Atypical Antipsychotics in the Treatment of Children and Adolescents: Clinical Applications

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Atypical antipsychotics offer superior safety and similar efficacy compared with conventional agents in adults with psychotic disorders. Consequently, atypical antipsychotics have been increasingly used in children and adolescents. Because most information now available on pediatric use comes from case reports and small open-label studies rather than large controlled trials, treatment in pediatric patients is often guided by experience with adults or based on limited evidence in youths. Although the literature contains reports on the use of each agent in this class in children, risperidone has been the focus of the greatest number of reports. However, the atypical antipsychotics are not interchangeable; each has a unique pharmacologic profile and may differ considerably in terms of adverse effects. Evidence on the use of atypical antipsychotics in children and adolescents is summarized in this review. *(J Clin Psychiatry 2004;65[suppl 6]:30–44)*

The atypical antipsychotics, which offer equal or better efficacy and superior safety compared with conventional antipsychotics, are well established in the treatment of adult patients with psychotic disorders.[1] Although most published research regarding these agents has focused on adult patients, the use of atypical antipsychotics in pediatric patients may be particularly attractive to clinicians treating young patients because these agents are associated with a low incidence of extrapyramidal symptoms (EPS, comprising dystonia, parkinsonism, and akathisia), as shown in studies in adults. The risk of EPS, especially with conventional antipsychotics, may be greater in young patients than in adults because the number of striatal dopamine D_2 receptors declines after childhood.[2]

Atypical antipsychotics carry lower risks of EPS and probably tardive dyskinesia in adults,[3–5] which is an important potential advantage when treating children or adolescents because young people often face long-term if not lifelong pharmacotherapy. However, non-neurologic adverse events, such as weight gain, may occur with atypical antipsychotics and can be distressing enough to compromise adherence to treatment with these drugs.[6] Weight gain is a greater problem with atypical antipsychotics than with conventional antipsychotic agents in both adults and children, and it has been theorized that the serotonin- and histamine-blocking activity of these drugs may interfere with satiety, thus contributing to weight gain through excessive intake of food.[7]

Favorable outcomes achieved with atypical antipsychotics in young patients with psychotic disorders have sparked interest in relation to children and adolescents with other psychiatric diagnoses, including mood disorders with and without psychotic symptoms, tic disorders, and conditions that may present with disruptive or aggressive behavior, including disruptive behavior disorders and pervasive developmental disorders (PDDs).

Overall, the literature on the use of atypical antipsychotics in pediatric patients is limited. Aside from a relatively small number of methodologically rigorous controlled studies, most of the published data come from anecdotal case reports and small open-label trials.[8,9] Uncertainties abound in the absence of definitive evidence for most conditions, and treatment in young patients is often guided by evidence and experience in adults. Dosing of antipsychotic drugs in children is often not based on pediatric pharmacokinetic studies or controlled dose-ranging trials.

Although no head-to-head comparisons have evaluated the risk of EPS with various antipsychotics in young people, data from adults suggest that high-potency conventional and atypical antipsychotics are associated with a higher risk of EPS.[10] In a review of the literature conducted by Tarsy et al.,[10] the risk among the atypical antipsychotics was potentially greatest with the high-potency

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agent risperidone (at higher doses), somewhat lower with olanzapine and ziprasidone, and lowest with clozapine and quetiapine. To minimize the risk of EPS, children should be started at the lowest possible dose with any of the antipsychotic agents, with gradual titration guided by clinical response.[11]

Among the atypical antipsychotics, clozapine has been considered the gold standard for efficacy in treatment-resistant adults with schizophrenia, and it carries a low risk of EPS. However, its use in children has been limited by concern about agranulocytosis,[12] which may occur in approximately 2% of adult patients over the course of 1 year of treatment, with the greatest risk in the first 4 months.[13] Clozapine has also been linked to impaired glucose tolerance in adults, weight increase in adults and children, and an increased risk of seizures and electroencephalographic changes in children and adolescents.[14] Thus, owing to its suboptimal adverse event profile, the use of clozapine is currently reserved for only the most treatment-resistant children and adolescents.

In adults, all other atypical antipsychotics are equally effective for the treatment of schizophrenia; however, there appear to be differences in their adverse event profiles. Among the first-line atypical antipsychotics, risperidone carries some risk of increased prolactin levels and a dose-related risk of EPS in adults.[14] Olanzapine has a relatively low risk of EPS in adults, but weight gain, impaired glucose tolerance, and sedation may be problems.[2,14] Quetiapine offers placebo-equivalent risks of EPS and prolactin elevation with minimal effect on weight when administered as long-term monotherapy, but sedation and dry mouth have been reported.[15] With ziprasidone, weight gain is not perceived to be a problem, and the risk of EPS is considered low.[16,17] Although this agent may cause prolongation of the QTc interval,[18] the actual risk of torsades de pointes is uncertain. In adults, aripiprazole carries a low risk of EPS and appears to have a minimal effect on weight but may cause sedation, light-headedness, and insomnia.[19]

The first-line atypical antipsychotics seem promising in the treatment of a variety of pediatric neuropsychiatric conditions, although there are relatively few data from controlled trials and no published head-to-head studies regarding between-drug comparisons of long-term safety. Given the generally low incidence of EPS caused by these agents reported in the medical literature, the most troublesome adverse event for patients and their families may be weight gain, which can contribute to noncompliance or forced discontinuation of treatment. For example, a prospective study in hospitalized adolescents concluded that weight gain was significantly greater with olanzapine than with risperidone, unrelated to dosage or efficacy, and more pronounced in this population than in adults.[20] A practical approach to averting major weight gain is to provide counseling before weight gain becomes problematic. The likelihood of increased appetite and the importance of proper diet and exercise during therapy should be emphasized.[8]

This review summarizes the experience to date with atypical antipsychotics in children and adolescents with schizophrenia and other neuropsychiatric disorders.

SCHIZOPHRENIA

There is general agreement that early-onset schizophrenia is often more disabling than adult-onset illness because of its severe impact on children's developing social skills and neurocognitive functions. The schizophrenia literature on young patients suggests that although conventional antipsychotics can be effective for many patients, high rates of adverse events have been reported; additionally, a substantial number of patients remain symptomatic[21–23] because earlier age at onset may be associated with nonresponse to conventional antipsychotics.[24] On the basis of a limited amount of controlled research and several open-label trials and case reports involving children and adolescents, atypical antipsychotics appear to be effective in pediatric patients.

Clozapine

In a randomized double-blind clinical trial, 21 children and adolescents (11 boys, 10 girls; mean age = 14 years) with early-onset schizophrenia diagnosed using *Diagnostic and Statistical Manual of Mental Disorders, Third Edition, Revised* (DSM-III-R) criteria were treated with clozapine or haloperidol.[25] Previous treatments with at least 2 different conventional antipsychotics were unsuccessful in this study cohort. After a drug-free washout period, patients received 6 weeks of treatment with clozapine (mean final dosage = 176 mg/day or 3.07 mg/kg/day) or haloperidol (16 mg/day or 0.29 mg/kg/day). Patients receiving haloperidol were prophylactically treated with benztropine. Clinical improvements on the Scale for the Assessment of Positive Symptoms (SAPS),[26] Scale for the Assessment of Negative Symptoms (SANS),[26,27] and Brief Psychiatric Rating Scale (BPRS)[28] were significantly greater with clozapine than with haloperidol.

