or odd social relatedness (Baker and Cantwell, 1991).

### Other Disorders

Other disorders that need to be differentiated from schizophrenia include schizotypal disorders, schizoid personality disorder, and other psychotic disorders (e.g., delusional disorders and schizophreniform disorder). Finally, 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 (Fish and Ritvo, 1979; Kumra et al., 1998; Towbin et al., 1993). Kumra et al., (1998) has characterized a group of children with deficits in attention, impulse control, affect regulation, and transient or subclinical psychotic symptoms as “multidimensionally impaired.” Such research highlights that fact that there are a number of children with complicated patterns of psychopathology that are not well described by our current diagnostic nosology. Whether such youth are at future risk for schizophrenia (or other disorders), or represent a distinct diagnostic entity themselves, requires further study.

## TREATMENT

The treatment of schizophrenia in children and adolescents requires therapies that are both *specific*—which are aimed at the characteristic symptomatology (positive and negative) constituting the disorder; and *general*—which relate to the psychological, social, educational, and cultural needs of the child and family as a result of or affecting the management of the disorder. Most youth with EOS will need multiple interventions to address the symptoms of the disorder, plus any other comorbid conditions (e.g., substance abuse), current or past biopsychosocial stressors, and psychological, social, and developmental sequelae associated with the illness (McClellan, in press). This comprehensive multimodal approach is the most effective way of reducing symptomatology, morbidity and relapse rates while maintaining the patient in their home and community.

Interventions may vary depending on the individual characteristics of the patient and the different stages of the disorder. An array of therapeutic services is needed, including comprehensive outpatient and community programs, with psychopharmacologic,

## AMERICAN ACADEMY OF CHILD AND ADOLESCENT PSYCHIATRY

psychotherapeutic, psychoeducational and case management services; family support, vocational, and rehabilitative assistance; specialized educational programs; inpatient/day patient psychiatric units with developmentally appropriate psychiatric, neurological, and medical services; and in some cases longer term residential programs.

There is a large body of research available in the adult literature on the treatment of schizophrenia. Unfortunately, only a few studies have been done examining interventions for EOS. However, since differences between early-onset and adult schizophrenia seem at most to be only quantitative and developmental (Beitchman, 1985; Werry, 1992), it is reasonable to assume that they are the same disorder (or more likely, the same group of disorders), and that research on treatment of adults should form the knowledge base for the treatment of early-onset cases. Clinicians must be aware of the limited research base, and be prepared to make clinical adjustments in care as appropriate given the developmental needs of their patients.

### PSYCHOPHARMACOLOGY

The efficacy of antipsychotic medications for the treatment for schizophrenia has been well established in adults (APA, 1997). These agents reduce psychotic symptoms, help prevent relapse, and improve overall long-term functioning. At this time, there are only a few randomized controlled trials examining their efficacy or safety in youth with EOS. The available studies and case reports, plus clinical experience, suggest that the pattern of response in youth is similar to that in adults. However, since treatment resistance to neuroleptics in adults with schizophrenia is associated with an earlier age of onset (Meltzer et al., 1997), youth with EOS may be less likely to respond adequately to medication therapy.

All but one of the available randomized controlled trials of antipsychotic medication in youth have examined traditional neuroleptics. Haloperidol (0.02 to 0.12 mg/kg) was found to be superior to placebo in reducing symptoms of thought disorder, hallucinations, and persecutory ideation in children with schizophrenia (Spencer et al., 1992). Loxitane and haloperidol were found to be superior to placebo, but did not differ from one another, in a study of 75 adolescents with schizophrenia (Pool et al., 1976). In a study that did not include a placebo control, both thiothixene and thioridazine improved psychotic symptoms in about 50% of youth (n = 21) diagnosed with chronic schizophrenia (Realmuto et al., 1984). Youth appear to have the same spectrum of side-effects noted in adults, e.g., extrapyramidal symptoms, sedation, tardive dyskinesia and neuroleptic malignant syndrome (Cambell et al., 1999; Earnst et al., 1998). However, the long-term use of neuroleptics in EOS has not been studied.

The advent of the novel antipsychotic agents, including clozapine, risperidone, olanzapine, and quetiapine, has been a major advance in the pharmacotherapy of schizophrenia. These agents are considered atypical since their antipsychotic properties stem, at least in part, from being serotonergic antagonists. Traditional neuroleptics are all dopamine antagonists (specifically D<sub>2</sub>) which is the mechanism responsible for their antipsychotic properties and characteristic side-effect profile that includes extrapyramidal symptoms (Ernst et al., 1998). The atypical agents effect a number of neurotransmitter systems, including both antidopaminergic and antiserotonergic activity.

In the adult literature, in comparison to traditional neuroleptics, the atypical agents are at least as effective for positive symptoms, and possibly more effective for negative symptoms (Meltzer et al., 1994). Clozapine has the best documented efficacy for treatment resistant

## AMERICAN ACADEMY OF CHILD AND ADOLESCENT PSYCHIATRY

schizophrenia, although further study is needed to determine its superiority over the newer atypical agents. Unfortunately, serious side-effects, including the potential for neutropenia and seizures, limit the use of clozapine. The other atypical antipsychotics are generally favored over traditional neuroleptics due to a lower risk for extrapyramidal symptoms. However, their potential for other serious side-effects, especially weight gain, is a significant clinical issue. Furthermore, they have not been in use long enough to provide sufficient clinical experience in regards to their long-term effectiveness and safety.

There are few studies examining the use of atypical neuroleptics in youth. In the NIMH study of youth with childhood onset schizophrenia ( $n = 21$ ), clozapine (mean final dose  $176 \pm 149$  mg/day) was superior to haloperidol ( $16 \pm 8$  mg/day) (Kumra et al., 1996). Both positive and negative symptoms improved. However, while on clozapine, five youth developed significant neutropenia and two had seizures. Therefore, although potentially more efficacious, clozapine's apparent increased risk for adverse reactions in youth raises concerns.

The other atypical agents have not been systematically studied with this age group (Toren et al., 1998). In an open label study of olanzapine for eight youths with treatment resistant childhood onset schizophrenia, Kumra and colleagues (1998) found that two subjects responded, and one partially responded, after an eight-week trial. There are other case reports and retrospective reviews describing positive responses for olanzapine (Mandoki, 1997), and risperidone (Armenteros et al., 1997; Grcevich et al., 1996; Lykes and Cueva, 1996; Quintana and Keshavan, 1995; Simeon et al., 1995). In addition quetiapine was noted to be safe and effective in an open label study treating 10 youth with either schizoaffective or bipolar disorder (McConville et al., 1999). There are also single case reports describing quetiapine's efficacy in a 14 year old boy with schizophrenia (Szigethy et al., 1998), and a 15 year old girl with an acute psychotic episode (Healy et al., 1999).

Systematic studies are needed to establish the efficacy and safety of atypical antipsychotic medications in juveniles. There has not yet been enough experience or research to describe all potential adverse effects in youth, especially with long-term usage. However, based on the adult literature, plus clinical experience, the use of these agents is justified for the treatment of EOS. Many clinicians use atypical agents, with the exception of clozapine, as the first drugs of choice, based on the noted efficacy and side-effect profile in the adult literature.

Other medications with some reported efficacy for schizophrenia in adults include lithium, benzodiazepines, and anticonvulsants (APA, 1997). However, the evidence supporting the antipsychotic activity of these agents is limited, and their use in youth with schizophrenia has not been studied.

