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Efficacy and Tolerability of Second-Generation Antipsychotics in Children and Adolescents With Schizophrenia

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Early-onset schizophrenia-spectrum (EOSS) disorders (onset of psychotic symptoms before 18 years of age) represent a severe variant associated with significant chronic functional impairment and poor response to antipsychotic treatment. All drugs with proven antipsychotic effects block dopamine D_2 receptors to some degree. The ongoing development of the dopamine and other neurotransmitter receptor systems during childhood and adolescence may affect clinical response and susceptibility to side effects in youth. A literature search was conducted of clinical trials of antipsychotics in children and adolescents with EOSS disorders between 1980 and 2007 from the Medline database, reference lists, and conference proceedings. Trials were limited to double-blind studies of duration of 4 or more weeks that included 15 or more patients. Ten clinical trials were identified. Antipsychotic medications were consistently found to reduce the severity of psychotic symptoms in children and adolescents when compared with placebo. The superiority of clozapine has been now demonstrated relative to haloperidol, standard-dose olanzapine, and "high-dose" olanzapine for EOSS disorders. However, limited comparative data are available regarding whether there are differences among the remaining second-generation antipsychotics (SGAs) in clinical effectiveness. The available data from short-term studies suggest that youth might be more sensitive than adults to developing antipsychotic-related adverse side effects (eg, extrapyramidal side effects, sedation, prolactin elevation, weight gain). In addition, preliminary data suggest that SGA use can lead to the development of diabetes in some youth, a disease which itself carries with it significant morbidity and mortality. Such a substantial risk points to the urgent need to develop therapeutic strategies to prevent and/or mitigate weight gain and diabetes early in the course of treatment in this population.

Key words: psychosis/atypical antipsychotic/weight management/metabolic syndrome/cognitive deficits/double-blind treatment trial

Introduction

Many clinicians view schizophrenia in childhood or adolescence as relatively rare; however, this belief is not fully accurate. Although the prevalence of childhood-onset schizophrenia (onset of psychotic symptoms before 13 years of age) is indeed very low (approximately 1/100 cases of schizophrenia),[1] the incidence of schizophrenia rises sharply at about 12–14 years of age.[2] Before 18 years of age, approximately 12%–33% of individuals with schizophrenia would develop the onset of their illness[3,4] and thus would be classified as having an early-onset schizophrenia-spectrum (EOSS) disorder.

When *Diagnostic and Statistical Manual of Mental Disorders, Third/Fourth Edition* (*DSM-III/IV*), criteria are rigorously applied, clinical and neurobiological studies have demonstrated a number of phenomenological similarities in the presentation of schizophrenia-spectrum disorders (ie, schizophrenia, schizoaffective disorder, schizophreniform disorder) in children/adolescents and adults with regard to the relative frequency of core psychotic symptoms (eg, auditory hallucinations, delusions, thought disorder), neurocognitive impairments, psychophysiological abnormalities, and the presence of structural brain abnormalities.[5,6] In comparison to adults with schizophrenia, there is an increased rate of premorbid abnormalities[7] and a rarity of well-formulated delusions reported by children/adolescents.[8] EOSS disorder patients frequently manifest early impairments in expressive language, motor function, and transient symptoms of pervasive developmental disorder well in advance of the first onset of psychotic symptoms.[7] However, children

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with EOSS disorder and autistic disorder can be distinguished on the basis of developmental history, clinical features, family history, and age at onset.[9] Higher rates of psychiatric comorbidity in EOSS disorder (ie, attention-deficit hyperactivity disorder, oppositional defiant disorder, and major depressive disorder) appear to be another important developmental difference between adults and youth with schizophrenia.[10] However, in children/adolescents pharmacological treatment of these comorbid conditions is rare that may reflect a lack of empirically driven guidelines for appropriate treatment and/or the hierarchical diagnostic system that is characteristic of *DSM-IV*.[10] It is important to note that psychotic symptoms are not specific to schizophrenia, and the differential diagnosis of EOSS disorder would include substance abuse, mood and anxiety disorders, and various medical conditions (eg, seizure disorders, infectious disease, metabolic and endocrine disorders, central nervous system lesions, etc). Also, there are a sizable number of children and adolescents with subsyndromal conditions who report psychotic symptoms that would not meet the severity/duration criteria required by *DSM-IV* to qualify for a diagnosis of schizophrenia.[11]

