Practice Parameter for the Assessment and Treatment of Children and Adolescents With Schizophrenia

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This Practice Parameter reviews the literature on the assessment and treatment of children and adolescents with schizophrenia. Early-onset schizophrenia is diagnosed using the same criteria as in adults and appears to be continuous with the adult form of the disorder. Clinical standards suggest that effective treatment includes antipsychotic medications combined with psychoeducational, psychotherapeutic, and educational interventions. Since this Practice Parameter was last published in 2001, several controlled trials of atypical antipsychotic agents for early-onset schizophrenia have been conducted. However, studies suggest that many youth with early-onset schizophrenia do not respond adequately to available agents and are vulnerable to adverse events, particularly metabolic side effects. Further research is needed to develop more effective and safer treatments. J. Am. Acad. Child Adolesc. Psychiatry, 2013;52(9):976–990. **Key Words:** schizophrenia, psychosis

Schizophrenia portends substantial morbidity and suffering to those afflicted and their families. Schizophrenia spectrum disorders often first present during adolescence and rarely in childhood. Since the last Practice Parameter for the Assessment and Treatment of Children and Adolescents with Schizophrenia was published,[1] knowledge of this topic has increased substantially. This revised version of the parameter presents the most up-to-date research findings and clinical standards regarding the assessment and treatment of this disorder.

METHODOLOGY

Earlier versions of this parameter were published in 1994 and 2001. The most recent literature search covered a 5-year period (January 2004 through August 2010) using PubMed, PsycInfo (Ovid), CINAHL (EBSCO), and Web of Science databases. The initial searches were inclusive and sensitive for PubMed using a combination of MeSH headings and key words. The search was adjusted for CINAHL and PsycInfo by "translating," where necessary, from the MeSH thesaurus to the CINAHL and PsycInfo thesauri, and using the same key words. The Web of Science search also was adjusted because this database responds only to key-word searching.

In PubMed, the search strategy from the Cochrane Review Group on schizophrenia was used (see below), yielding 282,328 results. This was refined to reflect treatment studies and reviews with limits for ages 0 to 18 years and English language applied, resulting in 3,662 articles. Search in CINAHL yielded an additional 55 articles, Web of Science 214 articles, and PsycInfo 24 articles. Once duplicates were removed, there were 3,186 articles.

The titles and abstracts of these articles were reviewed. Many studies identified in the search were conducted in a primarily adult population with only a few adolescent subjects. Articles with a focus on early-onset schizophrenia (EOS) treatment (87) were prioritized for inclusion. Additional selection criteria were based on the study's weight in the hierarchy of evidence (e.g., randomized controlled trials), attending to the quality of individual studies and the generalizability to clinical practice. The search was augmented by review of articles published before 2004, those nominated by expert review, those recently accepted for publication in peer-reviewed journals, and those pertaining to adult-onset schizophrenia treatment.

Search terms (this search statement was modeled after the Cochrane Review Group on Schizophrenia Specialised Register search strategies originally designed for the OVID database,

adjusted to work in the PubMed database): akathisia OR neuroleptic OR neuroleptics OR neuroleptic* OR parkinsonian* OR psychoses OR psychotic OR psychosis OR schizoaffective OR schizophren* OR tardive OR "childhood onset schizophrenia" OR "early onset schizophrenia" OR ((chronic OR paranoid) AND schizophren*) OR "Akathisia, Drug-Induced" [MeSH] OR "Dyskinesia, Drug-Induced" [MeSH] OR "Psychoses, Substance-Induced" [MeSH] OR ("Antipsychotic Agents" [MeSH] OR "Catatonia" [MeSH]) OR "Neuroleptic Malignant Syndrome" [MeSH] OR "Parkinsonian Disorders" [MeSH] OR "Schizophrenia and Disorders with Psychotic Features" [MeSH] OR "Schizophrenia, Childhood"[MeSH].

DEFINITIONS

EOS is defined as onset before 18 years of age. Onset before 13 years of age is often described as childhood-onset schizophrenia (COS). The diagnosis of schizophrenia in children and adolescents is made using the same criteria as in adults, following the criteria outlined by the *DSM-5*[2] or *International Classification of Diseases, 10th Revision*.[3] The *DSM-5* requires that two or more characteristic symptoms, i.e., hallucinations, delusions, disorganized speech, disorganized or catatonic behavior, and/or negative symptoms, must be present for at least 1 month (or shorter if successfully treated). During this active phase, hallucinations, delusions, or disorganized speech must be present. Evidence of the disorder must be present for at least 6 months and must be associated with a significant decline in social or occupational functioning. In children and adolescents, decline in function may include the failure to achieve age-appropriate levels of interpersonal or academic development. The *International Classification of Diseases, 10th Revision* diagnostic criteria are similar to the *DSM-5* criteria except that the total duration of illness required is at least 1 month.

Schizophrenia as defined by the *DSM-5* differs from the *DSM-IV-TR*[4] by the following: delusions, hallucinations, or disorganized speech are required for diagnosis and commenting and conversing hallucinations and bizarre delusions are no longer accorded special diagnostic status.