### Procedures For Use Of Medication

Treatment varies dependent on the phase of the illness and the patient's history of medication response and side-effects. General guidelines for the psychopharmacologic management of schizophrenia include:

*Baseline assessment.* Prior to initiating a medication trial, a thorough psychiatric and medical evaluation is needed. The targeted psychotic symptoms should be adequately documented. In the physical examination, any pre-existing abnormal movements should be documented to avoid later mislabeling them as medication side-effects. Baseline and follow-up laboratory tests, including renal and liver functions, blood counts, and electrocardiograms, may

## AMERICAN ACADEMY OF CHILD AND ADOLESCENT PSYCHIATRY

be indicated for specific antipsychotic agents.

*Medication choice.* In the adult literature, clozapine is the only antipsychotic agent with clearly documented superiority for treatment refractory schizophrenia. Further research comparing the atypical agents to traditional agents, and to each other, is needed. It has been suggested that the atypical agents are more efficacious for negative symptoms. Otherwise, besides clozapine, antipsychotic agents appear equal in their antipsychotic effects. Therefore, the choice of medication should be made based on the agent's relative potency, potential side-effects and the patient's history of medication response. Individual responses to different antipsychotics are variable, and if insufficient effects are evident after a 6-week trial using adequate dosages, a different antipsychotic agent should be tried. Clozapine, given its side-effect profile, is generally only used after a patient has either failed to respond to at least two therapeutic trials of other antipsychotic agents (at least one of which is an atypical antipsychotic) and/or developed significant side-effects (including tardive dyskinesia).

Depot antipsychotics have not been studied in pediatric age groups and have inherent risks with long-term exposure to neuroleptic side-effects. Therefore, they should only be considered in schizophrenic adolescents with documented chronic psychotic symptoms and a history of poor medication compliance. Depot agents are not recommended for children with VEOS.

*Informed consent.* Informed consent (which addresses the rationale for treatment and potential risks and benefits of the therapy) should be obtained from both the youth and the parents/guardians. If the psychotic state or developmental level of the patient precludes this, or if therapy is refused, invoking the relevant statutory mechanisms for involuntary treatment may become necessary. For patients under the legal age of consent, basic information regarding treatment should be provided in a developmentally appropriate manner.

Medication strategies vary somewhat depending on the stage of the illness, as outlined below:

*Acute phase.* Antipsychotic therapy should be implemented for a period of no less than 4 to 6 weeks, using adequate dosages, before efficacy of the medication choice is determined. Any immediate effects of the medication are more likely due to sedation, with the antipsychotic effects becoming more apparent after the first week or two. Instituting large dosages during the early part of treatment generally does not hasten recovery, and more often results in unnecessarily excessive doses and side-effects. For acutely psychotic and agitated patients, the short-term use of benzodiazepines as adjuncts to neuroleptics may help to stabilize the clinical situation. If no results are apparent after 4 - 6 weeks, or if side-effects are not manageable, a trial of a different antipsychotic should then be undertaken (APA, 1997).

*Recuperative phase.* This generally occurs after 4 - 12 weeks provided the acute phase can be controlled. As positive symptoms improve, the patient may have persistent confusion, disorganization, and dysphoria. During this period antipsychotic medication should be maintained since additional improvement may be noted over the 6 to 12 months following the acute presentation. Attempts to gradually lower the dosage may be indicated to decrease side-effects, including exacerbation of negative symptoms. This is especially true if high dosages were needed to control the acute psychotic phase. However, any lowering of the antipsychotic dose must be carefully monitored to avoid relapse.

*Recovery/residual phase.* In this phase, antipsychotic therapy has well-documented

## AMERICAN ACADEMY OF CHILD AND ADOLESCENT PSYCHIATRY

efficacy in preventing relapse. Approximately 65% of adult patients on placebo will have a relapse within 1 year of their acute psychotic phase, compared to 30% on neuroleptics (APA, 1997). Over 5 years, approximately 80 percent of adult patients have at least one relapse (Robinson et al., 1999). This risk is decreased with maintenance drug treatment. Therefore, most patients with schizophrenia need long-term antipsychotic medication therapy. Since a small percentage of patients do not relapse, a medication-free trial may be considered in newly diagnosed patients that have been symptom-free for at least 6 - 12 months. However, any evidence of the disorder warrants ongoing treatment. The medication dosage should be periodically reassessed to ensure that the lowest effective dose is being used. Many clinicians will wait one to six months between medication adjustments, unless the presence of worsening symptoms or adverse effects warrants more immediate action. Physician contact, however, should be maintained on a much more frequent basis (at least monthly) in order to adequately monitor symptom course, side-effects, and compliance, while also directing any necessary psychosocial interventions.

*Non-responders to antipsychotics.* A significant minority of patients with schizophrenia do not respond adequately to traditional neuroleptics. The atypical agents may be more effective for treatment resistant cases, although at this time clozapine is the only antipsychotic for which there is sufficient research to document its superiority in efficacy (Meltzer et al., 1994). Given clozapine's potential side-effects, it is generally only used in cases where patients have failed to respond (or have had significant side-effects) to two or more adequate trials of different antipsychotic agents, including at least one atypical agent.

A medication free trial may be indicated for some treatment resistant cases in order to reassess the diagnosis, or to assess whether adverse effects of the antipsychotic medication is confounding the clinical presentation. In one study, 23 percent of subjects with VEOS (n = 31) were found to have a diagnosis other than schizophrenia during a 4-week medication free period (Kumra et al., 1999). The other diagnoses included personality disorders, posttraumatic stress disorder, or atypical psychotic presentations in youth with multidimensional impairments. Medication-free trials will often need to be done in inpatient settings given the possibility of significant clinical deterioration.

### Medication Management and Side-effects

Clinical monitoring of both efficacy and side-effects is a necessary component of antipsychotic therapy that varies with the stages of the disorder. During the acute psychotic phase, either frequent outpatient visits, or often hospitalization is needed to address the degree of psychosis, as well as potential danger to self and/or others. Once the patient is stabilized, the monitoring should first occur at least weekly to help establish rapport and ensure compliance, with the frequency then decreasing as clinically indicated. Integrating the medication follow-up with ongoing psychosocial therapies helps to increase compliance and decrease relapse rates (see below).

It is important to carefully monitor for side-effects when prescribing antipsychotic agents. This is particularly important in youth since these agents have not been well studied in this population. Children and adolescents may have significant side-effects that are yet unrecognized, and may also have greater difficulties communicating their concerns given

## AMERICAN ACADEMY OF CHILD AND ADOLESCENT PSYCHIATRY

developmental issues. Antipsychotic medications produce a wide array of untoward effects, some of which may be serious and/or long-lasting. Side-effects are also a common reason for medication noncompliance, which increases the risk for relapse and greater morbidity. A complete review of all side-effects associated with antipsychotic medications is beyond the scope of this text. For a more detailed review, see Ernst et al., 1998.

*Conventional neuroleptics.* The side effect profile of an antipsychotic agent generally relates to its effects on different neurotransmitter receptors. For the traditional antipsychotics, potency refers to the degree of dopamine receptor blockade. High-potency agents (e.g., haloperidol) tend to produce extrapyramidal symptoms, whereas low-potency agents (e.g., thioridazine and chlorpromazine) have more anticholinergic side-effects, including sedation and potential deficits in memory. Important types of side-effects to be aware of include:

### 1) Neurologic

a) Acute Extrapyramidal Side-effects: Acute extrapyramidal side-effects often occur during the initial phases of treatment. Children and adolescents may be at higher risk for EPS than adults. Types of EPS include:

- i) Dystonia: A dystonic reaction involves the sudden spastic contraction of distinct muscle groups, often in the neck, eyes (oculogyric crisis) or torso (APA, 1997). Risk factors include young age, male gender, and the use of high potency agents. Dystonias are often quite distressing, and, in the case of laryngospasm, can be life threatening. They usually respond well to anticholinergic, or antihistaminic medications.
- ii) Parkinsonism: Antidopaminergic agents can induce symptoms of Parkinson's Disease, including bradykinesia, tremors, and rigidity (APA, 1997). Anticholinergic or mild dopaminergic agents (amantidine) are used to treat this. At times differentiating between Parkinson side-effects, and symptoms of the illness, i.e., negative symptoms, or in severe cases, catatonia, may be difficult.
- iii) Akathisia: Akathisia, a sense of severe restlessness frequently manifest as pacing or physical agitation, is commonly seen in patients treated with antipsychotics. It is often misinterpreted as psychotic agitation or anxiety, and is a common reason for medication noncompliance. It is, unfortunately, also at times difficult to treat. If clinically feasible, lowering the antipsychotic dose should be attempted. Antiparkinsonian agents are not consistently helpful, although relief has been reported with beta-blockers and benzodiazepines (APA, 1997).

