Use of Antipsychotics in Children and Adolescents

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The comparable efficacy and improved safety of the atypical antipsychotics compared with the traditional antipsychotic agents in the treatment of schizophrenia and other disorders in adults have prompted the use of these agents in children and adolescents. The atypical antipsychotics are increasingly being used in children and adolescents with a variety of different psychiatric diagnoses, including schizophrenia, bipolar disorder, autism/pervasive developmental disorders, conduct disorder, depression, anxiety disorders, tic disorders, delirium, and eating disorders. Unfortunately, clinical use of these agents in pediatric patients has far exceeded the limited evidence from randomized controlled trials. This article reviews the available evidence from the published literature on the use of the atypical antipsychotics in children and adolescents with schizophrenia, bipolar disorder, and maladaptive aggression associated with autism/pervasive developmental disorders and conduct disorder/disruptive behavior disorders. *(J Clin Psychiatry 2005;66[suppl 7]:29–40)*

In the early 1990s, the antipsychotics were the most commonly prescribed pharmacologic agents for child and adolescent psychiatric inpatients.[1] Since then, the role of the antipsychotics, particularly the atypical antipsychotics, has expanded and now includes more outpatients and children and adolescents with a variety of psychiatric disorders. Besides schizophrenia, bipolar disorder, aggressive/disruptive behavior, depression, anxiety disorders, tic disorders, delirium, and eating disorders are examples of conditions for which clinicians are prescribing the atypical antipsychotics.[2]

Despite the increased use of the atypical antipsychotics, data supporting their use in children and adolescents from randomized controlled trials are remarkably scarce. Because the disorders for which the atypical antipsychotics are used are generally chronic, severe, and disabling, it is extremely important that double-blind, placebo-controlled data become available in order to provide clinically meaningful information about efficacy and safety. This article will consider the extant data regarding the use of antipsychotics in the treatment of schizophrenia, bipolar disorder, and aggression in pediatric patients.

SCHIZOPHRENIA

The onset of schizophrenia often occurs in adolescence, with many patients experiencing their first psychotic episode before the age of 15 years.[3–6] Although childhood-onset schizophrenia is much less common than the adolescent-onset illness,[7,8] psychotic illnesses also occur in prepubertal children.[5] Childhood- and adolescent-onset schizophrenia is generally more severe and treatment-refractory than adult-onset illness and has a poorer prognosis.[3,4,7,9]

There are remarkably few randomized controlled trials to inform treatment decisions for adolescent-onset schizophrenia.[10,11] The information that is available is derived largely from single case reports, retrospective case series, chart reviews, and open-label studies. Although contemporary treatment is, out of necessity, guided by the findings of studies in adults, adolescents may not respond to treatment in the same manner as older patients. Young people with schizophrenia are a particularly challenging population to study and treat. Adolescents may respond well to treatment for a period of time only to rapidly and unexpectedly decompensate.[12] Moreover, diagnosis can be difficult, and many adolescents with psychosis who are referred to specialty psychiatric care from mental health clinicians do not fulfill diagnostic symptom criteria for

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schizophrenia.[13] Nonetheless, schizophrenia in adolescents may respond to antipsychotic treatment, and the atypical antipsychotics are increasingly being used in this age group.[10,14–17]

Antipsychotic Studies in Children and Adolescents With Schizophrenia

Traditional antipsychotics. There are only 2 controlled studies of acute treatment with the older, "traditional" antipsychotics in adolescents with schizophrenia. Long-term studies have not been conducted in this population. Of the 2 available trials, 1 was published nearly 30 years ago and remains the largest published, randomized, placebo-controlled, double-blind study of any antipsychotic, traditional or atypical, in adolescent patients. In this study, Pool and colleagues[18] compared the efficacy and adverse effects of a 4-week, double-blind, placebo-controlled trial of haloperidol (mean dose = 9.8 mg), loxapine (mean dose = 87.5 mg), or placebo in 75 adolescent inpatients with schizophrenia. Both active treatments resulted in significantly greater symptom improvement than placebo, but were associated with higher rates of extrapyramidal symptoms (EPS) and sedation. Extrapyramidal symptoms were observed in 73% of patients treated with haloperidol, 72% treated with loxapine, and 4% treated with placebo. Sedation occurred in 52% of patients in the haloperidol group, 81% in the loxapine group, and 25% in the placebo group. The second controlled study was a single-blind, 4- to 6-week comparison of thiothixene and thioridazine treatment of 21 adolescents with schizophrenia (mean age = 14.6 years).[19] Both antipsychotics improved baseline Brief Psychiatric Rating Scale (BPRS) symptom scores. However, at study endpoint, most patients remained ill, with a mean BPRS score of 32.2. Rates of sedation (75%) and orthostasis (38%) were high with thioridazine, as were rates of sedation (54%) and EPS (54%) for thiothixene.

Clinical outcomes for schizophrenia, including therapeutic response and adverse events, may in part be age-related. For example, poor response to treatment with traditional antipsychotics may be associated with an earlier age at onset of schizophrenia.[9] Indeed, the findings of the 2 controlled studies of traditional antipsychotics in adolescents with schizophrenia[18,19] demonstrate improvement, but not resolution, of positive symptoms.