Naturalistic data show that EOSS disorder is a chronic, disabling disease, which, in the majority of cases, requires long-term antipsychotic medication treatment.[3,12–16] Studies of antipsychotic medications in adults with chronic schizophrenia may provide guidance for the treatment of children and adolescents with schizophrenia, but the treatment of pediatric patients has unique developmental aspects. To date, all the drugs with proven antipsychotic effects block dopamine D_2 receptors to some degree. Although the pathophysiology of schizophrenia remains unclear, it has been hypothesized that increased dopaminergic neurotransmission in the mesolimbic pathways produces the positive symptoms of the disease.[17,18] Based on this working hypothesis, it is thought that antipsychotic medications work by blocking dopamine D_2 receptors, thus dampening psychotic symptoms.[19] Preclinical studies suggest that there are substantial changes occurring within the dopamine system and other neurotransmitter systems during mid to late adolescence in the prefrontal cortex (PFC) in normative development[20] that may have implications for understanding the mechanism of onset of schizophrenia that typically occurs during late adolescence and early adulthood.[21] The specific maturational changes in the dopamine receptor system include decreases in dopamine cell density[22]; peaking of basal dopamine levels,[23] dopamine turnover,[24] and dopaminergic PFC input[25]; and changes in D_1 and D_2 receptor concentrations in the striatum.[26,27] Overall, these data suggest that, relative to adulthood, adolescence is characterized by increases in basal PFC dopamine levels. These maturational changes in the dopamine receptor system (as well as other neurotransmitter systems) during childhood and adolescence could potentially have implications for clinical response as well as an increased susceptibility to side effects (eg, extrapyramidal side effects [EPS], prolactin elevation, sedation, weight gain) observed in youth exposed to antipsychotic drugs.

Aside from making the initial diagnosis, choice of antipsychotic is probably the most important decision that a child and adolescent psychiatrist makes in collaborating with the patient/family in treating a young patient with a schizophrenia-spectrum disorder. Over the past few years, second-generation antipsychotics (SGAs) have been preferred over first-generation antipsychotics (FGAs) in the treatment of EOSS disorder.[28] However, increasing concerns about the adverse side effects associated with SGA treatment in children and adolescents point to the need to reexamine the risk/benefit of these agents. This descriptive review aims to systematically examine the evidence from randomized, double-blind comparison studies supporting the use of antipsychotics in EOSS disorder. The implications of recent treatment research are discussed including the identification of high priority areas for future research in this population.

Methods

A systematic literature search using the Medline database was performed to identify all random assignment, controlled pediatric clinical trials of antipsychotics in children and adolescents with schizophrenia-spectrum disorders whose results were published in the peer-reviewed literature from 1970 to 2007. Because we were aware of several treatment studies that were recently completed, we queried investigators and contacted manufacturers to locate additional studies and included data obtained from conference proceedings. Trials limited to double-blind studies of duration of 4 or more weeks with 15 or more patients were included in this review.

Results

We identified 10 double-blind studies that met our criteria for final review. These studies and their findings are presented below and summarized in table 1 by drug class (FGA, 3 studies; SGA, 7 studies).

First-Generation Antipsychotics

There have been 3 major studies that have examined the efficacy of FGAs in the treatment of EOSS disorder. Two of these utilized placebo controls and found a modest but significant superiority of active medication for acute positive symptoms over placebo: a crossover trial of moderate dose haloperidol (average daily dose 95 CPZ equivalents) in 16 children[29] and a 3-arm, parallel group study comparing loxitane (average daily dose 875 CPZ equivalents), haloperidol (average daily dose 490 CPZ