BRIEF HISTORY

Descriptions of madness and insanity date to antiquity. In the early 20th century, Kraeplin characterized two forms of insanity, manic-depressive illness and dementia praecox.[5] Bleuler substituted the term *schizophrenia* (splitting of the mind) for *dementia praecox*,[6] given the observation that the illness was not associated with dementia, but rather with the loss of association of thought processes and the disruption of thought, emotions, and behavior.[7]

The original descriptions of the disorder recognized a typical pattern of onset during adolescence and young adulthood, with reports of rare cases in children. However, beginning with the works of Bender, Kanner, and others,[8] the concept of childhood schizophrenia was broadened to include syndromes defined by developmental lags in the maturation of language, perception, and motility (which also included infantile autism).[9] Hallucinations and delusions were not required criteria. This nosology was adopted by the *DSM-II*. As a result, the childhood schizophrenia literature from this period overlaps with that of autism and other pervasive developmental disorders.

Seminal work by Kolvin[10] and Rutter[11] established the distinctiveness of the various childhood psychoses and the similarity between child and adult schizophrenia. Therefore, beginning with the *DSM-III*, the diagnosis of schizophrenia in youth has been made using the same criteria as for adults, regardless of age of onset. Subsequent research has generally validated this decision.

EPIDEMIOLOGY

The worldwide prevalence of schizophrenia is generally held to be approximately 1%, with some variation noted across studies and populations. The male-to-female ratio is approximately 1.4 to 1.[12]

The prevalence of EOS has not been adequately studied. Onset before 13 years of age appears to be quite rare. The rate of onset then increases during adolescence, with the peak ages of onset for the disorder ranging from 15 to 30 years. EOS tends to occur more often in male individuals. As age increases, this ratio tends to even out. The diagnostic validity of schizophrenia in young children, e.g., younger than 6 years, has not been established.

CLINICAL PRESENTATION

Psychosis is defined as the severe disruption of thought and behavior resulting in the loss of reality testing. The diagnosis of psychosis is based on overt changes in a person's behavior

and functioning, with evidence of disrupted thinking evident on mental status examination.[13] Although psychotic symptoms are characteristic of schizophrenia, psychosis may present with other illnesses, including mood disorders, neurologic conditions, and acute intoxication.

The diagnostic assessment of schizophrenia in youth presents unique developmental concerns. Misdiagnosis is common, particularly at time of onset.[14-17] Conditions often misdiagnosed as schizophrenia in youth include bipolar disorder and other psychotic mood disorders,[17,18] personality disorders,[19] obsessive-compulsive disorder,[20] and developmental syndromes.[16] Comprehensive diagnostic assessments, which reconcile mental status findings with the rigorous application of diagnostic criteria, help improve accuracy.[14,21]

Most children who report hallucinations do not meet criteria for schizophrenia, and many do not have a psychotic illness.[22,23] Normative childhood experiences, including overactive imaginations and vivid fantasies, can be misinterpreted as psychosis. Distinguishing formal thought disorder from developmental disorders that impair speech and language function can be a challenge.[24] Expertise in childhood psychopathology and experience in assessing reports of psychotic symptoms in youth are important prerequisite skills for clinicians evaluating youth for possible psychosis.

Symptomatology

Schizophrenia is characterized by positive and negative symptoms. Positive symptoms refer to hallucinations, delusions, and thought disorder. Negative symptoms are those of deficits, i.e., flat affect, anergy, and paucity of speech or thought. Disorganized behavior may represent an independent third domain, including disorganized speech (e.g., incoherence, looseness of associations), bizarre behavior, and poor attention.[4]

Hallucinations, thought disorder, and flattened affect have been consistently found in EOS, whereas systematic delusions and catatonic symptoms occur less frequently.[25] Developmental variation in language and cognition may affect the range and quality of symptom presentation.

Cognitive Delays

Cognitive delays are common with EOS.[26] Deficits in memory, executive functioning, attention, and global impairments are generally noted. Children who later develop schizophrenia often have premorbid problems with verbal reasoning, working memory, attention, and processing speed.[27] Cognitive decline typically occurs at the time of onset of illness. Once established, intellectual deficits appear to be stable over time without continued deterioration.[28] These findings are consistent with those in the adult literature.

Premorbid Functioning

Premorbid abnormalities are evident in most youth who develop schizophrenia, especially those with COS.[29] Common premorbid difficulties include social withdrawal and isolation, disruptive behavior disorders, academic difficulties, speech and language problems, and cognitive delays. Because schizophrenia in youth often has an insidious onset, the gradual development of psychotic symptoms in a child with premorbid language delays and social withdrawal can be difficult to recognize.

Predicting which youth with premorbid characteristics of schizophrenia will eventually develop the disorder remains a challenge. Factors in high-risk youth that predict progression into the illness include familial risk for schizophrenia plus a recent deterioration in functioning; unusual, suspicious, or paranoid thought content; greater social impairment; and/or a history of substance abuse.[30]

ETIOLOGY

Schizophrenia is a heterogeneous disorder with multiple etiologies. To date, no single set of causes has been identified. Current evidence suggests that a multifactorial neurodevelopmental model best explains the development of schizophrenia, with multiple genetic and environmental exposures playing roles.[31] Neurobiological research suggests that EOS and adult-onset schizophrenia share etiologic factors, although EOS may be a more severe form.[32,33]

Genetic Factors

Family, twin, and adoption studies support a strong genetic component for schizophrenia. The lifetime risk of developing the illness is 5 to 20 times higher in first-degree relatives of affected probands compared with the general population. The rate of concordance between monozygotic twins is approximately 40% to 60%. Concordance rates in dizygotic twins and other siblings are 5% to 15%.[34] Genomewide association studies, using large collaborative international cohorts, have published findings implicating different

genomic loci and genes, including the major histocompatibility complex (6p21.1), MIR137, and ZNF804a.[35,36] For EOS, positive associations have been reported for several candidate genes, including those reported in the adult literature.[37]