Atypical antipsychotics. In adults, the risk of EPS, tardive dyskinesia, dysphoria, and impaired cognition is lower with the atypical antipsychotics compared with the traditional agents, and this newer class of drugs is associated with improvement in both positive and negative symptoms of schizophrenia.[20] It is not definitely known whether the benefits associated with the atypical antipsychotics in adults are manifested in young people as well.

Clozapine. The clinical trial experience with clozapine in adolescents with schizophrenia consists of 1 short-term controlled study,[21] 2 open-label studies,[22,23] and 1 retrospective analysis of long-term treatment,[24] all of which were conducted in treatment-refractory patients. In the short-term controlled study, clozapine was compared with haloperidol in a double-blind fashion in 21 adolescents with schizophrenia.[21] This population was severely ill and treatment-refractory with a mean ± SD age of 14 ± 2.3 years and an age at onset of less than 13 years. Patients were randomly assigned to receive a 6-week course of flexible doses with either clozapine (mean dose = 176 mg) or haloperidol (mean dose = 16 mg; with prophylactic benztropine). Clozapine was superior to haloperidol across all outcome measures and reduced both positive and negative symptoms. Although EPS did not occur in the clozapine-treated patients, other adverse events associated with clozapine were of concern. Of the 10 patients in the clozapine group, neutropenia occurred in 4, seizures in 2, and sedation in 9. One third of the clozapine-treated patients were withdrawn from the study because of adverse events.

The efficacy and safety of long-term treatment with clozapine in 36 adolescents and young adults with schizophrenia were assessed in a retrospective review.[24] This is the only published analysis of long-term treatment with clozapine in the adolescent population. Patients were treated with clozapine (mean dose = 330 mg; range, 50–800 mg) for a mean duration of 154 days. Clinical response included marked improvement in 75% of patients and remission in 11%. Adverse events consisted of leukopenia (3 patients), electroencephalographic (EEG) changes (16 patients), akathisia (4 patients), and coarse tremor (1 patient). Six of the 36 patients discontinued treatment because of adverse events, which included stupor, leukopenia, cardiotoxicity, and significant transaminase elevations.

On the basis of available data, clozapine appears to have a role in treating adolescents with treatment-refractory schizophrenia. As in adults, however, caution must be taken to monitor leukocyte counts. In addition, adolescents may be at increased risk of EEG abnormalities or seizures during clozapine therapy, and pretreatment electroencephalograms may be a reasonable consideration.[10]

Risperidone. There is 1 controlled trial of risperidone treatment in children and adolescents with schizophrenia and other psychotic illnesses[25] and 3 open-label studies of more homogeneous populations of adolescents with schizophrenia.[26–28] In the controlled trial, risperidone was compared with olanzapine and haloperidol in a double-blind fashion. Fifty children and adolescents (aged 8–19 years) were enrolled and randomly assigned to 1 of 3 treatment arms for 8 weeks. At endpoint, 74% of patients in the risperidone group, 88% in the olanzapine group, and 53% in the haloperidol group achieved significant reductions from baseline BPRS scores. Somnolence, EPS, and weight gain occurred in each treatment group.[25] Another group of investigators reported the findings of an 8-week, open-label comparison of risperidone, olanzapine, and

haloperidol in 43 adolescents with schizophrenia.[27] These investigators concluded that each of the 3 treatments resulted in significant clinical improvement by week 4 and that risperidone was less sedating than olanzapine or haloperidol.

Two other open-label studies of risperidone in adolescents have been reported. Zalsman and colleagues[28] treated 11 adolescents with first-episode schizophrenia with risperidone (mean dose = 3.1 mg/day) for 6 weeks. Although risperidone therapy resulted in statistically significant reductions in the Positive and Negative Syndrome Scale (PANSS) total, BPRS, and Clinical Global Impressions-Severity of Illness scale (CGI-S) scores compared with baseline, improvement in the PANSS negative subscale score was not observed. In the second study, 10 adolescents (aged 11–18 years) with schizophrenia were treated for 6 weeks with higher doses of risperidone (4–10 mg/day; mean dose = 6.6 mg/day).[26] This was a moderately ill population, with a mean baseline PANSS score of 70.7. Seven patients were treatment-resistant, and 3 were neuroleptic-naive. Significant improvements in the total PANSS score, including positive and negative symptom scores, were achieved. Adverse events were common and included mild, but transient, somnolence (8 patients); acute dystonia (2 patients); parkinsonian syndrome (3 patients); dose-related orofacial dyskinesia (1 patient); blurred vision (1 patient); and impaired cognition (1 patient). Eight of the 10 adolescents experienced weight gain (mean = 4.9 kg) during the study.

These limited data suggest a role for risperidone in the treatment of adolescent schizophrenia. Gradual dosage titration may lessen the rate and severity of adverse events. However, EPS and weight gain may be limiting factors for long-term therapy, but this remains an empirical question requiring further study.