Table 1. Characteristics of Studies Included in the Review

Authors	Drugs, Mean Daily Dose (SD)	Duration	Participants	Effectiveness	Adverse Effects	Limitations
Pool et al[30]	Loxapine, 87.5 mg; haloperidol, 9.8 mg; placebo	4 weeks	$N = 75$, mean age: ~15.5 years	Both treatments significantly reduced BPRS total ratings compared with placebo. No significant differences observed between active treatment groups.	EPS (eg, muscle rigidity) noted in 19 (73%) of 26 receiving loxapine and 18 (72%) of 25 subjects receiving haloperidol. Sedation also problematic.	Short duration of treatment; small sample size
Realmuto et al[31]	Thiothixene, 16.2 mg; thioridazine, 178 mg	6 weeks	$N = 21$, mean age: ~15.5 years	Both treatments significantly reduced BPRS total scores. Clinical improvement noted within the first 7 days of treatment.	Marked sensitivity to sedative effects of medication, dose reductions required for both medications	Short duration of treatment, small sample size
Spencer et al[29]	Crossover design: haloperidol, 1.8 mg, vs placebo	6 weeks	$N = 16$, mean age (SD): ~8.9 years	CGI-I much/very much improved: 12 (75%) of 16; marked reduction in severity of persecutory ideation and hallucinations	Sedation observed at optimal doses	Short duration of treatment, small sample size
Kumra et al[69]	Clozapine, 176 mg (149); haloperidol, 16 mg (8)	6 weeks	$N = 21$, mean age (SD): 14.0 ± 2.3 years	Clozapine > haloperidol in terms of positive (SAPS total) and negative symptoms (SANS total)	One third of clozapine-treated patients discontinued treatment prematurely due to neutropenia or seizures	Short duration of treatment
Sikich et al[64]	Risperidone, 4 mg (1.2); olanzapine, 12.3 mg (3.5); haloperidol, 5.0 mg (2)	8 weeks	$N = 50$, mean age (SD): 14.7 ± 2.7 years; broad range of children with psychotic disorders included	All treatments significantly reduced BPRS-C total scores from baseline to end point; CGI-I much/very much improved and ≥ 20% BPRS-C reduction: 74% risperidone, 88% olanzapine, 54% haloperidol	Prevalence of extrapyramidal symptoms and weight gain higher and more severe in youth compared with published data from adult studies	Short duration of treatment, differences in the diagnosis across the treatment groups, concomitant use of antidepressants and/or mood stabilizers
Shaw et al[68]	Clozapine, 327 mg (113); olanzapine, 18.1 mg (4.3)	8 weeks	$N = 25$, mean age: ~12 years	Clozapine > olanzapine with respect to improvement in negative symptoms (SANS)	Marked weight gain at 4 kg during the 8-week trial noted in both groups, at 2-year follow-up, 6 (40%) of 15 patients were observed to have dyslipidemia	Short duration of treatment, study powered to detect only large treatment effects

Table 1. Continued

Authors	Drugs, Mean Daily Dose (SD)	Duration	Participants	Effectiveness	Adverse Effects	Limitations
Kumra et al[70]	Clozapine, 403.1 mg (201.8); olanzapine, 26.2 mg (6.5)	12 weeks	N = 39, mean age (SD): 15.6 (2.1)	Clozapine > "high-dose" olanzapine with respect to improvement in negative symptoms (SANS) for 12 weeks, CGI much/very much improved and ≥30% BPRS reduction: 66% clozapine, 33% olanzapine	Five (13%) of 39 patients (3 clozapine, 2 olanzapine) gained >7% of their baseline body weight; high incidence of dyslipidemia and prediabetes seen with both drugs	Short duration of treatment, small sample size
Robb et al,[58] Findling et al[57]	Aripiprazole, 10 mg; aripiprazole, 30 mg; PBO	6 weeks	N = 302, mean age: 15.5 years (range, 13–17)	Aripiprazole (10-mg and 30-mg doses) > PBO in terms of improvement from baseline to end point on the PANSS Total Score compared with placebo (−26.7 and −28.6, respectively; placebo, -21.2; Last Observation Carried Forward (LOCF)	Mild to moderate severity of spontaneously reported Adverse Events (AEs): extrapyramidal disorder, somnolence, akathisia; mean change in weight from baseline was minimal (10 mg, no change; 30 mg, 0.2 kg)	No data available from drug-naive subjects to assess whether aripiprazole is truly "weight neutral"; high placebo response rate
Haas et al[52]	Risperidone, 1–3 mg; risperidone, 4–6 mg; PBO	6 weeks	N = 160, mean age (SD): 15.6 years (1.3)	Both risperidone groups > PBO on the PANSS Total Score (risperidone 1- mg: −19.9 and risperidone 4–6 mg: −20.7, respectively; placebo, −7.8; LOCF)	Higher dose risperidone group had a greater incidence of EPS, dizziness, and hypertonia compared with lower dose group	Short duration of treatment
Kryzhanovskaya et al[50]	Olanzapine, 11.1 mg (4.0); PBO	6 weeks	N = 107, mean age (SD): 16.2 years (1.3)	Olanzapine > PBO in terms of improvement from baseline to end point on the BPRS-C (P = .003) and CGI-S (P = .004), respectively. Treatment response rate was not significantly different between olanzapine (37.5%) and PBO (25.7%).	Mean olanzapine-induced weight gain (4.3 ± 3.3 kg) higher and more severe in youth compared with adult studies	Short duration of treatment, high placebo response rate