Emerging evidence shows that rare deletions and duplications are enriched in individuals with schizophrenia.[38-42] Structural mutations arising at genomic "hotspots," including 1q21.1, 15q13.3, and 22q11.2, may be responsible for 0.5% to 1.0% of cases. EOS appears to be associated with a higher rate of large cytogenetic abnormalities and rare structural variants[37] than reported in adults with the illness. These include 22q11.2 deletion syndrome (velocardiofacial syndrome),[43] which is associated with substantial rates of behavioral, cognitive, and psychiatric problems, including psychosis. Most rare copy number errors detected in affected persons are found at different genetic loci, and many are unique to one individual or family. Thus, the emerging research suggests that most affected persons have a different genetic cause, which has important implications for intervention and translational research.[44]

Environmental Exposures

Genetic and environmental factors interact to shape neurodevelopmental processes, affecting disease risk and progression.[45] Environmental exposures may mediate disease risk by different mechanisms, including direct neurologic damage, gene-by-environment interactions, epigenetic effects, and/or de novo mutations.[46] Numerous environmental factors have been hypothesized to contribute to the development of schizophrenia, including in utero exposure to maternal famine, paternal age, prenatal infections, obstetric complications, marijuana use, and immigration.[47]

Neuroanatomic Abnormalities

Structural brain aberrations most consistently reported in adults with schizophrenia include increased lateral ventricle volumes and decreases in hippocampus, thalamus, and frontal lobe volumes.[48] EOS is associated with similar abnormalities,[49,50] with limbic structures appearing to play a particularly important role.[51] Youth with EOS exhibit significant decreases in gray matter volumes[52,53] and decreased cortical folding.[54] Cortical abnormalities appear to be most profound in COS.[55] Follow-up longitudinal studies have shown that cortical thinning in COS may plateau in early adulthood, when it becomes similar to the adult regional pattern.[56,57] Structural brain findings found in EOS are theorized to stem from the disruption of neurodevelopmental processes emerging during adolescence.[58] In the National Institute of Mental Health COS cohort, unaffected siblings of patients shared similar patterns of cortical deficits, suggesting these are familial traits with variable impact on disease risk.[59,60]

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.[61] Psychosocial factors, including expressed emotion within the family setting, influence the onset and/or exacerbation of acute episodes and relapse rates. These interactions are complex and bidirectional. Being raised in a healthy home environment may be protective for children with a familial risk for schizophrenia.[62] Alternatively, 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.

COURSE AND OUTCOME

The course of schizophrenia varies across individuals. There are hallmark phases that are important to recognize when making diagnostic and therapeutic decisions.

Prodrome. Most patients experience some degree of functional deterioration before the onset of psychotic symptoms, including social withdrawal and isolation, idiosyncratic or bizarre preoccupations, unusual behaviors, academic failure, deteriorating self-care skills, and/or dysphoria. These changes may be associated with depression, anxiety, aggressive behaviors, or other conduct problems, including substance abuse, which often confuse the diagnostic picture. The prodromal phase may vary from an acute marked change in behavior to a chronic insidious deterioration.

Acute Phase. The acute phase is marked by prominent positive symptoms (i.e., hallucinations, delusions, disorganized speech and behavior) and a significant deterioration in functioning. This phase may last several months depending in part on the response to treatment.

Recuperative/Recovery Phase. After the acute phase, with the remission of the acute psychosis,

there is generally a several-month period when the patient continues to experience a significant degree of impairment. Negative symptoms (flat affect, anergia, social withdrawal) predominate, although some positive symptoms may persist. In addition, some patients will develop a post-psychosis depression characterized by dysphoria.

Residual Phase. Youth with EOS may have prolonged periods (several months or more) between acute phases when they do not experience significant positive symptoms. However, most patients will continue to be at least somewhat impaired owing to negative symptoms. Unfortunately, some affected individuals never progress to residual symptoms and remain chronically symptomatic despite adequate treatment.

Outcome

Follow-up studies of EOS, spanning periods up to several decades, have suggested moderate to severe impairment across the lifespan.[25] Poor long-term outcome is predicted by low premorbid functioning, insidious onset, higher rates of negative symptoms, childhood onset, and low intellectual functioning.[15,63-67] When followed into adulthood, youth with EOS have shown greater social deficits, lower levels of employment, and a lower likelihood to live independently compared with those with other childhood-onset psychotic disorders.[67,68]

Suicidality is prevalent in youth with schizophrenia spectrum disorders.[69] In follow-up studies, at least 5% of individuals with EOS died by completed suicide or by accidental death directly because of behaviors influenced by psychotic thinking.[17,70] As adults, individuals with schizophrenia are at higher risk of other morbidities, such as heart disease, obesity, human immunodeficiency virus, hepatitis, and diabetes.[71]

DIFFERENTIAL DIAGNOSIS

The effective treatment of schizophrenia relies on an accurate diagnosis and a thorough assessment to identify any other contributing medical or psychiatric conditions and/or psychosocial stressors. The proper assessment of psychosis in youth requires the gauging of potential symptom reports in the context of normal development. The mere fact that a child responds affirmatively to questions regarding hallucinations or delusions does not ipso facto mean the child is psychotic. Psychotic symptoms occur in the context of an illness, and psychotic illnesses are rare in youth, especially in children younger than 12 years. The accurate diagnosis of schizophrenia and other psychotic illnesses should be based on characteristic patterns of illness and overt signs on the mental status examination. Clinical features that help confirm a diagnosis of schizophrenia include deteriorating function, thought disorder, and bizarre behavior. There are several important diagnoses to rule out when assessing a youth for schizophrenia.