Olanzapine. Published data of olanzapine treatment of adolescent schizophrenia consist of small, open-label studies. Kumra and associates[29] assessed the efficacy and tolerability of olanzapine in 8 treatment-resistant children and adolescents (mean dose = 17.5 mg) and compared the results with an ongoing clozapine study in their group. Although olanzapine resulted in a moderate degree of symptom improvement, therapeutic benefits were greater for clozapine. Adverse events associated with olanzapine were increased appetite (6 patients), gastrointestinal disturbances (6 patients), headache (6 patients), somnolence (6 patients), insomnia requiring concomitant benzodiazepines (7 patients), and increased agitation (6 patients). Mean weight gain after 6 weeks of treatment with olanzapine was 3.4 kg. In another report, the efficacy and tolerability of a switch to olanzapine were assessed retrospectively for 8 children and adolescents with schizophrenia who were stable on clozapine treatment.[30] Olanzapine was as effective as clozapine, but better tolerated. Olanzapine has also been studied in an open trial of 16 non-treatment-resistant adolescents.[31] Olanzapine resulted in statistically significant improvements in symptom scores, but patients continued to have residual impairment after 8 weeks of treatment (mean PANSS total score = 72.7). Thirteen patients completed 8 weeks of treatment, and weight gain (mean = 6.5 kg; range, 1.1–13.4 kg) and sedation (9 patients) were the most commonly reported adverse events. A 1-year course of open-label olanzapine treatment of 20 patients aged 6 to 15 years with childhood-onset schizophrenia has been reported.[32] At endpoint, 74% of patients were considered to be treatment responders (i.e., 20% or greater improvement in BPRS total score), although negative symptoms and anxiety were less responsive than positive symptoms. Each of the 20 patients had an endpoint body mass index (BMI) above normal limits, and 4 of the 5 patients who withdrew prematurely from the study did so because of weight gain.

These data suggest that olanzapine is effective in adolescent schizophrenia, although possibly not as effective as clozapine for treatment-resistant patients. Only randomized, double-blind, placebo-controlled studies will be able to determine true differences in efficacy between these 2 drugs. In addition, the limited available data suggest that olanzapine may be associated with significant weight gain. An empirical characterization of the magnitude of weight gain that occurs during short-term and long-term olanzapine treatment is needed.

Quetiapine. The published data on quetiapine treatment of adolescent schizophrenia consist of 2 open-label studies in heterogeneous populations of patients with schizophrenia, schizoaffective disorder, bipolar disorder, psychotic depression, or psychosis not otherwise specified.[33–35] Results were reported for the entire group in both studies, which demonstrated improvement over baseline in positive and negative symptoms. In a long-term, open-label extension[33] of a 3-week pharmacokinetic study of 10 adolescents,[34] mean BPRS, CGI, and Scale for the Assessment of Negative Symptoms scores improved significantly. Quetiapine doses ranged from 333 mg/day to 695 mg/day (mean ± SD dose = 600 ± 122 mg/day), and patients completed at least 32 weeks of the extension study. Adverse events included somnolence, headache, postural tachycardia, and weight gain. In another open-label, flexible-dose, 8-week trial of 15 adolescents, the mean dose of quetiapine was 467 mg/day (range, 300–800 mg/day).[35] Mean BPRS, CGI, PANSS, and Young Mania Rating Scale (YMRS) scores improved significantly compared with baseline. Although modest weight gain (3.4 kg, adjusted for growth) was noted, elevated prolactin or cholesterol levels, electrocardiogram (ECG) changes, and EPS did not occur. There are no comparative or other long-term studies of quetiapine in this population.

Other atypical antipsychotics. Ziprasidone and aripiprazole are 2 newer atypical antipsychotics that are effective treatments of schizophrenia in adults.[36–38] Al-

though prolongation of the QTc interval has been reported to occur during ziprasidone therapy, the risk of arrhythmia is low in adult patients without arrhythmias or electrolyte imbalance and those who are not receiving concomitant treatment with drugs that prolong the conduction interval.[39] In addition, ziprasidone may be associated with a lower risk of significant weight gain than other atypical antipsychotics in adults.[39] Aripiprazole is another new atypical antipsychotic with unique receptor-binding properties, including partial agonism of the D_2 and 5-HT_{1A} receptors and antagonism of the 5-HT_{2A} receptor.[40,41] Overall, aripiprazole is well tolerated in adults, and rates of sedation, weight gain, anxiety, EPS, hyperprolactinemia, and QTc interval changes are similar to those with placebo in the adult population.[37] Neither ziprasidone nor aripiprazole has been examined in prospective studies of children or adolescents with schizophrenia. However, should controlled clinical trials of these agents demonstrate effectiveness in adolescents, and should the safety and tolerability profile of these newer agents be similar in young people as in adults, this information could be of benefit to pediatric patients.

Unmet Needs

The lack of data from controlled trials of the atypical antipsychotics in adolescents with schizophrenia is an especially significant unmet need because of the relatively common onset during the teenage years, severity of early-onset illness, and differences in response to treatment when compared with adults. There are several treatment domains that await the findings of rigorously controlled studies before the role of the atypical antipsychotics in adolescent schizophrenia is better understood. Data from older antipsychotics suggest that earlier age at onset is associated with a poor response to the traditional antipsychotics.[9] However, possible age-related differences in efficacy have not been rigorously tested in the newer agents. Also, because available studies have often enrolled diagnostically heterogeneous populations, the optimal dosing schedules needed for first-episode psychosis versus treatment-refractory illness are not yet known.