Note: EPS, Extrapyramidal side effects; BPRS, Brief Psychiatric Rating Scale; CGI-I, Clinical Global Impression—Improvement Scale; CGI-S, Clinical Global Impression—Severity of Illness; BRPS-C, Brief Psychiatric Rating Scale for Children; SAPS, Scale for the Assessment of Positive Symptoms, SANS, Scale for the Assessment of Negative Symptoms; PBO, placebo; PANSS, Positive and Negative Syndrome Scale.

equivalents), and placebo in 75 adolescents.[30] The third study directly compared a high-potency FGA thiothixene (average daily dose 324 CPZ equivalents, $n = 13$) with a lower potency FGA thioridazine (average daily dose 178 CPZ equivalents, $n = 7$) in adolescents.[31] All these studies found significant extrapyramidal symptoms affecting 70% of those treated with haloperidol or loxitane and 50% of those treated with thiothixene. In addition, all studies reported significant—often intolerable—sedation.

The side effect profile of the FGAs, particularly motor side effects and the development of tardive dyskinesia, has led to their decreased utilization among child and adolescent psychiatrists.[32] In general, side effects associated with FGAs occur along a continuum: agents with low dopamine D_2 binding affinity/potency typically produce marked sedation, orthostasis, and moderate weight gain and medications with high dopamine D_2 binding affinity/potency more frequently cause motor side effects that seem partially dose related. There have been no long-term studies demonstrating the safety of FGAs in children, and thus, data must be extrapolated from adult studies. Case reports of antipsychotic-related tardive dyskinesia (TD) have been reported in adults and children for all the available antipsychotics, including the SGAs.[33] In adults, TD is of particular concern, with an incidence of approximately 5% per year of FGA exposure and a spontaneous remission rate of 2.5%.[33] In 2 large adult studies, the incidence of TD over 5 years was 20%–25%.[34–36] In addition, adult data suggest that FGAs appear to have minimal benefit for neurocognitive symptoms in comparison to SGAs.[37] However, it remains unclear to what extent the improvements in cognition demonstrated for SGAs in adult studies reflect normalization of cognitive deficits, practice effects, lack of inclusion of a healthy control group in some studies, or reduced burden of EPS.

Second-Generation Antipsychotics

The current published practice parameter for the assessment and treatment of children and adolescents with schizophrenia[38] does not address the question of which antipsychotic to prescribe as a first-line agent for patients based on phase of illness, severity of clinical symptoms, and side effect risk. Concerns about the safety and lack of efficacy of the FGAs prompted a search for more effective agents with better tolerability. As a class, SGAs have affinity for both dopamine D_2 receptors as well as for serotonin 5-hydroxytryptamine $(5\text{-HT})_2$ and include clozapine, risperidone (and its active metabolite paliperidone), olanzapine, quetiapine, and ziprasidone.[39] In addition, aripiprazole, another novel antipsychotic that is a partial dopamine agonist, is often classified as an SGA. The SGAs have become the standard treatment for EOSS disorder.[38]

As a class, these agents have a reduced propensity to cause adverse motor side effects and prolactin elevations when compared with FGAs of similar potency. However, as with FGA agents, each of the SGAs tends to be more prone to certain adverse effects that exist along a spectrum.[40] These side effects appear directly related to the unique receptor-binding profiles of each of the SGAs. For example, some SGAs (eg, quetiapine, clozapine) rapidly dissociate from the dopamine D_2 receptor[41] possibly allowing normal surges in dopamine to overcome receptor blockade in the nigrostriatal and tuberoinfundibular pathways. In contrast, aripiprazole acts as a selective partial agonist at the dopamine D_2 receptor.[42] These unique features may result in the lower EPS liability and minimal effects on prolactin levels of clozapine, quetiapine, and aripiprazole compared with other SGAs such as risperidone in children.[43–47] Whether the improved tolerability of the SGAs will enhance treatment adherence in children and adolescents with EOSS disorder remains an important, but unanswered question.

Nonadherence to treatment is a widespread phenomenon among youth with schizophrenia, due to such factors as impaired cognition, lack of insight, and side effects associated with antipsychotic treatment. Also, the quality of relationships with clinicians during acute admission appears to be an important determinant of patients' and families' attitudes toward treatment. Enhancing such relationships may yield important clinical benefits.[48] To date, there has been little systematic research examining the benefits of psychological interventions aimed at promoting medication adherence in children/adolescents. Although there are no data available regarding the use of risperidone microspheres (Risperdal Consta) in children and adolescents, injectables and long-acting formulations of antipsychotics may also offer benefits in terms of ensuring treatment adherence in select patients.