The 11 patients treated with haloperidol were then given clozapine on an open-label basis and reassessed. With blinded or open-label use of clozapine, 20 of 21 patients showed at least some improvement. Clozapine produced more drowsiness and salivation, whereas haloperidol caused more insomnia. There were no cases of agranulocytosis with clozapine, but 5 patients developed neutropenia, and 3 patients had electroencephalographic abnormalities during open-label use of clozapine.

A number of short-term open-label trials have evaluated the use of clozapine in children and adolescents with schizophrenia or schizoaffective disorder. An open-label trial of clozapine was conducted in 11 pediatric patients with a mean age of 14 years.[29] After 6 weeks at a mean

dosage of 370.5 mg/day (range, 125–825 mg/day), patients showed mean improvements of 58% on the SAPS, 42% on the SANS, and 43.5% on the Bunney-Hamburg psychosis subscale.[30] On the BPRS, substantial (≥ 30%) improvement was seen in 6 of 11 patients compared with previous best treatment and in 9 of 11 patients compared with baseline conditions. Treatment was generally well tolerated, but weight gain was substantial (mean increase = 7 kg in 6 weeks). No patients showed evidence of adverse hematologic effects.

Another open-label trial of clozapine involved 11 patients with a mean age of 11.3 years who had schizophrenia resistant to prior treatments with at least 2 other antipsychotic agents.[31] After drug discontinuation and washout, clozapine was started at 12.5 to 25 mg/day and titrated to a mean dosage of 227 mg/day by week 16. Improvements were documented by reductions of 42% on the Clinical Global Impressions-Severity of Illness scale (CGI-S),[32] 70% on the BPRS, and 51% on the Positive and Negative Syndrome Scale (PANSS).[33] Seven patients had serious developmental disabilities, but the 4 patients who were not developmentally disabled showed the most dramatic benefits, with reductions of 53% on the CGI-S, 84% on the BPRS, and 70% on the PANSS. EPS from prior medication resolved, and there were no new-onset EPS. The most frequent adverse events were drowsiness, hypersalivation, and nonspecific changes in electroencephalography. Clinical improvement was sustained during long-term (up to 3 years) follow-up.

A retrospective study examined the clinical records of 36 adolescents (mean age = 11.3 years) with treatment-resistant schizophrenia who had participated in open-label clinical trials with clozapine.[34] Treatment with clozapine (mean dose = 330 mg/day; range, 50–800 mg/day) for 22 weeks resulted in complete remission in 11% of patients and clinical improvement in 75% of patients. Positive symptoms of schizophrenia were responsive to clozapine in 65% of patients; however, there were only modest improvements in negative symptoms. Leukopenia without agranulocytosis led to the discontinuation of clozapine in 2 patients. Electroencephalographic changes were noted in 44% of patients.

Very-early-onset schizophrenia refers to patients in whom the onset of symptoms occurs before age 13 years. A case report described a series of 4 patients, aged 10 to 12 years, who showed substantial improvement during treatment with clozapine after responding poorly to other treatments.[35] Extrapyramidal symptoms from previous medications decreased during treatment. The most common adverse events were excessive salivation and drowsiness.

Risperidone

The short-term effects of risperidone were assessed in an open-label trial of 10 adolescents (mean age = 15 years) with schizophrenia, including 7 adolescents nonresponsive to conventional antipsychotics and 3 adolescents who were antipsychotic-naive.[36] Following a 2-week washout period, eligible patients were given a 6-week trial of risperidone (mean dose = 6.6 mg/day; range, 4–10 mg/day). Benztropine was permitted for emergent instances of drug-induced parkinsonism or acute dystonic reactions, and lorazepam was permitted as a sedative. Clinically and statistically significant improvement in PANSS, BPRS, and CGI-S scores was observed with risperidone. No major adverse events were reported; however, weight gain (mean increase = 4.85 kg) and mild somnolence were reported in 8 patients. Benztropine was required in 3 patients for parkinsonian symptoms.

Treatment with risperidone was reviewed in a retrospective study in 16 adolescents (13 boys, 3 girls; mean age = 14.9 years) with diagnoses of schizophrenia, schizoaffective disorder, or schizophreniform disorder; previous antipsychotic therapy had been unsuccessful in 11 of the patients.[37] A main focus of the study was the effect on negative symptoms, assessed by 4 items (emotional withdrawal, motor retardation, blunted affect, disorientation) from the 22-item BPRS. Risperidone treatment was initiated at 1 mg twice daily and increased as needed to a mean dosage of 5.9 mg/day (range, 2–10 mg/day). Treatment resulted in significant improvements in BPRS total and negative scores and CGI-S score, and many patients who were taking other medications (e.g., antipsychotics, antiparkinsonian drugs, anticonvulsants, lithium) were able to discontinue their other treatments. The most common adverse event was transient sedation, and 3 patients developed EPS. Only 1 patient had to discontinue treatment because of adverse events (EPS and sedation).

In a case series, 3 of 4 adolescent patients with schizophrenia showed substantial clinical improvement, especially in negative symptoms, during treatment with risperidone without suffering EPS, cardiovascular effects, weight gain, or sedation.[38] During 6 months of follow-up at dosages of 4 to 5 mg/day, these benefits were maintained, suggesting that the patients did not develop tolerance to the effects of the drug.

Olanzapine

The intramural branch of the National Institute of Mental Health (NIMH) has extensively studied young patients with treatment-resistant early-onset schizophrenia (diagnosed by DSM-III-R criteria, with onset of psychotic symptoms by age 12 years and a poor response to 2 previous antipsychotics). As part of that avenue of research, data on open-label olanzapine treatment in 4 boys and 4 girls (mean age = 15.25 years) for 8 weeks were compared with data from 15 children and adolescents who had taken part in open-label 6-week NIMH trials of clozapine.[39] After a variable period of drug discontinuation and washout, treatment with olanzapine was started at 2.5 mg/day (or every other day for children with body weight ≤ 40 kg)

and increased to a mean dosage of 17.5 mg/day at 6 weeks. From baseline to week 8, olanzapine produced improvements of 33% in the Bunney-Hamburg total score, 19% in BPRS total score, 21% in SANS score, and 6% in SAPS score. However, none of the olanzapine patients were considered responsive (defined by a reduction of at least 20% in the BPRS total score) at 6 weeks, compared with 8 of 15 clozapine patients ($p = .01$). Likewise, in a subgroup of 4 olanzapine patients in whom previous treatment with clozapine had been effective but intolerable, clinical improvement at 6 weeks was greater with clozapine than with olanzapine. Olanzapine was moderately well tolerated, with a mean weight gain at 6 weeks (3.4 kg) similar to that seen with clozapine (5.0 kg). Although olanzapine does not seem to carry the risks of neutropenia and seizure activity associated with clozapine, this study suggests that clozapine offers greater efficacy in treatment-resistant schizophrenia in children and adolescent patients.