Medical Conditions

The list of medical conditions that can result in psychosis is exhaustive, including central nervous system infections, delirium, neoplasms, endocrine disorders, genetic syndromes (e.g., velocardiofacial [22q11] syndrome), autoimmune disorders, and toxic exposures.

Drugs of abuse that can result in psychotic symptoms include dextromethorphan, lysergic acid diethylamide, hallucinogenic mushrooms, psilocybin, peyote, cannabis, stimulants, and inhalants. Prescription drugs associated with psychosis, especially when used inappropriately, include corticosteroids, anesthetics, anticholinergics, antihistamines, and amphetamines. Typically, acute psychosis secondary to intoxication resolves within days to weeks once the offending drug is discontinued.

Adolescents with EOS appear to be at substantial risk for comorbid substance abuse.[72] Cannabis use in teenagers is associated with a higher risk of eventually developing psychosis.[73] When drug abuse precedes the development of schizophrenia, it is difficult to gauge whether the psychosis represents independent drug effects or the unmasking of the underlying illness in an individual with other neurobiological vulnerabilities.

Schizoaffective Disorder

By definition, schizoaffective disorder requires the presence of psychotic symptoms plus prominent mood episodes (meeting full criteria for mania or depression) that are present for a substantial duration of the illness. The *DSM-5* emphasizes the requirement of a full mood episode, which should be present for the majority of the total duration of the active and residual portions of the illness. These are important distinctions because mood symptoms, such as dysphoria, irritability, or grandiosity, are common in individuals with schizophrenia, and the reliability of the diagnosis of schizoaffective disorder in clinical settings has been poor.

Youth with schizoaffective disorder present with the same severity of psychotic symptoms and functional impairment as those with schizophrenia.[74] The stability of early-onset schizoaffective disorder as a diagnosis appears to vary over time and can be difficult to distinguish from schizophrenia.[15,21]

Affective Psychosis

Psychotic mood disorders (especially bipolar disorder) can present with different affective and psychotic symptoms. Full-blown mania in teenagers often presents with florid psychosis, including hallucinations, delusions, and thought disorder.[75] Psychotic depression may present with mood congruent or incongruent hallucinations or delusions.[76]

Alternatively, symptoms of schizophrenia, such as negative symptoms, may be confused with a mood disorder. The overlap in symptoms increases the likelihood of misdiagnosis. Longitudinal reassessment is needed to ensure diagnostic accuracy.

Atypical Reports of Psychotic Symptoms

Many children and adolescents report symptoms suggestive of hallucinations and delusions, yet do not present with overt evidence of psychosis.[22,23,77] In an epidemiologic survey, questions regarding possible psychotic symptoms had a high rate of false-positive results.[78] Reports suggestive of psychosis in children may stem from overactive imaginations, cognitive limitations, or simply misunderstanding the question.

Youth diagnosed with posttraumatic stress disorder, conduct problems, and/or depression have been found to report significantly higher rates of psychotic-like symptoms than controls.[22,23,77] Maltreated youth are particularly vulnerable to report such symptoms, which may represent dissociation and/or anxiety, including intrusive thoughts/worries, derealization, or depersonalization.[15,79-81] Individuals with childhood abuse histories are at greater risk for being diagnosed with psychotic illnesses as adults.[82,83] Of course, individuals with schizophrenia may have significant histories of trauma. A trauma history neither establishes nor rules out a schizophrenia spectrum disorder. The clinical task is to determine the nature of symptom reports to make an accurate diagnostic assessment. Differentiating trauma-related symptoms from true psychosis can be particularly challenging, yet has important implications for treatment and diagnostic specificity.[84]

Pervasive Developmental Disorders/Autism

Autism and pervasive developmental disorders are distinguished from schizophrenia by the absence of psychotic symptoms and by the predominance of the characteristic deviant language patterns, aberrant social relatedness, or repetitive behaviors. The younger age of onset and the absence of a normal period of development are also indicative. The premorbid abnormalities in EOS tend to be less pervasive and severe than those with autism.[10,11]

Youth with schizophrenia often have premorbid and/or comorbid problems with social oddities and aloofness, which may be characterized as autism spectrum disorders.[85] These symptoms are likely nonspecific markers of disrupted brain development[86] and may reflect potential shared etiologic mechanisms that are common to both syndromes.[85] Once psychotic symptoms become apparent, the diagnosis of schizophrenia takes precedence.

EVIDENCE BASE FOR PRACTICE PARAMETERS

In this parameter, recommendations for best assessment and treatment practices are stated in accordance with the strength of the underlying empirical and/or clinical support.