Placebo-Controlled Studies

As of the writing to this article, several US pharmaceutical manufacturers have short-term, placebo-controlled studies that are currently underway and/or that have been recently completed. It is possible that the patients included in these trials may not be "real-world" patients because they and their families must be willing to participate in a placebo-controlled trial. Also, while the carefully supervised conditions of a clinical trial allows children and adolescents with schizophrenia-spectrum disorders to be closely monitored, there remains some ethical concerns about withholding medications in children with EOSS disorder, particularly those who are severely ill, because it could be argued that participation in these trials may expose them to substantial risks.[49] To our knowledge, the results from 3 short-term placebo-controlled studies that have now confirmed the efficacy and tolerability of SGAs (risperidone, olanzapine, aripiprazole) relative to placebo in EOSS disorder have been presented at national meetings and the manuscripts for these data are currently under review.

A double-blind, flexible dose study randomized adolescents with schizophrenia to olanzapine (n = 72) or placebo (n = 35).[50] Improvements in overall psychopathology and illness severity were significantly greater in olanzapine-treated subjects (P = .003, .004, respectively). However, olanzapine-treated patients experienced somnolence, treatment-emergent liver enzyme abnormalities, prolactin elevation, and excessive weight gain (4.3 ± 3.3 vs 0.1 ± 2.8 kg, $P < .001$) compared with placebo. Although the profile of side effects appeared to be similar in adolescents vs adults, as seen in other studies,[44,51] the authors noted that the magnitude of olanzapine-induced weight gain may be greater in adolescents and was alarming in comparison to antipsychotic medications. Overall, the extant data might prompt clinicians to consider olanzapine as a "second-line" agent for children and adolescents with schizophrenia-spectrum disorders.

A double-blind, placebo-controlled study randomized patients to receive either risperidone 1–3 mg/day (n = 55), 4–6 mg/day (n = 51), or placebo (n = 54) for up to 6 weeks.[52] The mean change score in overall psychopathology was significantly greater in patients receiving "low-" or "high-" dose ranges of risperidone (1–3 mg: −21.3 ± 19.6; 4–6 mg: -21.2 ± 18.3) compared with placebo (−8.9 ± 16.1). The most commonly reported side effects were somnolence, agitation, and headache in the 1- to 3-mg group and extrapyramidal disorder, dizziness, and hypertonia in the risperidone 4- to 6-mg group.[52] The investigators reported no prolactin-related side effects or adverse reactions related to glucose or lipid metabolism in this short-term study.[52] However, risperidone treatment in children has been associated with galactorrhea, increased appetite, and moderate weight gain that can lead to metabolic problems and steatohepatitis.[51,53–56] Also, dose-dependent EPS[46,47] have been noted by other investigators and suggest that the overall benefit-risk profile of risperidone appears to be optimal in the lower dose ranges (1–4 mg) for children/adolescents.

A double-blind, placebo-controlled study randomized patients to aripiprazole 10 mg/day (n = 99), 30 mg/day (n = 97), or placebo (n = 98) for up to 6 weeks.[57,58] Improvement in overall psychopathology was significantly greater in the aripiprazole groups (10 mg, P = .04; 30 mg, P = .006) vs placebo.[58] The most commonly reported side effects were EPS, tremor, and somnolence.[57] The incidence of clinically significant weight gain (>7% increase) was modest in all treatment arms (placebo: 1.0%; 10 mg, 4%; 30 mg, 5.2%).[57] Although these data suggest that aripiprazole may be "weight neutral" in children and adolescents, a post hoc analysis in treatment-naive subjects was not conducted.