To avoid acute extrapyramidal symptoms, the use of prophylactic antiparkinsonian agents may be considered, especially in those at risk for acute dystonias or that have a previous history of dystonic reactions (APA, 1997). This is particularly true in patients where compliance may be an issue (e.g., those who are paranoid or otherwise distrust medication treatments). The need for antiparkinsonian agents should be reevaluated after the acute phase of treatment, or if doses are lowered, since many patients no longer need them during long-term therapy (APA, 1997).

b) Late Appearing Extrapyrimidal Side-effects.

## AMERICAN ACADEMY OF CHILD AND ADOLESCENT PSYCHIATRY

- i) **Tardive Dyskinesia:** Tardive dyskinesia (TD) is an involuntary movement disorder usually consisting of athetoid or choreic movements in the oro-facial region, but may affect any part of the body (Ernst et al., 1998). TD is a major public health concern in the treatment of schizophrenia, with both clinical and medicolegal implications. TD is typically associated with the long-term use of neuroleptics (Ernst et al., 1998). Withdrawal dyskinesia may occur with either gradual or sudden cessation of neuroleptic agents. As many as 50 percent of youth on neuroleptics may experience some form of tardive or withdrawal dyskinesia (Ernst et al., 1998, Kumra et al., 1998). Withdrawal dyskinesias almost always resolve over time, whereas tardive dyskinesia may persist even if the antipsychotic agent is discontinued.

Because there is no specific treatment for tardive dyskinesia other than discontinuing the medication, strategies for prevention and early detection need to be followed (APA, 1997). The concern over tardive dyskinesia should not outweigh the potential benefits provided by antipsychotics for patients with schizophrenia. However, adequate informed consent is necessary, and baseline measures of abnormal movements should be recorded. Once neuroleptic therapy has been started, assessment for dyskinesias should occur at least every 3 to 6 months. The Abnormal Involuntary Movement Scale (National Institute of Mental Health, 1985) is a useful measure for monitoring this problem.

If TD occurs, the medication should only be continued at the current dose if the patient is in full remission, and there is reason to believe that any change in dosage or agent will precipitate a relapse (APA, 1997). Otherwise, attempts should be made to either lower the dose, or switch to another medication, most likely an atypical antipsychotic.

- ii) **Tardive Dystonia:** Tardive dystonia is characterized by slow movements along the long axis of the body that culminate in spasms (Ernst et al., 1998). Facial spasms have also been noted. It can be quite disabling, and is often associated with tardive dyskinesia. The same strategies for treating TD should be used for tardive dystonia.
  - c) **Neuroleptic Malignant Syndrome.** Neuroleptic malignant syndrome (NMS) is a rare idiosyncratic reaction that may occur at any time during the course of antipsychotic therapy. It is characterized by severe rigidity, hyperthermia, confusion, markedly elevated creatinine phosphokinase, and unstable vital signs. If untreated, mortality rates of 5 – 20% are reported in adults (APA, 1997). There are case reports of NMS occurring in youth (Silva et al., 1999). Of 77 noted cases in juveniles, 9 percent died, and 20 percent has serious residual sequelae (Silva et al., 1998). When NMS is suspected, the antipsychotic agent should be discontinued and supportive medical care sought. Dopamine agonists (e.g., bromocriptine) and antispasticity agents (e.g., dantrolene) also have been used to treat adult patients with NMS (APA, 1997). In the available case reports of NMS in youth, bromocriptine and anticholinergic agents were helpful, but dantrolene was not (Silva et al., 1999). These reports, however, are not definitive, and further study is needed.
- 2) **Cognitive Effects.** Although there are no studies of cognitive changes with antipsychotic therapy in EOS, the potential for sedation, cognitive blunting, apathy, and memory deficits, especially when using low-potency agents with greater anticholinergic activity, raises



## AMERICAN ACADEMY OF CHILD AND ADOLESCENT PSYCHIATRY

concerns (Ernst et al., 1998). However, it is important to note that schizophrenia itself has a profound impact on cognition that may be ameliorated by medication therapy.

- 3) Other Side-effects. Other side-effects noted with traditional antipsychotic agents include sedation, orthostatic hypotension, weight gain, sexual dysfunction, hyperprolactinemia and lowered seizure threshold (APA, 1997). Some agents have specific side-effects, such as lenticular stippling with thioridazine or photosensitivity, elevated liver enzymes and cholestatic jaundice with phenothiazines (APA, 1997). Clinicians should be aware of the side-effect profiles for the different agents that they prescribe.

*Atypical Antipsychotic Agents.* One of the advantages of the atypical agents is that they are theoretically less likely to cause extrapyramidal side-effects (including tardive dyskinesia). However, some of these agents (e.g., risperidone) still have some antidopaminergic activity, and can produce extrapyramidal symptoms. They also have other potential side-effects, which, especially for clozapine, represent significant medical concerns.

For this discussion, clozapine will be considered separately from the other atypical agents. Clozapine, although quite effective, has significant side-effects that often limit its use. In the adult literature, the two major concerns are 1) seizures, which occur in approximately 3 % of patients; and 2) agranulocytosis, which occurs in approximately 1 % of patients, and is potentially fatal. The risk for seizures increases as the dose increases, especially if dosage changes are made rapidly (APA, 1997). The agranulocytosis is usually reversible, as long as the drug is stopped immediately. Other side-effects include sedation, weight gain, hypersalivation, elevated liver enzymes, orthostatic hypotension, tachycardia and fever (APA, 1997; Toren et al., 1998). Some case reports have also noted extrapyramidal side-effects in youth (Toren et al., 1998). Youth may have higher rates of side-effects on this agent, including seizures and agranulocytosis (Kumra et al., 1996).

Clozapine can only be used with an extensive monitoring protocol. Prior to starting therapy, there can be no evidence of a myeloproliferative disorder, or a prior history of agranulocytosis or granulocytopenia on clozapine (APA, 1997). Also, the baseline white blood cell count (WBC) needs to be a least 3500/mm<sup>3</sup>. The use of concurrent medications that also have the potential to lower blood counts (e.g., carbamazepine) should be avoided.

The trial should begin using low doses that increase gradually. Although there are not set dosage recommendations for juveniles, the NIMH protocol using starting doses of 6.25 to 25 mg/day, depending on the patients weight (Kumra et al., 1996). In adults, the starting dose is 12.5 mg once or twice per day, with subsequent increases of no more than 25 – 50 mg (added to the total daily dose) once or twice per week (APA, 1997). Although some investigators have suggested achieving blood levels in the range of 200 – 400 ng/ml, further research is needed to establish whether blood levels correlate with efficacy or side-effects.