- Clinical Standard [CS] is applied to recommendations that are based on rigorous empirical evidence (e.g., meta-analyses, systematic reviews, individual randomized controlled trials) and/or overwhelming clinical consensus
- Clinical Guideline [CG] is applied to recommendations that are based on strong empirical evidence (e.g., nonrandomized controlled trials, cohort studies, case-control studies) and/or strong clinical consensus
- Clinical Option [OP] is applied to recommendations that are based on emerging empirical evidence (e.g., uncontrolled trials or case series/reports) or clinical opinion, but lack strong empirical evidence and/or strong clinical consensus
- Not Endorsed [NE] is applied to practices that are known to be ineffective or contraindicated

The strength of the empirical evidence is rated in descending order as follows:

- Randomized, Controlled Trial [rct] is applied to studies in which subjects are randomly assigned to two or more treatment conditions

- Controlled Trial [ct] is applied to studies in which subjects are nonrandomly assigned to two or more treatment conditions
- Uncontrolled Trial [ut] is applied to studies in which subjects are assigned to one treatment condition
- Case series/report [cs] is applied to a case series or a case report

RECOMMENDATIONS

Recommendation 1. Psychiatric assessments for children and adolescents should include screening questions for psychosis. [CS]

In the psychiatric assessment, general inquiries should be made regarding changes in behavior or any evidence of problems with thinking or perceptions. Questions such as "Does your mind ever play tricks on you?," "Do you hear voices talking to you when no one is there?," and "Does your mind ever feel confused" help elicit possible symptoms. Youth with EOS can generally describe relevant aspects of their psychotic symptoms, although some will be too disorganized, confused, and/or paranoid to provide accurate details or relevant history. Parents, family members, teachers, and treatment providers are important sources of information for documenting overt changes in behavior and thinking.

It is important to gauge suspected psychosis in a developmental context. When evaluating youth, especially children younger than 12 years, the clinician must ensure that the child understands the question and that developmental considerations are taken into account. True psychotic symptoms are generally confusing to the individual and experienced as distressing external phenomena beyond the individual's control. Highly descriptive, detailed, organized, and/or situation-specific reports are less likely to represent true psychosis. Schizophrenia and other psychotic illnesses are associated with disorganized thinking and behavior and deterioration in functioning. Overt signs of the illness should be evident on the mental status examination and in descriptions of the child's behavior. Without overt evidence of psychosis, the validity of symptom reports suggestive of schizophrenia in children needs to be carefully scrutinized.

Recommendation 2. The diagnosis of schizophrenia in children and adolescents should follow *DSM-5* criteria, using the same criteria as for adults. [CS]

A comprehensive diagnostic assessment includes interviews with the child or adolescent and the family plus a review of past records and any other available ancillary information. Issues to address include overt evidence of psychotic symptoms (including mental status examination findings, symptom presentation, course of illness) and a pertinent review of systems and potential confounding factors (including any history of significant developmental problems, mood disorders, trauma, or substance abuse).

Diagnostic accuracy may be improved by using a structured diagnostic interview that is designed for youth and includes a module for psychotic illnesses.[87] Diagnostic status should be reassessed over time because clinical presentations of psychotic illnesses tend to change, especially during the first few years of illness.[88] In some cases, decreasing a child's medication burden (including attempting a medication-free trial if possible) may be indicated to clarify a complicated clinical presentation.

Recommendation 3. Youth with suspected schizophrenia should be carefully evaluated for other pertinent clinical conditions and/or associated problems, including suicidality, comorbid disorders, substance abuse, developmental disabilities, psychosocial stressors, and medical problems. [CS]

Youth with suspected schizophrenia require a thorough psychiatric and medical evaluation, including the assessment for common comorbid conditions, such as substance abuse or cognitive delays. When present, active psychotic symptoms are generally prioritized as the main target for treatment. Comorbid conditions, such as substance abuse, may respond better to treatment once acute symptoms of schizophrenia are stabilized. However, any life-threatening symptoms, such as suicidal behavior or severe aggressive behaviors, must be prioritized in the treatment plan.

There are no neuroimaging, psychological, or laboratory tests that establish a diagnosis of schizophrenia. The medical evaluation focuses on ruling out nonpsychiatric causes of psychosis and establishing baseline laboratory parameters for monitoring medication therapy. More extensive evaluation is indicated for atypical presentations, such as a gross deterioration in cognitive and motor abilities, focal neurologic symptoms, or delirium.

Assessments are obtained based on specific medical indications, e.g., neuroimaging studies

when neurologic symptoms are present or an electroencephalogram for a clinical history suggestive of seizures. Toxicology screens are indicated for acute onset or exacerbations of psychosis when exposure to drugs of abuse cannot otherwise be ruled out. Genetic testing is indicated if there are associated dysmorphic or syndromic features. Similarly, tests to rule out specific syndromes or diseases (e.g., amino acid screens for inborn errors of metabolism, ceruloplasmin for Wilson disease, porphobilinogen for acute intermittent porphyria) are indicated for clinical presentations suggestive of the specific syndrome in question. Broad screening for rare medical conditions is not likely to be informative in individuals with psychosis who do not present with other neurologic or medical concerns.

At the time of first diagnosis, routine laboratory testing typically assesses blood counts, liver and renal functions, and metabolic parameters and thyroid functions, which provide a general medical screen and serve as baseline assessments for medication monitoring. Neuropsychological testing cannot be used to establish the diagnosis but may be important for documenting cognitive deficits and for treatment and academic planning.

Recommendation 4. Antipsychotic medication is a primary treatment for schizophrenia spectrum disorders in children and adolescents. [CS]

The efficacy of antipsychotic medications in the acute treatment of adults with schizophrenia is well established.[89] In community settings, the atypical agents are often considered the preferred treatment. However, large adult trials, including the Clinical Antipsychotic Trials of Intervention Effectiveness study,[90[rct]] the Cost Utility of the Latest Antipsychotic Drugs in Schizophrenia study,[91[rct]] and the European First-Episode Schizophrenia Trial study,[92[rct]] raise questions as to whether second-generation (atypical) antipsychotics truly have superior efficacy than first-generation (typical) antipsychotics. Furthermore, many patients do not maintain the same medication treatment long term, often owing to lack of efficacy, side effects, or noncompliance.