As another part of the intramural NIMH trials, the pharmacokinetic profile of olanzapine was assessed in an open-label study of 4 boys and 4 girls (mean age = 15 years; all nonsmokers) with treatment-resistant schizophrenia as previously defined.[40] After a drug washout period, olanzapine treatment was started at 2.5 mg/day and increased to a maximum of 20 mg/day. Plasma concentrations of olanzapine rose with increasing doses and declined from peak levels in a log-linear fashion, with an elimination half-life of 37.2 hours. Peak plasma drug concentrations in these pediatric patients were similar to those seen in adult nonsmokers and higher than the concentrations seen in adult smokers, probably because drug clearance is accelerated in smokers via induction of the hepatic cytochrome P450 (CYP) 1A2 isoenzyme. There were no significant sex-related differences in pharmacokinetic parameters and no observed correlation between plasma drug levels and changes in BPRS scores. Adverse events were mostly mild and included increased appetite, constipation, nausea and vomiting, headache, and somnolence.

In contrast to the NIMH intramural trials, treatment resistance was not an entry criterion in an 8-week open-label trial of olanzapine in 16 adolescents (12 boys, 4 girls; mean age = 13.8 years) with schizophrenia-spectrum disorders.[41] Olanzapine treatment was initiated at 2.5 mg/day and increased to a mean dosage of 12.4 mg/day. All but 3 patients completed the study. Treatment resulted in significant improvements in the PANSS total, positive, and negative scores and CGI-S scores. Although the drug was generally well tolerated (the most common adverse events were increased appetite and sedation), EPS developed in 2 patients, and weight gain was significant (mean increase = 6.5 kg).

Quetiapine

An 8-week open-label trial of quetiapine was conducted in 15 adolescents (mean age = 15 years) with psychotic disorders.[42] Treatment began at 25 mg/day on day 1, with daily doubling of dosage to reach 200 mg/day on day 4, and increased as tolerated thereafter. Mean dosage at the end of the study was 467 mg/day (range, 300–800 mg/day). End-of-study assessments (BPRS, CGI, PANSS, Young Mania Rating Scale [YMRS][43]) showed significant reductions in psychotic symptoms from baseline ($p < .001$ for all measures) with no reports of severe adverse events. Weight gain was noted; after correction for expected growth, the mean increase was 3.4 kg. The leukocyte count declined during the course of the study, but there were no elevations in serum prolactin or cholesterol, no notable changes on electrocardiographic or ophthalmic examination, and no significant EPS, leading the investigators to conclude that quetiapine seemed to be effective and well tolerated in adolescents with psychotic disorders.

Studies in adults have shown that quetiapine is extensively metabolized (mainly via the CYP3A4 isoenzyme), with less than 1% of an administered dose excreted unchanged, and plasma drug levels vary in a linear fashion across the recommended dosage range. The pharmacokinetic profile of quetiapine in adolescents was assessed in an open-label study in 10 patients with a mean age of 13.6 years with schizoaffective disorder or bipolar disorder with psychotic features.[44] Patients were grouped by age (12–14 years and 15–17 years) to examine whether there were any age-related effects. After a 2-day washout period, quetiapine treatment was started at 25 mg twice daily on day 3, and the dosage was increased in a stepwise manner during the ensuing 18 days to a final dosage of 400 mg twice daily. That dosage was given on days 21 and 22, and a final 400-mg dose was given on the morning of day 23, the last day of the trial.

As in adults, pharmacokinetics were found to be dose proportional. There were no significant differences between adults and older or younger adolescents in time to peak concentration after oral dosing (1.5 hours for adults, 0.5–3.0 hours for adolescents) or half-life (6 hours for adults, 5.3 hours for adolescents), suggesting that dosage adjustments are not necessary for treatment in adolescents. There were no withdrawals from the study. Extrapyramidal symptoms from prior medication were reduced significantly and prolactin levels were unaffected, but 6 patients gained weight (mean increase = 1.5 kg). Adverse events, all of which were mild to moderate, included orthostatic hypotension and tachycardia, transient insomnia (which resolved as the dosage was increased), and a decrease in levothyroxine (T_4). Efficacy measurements, also assessed during treatment, showed significant improvements in BPRS total score and CGI-S score; in addition, there were significant reductions in negative symptoms as measured by the SANS.

In an extended follow-up to the pharmacokinetics study, the same 10 patients participated in a long-term open-label trial of quetiapine. All patients completed at least 32 weeks

of treatment at dosages ranging from 300 to 800 mg/day; weight gain varied, but there was no evidence of EPS, tardive dyskinesia, or hyperprolactinemia during that time.[45]

BIPOLAR DISORDER

The onset of bipolar disorder can occur in childhood or adolescence. It is the most prevalent disorder with psychosis in the first 2 decades of life.[46] Treatment of bipolar disorder in pediatric patients generally requires at least 4 weeks of treatment with an antimanic agent at adequate doses (and for some agents, confirmed plasma drug levels) to assess effectiveness. For patients who have clearly suffered from a manic episode, treatment should be considered a long-term proposition. The relapse rate for bipolar disorder is high, partially perhaps because of medication noncompliance. Even if symptoms of the mood disorder improve, the functional level of patients may not always show comparable improvement.[47]

Traditionally, the mood stabilizer lithium has been the mainstay of treatment; however, limited controlled clinical data exist regarding its use in young people. In a 6-week, double-blind, placebo-controlled trial enrolling 25 adolescents (mean age = 16.3 years) with bipolar disorder and a secondary substance dependency disorder, treatment with lithium was found to be associated with fewer positive drug screens and superior overall functioning than treatment with placebo.[48] In children and adolescents, lithium may cause gastrointestinal disturbances, sedation, tremor, polyuria (secondary to inhibition of vasopressin), hypothyroidism, and weight gain.[46] Although anticonvulsants, such as divalproex sodium or carbamazepine, may provide greater therapeutic benefit than lithium in adult patients with mixed mania or rapid-cycling bipolar disorder,[49] there are no data to confirm or refute whether mixed mania or rapid-cycling bipolar disorder is better treated with these anticonvulsants than with lithium in children or adolescents.

Valproate is an anticonvulsant with mood-stabilizing activity that has been used in adults to treat manic symptoms in bipolar disorder. In children and adolescents, adverse events that occur relatively frequently include nausea and vomiting, increased appetite and weight gain, sedation, tremor, and, less frequently, thrombocytopenia.[46] Unfortunately, monotherapy with mood stabilizers may not be adequate to control the symptoms of bipolar disorder in children and adolescents. In a 6-week open-label study conducted by Kowatch et al.,[50] more than half of the adolescents (mean age = 11.4 years) receiving monotherapy with lithium, divalproex sodium, or carbamazepine did not respond. As a result, combination therapy with mood stabilizers, atypical antipsychotics, or stimulants may be needed.