BIPOLAR DISORDER

Bipolar disorder is increasingly being diagnosed in children and adolescents. The estimated prevalence rate of bipolar disorder in pediatric patients varies, but was found in one study to be roughly 6% in a clinical sample.[42] Childhood- and adolescent-onset bipolar disorder is associated with severe disability, comorbid substance abuse, and impaired educational achievement.[43] Treatment of bipolar disorder in children and adolescents in general is remarkably understudied,[43] and there are very few randomized, controlled studies of mood stabilizers[44] or psychotherapy[45] in this population.

Antipsychotic Studies in Children and Adolescents With Bipolar Disorder

The older antipsychotics, such as haloperidol, traditionally have been used as second-line treatment of the manic phase of bipolar disorder in adults.[46,47] However, the risk of tardive dyskinesia and EPS limited their use. Recently, the atypical antipsychotics were shown to be an effective and better tolerated treatment of bipolar disorder in adults[48–51] and are assuming an increasingly prominent role as part of the complex combination therapy for this illness. A very limited evidence base, consisting of 1 small randomized controlled trial, 2 open-label studies, 3 case reports, and 3 retrospective chart reviews, suggests a possible role for the atypical antipsychotics in the treatment of bipolar disorder in children and adolescents.

Clozapine. The literature on the use of clozapine in pediatric bipolar disorder consists of a single case study,[52] 1 small retrospective review,[53] and a small open-label study.[54] The most rigorously collected data available were gathered by Masi and colleagues,[54] who administered a 15- to 28-day open-label course of clozapine (mean dose = 142.5 mg) to 10 adolescents with severe acute or mixed mania who had not responded to prior mood stabilizers or traditional antipsychotics. Two patients received clozapine monotherapy, and in 8 patients, clozapine was administered as an adjunct to lithium and valproic acid. The mean ± SD time to onset of a clinically significant response was 15.6 ± 3.6 days, and all patients were considered responders. Although leukopenia and seizures did not occur, the observed adverse events were not trivial. Somnolence, enuresis, sialorrhea, and increased appetite were reported. After 6 months of continued treatment, the mean ± SD weight gain in this cohort was 7 ± 3 kg.

Risperidone. Risperidone has also been shown to be effective in the treatment of mania in adults both in combination with a mood stabilizer[55] and as monotherapy.[56] Published data about the efficacy of risperidone in young patients with bipolar disorder consist of 1 retrospective chart review.[57] In this report, treatment response was assessed for 28 children and young adolescents with bipolar disorder. The mean dose of risperidone was 1.7 mg, and the mean duration of treatment was 6.1 months. Response, which was defined as a score of 1 (very much improved) or 2 (much improved) on the CGI-Improvement scale (CGI-I), was achieved by 82% of patients. Adverse events included weight gain, somnolence, and sialorrhea.

Olanzapine. A relatively robust body of literature documents the efficacy of olanzapine in the acute treatment of mania in adults[58–60] and as maintenance therapy of bipolar disorder in adults.[61] Published data on the use of olanzapine in the treatment of pediatric bipolar disorder are sparse and consist of 1 retrospective chart review[62] and an open-label trial in children and adolescents.[63] In the open-label trial, Frazier and associates administered an 8-week course of olanzapine monotherapy (2.5–20 mg) to 23

children and young adolescents with bipolar disorder.[63] Using criteria defined a priori, 61% of the 22 patients who completed the study were rated as responders. Weight gain was a significant adverse event, with a mean ± SD gain of 5 ± 2.3 kg after 8 weeks of treatment.

Quetiapine. Published data with quetiapine treatment of mania or bipolar disorder in children or adolescents consist of 2 case reports[64,65] and 1 controlled study.[66] In the only placebo-controlled study of any atypical antipsychotic in this population, 30 adolescents with mania or mixed bipolar I disorder were randomly assigned to receive a 6-week course of quetiapine (mean dose = 432 mg) plus valproate (20 mg/kg) or valproate plus placebo.[66] Patients who were randomly assigned to the quetiapine/valproate group achieved a significantly greater improvement in YMRS scores compared with the valproate/placebo group. Response, which was defined as a 50% or greater improvement in baseline YMRS scores, was achieved by 87% of the quetiapine plus valproate group and 53% of the valproate plus placebo group ($p = .05$). Adjunctive therapy with quetiapine was well tolerated. Sedation in the quetiapine group (80%) was significantly more common than in the placebo group (33%; $p = .03$).

Other atypical antipsychotics. Ziprasidone and aripiprazole are newer atypical antipsychotics that have been studied in adults with bipolar disorder and have been shown to be effective and well tolerated.[50,67,68] With the exception of 1 retrospective review of 13 adolescents treated with ziprasidone (3 of whom had bipolar disorder),[69] neither ziprasidone nor aripiprazole has been studied in prospective trials in pediatric patients with bipolar disorder.

Unmet Needs

Limited data suggest that the atypical antipsychotics may be useful as monotherapy or adjunctive therapy in the treatment of pediatric bipolar disorder. However, given the increasing use of the atypical antipsychotics in children and adolescents with bipolar disorder, the data from randomized controlled trials are too few to guide treatment decisions. Of interest is an ongoing study that is comparing the safety and efficacy of risperidone, lithium, and valproic acid in the treatment of mania or bipolar disorder in children and young adolescents. The Treatment of Early Age Mania study is a multicenter study sponsored by the National Institute of Mental Health that is a rigorously controlled assessment of a 2- to 4-month course of treatment.[70] It is hoped that the results of this study will better inform treatment decisions in this patient population, especially with regard to combination therapy and patient subtypes.