Antipsychotic agents are also considered first-line treatment for schizophrenia spectrum disorders in youth, with second-generation agents typically being the treatments of first choice.[93] It is recommended that these agents are used in conjunction with psychotherapeutic interventions (Recommendation 9).

Several controlled trials of antipsychotic agents for EOS have been conducted, although all have limitations and more studies are needed. Older studies support the use of loxapine[94[rct]] and haloperidol.[95[rct]] For adolescents with EOS, industry-sponsored randomized controlled acute trials support the efficacy of risperidone (n = 257)[96[rct]] and aripiprazole (n = 302).[97[rct]] An industry-sponsored trial found olanzapine to be superior to placebo on symptom ratings of psychosis (n = 107). However, the overall response rate for olanzapine was low (38%) and did not differ from placebo.[98[rct]]

There are few studies comparing the efficacy and safety of different agents for EOS. In youth with more broadly defined psychotic disorders (n = 50), olanzapine was maintained significantly longer than risperidone and haloperidol.[99[rct]] The proportion of responders at 8 weeks for olanzapine (88%), risperidone (74%), and haloperidol (53%) was not significantly different. Sedation, extrapyramidal side effects (EPSs), and weight gain were common in all three groups. A small randomized controlled 6-week trial of adolescents with first-onset psychosis (n = 22) found no significant differences in efficacy or tolerability between risperidone and quetiapine.[100[rct]] Similarly, an 8-week study of youth with different psychotic illnesses (n = 30) found no differences in efficacy among olanzapine, risperidone, and quetiapine.[101[rct]]

A national survey of Medicaid claims from 2001 to 2005 found that approximately 75% of youth diagnosed with a schizophrenia-related disorder discontinued their atypical antipsychotic medication (aripiprazole, risperidone, quetiapine, olanzapine, or ziprasidone, N = 1745) within 18 months of initiating treatment.[102[cs]] There were no differences in rates of treatment discontinuation or the need for psychiatric hospitalization among the different agents. A naturalistic follow-up study of youth with first-onset psychosis (n = 109),[103[cs]] found that the agents used most often by providers were risperidone, quetiapine, and olanzapine. The three agents did not differ in measurements of symptom decrease. Olanzapine caused more weight gain, whereas risperidone was associated with more neurologic side effects.

The Treatment of Early Onset Schizophrenia Spectrum Disorders Study (TEOSS) compared olanzapine, risperidone, and molindone for youth with EOS spectrum disorders, using a randomized double-blind design. Fewer than 50% of participants (n = 119) responded over

8 weeks of acute treatment.[104][rct] There were no significant differences found among the treatment groups in response rates or magnitude of symptom decrease. Patients receiving olanzapine gained significantly more weight than participants in the other two treatment arms. There were no statistically significant differences in mean EPS ratings among groups. However, all patients in the molindone group received prophylactic benztropine therapy, which likely influenced the rate of EPS.

Subjects in the TEOSS who were rated as responders after 8 weeks of therapy were allowed to continue their medication for up to an additional 44 weeks of maintenance treatment. Only 12% of subjects completed 12 months of therapy on their originally assigned medication.[105][rct] There were no significant differences among molindone, risperidone, and olanzapine in long-term treatment outcomes. Symptom improvements evident at 8 weeks tended to plateau. Thus, evidence from the TEOSS suggests that none of the agents worked sufficiently well and all had potential problems with side effects.

At this time, most atypical and traditional agents, with the exception of clozapine, can be used as primary treatment options for EOS. Risperidone, aripiprazole, quetiapine, paliperidone, and olanzapine are approved by the Food and Drug Administration for treating schizophrenia in adolescents 13 years and older. Haloperidol and molindone are approved by the Food and Drug Administration for treating schizophrenia in youth 13 years and older. However, the production of molindone was discontinued by the manufacturer.

Safety and effectiveness data addressing the use of antipsychotic medications for EOS remain limited and for the most part reflect short-term use. Comparative trials are generally lacking. The choice of which agent to use first is typically based on Food and Drug Administration approval status, side effect profile, patient and family preferences, clinician familiarity, and cost. 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. The risk for weight gain with olanzapine may limit its use as a first-line agent. An industry-sponsored trial of ziprasidone for adolescents with schizophrenia was terminated prematurely in 2009 because of a lack of efficacy. Therefore, ziprasidone probably should not be considered for this population unless other data supporting efficacy become available.

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

Recommendation 5. Ongoing medication therapy should be provided to most youth with schizophrenia to improve functioning and prevent relapse. [CS]

Most individuals with schizophrenia need long-term treatment and are at significant risk of relapse if their antipsychotic medication is discontinued.[89] Most youth with EOS remain chronically impaired, even with treatment.[64,66,68,70,105] Patients should maintain regular physician contact to monitor symptom course, side effects, and adherence. The goal is to maintain the medication at the lowest effective dose to minimize potential adverse events. Many youth will continue to experience some degree of positive or negative symptoms, requiring ongoing treatment. The patient's overall medication burden should be reassessed over time, with the goal of maintaining effective dosages and minimizing side effects. Adjustments in medications should be gradual, with adequate monitoring for changes in symptom severity. After a prolonged remission, a small number of individuals may be able to discontinue antipsychotic medications without re-emergence of psychosis. In these situations, periodic longitudinal monitoring is still recommended because some of these patients may eventually experience another psychotic episode.