Active-Comparator Controlled Studies

To our knowledge, there are very limited data from controlled treatment trials that have compared the effectiveness of SGAs vs FGAs typically used as first-line treatments for children and adolescents with schizophrenia-spectrum disorders. At present, the appropriate positioning of the FGAs within treatment algorithms for EOSS disorder remains controversial, particularly in light of recent adult data from the Clinical Antipsychotic Trials of Antipsychotic Effectiveness study (CATIE)[59] and Cost Utility of the Latest Antipsychotic Drugs in Schizophrenia Study (CUtLASS-1)[60] involving adults with schizophrenia. Also, a recent meta-analysis of the treatment of EOSS disorder concluded that the FGAs were more effective and caused less weight gain than SGAs. However, there were several methodological flaws in this meta-analysis (eg, absence of control group in several studies, cohort effects by year of study, differences in the quality of studies, limited sample size of most studies included) that cast doubts on the validity of its conclusions.[61]

In adults, the CATIE trial was a publicly funded, direct, randomized, double-blind trials of multiple SGAs in comparison to a mid-potency FGA. Although there appeared to be a modest effectiveness advantage for olanzapine as compared with perphenazine, risperidone, and quetiapine in the CATIE trial, no advantage was observed for the other SGAs vs perphenazine.[59] Further, olanzapine was associated with more adverse effects, particularly related to weight and related metabolic abnormalities.[59] It should be noted that the results from the CATIE study differed significantly from some pharmaceutical company–sponsored short-term trials using haloperidol as the comparator.[62,63]

In children and adolescents, the Treatment of Adolescent Psychosis Study, an 8-week, double-blind study that compared risperidone, olanzapine, and haloperidol in 50 pediatric subjects (ages 8–19 years) with psychosis (60% of whom had EOSS disorder) found no statistical difference in the response rate or symptom reduction between agents, although there was a numeric trend favoring the 2 SGAs. Further, the time to all-cause treatment discontinuation was significantly longer in the olanzapine group than either the risperidone or haloperidol group ($P < .05$). However, there was significant weight gain (especially with the SGAs) and frequent extrapyramidal symptoms noted across treatment conditions even with the 2 SGAs.[64]

Also in children, a federally funded, 8-week, randomized, flexible dose, double-blind trial—the "Treatment of Early-Onset Schizophrenia Spectrum Disorders (TEOSS)" study—compared 2 SGAs (risperidone and olanzapine) to a weight-neutral FGA (molindone) in youth 8–18 years of age with EOSS disorder. TEOSS enrolled 119 youth[65]; initial publication of results from the study is anticipated within 1 year. Interestingly, weight gain associated with olanzapine treatment in this study was significantly greater than weight gain associated with either of the other 2 agents studied and led the

National Institute of Mental Health Data and Safety Monitoring Board to close randomizations to the olanzapine arm prematurely.[65] Preliminary analyses of the data revealed that there were significant reductions in positive symptoms observed with all 3 medications; however, adequate response was achieved in fewer than half of youth with EOSS disorder (Dr Lin Sikich, 2007).

After risperidone becomes available in a generic formulation, one important question for EOSS disorder treatment research will be to clearly define the potential advantages and cost-effectiveness of the other SGAs with respect to risperidone, particularly as policy makers and third-party payers question the incremental costs associated with these treatments. In children and adolescents with EOSS disorder, an open-label pilot study comparing 2 SGAs with ''continuously high'' dopamine D_2 receptor occupancy (ie, olanzapine and risperidone) with quetiapine, which is associated with only ''transiently high'' D_2 receptor occupancy,[66] found superior reduction in overall psychopathology for risperidone as compared with quetiapine but quetiapine had a more favorable side effect profile.[67] These preliminary data provide evidence for a hypothesis that there may be important differences in treatment outcome among currently available SGAs in EOSS disorder. However, to our knowledge, there have been no published double-blind studies that have compared the effectiveness of risperidone with other SGAs that may be comparable in terms of effectiveness but which may have the potential for significantly fewer adverse effects (eg, quetiapine, ziprasidone, aripiprazole).

Controlled Studies in Treatment-Refractory EOSS Disorder

Clozapine is generally reserved as a second-line intervention for pediatric patients with treatment-refractory schizophrenia due to its potential toxicities with regard to seizures and hematological adverse events.[68–70] In adults, clozapine has been shown consistently to have several advantages over FGAs in terms of overall clinical response and reduction of positive symptoms,[71] lower rates of EPS,[71–73] and tardive dyskinesia.[74,75] Initial open-label studies of clozapine used to treat children with EOSS disorder demonstrated a similar effectiveness for both positive and negative symptoms[76–80] and aggressive outbursts.[81]