MALADAPTIVE AGGRESSION

Aggressive behaviors in children and adolescents are common and normative and serve an important evolutionary purpose.[71] However, aggressive behavior in children and adolescents is considered inappropriate or maladaptive when it occurs in circumstances that are independent of an expected social context or in the absence of expected antecedent social cues. Maladaptive aggression may also be disproportionate to its cause in intensity, frequency, or duration or fail to terminate appropriately after a task has been achieved.[72] Aggressive episodes with these characteristics raise the suspicion of the presence of another psychiatric disorder, such as psychosis, pervasive developmental disorder, attention-deficit/hyperactivity disorder (ADHD), posttraumatic stress disorder, or subaverage intelligence[71] or the need for treatment with aggression as a target symptom.[72]

From a phenomenological point of view, maladaptive aggression can be loosely defined as physical or verbal behavior that intentionally or unintentionally causes harm to self, others, or inanimate objects.[73] In pediatric patients, maladaptive aggression is a hallmark feature of oppositional defiant disorder and conduct disorder. In addition, maladaptive aggression can present as a secondary phenomenon of other psychiatric disorders, such as language disorders, pervasive developmental disorders, psychosis, ADHD, posttraumatic stress disorder, and mood disorders.[12,71] Maladaptive aggression can be very difficult to treat and accounts for high rates of hospitalization and institutionalization.[73–75]

Antipsychotic Studies in Children and Adolescents With Maladaptive Aggression

Aggression is one of the most common reasons for psychotropic drug use in children and adolescents in residential treatment facilities.[74] Currently, the atypical antipsychotics are the most widely used class of pharmacologic agents in the treatment of aggression and other behavioral disturbances in young persons.[76–78] Despite the widespread use of atypical antipsychotics, the psychopharmacology of maladaptive aggression in children and adolescents is tremendously understudied and remains an open arena for clinical investigation.[73,77]

Autistic disorder and other pervasive developmental disorders. Haloperidol and other traditional antipsychotics have been shown to be effective treatment of behavioral disturbances in children and adolescents with autism or other pervasive developmental disorders.[79–81] However, concerns about EPS and tardive dyskinesia have limited the use of these agents. The atypical antipsychotics are being used in this population, and risperidone is the most extensively studied drug in this class. The findings of open-label studies, case series, and chart reviews suggest efficacy for the other atypical agents, with the possible exception of quetiapine. There are no published data from rigorously controlled long-term studies to guide maintenance treatment in these patients.

Controlled trials. To date, risperidone is the only atypical antipsychotic that has been studied under double-blind,

randomized, placebo-controlled conditions in pediatric patients with maladaptive aggression and other behavioral disturbances associated with autism and pervasive developmental disorders. Two 8-week trials of 180 patients evaluated the efficacy of risperidone in this population.[82,83] Compared with placebo, risperidone resulted in significantly greater improvements in irritability as measured by the Aberrant Behavioral Checklist irritability subscale in the studies by McCracken et al.[82] (risperidone, 57% reduction; placebo, 14% reduction) and Shea et al.[83] (risperidone, 64% reduction; placebo, 31% reduction). Risperidone was also superior to placebo on secondary efficacy measures, including the CGI-I[82,83] and the conduct problem and other subscales of the Nisonger Child Behavior Rating Form.[83] A separate analysis of the patients from the study by McCracken and coworkers[82] was conducted to determine the effect of risperidone treatment on the symptoms of concern to parents.[84] Using a 9-point parent-defined target symptom score, it was shown that, compared with placebo, risperidone significantly improved the rate and severity of tantrums, aggression, and hyperactivity, which were the symptoms of most concern to the parents. Somnolence and moderate weight gain (mean increase of 2.7 kg) were more common with risperidone compared with placebo,[82,83] and rates of EPS were low and similar to those with placebo.[83]

Open-label studies. A larger literature exists for open-label or naturalistic studies of the atypical antipsychotics, which suggests possible efficacy in pediatric patients with autism or other pervasive developmental disorders. To date, several studies have been published that describe experience with risperidone,[85–94] olanzapine,[95–98] quetiapine,[99–101] ziprasidone,[102] and aripiprazole.[103] In these uncontrolled studies, a total of 302 patients (3–28 years of age) were enrolled and treated for periods ranging from 4 weeks to nearly 4 years. Most studies were less than 6 months in duration,* but several included patients who were followed for more than 1 year.[89,94,98,99] Young adults[97,99,102] and children under the age of 5 years[87,89,90,92,105] were included in some studies.

Measures of disruptive behavior and CGI scores improved in studies of risperidone, ziprasidone, aripiprazole, and olanzapine. Efficacy was not observed in 2 of the 3 quetiapine studies[100,101] and in 1 olanzapine study.[95] Two studies evaluated longer courses (≥ 1 year) of risperidone and found that effectiveness was sustained.[89,94] Extrapyramidal symptoms were rare, but somnolence and weight gain, the latter of which was marked in some patients, were noted in the risperidone,[85–88,90–93,104] olanzapine,[95–97] quetiapine,[101] and aripiprazole[103] studies.