Weekly blood cell counts are obtained during the first 6 months of treatment, than every two weeks thereafter, including testing during the 4 weeks after the medication is stopped. The following guidelines are recommended by the APA (1997):

- 1) If the WBC drops below 2000/mm<sup>3</sup>, or the absolute neutrophil count (ANC) drops below 1000/mm<sup>3</sup>, the medication must be stopped immediately, and the patient monitored for infection, with daily checks of their blood cell counts. Further hematological consultation and assessment may be necessary.
- 2) If the WBC drops between 2000 - 3000/mm<sup>3</sup>, or the ANC drops between 1000 - 1500/mm<sup>3</sup>,

## AMERICAN ACADEMY OF CHILD AND ADOLESCENT PSYCHIATRY

the medication must be stopped immediately, and the patient monitored for infection, with daily checks of their blood cell counts. Clozapine may be resumed with a WBC greater than 3000, or an ANC above 1500, and no signs of infection. Counts should then be done biweekly until the WBC is greater than 3500.

- 3) If the WBC is between 3000 - 3500/mm<sup>3</sup>; or if the WBC has dropped 3000/mm<sup>3</sup> over 1 to 3 weeks; or if immature cell forms are present, repeat the count. If the WBC remains between 3000 – 3500/mm<sup>3</sup> and the ANC is greater than 1500/mm<sup>3</sup>, follow the counts (with a differential) biweekly until the WBC is greater than 3500/mm<sup>3</sup>. If the counts drop below 3000/mm<sup>3</sup>, or the ANC below 1500/mm<sup>3</sup>, follow the guidelines listed above.

The other atypical antipsychotic medications are generally better tolerated than traditional antipsychotic medications and clozapine. Potential adverse effects include:

1. Weight Gain: The weight gain associated with atypical antipsychotic agents may be extreme (Toren et al., 1998), and to date is the most common significant problem associated with their use.
2. Neurologic: Extra-pyramidal side-effects and neuroleptic malignant syndrome can theoretically occur with any of the atypical agents, however the risk for these problems is less than that for traditional neuroleptics (Leucht et al., 1999). Of the atypical agents, risperidone appears to be the most likely to produce EPS (Leucht et al., 1999), including case reports in youth (Mandoki, 1995). There are also case reports of neuroleptic malignant syndrome and tardive dyskinesia in adults and teenagers on risperidone (APA, 1997; Feeney and Klykylo, 1996; Toren et al., 1998).
3. Cognitive: The atypical antipsychotics have shown consistent benefits in fine motor function, memory and executive function in adult studies, and appear to cause less cognitive difficulties than traditional neuroleptics (Gallhofer et al., 1996; Purdon, 1999). Within the atypical agents, there may be some differences in regards to their impact on cognitive performance (Gallhofer et al., 1999; Purdon et al., 1999).
4. Cardiac: Orthostatic hypotension can be a problem (Toren et al., 1998). In adults, minor electrocardiogram changes, specifically QT prolongation, have been associated with atypical antipsychotics. While this has generally not been a clinically significant issue, it raises concerns since youth may be more susceptible to the cardiac effects of medications (e.g., tricyclic antidepressants).
5. Hematologic: Although primarily associated with clozapine, agranulocytosis can occur with any antipsychotic agent (Ernst et al., 1998). This is one report of leukocytopenia in a teenage boy on risperidone (Edleman, 1996), and one unpublished report of a precipitous drop in absolute neutrophil count and platelets in a 12 year old boy on quetiapine (McClellan, personal communication).
6. Hepatic: Atypical agents may produce elevations in hepatic transaminases. These elevations are often transient and generally resolve with cessation of the drug. There are two reported cases of adolescent males developing liver enzyme abnormalities and fatty infiltrates, associated with obesity, while on risperidone (Kumra et al., 1997). Thus it may be prudent to check baseline liver functions prior to initiating treatment, with periodic monitoring during ongoing therapy (Kumra et al., 1997).
7. Ocular: Quetiapine therapy was associated with the development of cataracts in studies of dogs. This adverse effect has not been reported in humans, but the FDA still recommends

## AMERICAN ACADEMY OF CHILD AND ADOLESCENT PSYCHIATRY

obtaining baseline and 6 month follow-up eye exams when prescribing quetiapine.

8. Other Side-effects: Other common side-effects include sedation, activation, and dizziness.

A broader concern is that these agents are relatively new, and have not yet been studied for use in a juvenile population. However, they are widely used in clinical practice, and in many settings are considered the standard of care treatment for psychotic symptoms. Further studies and clinical experience is necessary to establish their side effect profiles, especially with long-term use.

### PSYCHOSOCIAL THERAPIES

The morbidity of EOS stems both from the pathogenic manifestations of the disorder, and from the resultant deviations in normal development. Therapeutic interventions must address the needs of the child as an individual, rather than focus solely on those needs specific to a diagnosis of schizophrenia. Hence, the goal of therapy is to help the child return to his or her premorbid level of functioning while also promoting the mastery of age-appropriate developmental tasks. Treatment should be broad based, and able to address any comorbid psychiatric condition (e.g., substance abuse), ongoing environmental and/or psychological stressors, or any other factors complicating recovery.

In adults, although traditional psychotherapeutic approaches have not been found to be effective for treating schizophrenia, there is ample evidence supporting learning based therapies that incorporate cognitive-behavioral strategies and social skills training (Heinsein et al., 2000). Psychoeducational interventions including strategies to improve family functioning, problem-solving and communication skills, and relapse prevention have been shown to decrease relapse rates (APA, 1997). Although most of the available treatment literature derives from studies of patients with adult-onset schizophrenia, much of it remains applicable to those with EOS as long as developmental issues are addressed.

Research regarding expressed emotion has been in part the theoretical basis for family interventions. Expressed emotion refers to attributes of overprotectiveness or criticism expressed towards the patient. Relapse rates are higher for patients with schizophrenia that live in families characterized as having high expressed emotion (Leff & Vaughn, 1985). Family intervention programs, in conjunction with medication therapy, have been shown to significantly decrease schizophrenia relapse rates (APA, 1997). However, it is important to note that the mechanisms behind expressed emotion are complex, interactive, and bi-directional. The presence of difficult family interactions may not be causal, but rather a reaction to the collection of difficulties the patient brings to the family setting.

Another important psychoeducational modality is social skills training. Individuals with schizophrenia often have major deficits in social and life skills. These programs focus on improving the patient's strategies for dealing with conflict and avoidance; identifying the correct meaning, content and context of verbal messages within their families; and enhancing their socialization and vocational skills. The combination of family treatment, social skills training and medication therapy also has been shown to decrease relapse rates (Hogarty et al., 1986).

Although most of the available literature deals with adults, there are some studies addressing psychosocial interventions for EOS. Rund et al., (1994) examined the effectiveness of a psychoeducational treatment program in comparison to standard community treatment, in a sample of adolescents with schizophrenia (12 subjects per group). The treatment program

## **AMERICAN ACADEMY OF CHILD AND ADOLESCENT PSYCHIATRY**

included parent seminars, problem-solving sessions, milieu therapy (while the subjects were hospitalized), and networks (reintegrating the subjects back into their schools and communities).

Medication therapy was also provided. Youth in the comparison group (community treatment) received a mixture of individual psychotherapy, milieu therapy, and medications. Outcome was assessed after two years. The psychoeducational treatment program had lower rates of rehospitalization, and was more cost-effective. Subjects with poor premorbid psychosocial functioning benefited the most from the psychoeducational interventions. Clinical improvement was associated with the families expressed emotion ratings changing from high to low.

Although more research is needed in this area, family treatment and social skills training should be considered helpful adjuncts to medication treatment for children and adolescents with schizophrenia.

Given the above findings, children and adolescents with schizophrenia should benefit from the combination of individual, family, and/or group therapies as adjuncts to medication therapy. Such treatment should be developed in accordance with the developmental level of the child and should focus on psychoeducational information regarding the symptomatology, etiological factors, prognosis, and treatment factors for schizophrenia. Cognitive-behavioral strategies, such as social skills, problem-solving strategies, and self-help skills are important elements of the treatment plan. Supportive family and individual therapies are also essential, given the morbidity of the disorder and the resultant disruption in the lives of the patient and their families. Other therapies may be needed to address comorbid illnesses and/or complicating individual or family factors. One of the long-term needs is to maintain a consistent, stable therapeutic relationship, which both serves to better monitor relapse and noncompliance, while also focusing on the more disabling negative symptoms of the disorder (i.e., social withdrawal, problems with relationship building, apathy, and anhedonia).