From a preclinical standpoint, olanzapine is more similar to clozapine than any other SGA in terms of a significant affinity for 5-HT_{2a} and D_4 receptors in comparison to D_2 receptors and a significant affinity for 5-HT_{2c}, 5-HT_3, 5-HT_6, D_3, D_1, muscarinic (especially M_1), α_1, and H_1 receptors.[82,83] However, the drugs are by no means identical from a pharmacological standpoint and an initial pilot study in treatment-refractory youth with EOSS disorder suggested that there may be important differences in clinical effectiveness between the 2 compounds.[84] These preliminary findings were confirmed in 2 head-to-head comparisons that compared clozapine with olanzapine at both standard[68] and higher-than-customary doses (up to 30 mg/day)[70] in children with EOSS disorder who had primarily failed at least 2 trials of SGAs. Although olanzapine was shown to be effective for some treatment-refractory children and adolescents with schizophrenia in both studies, clozapine was found to be superior in terms of reduction of negative symptoms and less consistently in terms of severity of illness and overall clinical response.[68,70]

Because of clinicians' concern regarding clozapine's side effects (eg, agranulocytosis, weight gain, diabetes) and a reluctance on the part of patients/families to submit to frequent blood testing, we believe that clozapine therapy remains underutilized. Although clozapine is often considered a treatment of last resort, some clinicians will attempt to switch patients who have been stabilized on clozapine to another drug after they have been discharged from hospital. For these reasons and due to the relative rarity of EOSS disorder, it has been difficult to conduct systematic, long-term studies of the safety of clozapine treatment in children/adolescents. However, there are some long-term safety data for clozapine. In a retrospective chart review of 172 hospitalized children with serious emotional disturbances treated with clozapine (median observation period 8 months), the cumulative probability of developing a hematological adverse event (mainly neutropenia) over a 1-year period was 16.1%, which seems somewhat higher than what typically has been reported in adult studies.[85] However, the probability of developing agranulocytosis in this pediatric sample was 0.99%, which is comparable to that observed in adult studies.[85]

Weight Gain and Metabolic Side Effects Associated With SGA Treatment

Weight gain has emerged as one of the most significant and problematic side effects for children and adolescents treated with SGAs and a significant barrier to treatment adherence. Though considered a class effect associated with all SGAs, a recent review in children and adolescents indicated that the risk of weight gain is more substantial with clozapine and olanzapine, moderate with risperidone and quetiapine, and low with ziprasidone and aripiprazole.[45] Treatment with SGAs is associated with a general increase in caloric intake[86] that can cause a rapid increase in body weight for 50%–60% of children and adolescents in the first few months of therapy that may not reach a plateau even after 1 year of treatment.[45] These changes clearly exceed the expected weight changes associated with normal growth as indicated by a prospective naturalistic study that tracked body mass index

percentile scores up to 1 year.[45] The medical consequences of weight gain in children and adolescents include the metabolic syndrome and insulin resistance, which can then lead to type 2 diabetes.[87] A 10-year naturalistic study revealed that the Kaplan-Meier estimate for new-onset diabetes mellitus was approximately 43% for adults treated with clozapine.[88] Although there are no comparable long-term data for children, there are emerging data suggesting alarming levels of metabolic adverse effects (eg, impaired glucose tolerance, dyslipidemia) in pediatric subjects treated long term with SGAs (up to 1 year), including antipsychotic-naive patients.[44]

At present, the mechanism underlying the development of obesity and insulin resistance in children and adolescents treated with SGAs is not fully understood. There are some animal data that appetite stimulation/weight gain associated with SGAs (ie, clozapine, olanzapine) is mediated by activation of hypothalamic AMP-protein kinase that has been linked to blockade of the histamine H_1 receptor.[89] It is thought that both obesity and some direct drug effect on glucose metabolism contribute to the problem of insulin resistance in adults with schizophrenia.[88] Based on this working model, it is possible that interventions designed to limit weight gain during the initial phases of treatment, when weight gain with SGAs such as risperidone is most likely to occur,[90] may diminish the likelihood of long-term adverse metabolic consequences.

There are no good treatment guidelines regarding the best therapeutic strategy to address treatment-emergent obesity, diabetes, or hyperlipidemia in children or adolescents treated with SGAs. In some cases, children and adolescents can be managed with nonpharmacological therapy directed at minimizing the occurrence of these adverse events (eg, nutritional counseling). However, when these problems are severe or fail to respond to behavioral interventions, clinicians frequently contemplate a change in antipsychotic medication and/or the addition of a weight-loss agent (possible agents that have been put forward include metformin, orlistat, amantidine, and sibutramine). However, this is an area in which further research is needed. There are concerns that amantadine and sibutramine could exacerbate psychiatric symptomatology and that orlistat may be poorly tolerated due to flatulence and associated stigmatization.