Recommendation 6. Some youth with schizophrenia spectrum disorders may benefit from adjunctive medication treatments to address side effects of the antipsychotic agent or to alleviate associated symptomatology (e.g., agitation, mood instability, depression, explosive outbursts). [CG]

Adjunctive medications commonly used in clinical practice include antiparkinsonian agents (extrapyramidal side effects), β-blockers (akathisia), mood stabilizers (mood instability, aggression), antidepressants (depression, negative symptoms), and/or benzodiazepines (anxiety, insomnia, akathisia). Benzodiazepines also are used as primary treatments for catatonia.[106] There are no studies systematically addressing the use of adjunctive agents in youth with schizophrenia. Although adjunctive agents are widely used in adults with

schizophrenia, further research is needed to establish their efficacy.[107] Medication trials need to be conducted systematically to avoid unnecessary polypharmacy. Although youth with schizoaffective disorder are often assumed to need concurrent antidepressants or mood stabilizers, these practices have not been systematically studied. In the TEOSS, there were no significant differences in treatment response between patients with schizophrenia and those with schizoaffective disorder.[104]

The ω-3 fatty acids have been suggested to be potentially useful as an adjunctive treatment for schizophrenia or as preventive therapy.[108] One randomized controlled trial found that ω-3 fatty acids helped delay the onset of psychosis in high-risk patients.[109[rct]] As of yet, this study has not been replicated, and at this time there are no interventions with conclusive evidence for treating prodromal psychosis.[110]

Recommendation 7. A trial of clozapine should be considered for youth with treatment resistant schizophrenia spectrum disorders. [CS]

Clozapine is the only antipsychotic agent for which there is established superiority over other agents. For treatment-refractory EOS, clozapine was more beneficial than haloperidol (n = 21) or high-dose olanzapine (n = 39) for positive and negative symptoms (n = 21)[111[rct],112[rct]] and superior to olanzapine for negative symptoms (n = 25).[113[rct]] A naturalistic follow-up study of EOS found clozapine more effective than haloperidol, risperidone, or olanzapine (n = 47).[114[cs]] However, owing to potential side effects, clozapine is reserved for treatment refractory cases, i.e., patients with two or more failed trials of a first-line antipsychotic agent.

Before using clozapine, it is important to review the child's clinical status and treatment history to ensure that the presentation accurately reflects treatment refractory schizophrenia. For complicated cases or the apparent diagnosis of schizophrenia in a younger child (e.g., <12 years), a diagnostic second opinion may be warranted.

When using clozapine, systematic monitoring of side effects, including following established protocols for blood count monitoring, is required. White blood cell and absolute neutrophil counts are obtained at baseline and weekly for the first 6 months to monitor the risk for agranulocytosis. These protocols require a coordinated effort among the pharmacy, laboratory, and physician to ensure that the blood count parameters are being monitored concurrently with prescriptions.

Recommendation 8. Baseline and follow-up monitoring of symptoms, side effects, and laboratory tests should be performed as indicated. [CS]

Antipsychotic medications need to be monitored systematically for side effects (for specific recommendations, see the American Academy of Child and Adolescent Psychiatry [AACAP] Practice Parameter for the Use of Atypical Antipsychotic Medications in Children and Adolescents).[115] When using second-generation antipsychotic agents, it is particularly important to monitor metabolic functions and weight gain. Youth appear to be particularly prone to metabolic side effects, including the long-term risks of diabetes and hyperlipidemia.

In a naturalistic study, youth naive to antipsychotic therapy (n = 272, 4–19 years old) gained on average 4.4 kg on aripiprazole, 5.3 kg on risperidone, 6.1 kg on quetiapine, and 8.5 kg on olanzapine over approximately 12 weeks of treatment.[116] Indications for treatment included psychosis, mood disorders, and/or disruptive behavior disorders. A comparison group of psychiatrically ill youth not receiving an antipsychotic agent (n = 15) gained only 0.2 kg over the same time period. Significant increases in cholesterol and/or triglycerides were noted in subjects taking olanzapine, quetiapine, and risperidone.

These data highlight the significant risk of weight gain with second-generation agents in children and adolescents and portend long-term risks for cardiovascular and metabolic problems. Thus, it is important that metabolic functions and risk factors are systematically monitored, including body mass index, fasting glucose, fasting triglycerides, fasting cholesterol, waist circumference, high-density lipoprotein/low-density lipoprotein, blood pressure, and symptoms of diabetes.[117] Although the metabolic risks are widely recognized, most patients taking antipsychotic medications are not adequately monitored.[118]

Consensus guidelines recommend the following[119]:

- At baseline, assess the patient's and/or family history of obesity, diabetes, cardiovascular disease, dyslipidemia, or hypertension.
- Assess and document the patient's body mass index at baseline, at 4, 8, and 12 weeks, and at least every 3 months thereafter, or more often as indicated.

- Assess and document the patient's fasting glucose, fasting lipid profile, and blood pressure at baseline and after 3 months of treatment. If the results are normal after 3 months of treatment, glucose and blood pressure monitoring is recommended annually. If the lipid profile is normal after 3 months, follow-up monitoring is recommended at least every 5 years.