The complexity of treating youth with EOS often requires a continuum of services and treatment providers. In addition to psychopharmacology management and psychotherapy, many of these youth need extensive case management and community support services. Such services may include crisis intervention, family support programs, and in-home services. Families also may benefit from being involved in a parent advocacy group.

Appropriate special education services are also a necessary component of a comprehensive treatment program. Children and adolescents with schizophrenia generally do not do well in standard classroom settings, and often need a specialized classroom with low levels of stimulation, an individualized curriculum that recognizes their potential cognitive impairments, and a teaching staff specifically trained to deal with emotionally disturbed youth. Day treatment or partial hospitalization programs, with both educational and mental health services, are often indicated. Specific attention should be paid to the long-term needs of these patients, with provision of vocational and independent life skills training.

### **ELECTROCONVULSIVE THERAPY**

Electroconvulsive therapy (ECT) has been found to be effective for adult schizophrenic patients during the acute phases of their illness, with ECT plus antipsychotic medications being the most effective (APA, 1997). It is generally used for patients who either do not adequately respond to, or cannot tolerate, antipsychotic medications. There is insufficient information available to make a judgment regarding its use in youth with EOS (Bertagnoli and Borchardt,

## **AMERICAN ACADEMY OF CHILD AND ADOLESCENT PSYCHIATRY**

1990; AACAP, in preparation). ECT may be used in children and adolescents with EOS that are either medication nonresponders, cannot tolerate medications, have a medical contraindication to medications (e.g., pregnancy), or a clinical presentation for which ECT may be particularly indicated (e.g., catatonia). The clinician must balance the relative risks and benefits of ECT treatment against of the morbidity of the disorder, the attitudes of the patient and family, and the availability of other treatment options. Obtaining informed consent from the parents, including a detailed discussion of the potential cognitive deficits, is necessary.

### **CONFLICT OF INTEREST**

As a matter of policy, some of the authors to this practice parameter is in active clinical practice and may have received income related to treatments discussed in this parameter. Some authors may be involved primarily in research or other academic endeavors and also may have received income related to treatments discussed in this parameter. To minimize the potential for this parameter to contain biased recommendations due to conflict of interest, the parameter was reviewed extensively by Work Group members, consultants, and Academy members; authors and reviewers were asked to base their recommendations on an objective evaluation of the available evidence. Authors and reviewers who believed that they might have a conflict of interest that would bias, or appear to bias, their work on these parameters were asked to notify the Academy.

### **SCIENTIFIC DATA AND CLINICAL CONSENSUS**

Practice parameters are strategies for patient management, developed to assist clinicians in psychiatric decision-making. This parameter, based on evaluation of the scientific literature and relevant clinical consensus, describes generally accepted approaches to assess and treat specific disorders or to perform specific medical procedures. The validity of scientific findings was judged by design, sample selection and size, inclusion of comparison groups, generalizability, and agreement with other studies. Clinical consensus was determined through extensive review by the members of the Work Group on Quality Issues, child and adolescent psychiatry consultants with expertise in the content area, the entire Academy membership, and the Academy Assembly and Council.

These parameters are not intended to define the standard of care; nor should they be deemed inclusive of all proper methods of care or exclusive of other methods of care directed at obtaining the desired results. The ultimate judgment regarding the care of a particular patient must be made by the clinician in light of all the circumstances presented by the patient and his or her family, the diagnostic and treatment options available, and available resources. Given inevitable changes in scientific information and technology, these parameters will be reviewed periodically and updated when appropriate.

## AMERICAN ACADEMY OF CHILD AND ADOLESCENT PSYCHIATRY

### REFERENCES

*References marked with an asterisk are particularly recommended.*

Akbadian S, Bunney JWE, Potkin SG, Wigal SB, Hagman JO, Sandman CA, Jones EG (1993), Altered distribution of nicotinamide-adenine dinucleotide phosphate-diaphorase cells in frontal lobe of schizophrenics implies disturbances of cortical development. *Arch Gen Psychiatry* 50:169-177

Alaghband-Rad J, Hamburger SD, Giedd JN, Frazier JA, Rapoport JL (1997), Childhood-onset schizophrenia: biological markers in relation to clinical characteristics. *Am J Psychiatry* 154:64-68

Alaghband-Rad J, McKenna K, Gordon CT, Albus KE, Hamburger SD, Rumsey JM, Frazier JA, Lenane MC, Rapoport JL (1995), Childhood-onset schizophrenia: the severity of premorbid course. *J Am Acad Child Adolesc Psychiatry* 34(10):1273-1283

Altman H, Collins M, Mundy P (1997), Subclinical hallucinations and delusions in nonpsychotic adolescents. *J Child Psychol Psychiatry* 38:413-420

American Academy of Child and Adolescent Psychiatry (1997a), Practice Parameter for the Assessment and Treatment of Children and Adolescents with Bipolar Disorder. *J Am Acad Child Adolesc Psychiatry* 36(10, Suppl):177-193

American Academy of Child and Adolescent Psychiatry (1997b), Practice Parameter for Psychiatric Assessment of Children and Adolescents. *J Am Acad Child Adolesc Psychiatry* 36(10, Suppl):4-20

American Academy of Child and Adolescent Psychiatry (1998a), Practice Parameter for the Assessment and Treatment of Children and Adolescents with Depressive Disorders. *J Am Acad Child Adolesc Psychiatry* 37(10, Suppl):63-83

American Academy of Child and Adolescent Psychiatry (1998b), Practice Parameter for the Assessment and Treatment of Children and Adolescents with Obsessive-Compulsive Disorder. *J Am Acad Child Adolesc Psychiatry* 37(10, Suppl):27-45

American Psychiatric Association (1980), *Diagnostic and Statistical Manual of Mental Disorders, 3rd edition (DSM-III)*. Washington, DC: American Psychiatric Association

American Psychiatric Association (1987), *Diagnostic and Statistical Manual of Mental Disorders, 3rd edition-revised (DSM-III-R)*. Washington, DC: American Psychiatric Association

American Psychiatric Association (1992), *Tardive Dyskinesia: A Task Force Report*. Washington, DC: American Psychiatric Press

## AMERICAN ACADEMY OF CHILD AND ADOLESCENT PSYCHIATRY

American Psychiatric Association (1994), *Diagnostic and Statistical Manual of Mental Disorders, 4<sup>th</sup> edition (DSM-IV)*. Washington, DC: American Psychiatric Association

\*American Psychiatric Association (1997), Practice guideline for the treatment of patients with schizophrenia. *Am J Psychiatry* 154(4, Suppl):1-63

Armenteros JL, Fennelly BW, Hallin A, Adams PB, Pomerantz P, Michell M, Sanchez LE, Campbell M (1995), Schizophrenia in hospitalized adolescents: clinical diagnosis, DSM-III-R, DSM-IV, and ICD-10 criteria. *Psychopharmacol Bull* 31(2):383-387

Armenteros JL, Whitaker AH, Welikson M, Stedje DJ, Gorman J, (1997), Risperidone in adolescents with schizophrenia: an open pilot study. *J Am Acad Child Adolesc Psychiatry* 36(5):694-700

Asarnow JR, Ben-Meir S (1988), Children with schizophrenia spectrum and depressive disorders: a comparative study of premorbid adjustment, onset pattern and severity of impairment. *J Child Psychol Psychiatry* 29:477-488

Asarnow JR, Goldstein MJ, Ben-Meir S (1988), Parental communication deviance in childhood onset schizophrenia spectrum and depressive disorders. *J Child Psychol Psychiatry* 29:825-838