In addition to the mood stabilizers, there is evidence from various studies that antipsychotics may have a role in the treatment of pediatric mania. In adults with mania, antipsychotic monotherapy may be less effective than lithium monotherapy, and it is not clear how much of the effect of these drugs is solely secondary to sedation. In general, it appears that the response to treatment of bipolar disorder is similar in children and adults.[51] Among the atypical antipsychotics, clozapine has been described as being helpful in approximately three fourths of adults with treatment-resistant bipolar disorder, and case reports suggest similar effectiveness in children.[51] A chart review study indicated that risperidone is beneficial in children with bipolar disorder.[52] Olanzapine has also been described as being effective in children with bipolar disorder,[53–55] but adverse events and weight gain may force discontinuation of treatment.[56] A controlled study found that the addition of quetiapine to treatment with divalproex sodium was beneficial in 30 adolescents with bipolar mania.[57] Additional information regarding the use of atypical antipsychotics in the treatment of pediatric bipolar disorder is provided in the following sections.

Clozapine

Clozapine is effective in adults with treatment-resistant bipolar disorder. Case reports suggest clozapine is also useful in some young people with treatment-resistant bipolar disorder.[58] For example, open-label treatment with clozapine was reviewed from the charts of 9 boys and 1 girl with a mean age of 9.9 years who had a history of poor response to conventional antipsychotics or mood stabilizers. Of these 10 patients, 5 had bipolar disorder (mixed type), 4 had schizophrenia, and 1 had psychotic disorder not otherwise specified (NOS). Clozapine treatment was started at 12.5 mg/day and titrated to a mean dosage of 128 mg/day. After 6 weeks, the group showed significant improvements in the CGI-S score and the Children's Global Assessment Scale (CGAS)[59] score. Adverse events were reported in 9 of 10 patients (weight gain and sedation were the most common problems), but no patients discontinued because of adverse events.[58]

Risperidone

Open-label treatment with low- to moderate-dose risperidone was assessed in 11 children aged 5 to 16 years who had diverse diagnoses, including attention-deficit/hyperactivity disorder (ADHD) and bipolar disorder associated with aggressive behavior.[60] Eight children, all of whom had shown poor responses to previous therapy with mood stabilizers, responded well, usually within days. The most common adverse events were weight gain and sedation.

A retrospective chart review was conducted in 28 young patients (mean age = 10.4 years) with bipolar mania treated with risperidone.[52] Over an average of 6 months, mean dosage was 1.7 mg/day. Treatment was successful in reducing manic and aggressive symptoms in 23 patients, psychotic

symptoms in 19 patients, and ADHD symptoms in 2 patients, as defined by ratings of much or very much improved on the Clinical Global Impressions-Improvement scale (CGI-I).

Olanzapine

An open-label study of olanzapine was conducted in 23 patients aged 5 to 14 years (mean = 10.3 years) diagnosed with a manic, hypomanic, or mixed-episode bipolar disorder. The mean duration of illness was 4.4 years, and the rates of comorbidity were high.[55] In all but 1 of the patients, prior therapy with stimulants, mood stabilizers, selective serotonin reuptake inhibitors (SSRIs), antidepressants, and antipsychotics was unsuccessful. Treatment with olanzapine, approved as monotherapy for acute mania in adults with bipolar disorder type I, was started at 2.5 mg/day and increased to a mean dosage of 9.6 mg/day by the end of the 8-week study period. Treatment reduced both manic and depressive symptoms and aggression, as indicated by significant improvements that included reductions of 62% in YMRS score; 37% to 40% in CGI-S scores for bipolar disorder, mania, and depression; 32% in Children's Depression Rating Scale[61] score; 62% in BPRS total score; and 90% in BPRS positive score. In all, 14 of 23 patients were considered responders based on a 30% or greater improvement on the YMRS and CGI scores for mania. Treatment was well tolerated, and compliance was good. There were no significant mean changes in ratings of EPS, although 2 patients developed akathisia. The most frequent adverse events were increased appetite, somnolence, abdominal pain, mild prolactin elevations, and a statistically significant increase in weight (mean = 5 kg).

One case report[54] describes the use of olanzapine in 3 prepubertal children with bipolar disorder and acute mania. Addition of olanzapine to ongoing treatment with a mood stabilizer (lithium or divalproex sodium) produced dramatic clinical improvement, although the patients experienced sedation and weight gain. Sedation normalized the sleep pattern, which may have helped resolve the manic symptoms, and the weight gain may have been due in part to the adjunctive mood stabilizers.

Quetiapine

A double-blind study was conducted to assess the value of adding quetiapine to divalproex sodium in 30 adolescents with acute bipolar mania.[57] While receiving divalproex sodium, patients were randomly assigned to 6 weeks of combination treatment with quetiapine (adjusted to 450 mg/day) or placebo. As judged by the YMRS scores, the response was significantly better with combined divalproex sodium and quetiapine than with divalproex sodium alone. Treatment was generally well tolerated, and there were no significant between-group differences on measures of safety; however, the incidence of sedation was significantly higher in the quetiapine group.

In an individual case report, quetiapine (titrated to 450 mg/day) was used successfully in a 9-year-old girl with severe mania.[62] In another case report,[63] a 17-year-old boy with bipolar disorder and a 6-year history of substance abuse, depression, aggression, and psychosis was treated with quetiapine after all previous treatments (lithium, risperidone, divalproex sodium, olanzapine, and fluoxetine) had failed to provide adequate control of mania, auditory hallucinations, and insomnia. Quetiapine adjusted to 600 mg/day resulted in correction of sleep disturbances and disappearance of hallucinations, with no evidence of recurrent psychosis, mania, or behavioral problems during the ensuing year.

PERVASIVE DEVELOPMENTAL DISORDERS

The PDDs form a group of 5 disorders that includes autistic disorder, Asperger's disorder, childhood disintegrative disorder, Rett disorder, and PDD-NOS. Patients with PDD often have difficulties with aggression, agitation, stereotypical behavior, and hyperactivity and have impairments in communication and problems forming appropriate social relationships.

The diagnosis of autism requires evidence of qualitative impairment in social interaction and communication and restricted, repetitive, stereotyped behaviors and interests.[64] These core symptoms appear by age 3 years and often continue throughout life. They are frequently accompanied by maladaptive behaviors, such as aggression, self-injury, tantrums, and sleep disturbances.

The causes of autism are unclear, but it may result from an aberrance in brain pathways involved in social and communicative activity. Dysfunction in the serotonergic system may contribute to the psychopathologic features of autistic disorder; many patients with autism show high blood levels of serotonin.[65] Hyperserotonemia, seen in approximately one third of autistic children, is associated with an increased risk of autism in a sibling.[66] The fact that genetics may be an important risk factor in the development of autistic disorder is suggested by the substantially increased risk (sibling recurrence risk of 3%–5%) of autism in a younger sibling of an autistic child.[67] Moreover, concordance rates for autism are higher in identical twins than in fraternal twins.[65] However, the clinical manifestations of autism have not been linked to specific chromosomal abnormalities.