These consensus guidelines were developed for all age groups. Recommendations for pediatric patients suggest following up on metabolic parameters every 6 months, with more frequent monitoring as clinically indicated.[120]

All patients prescribed antipsychotic agents should be advised of the importance of a healthy lifestyle, including cessation of smoking, healthy diet, and routine exercise.[117,120] If a patient develops significant weight gain or evidence of metabolic syndrome (obesity, hypertension, dyslipidemia, and insulin resistance), the options include switching to a different antipsychotic agent with lower metabolic risk or adding an agent that targets metabolic problems (e.g., metformin).[120] Clinically significant abnormalities (e.g., hypercholesterolemia) should be targeted for specific treatment and may require referral for specialty care.[120]

EPSs, including dystonia, akathisia, tardive dyskinesia, and neuroleptic malignant syndrome, may occur with traditional or atypical agents and need to be periodically assessed throughout treatment. Standardized measurements, such as the Abnormal Involuntary Movement Scale[121] and the Neurological Rating Scale,[122] are helpful for monitoring for abnormal movements and neurologic side effects.

To avoid acute EPSs, the use of prophylactic antiparkinsonian agents may be considered, especially in those at risk for acute dystonias or have a history of dystonic reactions. The need for antiparkinsonian agents should be re-evaluated after the acute phase of treatment or if doses are lowered, because many patients do not need them during long-term therapy.

Other potential adverse events noted with antipsychotic agents include sedation, orthostatic hypotension, sexual dysfunction, hyperprolactinemia, electrocardiographic changes (including prolongation of the corrected QT interval), elevated liver transaminases, and steatohepatitis.[93] In adults, traditional and atypical antipsychotic agents are associated with an increased risk of sudden death.[123] Sudden death is very rare in pediatric populations. However, clinicians should be aware of the potential impact of these agents on cardiac functioning, including corrected QT interval prolongation, and monitor appropriately.

Recommendation 9. Psychotherapeutic interventions should be provided in combination with medication therapies. [CG]

In adults with schizophrenia, interventions found to be helpful include cognitive-behavioral therapies, social skills training, cognitive remediation, and family interventions. The goals of treatment include symptom reduction, improving social/occupational functioning, enhancing quality of life, and decreasing the risk for relapse.[124] In addition, interventions addressing comorbid conditions, such as substance abuse, are important to lower the risk of relapse and improve quality of functioning.

There are very few studies of psychosocial treatments for youth with schizophrenia. Psychoeducation, including parent seminars, problem-solving sessions, milieu therapy (while the subjects were hospitalized), and networks (reintegrating the subjects back into their schools and communities), was associated with lower rates of rehospitalization in a small sample of adolescents with EOS.[125[ut]] In a separate study, youth who received cognitive remediation plus psychoeducational treatment showed greater improvements in early visual information processing at 1-year follow-up, although no significant short-term improvements were found.[126[rct],127[rct]] A 3-month trial of cognitive remediation therapy, in comparison with standard therapy, was associated with improvements in planning ability and cognitive flexibility in adolescents with schizophrenia.[128[rct]]

Although further studies are needed, youth with EOS should benefit from adjunctive psychotherapies designed to remediate morbidity and promote treatment adherence. Strategies for the patient include psychoeducation regarding the illness and treatment options, social skills training, relapse prevention, basic life skills training, and problem-solving skills or strategies. Psychoeducation for the family is also indicated to increase their understanding of the illness, treatment options, and prognosis and to develop strategies to cope with the patient's symptoms. Some youth will need specialized educational programs and/or vocational training programs to address the cognitive and functional deficits associated with the illness.

Recommendation 10. Electroconvulsive therapy may be used with severely impaired

adolescents if medications are not helpful or cannot be tolerated. [OP]

Research evidence supports the use of electroconvulsive therapy (ECT), typically in combination with antipsychotic therapy, as a treatment for schizophrenia in adults.[129] ECT is generally used for patients who do not adequately respond to or cannot tolerate antipsychotic medications or those with catatonia.[106] ECT has not been systematically studied in youth with EOS.[130] The clinician must balance the relative risks and benefits of ECT against 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.

PARAMETER LIMITATIONS

The AACAP Practice Parameters are developed to assist clinicians in psychiatric decision making. These parameters are not intended to define the sole standard of care. As such, the parameters should not 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 other available resources. &

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AACAP Practice Parameters are developed by the AACAP CQI in accordance with American Medical Association policy. Parameter development is an iterative process among the primary author(s), the CQI, topic experts, and representatives from multiple constituent groups, including AACAP membership, relevant AACAP committees, the AACAP Assembly of Regional Organizations, and the AACAP Council. Details of Parameter development process can be accessed on the AACAP website. Responsibility for Parameter content and review rests with the author(s), the CQI, the CQI Consensus Group, and the AACAP Council.

AACAP develops patient-oriented and clinician-oriented Practice Parameters. Patient-oriented Parameters provide recommendations to guide clinicians toward best assessment and treatment practices. Recommendations are based on critical appraisal of the empirical evidence (when available) and clinical consensus (when not) and are graded according to the strength of the empirical and clinical support. Clinician-oriented Parameters provide clinicians with the information (stated as principles) needed to develop practice-based skills. Although empirical evidence may be available to support certain principles, principles are based primarily on clinical consensus. This Parameter is a patient-oriented Parameter.

The primary intended audience for AACAP Practice Parameters is child and adolescent psychiatrists; however, the information contained therein may be useful for other mental health clinicians.

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