Conduct disorder and disruptive behavior disorders. Different psychopharmacologic strategies have been studied in the treatment of aggressive behaviors in children and adolescents with conduct disorder, including methylphenidate,[104,106] anticonvulsants,[107–112] and traditional antipsychotics.[109] However, modest efficacy and adverse effects limit their widespread use, and the atypical antipsychotics have largely replaced the older agents in this population. Although children and adolescents with conduct disorder or disruptive behavior disorders are being treated with the atypical antipsychotics, there are very few randomized controlled trials. Most recent studies have been conducted in patients with subaverage intelligence. The extant literature consists almost exclusively of risperidone studies, with 1 pharmacokinetic study of aripiprazole.

Studies in patients with average intelligence. There are 2 published reports describing treatment of conduct disorder in children and adolescents of average intelligence.[113,114] The efficacy of risperidone was assessed in a 10-week, randomized, double-blind, placebo-controlled pilot study of 20 patients between the ages of 5 and 15 years.[114] Compared with placebo, risperidone resulted in significantly greater improvements in the Rating of Aggression Against People and/or Property (RAAPP) and CGI-I scores ($p = .01$). The most commonly reported adverse events were increased appetite, somnolence, headache, and weight gain. Risperidone was not associated with EPS in this study.[114] The use of aripiprazole in 23 children and adolescents with conduct disorder was evaluated in a 14-day pharmacokinetic, pharmacodynamic, and safety study.[113] Although this study was not designed to assess efficacy, the RAAPP and CGI-S scores were measured at baseline and at the 14-day endpoint. Administration of aripiprazole resulted in improvement in RAAPP scores. At baseline, 74% of patients had severe (9%) or moderately severe (65%) symptoms; at endpoint, 87% of patients had mild (65%) or no symptoms (22%). Similarly, more patients had CGI-S scores of normal or borderline at endpoint compared with baseline. The most commonly reported adverse events associated with aripiprazole were gastrointestinal disturbance and somnolence, both of which appeared to be dose-related.

Studies in patients with subaverage intelligence. The short-term efficacy of risperidone in the treatment of behavior disturbances and aggression associated with disruptive behavior disorders in patients with subaverage intelligence has been assessed in 4 randomized, double-blind, placebo-controlled studies of 4 or 6 weeks' duration. A total of 279 children and adolescents, aged 5 to 14 years, were enrolled in the controlled studies.[115–118] Risperidone was superior to placebo on measures of aggressive or disruptive behavior, including the Nisonger Child Behavior Rating Form conduct problem subscale, several subscales from the Aberrant Behavior Checklist, and the Behavior Problems Inventory aggressive/destructive behavior subscale. Headache, somnolence, increased

*References 85, 86, 90–93, 95–97, 100, 101, 103, 104.

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appetite, and moderate weight gain were commonly reported adverse events. Rates of EPS were similar to those with placebo.[115–118] The findings of 1 open-label study of risperidone in this population also suggest effectiveness.[119]

Three long-term, open-label studies of risperidone treatment of disruptive behavior disorders in children aged 5 to 14 years with subaverage intelligence have been published.[120–122] Turgay and associates[122] enrolled 77 patients in a 48-week, open-label extension of a 6-week, placebo-controlled study.[118] Risperidone-naive patients who were switched from the placebo arm to open-label risperidone exhibited significant improvement on the conduct problem subscale score of the Nisonger Child Behavior Rating Form after 1 week, which was comparable to mean scores for patients in the risperidone treatment arm of the short-term study. Mean clinical response in both groups (mean risperidone dose = 1.4 mg/day) was maintained through study endpoint. Croonenberghs and colleagues[120] observed similar results with regard to the onset and durability of response on the Nisonger Child Behavior Rating Form scores in their study of 504 patients. The mean dose of risperidone in this study was 1.6 mg/day. Findling and associates[121] studied risperidone treatment in a 48-week, open-label extension study of 107 children who had completed at least 2 weeks of a randomized, double-blind, placebo-controlled study.[116] Clinical response was sustained for patients who remained on risperidone treatment. Patients who were crossed over from placebo to risperidone achieved a rapid and statistically significant response on the conduct problem subscale score of the Nisonger Child Behavior Rating Form. The most commonly reported adverse events in all 3 studies were somnolence and headache; rates of treatment-emergent movement disorders were low.[120–122]

Unmet Needs

The improved safety and tolerability of the atypical antipsychotics in adults have resulted in a greatly increased use of these agents in children and adolescents with maladaptive aggression and other behavioral disturbances associated with autism/pervasive developmental disorders and conduct disorder/disruptive behavior disorders. However, the relative paucity of controlled studies is of concern. Dose-ranging studies are needed to identify optimal doses that are associated with the lowest risk of adverse effects. In addition, maintenance studies are needed to better inform decisions about continuing long-term treatment in children and adolescents. The effects of antipsychotic treatment and other forms of therapy have not been adequately studied in different subtypes of aggression, including acute versus subacute/chronic, and aggression in the context of other primary diagnoses.