Treatment of autism should be multimodal and should include speech therapy, social skills training, special educational planning, and support services to families. Medications are prescribed to young people with autistic disorder to reduce dysfunctional behaviors so that other treatment modalities can be applied more effectively.[68] Various medications have been studied as potential treatments for young people with autistic disorder. These include stimulants, mood stabilizers, anxiolytics, antide-

pressants, and antipsychotics. Conventional antipsychotics have been reported as sometimes being helpful in reducing dysfunctional behaviors, but concerns about safety can limit their use. For example, dyskinesias developed in 24 (29%) of 82 autistic children treated with haloperidol; of these 24 cases, 5 represented tardive dyskinesia (onset during treatment), and 19 represented withdrawal dyskinesia (onset after discontinuation).[69] Atypical antipsychotics have a lower risk of EPS, which may reflect activity at serotonergic receptors or shorter binding time at dopaminergic receptors.[70]

Clozapine

Limited data are available regarding the use of clozapine in children and adolescents with PDD. As with schizophrenia and bipolar disorder, the administration of clozapine in young people with PDD is typically reserved for those who are treatment resistant.

Zuddas et al.[71] reported on successful treatment with clozapine in two 8-year-old boys and one 12-year-old girl with autistic disorder and marked hyperactivity and aggressiveness. These children experienced minimal effectiveness with conventional antipsychotics. After 3 months of treatment with clozapine, a marked reduction in scores on the Children's Psychiatric Rating Scale (CPRS)[32] was noted in all 3 children, and a 40% improvement was observed on items of fidgetiness, hyperactivity, abnormal object relationships, and negativism. The boys continued to improve, with a further reduction in CPRS scores after 8 months of therapy. However, in the girl, CPRS and Self-Injurious Behavior Questionnaire[72] scores returned to pretreatment levels after 5 months of therapy. Transient sedation and enuresis were reported in all 3 children.

The successful use of clozapine was also reported in a 17-year-old boy with autism, mental retardation, and aggression.[73] After 15 days of treatment with clozapine, 275 mg/day, an improvement in CPRS score and problem behaviors was observed. The only adverse events were mild constipation and hypersalivation.

Risperidone

Most of the published reports on the use of atypical antipsychotic drugs to treat autism discuss treatment with risperidone, which seems effective in reducing hyperactivity, aggression, and repetitive behaviors.[12,74] Its use in children with autism and other PDDs is based in part on favorable results in adults. For example, in a controlled trial in adults with PDD, treatment response was seen in 8 of 14 patients receiving risperidone monotherapy versus 0 of 16 patients receiving placebo.[75]

In what may be the largest published controlled study to date, 101 children (82 boys, 19 girls; mean age = 8.8 years; range, 5–17 years) with autism and serious behavioral problems, including severe tantrums, aggression, or self-injurious behavior, participated in a double-blind trial of risperidone (N = 49) versus placebo (N = 52).[70] At the end of the acute 8-week study, patients taking placebo who showed no improvement and patients treated with risperidone who had a positive response were offered open-label treatment with risperidone for 4 to 6 months. After withdrawal of other medications and a drug-free washout period, risperidone was initiated at 0.25 mg at bedtime in children weighing < 20 kg or 0.5 mg at bedtime in children weighing ≥ 20 to 45 kg. The dosage was adjusted gradually to a maximum of 2.5 mg/day in children weighing 20 to 45 kg and to 3.5 mg/day in children weighing > 45 kg; mean dosage was 1.8 mg/day. Mean scores on the irritability subscale of the Aberrant Behavior Checklist[76] were reduced by 57% in the risperidone group versus 14% in the placebo group ($p < .001$). A positive response, defined as a 25% or greater improvement in the irritability score and a rating of much or very much improved on the CGI-I scores, was documented in 69% of risperidone patients versus 12% of placebo patients ($p < .001$). Of the 34 patients who responded to risperidone, 23 maintained the benefit achieved for 6 months. Mean weight gain was significantly greater with risperidone than placebo (2.7 vs. 0.8 kg; $p < .001$). There were no serious adverse events, no withdrawals because of adverse events, and no cases of EPS in either group. Withdrawals for lack of effectiveness were reported in 6% of risperidone patients versus 23% of placebo patients ($p = .001$). Although risperidone was safe and effective in controlling behavior problems in this trial, it did not improve the core symptoms that constitute the diagnostic symptom criteria of autism.

An extended, double-blind, placebo-controlled, crossover study was conducted to assess weight changes during acute and maintenance treatment with risperidone for aggressiveness, destructiveness, and self-injury in autism patients of various ages, including 5 children (ages 8–12 years) and 6 adolescents (ages 13–16 years).[77] At low-to-moderate dosages, risperidone was effective in reducing behavioral problems. Mean weight gain after 12 weeks of acute treatment was 3.8 kg in children and 4.2 kg in adolescents; mean weight gain from baseline to study end (approximately 1 year, including a 6-month maintenance period) was 8.2 kg in children and 8.4 kg in adolescents. Weight decreased during the placebo phase between acute and maintenance treatment, and there was a close correlation of weight change with initiation and discontinuation of risperidone.

A number of open-label trials of various durations (12 weeks to 7.4 months) have also evaluated the use of risperidone in children and adolescents with PDDs. A 12-week open-label trial of risperidone evaluated 18 patients (15 boys, 3 girls, mean age = 10.2 years; range, 5–18 years) with autism or other PDDs, including 14 patients with moderate-to-profound mental retardation.[78] After a drug-free washout period, risperidone treatment was started at 0.5 mg at bedtime and titrated to a mean dosage of 1.8

mg/day. Twelve patients were responders (much or very much improved on the CGI-Global Improvement scale). Treatment significantly reduced repetitive behaviors and aggression but did not affect abnormal motor activity or language. Weight gain was substantial; 12 of 18 patients gained a mean of 8.1 kg over 12 weeks. Sedation occurred in 6 patients; there were no cases of EPS or seizures.

A 16-week open-label trial of risperidone was conducted in 10 preschool children (mean age = 4.7 years) with autism or PDD-NOS[79]; all had behavioral problems, and 9 had mental retardation. Risperidone treatment was started at 0.25 mg/day and titrated to a maximum of 0.50 mg/day. The 8 children who completed the trial showed modest improvement as measured by the Childhood Autism Rating Scale,[80] CPRS, CGAS, and CGI-Global Improvement scale. There were no instances of behavioral deterioration, and the adverse events that led to 2 dropouts were not severe.

In another report of open-label treatment with risperidone,[12] 6 patients with PDD (mean age = 10.7 years; range, 7.3–14.8 years) showed rapid and significant improvement in behavior (reductions in temper tantrums, aggression, and mood instability) but not in language use or socialization; 5 of the patients had not improved on previous treatment. Weight gain and sedation were the most common adverse events.