Asarnow JR, Thompson MC, Goldstein MJ (1994), Childhood onset schizophrenia: a follow-up study. *Schizophr Bull* 20(4):647-670

Asarnow JR, Asamen J, Granholm E, Sherman T, Watkins JM, Williams ME (1994), Cognitive/neuropsychological studies of children with a schizophrenic disorder. *Schizophr Bull* 20(4):647-670

Baker L, Cantwell DP (1991), Disorders of language, speech, and communication. In: *Child and Adolescent Psychiatry: A Comprehensive Textbook*, Lewis M, ed. Baltimore: Williams & Wilkins, pp 516-521

Baltaxe CAM, Simmons III JQ (1995), Speech and language disorders in children and adolescents with schizophrenia. *Schizophr Bull* 21(4):677-692

Beitchman JH (1985), Childhood schizophrenia: a review and comparison with adult-onset schizophrenia. *Psychiatr Clin North Am* 8:793-814

Bertagnoli M, Borchardt CM (1990), A review of ECT for children and adolescents. *J Am Acad Child Adolesc Psychiatry* 29:2302-2307

Bettes B, Walker E (1987), Positive and negative symptoms in psychotic and other psychiatrically disturbed children. *J Child Psychol Psychiatry* 28:555-567

## AMERICAN ACADEMY OF CHILD AND ADOLESCENT PSYCHIATRY

- \*Campbell M, Rapoport JL, Simpson GM (1999), Antipsychotics in children and adolescents. *J Am Acad Child Adolesc Psychiatry* 38:537-545
- Cantor S, Evans J, Pearce J, Pezzot-Pearce P (1982), Childhood schizophrenia, present but not accounted for. *Am J Psychiatry* 139:758-762
- Caplan R (1994), Communication deficits in children with schizophrenia spectrum disorders. *Schizophr Bull* 20:671-674
- Caplan R, Guthrie D, Gish B, Tanguay P, David-Lando G (1989), The Kiddie Formal Thought Disorder Scale: clinical assessment, reliability, and validity. *J Am Acad Child Adolesc Psychiatry* 28:408-416
- Caplan R, Guthrie D, Komo S (1996), Conversational repair in schizophrenic and normal children. *J Am Acad Child Adolesc Psychiatry* 35(7):950-958
- Carlson GA (1990), Child and adolescent mania: diagnostic considerations. *J Child Psychol Psychiatry* 31:331-342
- Del Beccaro MA, Burke P, McCauley E (1988), Hallucinations in children: a follow-up study. *J Am Acad Child Adolesc Psychiatry* 27:462-465
- Edleman RJ (1996), Risperidone side-effects [letter]. *J Am Acad Child Adolesc Psychiatry* 35:4-5
- \*Ernst M, Malone RP, Rowan AB, George R, Gonzalez NM, Silva RR (1998), Antipsychotics (neuroleptics). In: *Practitioner's Guide to Psychoactive Drugs for Children and Adolescents* (2<sup>nd</sup> ed), Werry JS, Aman MG, eds. New York: Plenum Press, pp 297-328
- Eggers C (1978), Course and prognosis in childhood schizophrenia. *J Autism Child Schizophr* 8:21-36
- Eggers C (1989), Schizo affective psychosis in childhood: a follow-up study. *J Autism Dev Disord* 19:327-334
- Eisner A, McClellan J (1998), Substances of abuse. In: *Practitioner's Guide to Psychoactive Drugs for Children and Adolescents* (2<sup>nd</sup> ed), Werry JS, Aman MG, eds. New York: Plenum Press, pp 297-328
- Facts and Comparisons, Inc (1992), *Drug Facts and Comparisons*. St. Louis: JB Lippincott Co, p. 265
- Famularo R, Kinscherff R, Fenton T (1992), Psychiatric diagnoses of maltreated children:



## AMERICAN ACADEMY OF CHILD AND ADOLESCENT PSYCHIATRY

- preliminary findings. *J Am Acad Child Adolesc Psychiatry* 31:863-867
- Feeney DJ, Klykylo W (1996), Risperidone and tardive dyskinesia [letter]. *J Am Acad Child Adolesc Psychiatry* 35(11):1421-1422
- Fish B, Marcus J, Hans SL, Auerbach JG, Perdue S (1992), Infants at risk for schizophrenia: sequelae of a genetic neurointegrative defect. *Arch Gen Psychiatry* 49:221-235
- Fish B, Ritvo E (1979), Psychoses of childhood. In: *Basic Handbook of Child Psychiatry*, Noshpitz JD, Berlin I, eds. New York: Basic Books, pp 249-304
- Frazier JA, Alagband-Rad J, Jacobsen L, Lenane MC, Hamburger S, Albus K, Smith A, McKenna K, Rapoport JL (1997), Pubertal development and onset of psychosis in childhood onset schizophrenia. *Psychiatry Res* 70:1-7
- Frazier JA, Giedd JN, Hamburger SD, Albus KE, Kaysen D, Vaituzis AC, Rajapakse JC, Lenane MC, McKenna K, Jacobsen LK, Gordon CT, Breier A, Rapoport JL (1996), Brain anatomic magnetic resonance imaging in childhood-onset schizophrenia. *Arch Gen Psychiatry* 53:617-624
- Gallhofer B, Bauer U, Lis S, Krieger S, Gruppe H, 1996. Cognitive dysfunction in schizophrenia: comparison of treatment with atypical antipsychotic agents and conventional neuroleptic drugs. *European Neuropsychopharmacology* 6 (S2): 13-20.
- Garralda ME (1984a), Hallucinations in children with conduct and emotional disorders: I. The clinical phenomena. *Psychol Med* 14:589-596
- Garralda ME (1984b), Hallucinations in children with conduct and emotional disorders: II. The follow-up study. *Psychol Med* 14:597-604
- Garralda ME (1985), Characteristics of the psychoses of late onset in children and adolescents: a comparative study of hallucinating children. *J Adolesc* 8:195-207
- Goldberg TE, Karson CN, Leleszi JP, Weinberger DR (1988), Intellectual impairment in adolescent psychosis: a controlled psychometric study. *Schizophr Res* 1(4):261-266
- Gordon CT, Frazier JA, McKenna K, Giedd J, Zametkin A, Zahn T, Hommer D, Hong W, Kaysen D, Albus KE, Rapoport JL (1994), Childhood-onset schizophrenia: an NIMH study in progress. *Schizophr Bull* 20:697-712
- Grcevich SJ, Findling RL, Rowane WA, Friedman L, Schulz SC (1996), Risperidone in the treatment of children and adolescents with schizophrenia: a retrospective study. *J Child Adolesc Psychopharmacol* 6:251-257