SAFETY OF ATYPICAL ANTIPSYCHOTICS IN PEDIATRIC PATIENTS

The atypical antipsychotics have been embraced by many clinicians who treat children and teenagers despite the scarcity of empirical data supporting their use in pediatric patients. The relative willingness of clinicians to use the atypicals in children and adolescents is largely based on data from studies in adults that demonstrate a generally more tolerable adverse event profile compared with the older agents. The safety and tolerability of the atypical antipsychotics in children and adolescents are especially important considerations, particularly given the unknown effects of these drugs on the developing brain and the likelihood of long-term treatment beginning at an early age. Adverse events associated with the atypical antipsychotic agents may be particularly burdensome in young people, who have been noted to be susceptible to sedation, motor disturbances, rapid and clinically significant weight gain, and mania.[73] Clozapine remains of unique concern because of the increased risk of seizures and agranulocytosis. Moreover, the effect of weekly blood drawing on treatment adherence by children and adolescents and their families should not be discounted.

Dosing and Titration

As with other illnesses, both medical and psychiatric, children and adolescents should not be viewed as small adults. The pharmacokinetic properties of the atypical antipsychotics have been studied in a small number of adolescents[34,113,123,124] and children.[113,123,124] It is not known if these agents possess age-related pharmacodynamic properties requiring dosing strategies that are different in children and adolescents compared with adults. Nonetheless, it has been suggested that the doses of atypical antipsychotics used in adults are also effective in adolescents with psychotic illnesses.[2,34] However, the rate of dosage titration in younger patients may need to be slower than in adults in an attempt to minimize the rate and severity of adverse events.[15]

Extrapyramidal Symptoms

Adverse events associated with the traditional antipsychotics, particularly EPS, are more frequent and severe in younger patients. A retrospective review of 215 hospitalized patients with psychosis aged 10 to 60 years demonstrated that EPS were almost universal in patients 10 to 19 years of age, but rates of EPS declined as a function of age. Of the patients with EPS, rates of dystonia and parkinsonism were also markedly higher in the younger cohort.[125] A double-blind, placebo-controlled comparison of the effects of biperiden administration (6 mg/day) to neuroleptic-naive, first-episode patients with schizophrenia 13 to 58 years of age (mean age = 26.4 years) during the first week of haloperidol (15 mg/day) treatment

confirmed that younger patients had the highest rates of dystonia.[126] Rates of EPS following short-term treatment in adolescents are high and range from 54% with thiothixene to 73% with haloperidol.[18,19]

Positron emission tomography studies have shown that neuroleptic-induced EPS are related to dopamine D_2 receptor occupancy, with occupancy rates greater than 80% associated with increased rates of EPS.[127,128] The density of D_2 receptors decreases with age and is therefore higher in children and adolescents than in adults.[129] Thus, it has been postulated that the increased number of D_2 receptors in children and adolescents compared with adults is a key factor underlying the vulnerability of young patients to EPS.[130] Although the atypical antipsychotics are associated with lower rates of EPS compared with the older agents, these adverse events do occur in children[21,117] and should be carefully monitored in all patients, especially when doses at the upper limit of the dosing range are used.

Weight Gain

Weight gain has been noted in young patients during treatment with clozapine,[54] olanzapine,[29,31,63] risperidone,[26,82,115] or quetiapine.[35] However, the comparative propensity of the other atypicals to cause weight gain in children and adolescents is not known with certainty. In one naturalistic study of 109 adolescent and young adult psychiatric inpatients with schizophrenia spectrum disorders, obesity defined as a BMI in the top 10th percentile was associated with clozapine (64%), other atypical antipsychotics (56%), traditional antipsychotics (30%), and no antipsychotic treatment (28%).[131] The findings of short-term olanzapine studies demonstrate mean weight gain of 3.4 kg,[29] 5 kg,[63] and 6.5 kg.[31]

There has been some concern regarding weight gain during long-term risperidone treatment.[132] Another group conducted a retrospective review of 6 months of risperidone treatment in 37 child and adolescent inpatients and compared weight gain in these patients with that in 33 age-matched, neuroleptic-naive psychiatric inpatients.[133] Risperidone was associated with clinically significant weight gain (≥ 7% increase in baseline weight) in 78% of patients compared with 24% of controls ($p < .001$). The onset of significant risperidone-associated weight gain occurred in the first 2 months of treatment and progressed without abating at a mean rate of 1.2 kg/month. However, these findings were not replicated by other long-term risperidone studies.[121,122]

Clinically significant weight gain may be an especially salient obstacle for antipsychotic treatment adherence in adolescents. Moreover, the long-term effects of increased body weight on the risk of cardiovascular disease and diabetes in adolescents are not known. Patients and their parents should be counseled about the benefits of treatment and the risks associated with the possibility of significant weight gain before beginning treatment. Efforts at educating patients about the importance of a balanced diet and regular physical activity are warranted. It is recommended that weight and BMI should be monitored at baseline and at regular intervals throughout treatment. Weight management strategies and monitoring of serum glucose and lipid levels are suggested for patients with weight gain in excess of 5 BMI units.[78] One program of multimodal weight control that includes nutrition, exercise, and behavioral interventions has been shown to be effective in adults over the course of 3 months and 1 year in achievement of weight loss, reduction in BMI, and improvements in markers for diabetes and cardiovascular disease.[134,135]