A long-term open-label study of risperidone was conducted in 11 children and adolescents (8 boys, 3 girls; mean age = 12.3 years; range, 7–17 years) with autism or PDD-NOS, all of whom suffered from mental retardation and also had severe behavioral problems not responsive to prior treatment with conventional antipsychotics.[81] Risperidone was started at 0.5 mg/day and titrated to the lower of 2 doses, a maximum of either 6 mg/day or 0.1 mg/kg/day. Although 1 patient had persistent or worsening behavior problems and was discontinued from the study, the other 10 were considered responders, as defined by ratings of much or very much improved on the CGI-Global Improvement scale. After 6 months of treatment, 7 patients elected to continue treatment for another 6 months and had no further changes in clinical status; the 3 patients who did not continue showed progressive behavioral degeneration. A mean weight gain of 7.2 kg occurred in 6 patients over the first 6 months. Mild sedation occurred, but was transient. There were no cases of EPS in the first 6 months, but 2 of the 7 patients who continued treatment developed facial dystonia. As other studies reported, the main benefit was to behavioral symptom control rather than to the core symptoms of autism.

In an open-label trial of risperidone, 13 of 14 children and adolescents with PDD experienced benefit, with improved attention and reduction in obsessive behaviors; 10 patients had marked reductions in agitation and anxiety, and 10 were managed on risperidone monotherapy with no relapses during a follow-up period of 2 to 14 months (mean = 7.4 months).[66] The most common adverse event was drowsiness, which was managed by dosage reduction.

Olanzapine

An open-label trial was conducted in 12 children with autistic disorder (8 boys, 4 girls; mean age = 7.8 years; range, 4.8–11.8 years) who were randomly assigned to receive 6 weeks of treatment with olanzapine or haloperidol (6 patients each).[68] After drug washout, olanzapine was initiated at 2.5 mg/day or every other day, depending on weight, and titrated to a mean dosage of 7.9 mg/day. On the CGI scales, a rating of very much improved was recorded in 1 patient in each group; much improved in 4 olanzapine patients and 2 haloperidol patients; and minimally improved in 1 olanzapine patient and 3 haloperidol patients. Between-group differences were not significant, but improvement from baseline was statistically significant ($p = .005$) only in the olanzapine group. Sedation and weight gain occurred in both groups, but mean weight gain was greater with olanzapine than with haloperidol (4.09 vs. 1.45 kg; $p = .04$).

In a noncomparative open-label trial, olanzapine was used in 8 patients (children, adolescents, and adults) with autism or PDD-NOS; 7 of the 8 patients had comorbid mild-to-moderate mental retardation.[82] Olanzapine was started at 2.5 mg/day and titrated to a mean dosage of 7.8 mg/day at week 12. Of 7 patients who completed 12 weeks of treatment, 6 were rated as responders (much or very much improved on CGI); responsiveness was not associated with age, IQ, dose of olanzapine, or severity of autistic symptoms. Of the 6 responders, 4 maintained improvement for another 2 to 4 months. Weight gain (mean increase = 8.3 kg) and sedation were the most frequent adverse events. There was no evidence of EPS or hepatotoxicity.

Quetiapine

In a series of 6 boys (mean age = 10.9 years; range, 6.2–15.3 years) with autism and mental retardation, open-label quetiapine treatment was started at 25 mg at bedtime and adjusted to a mean dosage of 225 mg/day.[83] Two patients completed 16 weeks of treatment; 3 patients dropped out because of lack of response (sedation precluded dosage increase) and 1 because of a possible seizure. The 2 completers showed much or very much improvement in CGI scores, but there was no statistically significant improvement from baseline to end of the study for the group as a whole. Four patients gained a mean of 2.9 kg, mainly during the first few weeks of the trial.

Data from a retrospective chart review of 14 children and adolescents with autism spectrum disorders or mental retardation indicated that quetiapine might be beneficial in improving conduct, hyperactivity, and inattention.[84] In the 10 patients with autism (mean age = 12.0 years; range, 5–19 years), significant improvements were seen in scores

on the Conners Parent Scale[85] for conduct, inattention, and hyperactivity. No differences were seen in scores for learning-related, psychosomatic, or anxiety symptoms. Among the 4 patients with mental retardation (mean age = 15.5 years; range, 10–19 years), significant improvement was seen in scores on the conduct subscale of the Conners Parent Scale, but not for the other subscale scores. Nine of the 14 patients were considered responders based on CGI-Global Improvement scores. Adverse effects in the group as a whole were mild, and no patients discontinued treatment.

Ziprasidone

Ziprasidone was studied in 12 young patients (10 boys, 2 girls; mean age = 11.6 years; range, 8–20 years) with autism or PDD-NOS; 11 patients were mentally retarded, and 11 had received prior antipsychotic treatment that usually resulted in an inadequate response or adverse events, mainly weight gain.[86] Five patients were taking other atypical antipsychotics at baseline; these were gradually discontinued during the first few weeks of treatment with ziprasidone. Ziprasidone was started at 20 mg at bedtime and titrated to a final mean dosage of 59 mg/day. After 6 to 30 weeks (mean = 14 weeks) of treatment, 6 of the 12 patients were responders (much or very much improved on the CGI), but 2 patients with comorbid bipolar disorder were rated as much worse. The most frequently reported adverse event was sedation. Among patients who had gained excessive weight during prior treatment with other atypical antipsychotics, weight increased further during treatment with ziprasidone in 1 patient, did not change in 3, and decreased in 4. Among all 12 patients, 5 lost weight, 5 showed no change, and 1 gained weight (1 patient had no follow-up weight measurement after baseline), and the mean change in weight for the entire group was a loss of 2.64 kg.

TIC DISORDERS AND OBSESSIVE-COMPULSIVE DISORDER

Tic disorders are differentiated into 2 main types: transient and chronic. Both transient and chronic tics may involve motor or phonic tics; however, they differ in terms of duration. Transient tic disorder is present for < 1 year, whereas chronic tics are present for > 1 year. Tourette's syndrome (TS) is a chronic form of tic disorder in which both motor and phonic tics are present. Chronic tics and TS tend to worsen during childhood and then decline in severity by early adulthood.[87]

A clinically relevant tic is defined by daily occurrence in all settings, drawing the attention of other people, and interfering with the patient's normal activities. The overall prevalence of tics is high; a community-based survey identified tics in 339 of almost 1600 schoolchildren (21%).[88] A survey from England yielded similar results for tics overall (19% in a large sample of children aged 13–14 years), but the prevalence of tics fulfilling the diagnostic criteria for TS was only 1% to 2%.[89] Tic disorders in young people are often complicated by comorbid obsessive-compulsive disorder (OCD), ADHD, anxiety, depression, phobias, impulsivity, and behavioral problems; these ancillary problems are often the principal reason for seeking treatment.[87] However, motor tics and behavioral problems are independent phenomena, and most children with motor tics have mild conditions and no comorbid behavioral problems.[90]

Antipsychotics may be the most widely used agents in treating patients with TS. Good results have been reported with conventional antipsychotics, such as haloperidol and pimozide, but the high doses used often caused treatment-limiting adverse events such as EPS, dysphoria, and the risk of prolonged QTc interval on electrocardiograms with pimozide.[91] Atypical antipsychotics may offer greater safety and tolerability in patients with TS, but the effectiveness of the various atypical antipsychotics appears to differ. For example, clozapine has not been effective in this role,[92,93] possibly because of its relatively weak dopamine-blocking activity.[87] Among the atypical antipsychotics, the most extensive experience to date in the treatment of tics has been with risperidone. Among other types of medications used in patients with tics, the α_2-agonists clonidine and guanfacine have been studied in previous clinical trials,[87,91] whereas experience with other agents is largely anecdotal.