## AMERICAN ACADEMY OF CHILD AND ADOLESCENT PSYCHIATRY

- Green WH, Campbell M, Hardesty AS, Grega DM, Pardon-Gayol M, Shell J, Erlenmeyer-Kimling L (1984), A comparison of schizophrenic and autistic children. *J Am Acad Child Psychiatry* 23:399-409
- Green WH, Padron-Gayol M (1986), Schizophrenic disorder in childhood: its relationship to DSM-III criteria. In: *Biological Psychiatry*, Shagass C, ed. Amsterdam: Elsevier Science Publishing, pp 1484-1486
- Green WH, Padron-Gayol M, Hardesty AS, Bassiri M (1992), Schizophrenia with childhood onset: a phenomenological study of 38 cases. *J Am Acad Child Adolesc Psychiatry* 31:968-976
- Hafner H, Nowotny B (1995), Epidemiology of early-onset schizophrenia. *Eur Arch Psychiatry Clin Neurosci* 245:80-92
- Healy E, Subotsky F, Pipe R (1999), Quetiapine in adolescent psychosis. *J Am Acad Child Adolesc Psychiatry* 38:1329
- Heinssen RK, Liberman RP, Kopelowicz A (2000), Psychosocial skills training for schizophrenia: lessons from the laboratory. *Schizophr Bull*, 26:21-46
- Hogarty GE, Anderson CM, Reiss DJ et al. (1986), Family psychoeducation, social skills training, and maintenance chemotherapy in the aftercare treatment of schizophrenia: I. One-year effects of a controlled study on relapse and expressed emotion. *Arch Gen Psychiatry* 43:633-642
- Hollis C (1995), Child and adolescent (juvenile onset) schizophrenia. A case control study of premorbid developmental impairments. *Br J Psychiatry* 166(4):489-495
- Hornstein JL, Putnam FW (1992), Clinical phenomenology of child and adolescent dissociative disorders. *J Am Child Adolesc Psychiatry* 31:1077-1085
- Jacobsen LK, Giedd JN, Berquin PC, Krain AL, Hamburger SD, Kumra S, Rapoport JL (1997), Quantitative morphology of the cerebellum and fourth ventricle in childhood-onset schizophrenia. *Am J Psychiatry* 154:1663-1669
- Jacobsen LK, Rapoport JL (1998), Research update; Childhood-onset schizophrenia: implications of clinical and neurobiological research. *J Child Psychol Psychiatry* 39:101-113
- Joyce PR (1984), Age of onset in bipolar affective disorder and misdiagnosis of schizophrenia. *Psychol Med* 14:145-149
- Kemper TL, Bauman ML (1993), The contribution of neuropathologic studies to the

## AMERICAN ACADEMY OF CHILD AND ADOLESCENT PSYCHIATRY

- understanding of autism. *Neurol Clin* 11:175-187
- Kenny JT, Friedman L, Findling RL, Swales TP, Strauss ME, Jesberger JA, Schulz SC (1997), Cognitive impairment in adolescents with schizophrenia. *Am J Psychiatry* 154:1316-1315
- Kilgus MD, Pumariega AJ, Cuffe SP (1995), Influence of race on diagnosis in adolescent psychiatric inpatients. *J Am Acad Child Adolesc Psychiatry* 34:67-72
- King RA, Noshpitz JD (1991), *Pathways of Growth: Essentials of Child Psychiatry, Vol. II: Psychopathology*. New York: John Wiley and Sons
- \*Kolvin I (1971), Studies in the childhood psychoses. *Br J Psychiatry* 6:209-234
- Kumra S, Briguglio C, Lenane M, Goldhar L, Bedwell J, Venuchekov J, Jacobsen LK, Rapoport JL (1999), Including children and adolescents with schizophrenia in medication-free research. *Am J Psychiatry* 156:1065-1068
- Kumra S, Jacobsen LK, Lenane M, Zahn TP, Wiggs E, Alaghband-Rad J, Castellanos FX, Frazier JA, McKenna K, Gordon CT, Smith A, Hamburger S, Rapoport JL (1998), "Multidimensionally impaired disorder": is it a variant of very early-onset schizophrenia? *J Am Child Adolesc Psychiatry* 37:91-99
- Kumra S, Frazier JA, Jacobsen LK, McKenna K, Gordon CT, Lenane MC, Hamburger SD, Smith AK, Albus KE, Alaghband-Rad J, Rapoport JL (1996), Childhood-onset schizophrenia. A double-blind clozapine-haloperidol comparison. *Arch Gen Psychiatry* 53:1090-1097
- Kumra S, Herion D, Jacobsen LK, Briguglia C, Grothe D (1997), Case study: risperidone-induced hepatotoxicity in pediatric patients. *J Am Child Adolesc Psychiatry* 36:701-705
- Kumra S, Jacobsen LK, Lenane M, Smith A, Lee P, Malanga CJ, Karp BI, Hamburger S, Rapoport JL (1998), Case series: spectrum of neuroleptic-induced movement disorders and extrapyramidal side-effects in childhood-onset schizophrenia. *J Am Child Adolesc Psychiatry*, 37:221-227
- Leff J, Vaughn C (1985), *Expressed Emotion in Families: Its Significance for Mental Illness*. New York: Gilford Press
- Leucht S, Pitschel-Walz G, Abraham D, Kissling W (1999), Efficacy and extrapyramidal side-effects of the new antipsychotics olanzapine, quetiapine, risperidone, and sertindole compared to conventional antipsychotics and placebo. A meta-analysis of randomized controlled trials. *Schizophr Res* 35(1):51-68

## AMERICAN ACADEMY OF CHILD AND ADOLESCENT PSYCHIATRY

- Lofgren DP, Bemporad J, King J, Lindem K, O'Driscoll G (1991), A prospective follow-up study of so-called borderline children. *Am J Psychiatry* 148:1541-1547
- Loranger A (1984), Sex differences in age at onset of schizophrenia. *Arch Gen Psychiatry* 41:157-161
- Lykes WC, Cueva JE (1996), Risperidone in children with schizophrenia. *J Am Acad Child Adolesc Psychiatry* 35:405-406
- Mandoki MW (1995), Risperidone treatment of children and adolescents: increased risk of extrapyramidal side-effects. *J Child Adolesc Psychopharmacol* 5:49-67
- Mandoki M (1997), Olanzapine in the treatment of early-onset schizophrenia in children and adolescents. *Biol Psychiatry* 41(Supplement):7S-22S
- \* McClellan, J.: Early Onset Schizophrenia. In BJ Sadock and VA Sadock (eds) (2000), *Comprehensive Textbook of Psychiatry/VII*: pps 2782 – 2789, Lippencott Williams and Wilkins, Philadelphia, PA.
- McClellan J, McCurry C (1999), Early onset psychotic disorders: diagnostic stability and clinical characteristics. *Eur Child Adolesc Psychiatry* 8(Supplement 2): 1S-7S
- McClellan J, McCurry C (1998), Neurocognitive pathways in the development of schizophrenia. *Seminars in Clinical Neuropsychiatry* 3(4):320-332
- McClellan J, McCurry C, Snell J, DuBose A (1999), Early onset psychotic disorders: course and outcome over a two year period. *J Am Acad Child Adolesc Psychiatry* 38:1380-1389
- McClellan JM, Werry JS, Ham M (1993), A follow-up study of early onset psychosis: comparison between outcome diagnoses of schizophrenia, mood disorders and personality disorders. *J Autism Dev Disord* 23:243-262
- McConville B, Arvanitis L, Thyrum P, Smith K (1999), Pharmacokinetics, tolerability, and clinical effectiveness of quetiapine in adolescents with selected psychotic disorders. *Eur Neuropsychopharmacol* 9 (supplement 5):S267
- McKenna K, Gordon CT, Lenane M, Kaysen D, Fahey K, Rapoport JL (1994), Looking for childhood-onset schizophrenia: the first 71 cases screened. *J Am Acad Child Adolesc Psychiatry* 33:636-644
- McGlashan TH (1988), Adolescent versus adult onset of mania. *Am J Psychiatry* 145:221-223
- Meltzer HY, Lee MA, Ranjan R (1994), Recent advances in the pharmacotherapy of schizophrenia. *Acta Psychiat Scand* 90(suppl 384):95-101