Hyperprolactinemia

Hyperprolactinemia is an adverse event that can also complicate treatment with atypical antipsychotics. Modest and transient increases in serum prolactin levels have been reported in adults during clinical trials of clozapine, olanzapine, and quetiapine[136,137] and in children and adolescents during short-term treatment with olanzapine.[138] Although risperidone is an atypical antipsychotic that has been associated with increased prolactin levels in adults,[139] the findings of long-term studies in children and adolescents reveal only transient and asymptomatic elevations in baseline prolactin concentrations.[120–122] The long-term sequelae of hyperprolactinemia are not known, but in theory could include delayed sexual maturation, sexual dysfunction, menstrual abnormalities, infertility, galactorrhea, gynecomastia, and osteoporosis.[137,139,140] Reduced bone mineral density in premenopausal women has been reported during risperidone treatment.[139]

QTc Interval Prolongation

Cardiac effects, namely a prolongation in the corrected QT (QTc) interval, have been noted with both the traditional and atypical antipsychotics. Prolongation of the QTc interval is of concern because of increased risk of ventricular arrhythmia (i.e., torsades de pointes). QTc intervals longer than 500 msec are associated with greatly increased risk of torsades de pointes. Of the antipsychotics, ziprasidone and thioridazine are associated with the greatest degree of QTc interval prolongation, and fatalities have occurred in adults during treatment with thioridazine.[141,142] A study that administered the highest recommended doses of the atypical antipsychotics to adults under controlled conditions found that QTc prolongation with ziprasidone was only 10 msec greater than with risperidone, quetiapine, olanzapine, or quetiapine.[73] Treatment with ziprasidone is considered safe for adult patients without arrhythmias or electrolyte imbalance and for those who are not being treated with other drugs that prolong the conduction interval.[39]

One retrospective series of 13 adolescents with various psychiatric diagnoses who were treated with ziprasidone revealed that 1 patient demonstrated prolongation of the

QTc interval on follow-up ECG.[69] A prospective study of 20 children and adolescents who were treated with low-dose ziprasidone (≤ 40 mg/day) for up to 6 months found that the mean QTc prolongation of 28 msec was not related to dose.[143] No adverse cardiac events were observed during a 6-week course of treatment with ziprasidone in an open-label study of 12 children and adolescents with autism.[102] However, peak QTc intervals of approximately 450 msec[143] in 3 patients suggest the need for ECG monitoring and caution in at-risk patients and those receiving higher doses of ziprasidone. Although careful monitoring is rational for pediatric patients being treated with ziprasidone, there is a great need for rigorously conducted studies in large patient samples in order to better characterize the cardiovascular profile of ziprasidone and other atypical antipsychotics.

Mania

Treatment-emergent mania or hypomania has been reported in association with risperidone, olanzapine, and ziprasidone.[144,145] A review of the literature summarized the clinical course of treatment-emergent mania in 58 adults treated with risperidone, quetiapine, olanzapine, or ziprasidone and 2 adolescents treated with olanzapine or ziprasidone.[144,146] Mania reported during risperidone or olanzapine treatment was possibly dose-related and was transient in some cases and remittent in others after a reduction in risperidone dose, substitution of another agent, or the addition of a mood stabilizer. Three patients were rechallenged with the atypical antipsychotic, and mania returned in all patients.[147–149]

These reports included 2 adolescents, a 16-year-old boy with pervasive developmental disorder who became manic within 2 to 3 weeks of beginning olanzapine treatment[150] and a 17-year-old girl with schizophrenia who became manic within 3 days of beginning ziprasidone treatment.[145] Symptoms of mania in both adolescents remitted upon discontinuation of the atypical antipsychotic. It is important to note that the atypical antipsychotics have been shown to be effective in adults with mania, and a determination of a causal role, if any, for these agents in treatment-emergent mania in children and adolescents awaits the findings of well-controlled prospective studies.

CONCLUSIONS

The availability of the atypical antipsychotics, which are effective in adults with schizophrenia and mania and are associated with a lower risk of EPS and tardive dyskinesia in adults, has changed the landscape of psychopharmacology. On the basis of the findings of controlled studies in adults, the atypical antipsychotics are now becoming widely used in adolescents and children with psychiatric illness. A small, but emerging, evidence base in conjunction with broadening clinical experience supports the use of these agents in children and adolescents with schizophrenia, bipolar disorder, pervasive developmental disorders, disruptive behavior disorders, and other diagnoses (e.g., tic disorders). However, controlled studies are urgently needed to determine optimal dosing regimens, comparative efficacy and safety, and the risk:benefit ratio associated with the use of the atypicals in young patients.

Taken in the aggregate, the spectrum of adverse events associated with the atypical antipsychotics are generally not acutely life-threatening. Clozapine-induced agranulocytosis, however, is the exception. Nonetheless, the development of EPS, rapid and substantial weight gain, and daytime somnolence can be very troublesome and poorly accepted and may discourage patients and their parents from adhering to treatment, especially in the long term. The need to understand the acute and long-term effects of these medications on growing and developing children and adolescents is urgent and must be studied in controlled clinical trials with adequate numbers of patients as well as stringent methodological rigor.

Drug names: aripiprazole (Abilify), benztropine (Cogentin and others), biperiden (Akineton), clozapine (Clozaril, FazaClo, and others), haloperidol (Haldol and others), lithium (Lithobid, Eskalith, and others), loxapine (Loxitane and others), methylphenidate (Ritalin, Metadate, and others), olanzapine (Zyprexa), quetiapine (Seroquel), risperidone (Risperdal), thiothixene (Navane and others), valproic acid (Depakene and others), ziprasidone (Geodon).

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