Comorbid OCD in patients with TS is generally treated with SSRIs,[94,95] and comorbid ADHD is generally treated with short-term use of psychostimulants.[96] Among other types of drugs, lithium does not appear beneficial in the treatment of OCD, but clomipramine may be another option.[97] In patients with comorbid tic disorders and OCD resistant to monotherapy with an SSRI, the addition of an antipsychotic agent to the regimen may be helpful.[98,99] There are no clearly defined predictors of response to drug treatment in young patients with OCD, but severe symptoms, parental psychopathology, and comorbid tic disorders or PDD have been identified as possible predictors of poorer outcome.[100]

The long-term effectiveness of pharmacotherapy in pediatric patients with tic disorders and related comorbid conditions is uncertain because of the relative paucity of controlled studies in this population and because of the potentially confounding effects of spontaneous changes in symptom severity over time among these patients.

Risperidone

A 12-week double-blind comparison of risperidone and pimozide was conducted in 50 children and adults (ages 11–50 years) with TS.[101] The proportions of patients showing significant improvement were similar for the 2 groups: 14 (54%) of 26 patients given risperidone (mean dosage at

end of study = 3.8 mg/day) and 9 (38%) of 24 treated with pimozide (2.9 mg/day). Tic severity total scores were reduced by more than half in both groups. A separate analysis in the pediatric subgroup revealed results similar to those in the whole sample. The risperidone group showed significant improvement in comorbid OCD symptoms, and the incidence of EPS in the risperidone group (4/26; 15%) was less than half of the incidence in the pimozide group (8/24; 33%). Other adverse events included depression, fatigue, and somnolence; among patients younger than age 18 years, weight gain was greater with risperidone (4.5 kg) than with pimozide (2.7 kg).

A randomized double-blind comparison of risperidone and clonidine was recently conducted in 21 children and adolescents (ages 7–17 years) with TS; 20 of the patients had symptoms of comorbid OCD or ADHD.[102] After 8 weeks of treatment, between-group differences in efficacy outcomes were nonsignificant. Tic severity was reduced 21% with risperidone (mean dosage at end of study = 1.5 mg/day) and 26% with clonidine (0.175 mg/day). Obsessive-compulsive symptoms declined in 5 of 8 risperidone patients and 4 of 12 clonidine patients; ADHD symptoms declined in 2 of 7 risperidone patients and 6 of 12 clonidine patients. Mild-to-moderate sedation was the most frequent adverse event, and there were no cases of clinically important EPS in either group. Mean weight gain was not significantly greater with risperidone than with clonidine (2.1 kg vs. 0.1 kg).

Risperidone in the treatment of TS was also assessed in a double-blind, placebo-controlled, 8-week trial in a mixed population of 48 adolescent and adult patients.[103] Improvement in the severity ratings for TS was significantly greater with risperidone (median dosage at end of study, 2.5 mg/day) than with placebo. The greatest improvements on the CGAS were seen in risperidone-treated patients who had poor scores at baseline. Treatment with risperidone caused worsening tremor in patients with tremor at baseline and a greater degree of hypokinesia than was seen in the placebo group; there were no significant between-group differences in other forms of EPS. There was no increase in obsessive-compulsive symptoms with risperidone; the incidence rates of fatigue and somnolence were significantly higher with risperidone than with placebo.

In an 8-week, double-blind trial in medication-free patients with TS, 26 children and 8 adults received risperidone (mean dosage = 2.5 mg/day) or placebo.[104] Tic severity was reduced by 36% in the 12 children randomly assigned to risperidone versus 9% in the 14 children randomly assigned to placebo ($p = .004$). Treatment with risperidone was associated with a mean (including all patients) weight gain of 2.8 kg, but there were no reports of EPS or abnormalities or clinically significant changes in cardiac conduction or laboratory test measurements.

Open-label risperidone was assessed in an 11-week trial in 7 children and adolescents (5 boys, 2 girls; mean age = 13 years; range, 11–16 years) with TS and other chronic tic disorders.[105] Five patients were diagnosed with comorbid OCD, ADHD, or depression, and none of the 7 patients had responded to prior treatment with haloperidol, clonidine, or SSRIs. Risperidone, started at 0.5 mg at bedtime and titrated as needed, reduced tic severity by 18% to 66% in all 7 patients. However, OCD symptoms improved in only 1 of the 3 children who were also receiving treatment for this condition. All 7 patients gained weight (3.6–6.4 kg; $p = .0001$). None of the patients developed EPS.

The experience with atypical antipsychotics in children with OCD as a primary diagnosis in the absence of a tic disorder is limited. Unexpected adverse events from treatment with risperidone were reported in 2 adolescent boys (ages 13 and 18 years) with obsessive-compulsive symptoms and a history of separation anxiety and a 10-year-old boy with ADHD and evidence of a mood disorder.[106] In all 3 boys, the addition of low-dose risperidone to other treatment (e.g., methylphenidate, fluoxetine, or divalproex sodium) led to severe separation anxiety, which resolved when risperidone was discontinued; subsequent treatment with olanzapine in 2 of these patients did not cause recurrence of anxiety.

Other Atypical Antipsychotics

A 6-week open-label trial of olanzapine was conducted in 14 patients, including 2 older adolescents with TS.[107] Olanzapine was initiated at 10 mg/day and titrated to a mean dosage of 15 mg/day by study end, resulting in a significant decrease in tic severity. The response was slightly better in patients who had never received antipsychotic drugs than in those who had responded poorly to previous therapy. Mild sedation was reported, and 2 patients experienced weight gain.

Experience to date with the use of quetiapine in patients with TS is limited to case reports. In a 19-year-old woman with a distressing motor tic since age 3 years, treatment with haloperidol and risperidone had produced a variety of intolerable adverse events, but quetiapine monotherapy at 100 mg/day produced satisfactory control of symptoms.[108] Similarly, 2 boys (ages 11 and 13 years) with TS and comorbid ADHD, OCD, and behavior problems were treated successfully with quetiapine after previous treatment had proved inadequate or intolerable.[109] Both patients had experienced weight gain from antipsychotic therapy with risperidone or haloperidol. Quetiapine adjusted to 100 to 150 mg/day resulted in clinical stabilization with tic reduction, weight loss, and no EPS.

A randomized 8-week pilot study of ziprasidone versus placebo was conducted in 28 children and adolescents (ages 7–17 years) with TS or other chronic tic disorder.[17] Ziprasidone was started at a low dosage and titrated to a mean dosage of 28 mg/day that remained relatively constant over the last 4 weeks of the trial. Active treatment

was significantly more effective than placebo, as shown by tic severity reductions of 35% with ziprasidone versus 7% with placebo. The most frequent adverse event was mild, transient sedation; treatment with ziprasidone did not result in significant weight gain or electrocardiographic changes.