## AMERICAN ACADEMY OF CHILD AND ADOLESCENT PSYCHIATRY

- Meltzer HY, Rabinowitz J, Lee MA, Cola PA, Ranjan R, Findling RL, Thompson PA (1997), Age at onset and gender of schizophrenic patients in relation to neuroleptic resistance. *Am J Psychiatry* 154(4):475-482
- National Institute of Mental Health (1985), Abnormal Involuntary Movement Scale. *Psychopharmacol Bull* 21:1077-1080
- Nicholson R, Rapoport J (1999), Childhood-Onset Schizophrenia: Rare but worth studying. *Biol Psychiatry*, 46:1418-1428.
- Pool D, Bloom W, Mielke DH, Roniger JJ Jr, Gallant DM (1976), A controlled evaluation of loxitane in seventy-five adolescent schizophrenia patients. *Current Therapeutic Research Clinical and Experimental* 19:99-104
- Purdon SE, Jones BD, Stip E, Labelle A, Addington D, David SR, Breier A, Tollefson GD (2000). Neuropsychological change in early phase schizophrenia during 12 months of treatment with olanzapine, risperidone, or haloperidol. The Canadian Collaborative Group for research in schizophrenia. *Arch Gen Psychiatry* 57:249-58
- Quintana H, Keshavan M (1995), Case study: risperidone in children and adolescents with schizophrenia. *J Am Acad Child Adolesc Psychiatry* 34:1292-1296
- Rapoport JL, Giedd JN, Blumenthal J, Hamburger S, Jeffries N, Fernandez T, Nicolson R, Bedwell J, Lenane M, Zijdenbos A, Paus T, Evans A (1999), Progressive cortical change during adolescence in childhood-onset schizophrenia. A longitudinal magnetic resonance imaging study. *Arch Gen Psychiatry* 56:649-654
- Rapoport JL, Giedd J, Kumra S, Jacobsen L, Smith A, Lee P, Nelson J, Hamburger S (1997), Childhood-onset schizophrenia: progressive ventricular change during adolescence. *Arch Gen Psychiatry* 54:897-903
- Realmuto GM, Erikson WD, Yellin AM, Hopwood JH, Greenberg LM (1984), Clinical comparison of thiothixene and thioridazine in schizophrenic adolescents. *Am J Psychiatry* 141:440-442
- Remschmidt H, Martin M, Schulz E, Gutenbrunner C, Fleischhaker C (1991), The concept of positive and negative schizophrenia in child and adolescent psychiatry. In: *Positive Versus Negative Schizophrenia*, Marneros A, Andreasen NC, Tsuang MT, eds. Springer-Verlag Berlin Heidelberg, pp 219-242
- Robinson D, Woerner MG, Alvir JM, Bilder R, Goldman R, Geisler S, Koreen A, Sheitman B, Chakos M, Mayerhoff D, Lieberman JA (1999), Predictors of relapse following response from a first episode of schizophrenia or schizoaffective disorder. *Arch Gen Psychiatry*

## AMERICAN ACADEMY OF CHILD AND ADOLESCENT PSYCHIATRY

56:241-247

- Rund, BR, Moe, L, Sollien, T, Fjell, A, Borchgrevink, T, Hallert, M, Naess, PO (1994), The Psychosis Project: Outcome and cost-effectiveness of a psychoeducational treatment programme for schizophrenic adolescents. *Acta Psychiatrica Scandinavica*, 89:211-218.
- Russell AT, Bott L, Sammons C (1989), The phenomenology of schizophrenia occurring in childhood. *J Am Acad Child Adolesc Psychiatry* 28:399-407
- Rutter M (1972), Childhood Schizophrenia reconsidered. *Journal of Autism and Childhood Schizophrenia*, 2, 315-337
- Spencer EK, Kafantaris V, Padron-Gayol MV, Rosenberg C, Campbell M (1992), Haloperidol in schizophrenic children: early findings from a study in progress. *Psychopharmacol Bull* 28:183-186
- Silva RR, Munoz DM, Alpert M, Perlmutter IR, Diaz J (1999), Neuroleptic malignant syndrome in children and adolescents. *J Am Acad Child Adolesc Psychiatry* 38:187-194
- Simeon JG, Carrey NJ, Wiggins DM, Milin RP, Hosenbocus SN (1995), Risperidone effects in treatment-resistant adolescents: preliminary case reports. *J Child Adolescent Psychopharmacology* 5:69-79
- Szigethy E, Brent S, Findling RL (1998), Quetiapine for refractory schizophrenia. *J Am Acad Child Adolesc Psychiatry* 37:1127-1128
- Thomas MA, Ke Y, Levitt J, Caplan R, Curran J, Asarnow R, McCracken J (1998), Preliminary study of frontal lobe 1H MR spectroscopy in childhood-onset schizophrenia. *J Magn Reson Imaging* 8: 841-846
- Toren P, Laor N, Weizman A (1998), Use of atypical neuroleptics in child and adolescent psychiatry. *J Clin Psychiatry* 59:644-656
- Towbin KE, Dykes EM, Pearson GS, Cohen DJ (1993), Conceptualizing “borderline syndrome of childhood” and “childhood schizophrenia” as a developmental disorder. *J Am Acad Child Adolesc Psychiatry* 32:775-782
- Usiskin SI, Nicolson R, Krasnewich DM, Yan W, Lenane M, Wudarsky M, Hamburger SD, Rapoport, JL (1999), Velocardiofacial syndrome in childhood-onset schizophrenia. *J Am Acad Child Adolesc Psychiatry* 38:1536-1543
- Volkmar FR, Cohen DJ (1991), Comorbid association of autism and schizophrenia. *Am J Psychiatry* 148:1705-1707

## AMERICAN ACADEMY OF CHILD AND ADOLESCENT PSYCHIATRY

- Volkmar FR, Cohen DJ, Hoshino Y et al. (1988), Phenomenology and classification of the childhood psychoses. *Psychol Med* 18:191-201
- Volkmar FR (1999), Practice Parameters for the Assessment and Treatment of Children, Adolescents, and Adults with Autism and other Pervasive Developmental Disorder. *J of Am Acad Child Adolesc Psychiatry* 38:2, 32S- 54S
- Walters V, McClellan, JM (1998), Psychotic symptoms in seriously mentally ill youth. Poster Presentation at the Annual Meeting of the American Academy of Child and Adolescent Psychiatry, Anaheim, CA
- Watkins JM, Asarnow RF, Tanguay P (1988), Symptom development in childhood onset schizophrenia. *J Child Psychol Psychiatry* 29:865-878
- Weinberger D (1987), Implications of normal brain development for the pathogenesis of schizophrenia. *Arch Gen Psychiatry* 44:660-669
- Werry JS (1979), Psychoses. In: *Psychopathological Disorders of Childhood, 2nd ed*, Quay HC, Werry JS, eds. New York: Wiley, pp 43-89
- \*Werry JS (1992), Child and adolescent (early onset) schizophrenia: a review in light of DSM-III-R. *J Autism Dev Disord* 22:601-624
- Werry JS, McClellan J (1992), Predicting outcome in child and adolescent (early onset) schizophrenia and bipolar disorder. *J Am Acad Child Adolesc Psychiatry* 31:147-150
- Werry JS, McClellan J, Andrews L, Ham M (1994), Clinical features and outcome of child and adolescent schizophrenia. *Schizophr Bull* 20:619-630
- \*Werry JS, McClellan J, Chard L (1991), Early-onset schizophrenia, bipolar and schizoaffective disorders: a clinical follow-up study. *J Am Acad Child Adolesc Psychiatry* 30:457-465
- \*Werry JS, Taylor E (1994), Schizophrenia and allied disorders. In: *Child and Adolescent Psychiatry: Modern Approaches, 3rd ed*, Rutter M, Hersov L, Taylor E, eds. Oxford: Blackwell Scientific, pp 594-615
- World Health Organization (1992), The ICD-10 Classification of Mental Health and Behavioural Disorders: Clinical Descriptions and Diagnostic Guidelines. World Health Organization, Geneva
- Zahn TP, Jacobsen LK, Gordon CT, McKenna K, Frazier JA, Rapoport JL (1997), Autonomic nervous system markers of psychopathology in childhood-onset schizophrenia. *Arch Gen Psychiatry* 54:904-912