Despite some initial data regarding the effectiveness of metformin to address weight gain and obesity in children treated with psychotropic drugs,[91] questions have been raised regarding both the use and long-term safety of pharmacological approaches as therapeutic/preventive strategies for limiting antipsychotic-induced weight gain.[92] How long do these interventions need to be continued? What are the consequences of the intervention? It is thought that lifestyle modification early in the course of antipsychotic treatment remains a promising avenue for preventing weight gain and other adverse outcomes in the majority of children receiving antipsychotic medications.[92,93]

Evidence-based behavioral interventions that have been developed for obese nonpsychiatrically ill children[94–96] emphasize diet modifications, increase in physical activity, and other behavioral interventions similar to programs that have been developed for adults with chronic and first-episode schizophrenia.[97] To our knowledge, no specific programs have been specifically tailored for use in acutely ill adolescents with schizophrenia-spectrum disorders who, in the majority of cases, are of normal weight prior to SGA treatment. Recent monitoring recommendations for weight gain and metabolic and endocrine side effects in youth exposed to antipsychotics have been put forward by Correll and Carlson (2006)[55]; however, a more formal consensus statement is currently being developed by the American Academy of Child and Adolescent Psychiatry and will be published shortly.

Future Priorities

There are several gaps in our knowledge base regarding the treatment of EOSS disorder. In particular, most of the studies reviewed herein have focused on short-term reductions in symptomatic outcomes and have not measured functional outcomes. Also, there has been a dearth of information regarding the utility of adjunctive psychosocial treatments and there have been relatively few head-to-head comparisons of currently available SGAs. In addition, there is a clear need for studies that examine the mechanisms by which antipsychotics medication work in pediatric populations and studies of interventions designed to address important adverse events such as antipsychotic-induced weight gain.

To date, a major obstacle to conducting informative treatment studies in EOSS disorder has been subject recruitment. There are a number of reasons for this problem that have been examined in detail elsewhere.[64] For example, substance misuse is a frequent comorbidity in youth with schizophrenia, and it is difficult to determine that psychotic symptoms are not substance induced particularly when treatment needs to be initiated symptomatically. Thus, these patients may not be included in clinical trials. The problem of subject recruitment has been overcome in recent industry and federally sponsored trials with the use of multisite studies. In addition, we would argue that intervention studies in this population should consider incorporating features of both efficacy and effectiveness trial designs. For example, although for scientific reasons it may be preferable to exclusively focus on patients with schizophrenia who do not require the addition of mood-stabilizing drugs, a sizable proportion of children and adolescents with schizophrenia-spectrum disorders present while taking such medications and acutely tapering them prior to randomization could

destabilize them, jeopardize their safety, and/or prevent their retention in a clinical trial. Thus, consideration should be given to designing protocols that include patients who have been on stable doses of such medications for at least 30 days and permit continuing them throughout the study. Lastly, the inclusion of a psychosocial treatment as a platform could enhance subject recruitment and retention.

Summary

A substantial proportion of individuals who develop schizophrenia will have the onset of their illness during early adolescence. An early onset of psychosis bodes poorly for prognosis, with an increased likelihood of chronic, treatment-resistant symptoms and disability. Until recently, there were few well-controlled treatment trials that focused on the treatment of EOSS disorder. There is an emerging consensus that aripiprazole and risperidone are effective drugs for the first-line treatment of acute exacerbation of psychosis in adolescents with schizophrenia, and both drugs may soon have a formal FDA indication for this population. Initial data had suggested that the olanzapine and risperidone were clinically more effective than a high-potency FGA, haloperidol, in adolescents with psychosis.[64] However, as seen in the CATIE trial in adults,[59] emerging data from TEOSS suggest that these differences are probably not clinically significant and that a substantial proportion of youth with schizophrenia respond poorly to currently available first-line antipsychotic treatments. To date, studies involving clozapine in treatment-refractory EOSS disorder have consistently demonstrated the superiority of clozapine with respect to haloperidol[98] and olanzapine at standard doses[68] and olanzapine at higher-than-customary doses[70] with respect to reduction in negative symptoms and, less consistently, with respect to overall response.[70,98] Across treatment studies of EOSS disorder, the emerging data indicate that adolescents might be particularly vulnerable to side effects (weight gain, metabolic problems, elevation in prolactin levels, sedation) suggesting limited generalizability of adult studies to younger patients.

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