DISRUPTIVE BEHAVIOR DISORDERS

Disruptive behavior disorders in children and adolescents include oppositional defiant disorder (ODD), defined as a 6-month history of anger, hostility, defiance, resentment, and uncooperativeness causing significant impairment in social or educational activities; conduct disorder, defined as a 12-month history of aggression or bullying, property destruction, theft or deceit, and rule violations; and disruptive behavior disorder NOS, a definition used for young people with clinically significant symptoms of either or both conditions. In young people with ODD or conduct disorder, aggression is common and is the most frequent cause of psychiatric hospitalization.[110] In addition, the behavior of these children tends to interfere with school attendance and family life.[111] Thus, despite heterogeneous symptom criteria, most studies of ODD and conduct disorder tend to focus their evaluations on the symptom of aggression.

Aggression may be overt (physical assault, temper tantrums) or covert (lying, cheating, vandalism, or theft). However, aggression itself is not a diagnosis per se. Aggression may be seen in a wide variety of patients. For example, in patients with schizophrenia and other psychotic disorders, aggression may result from paranoid delusions or a mistaken perception of threat. In patients with bipolar disorder, anger outbursts seem to occur more often in the manic, hypomanic, and mixed phases than in the depressive phase of the illness.

Drug treatment for young people with problematic disruptive behavior disorders should be used in an attempt to treat the underlying condition in which the problem arises (e.g., stimulants for ADHD, lithium for bipolar disorder, antipsychotics for schizophrenia). Benzodiazepines may be effective in reducing agitation and irritability in elderly patients and patients with dementia but may also cause excessive sedation and paradoxical behavioral disinhibition, especially in younger patients.[112,113]

No drug is specifically labeled for the treatment of conduct disorder in the United States even though antipsychotics are the most frequently used agents for patients with behavioral problems associated with other neuropsychiatric disorders. Controlled studies have shown that conventional antipsychotic agents[111,114,115] and risperidone[116,117] are consistently superior to placebo or equivalent to an active comparator. However, it is generally recommended that nonpharmacologic interventions be considered as first-line therapy for severe behavioral problems in children without comorbid developmental disabilities. Other types of drugs shown to be effective in children with conduct disorder include lithium[111,118] and methylphenidate.[119] Because conduct disorder often appears in the context of ADHD, the antiaggression effects of methylphenidate and other stimulants were assessed in a meta-analysis of 28 studies involving a total of 683 children and adolescents (88% boys; mean age = 9.7 years; range, 7.7–14.4 years) with ADHD and, in most cases, comorbid conduct disorder or ODD. The analysis demonstrated that stimulants significantly reduce aggression independent of their effects on the core symptoms of ADHD.[120]

In view of the increased risk of EPS in young patients,[2] atypical antipsychotics would seem preferable to conventional antipsychotics in this patient population. Notably, aggression may occur in patients suffering from a variety of primary diagnoses and is the most common target symptom for which antipsychotics are used in children and adolescents.[8] Most of the experience with atypical antipsychotics in children with behavioral problems has been with risperidone.[110]

Risperidone

Behavior problems in young patients with subaverage intelligence may be difficult to manage. However, risperidone has been used effectively in this setting. A double-blind placebo-controlled study of risperidone was conducted in 13 patients (5 boys, 8 girls; ages 6–14 years) with low IQ (66–85) and persistent behavioral problems that included symptoms of hostility, aggressiveness, irritability, agitation, or hyperactivity.[121] During the 4-week trial, risperidone dosage was titrated to a mean of 1.2 mg/day. All patients completed treatment. Treatment with risperidone resulted in significant improvement in Aberrant Behavior Checklist scores for irritation and hyperactivity from baseline to endpoint and for treatment versus placebo at endpoint. Behavioral disturbances improved from severe to mild in 3 of 6 risperidone-treated patients versus 0 of 7 placebo-treated patients. On the CGI-I, 5 of 6 risperidone-treated patients were rated as much or very much improved, whereas 7 of 7 placebo-treated patients were rated as unchanged or minimally improved. The onset of effect with risperidone was rapid, and there were no significant between-group differences in tolerability, including weight gain.

A jointly designed pair of trials of identical structure assessed risperidone in the treatment of behavioral problems in a total of 228 children (ages 5–12 years) with low IQ (36–84) and, frequently, comorbid ADHD.[122,123] After a 1-week, single-blind, placebo run-in, patients were randomly assigned to 6 weeks of treatment with risperidone or placebo. Findings in the 2 studies were similar. From baseline to endpoint, reductions in the mean scores on all subscales of the Nisonger Child Behavior Rating Form[124] were significantly greater for risperidone (mean dosages = 1.16 mg/day and 0.98 mg/day) than for placebo. The

effectiveness of risperidone was not altered by the presence or absence of comorbid ADHD, the use of stimulants to treat ADHD, or differences in IQ. Common adverse events included somnolence, headache, increased appetite, weight gain, and dyspepsia. There were few discontinuations owing to adverse events and no significant between-group difference in the incidence of EPS, although the mean increase in weight was greater with risperidone (2.2 kg in both trials) than with placebo (0.2 and 0.9 kg). In an interesting subanalysis excluding patients who developed somnolence, clinical improvement was still significantly greater with risperidone than with placebo, indicating that the effectiveness of the drug was not a function of sedation.

In a follow-up to the pair of studies in low-IQ children with behavioral problems, 77 children who had participated in the double-blind trials entered a 48-week open-label extension study of risperidone.[125] At a mean dosage of 1.38 mg/day, treatment produced rapid improvement in those who had received placebo during the double-blind trial, whereas those who had received risperidone in the double-blind trial maintained the benefits they had achieved. Although there were no severe adverse events, 20 patients developed mild-to-moderate EPS. Boys showed a statistically significant increase in prolactin levels at endpoint, although the mean level was still within normal limits. Many patients reported somnolence or weight gain, although close to half of the weight gain could be attributed to normal growth.

An open-label study of risperidone was conducted in 15 young patients (12 boys, 3 girls; mean age = 10 years; range, 7.5–13.4 years) with a primary diagnosis of ODD, conduct disorder, or disruptive behavior disorder NOS.[126] Ten of the children had learning difficulties, and 13 had personality traits suggestive of borderline pathology or multiple complex developmental disorder. All were receiving "milieu therapy," a comprehensive inpatient regimen employing behavior modification techniques, family therapy, occupational therapy, music and art therapy, and other approaches. After at least 2 weeks of milieu therapy without adjunctive pharmacotherapy, risperidone was started at 0.5 to 1.0 mg/day and titrated to maintenance dosages of 1 to 2 mg/day. Mean scores on the CGAS (scored on a scale of 1 to 100, representing worst condition to best) improved from 21.9 at admission to 26.8 after a period of milieu therapy alone and to 50.3 after milieu therapy plus risperidone. Combined therapy was significantly better than milieu therapy alone in terms of absolute improvement ($p < .0001$) and weekly rates of improvement ($p < .001$). Notably, improvements were lost when risperidone was discontinued. Two patients reported adverse events (weight gain of 3.8 kg and tremor), both tolerable. The lack of specific diagnostic measurements by an independent observer and the absence of a control group limit the interpretability of these findings.

Other Atypical Antipsychotics

Few controlled data are available for clozapine or olanzapine in children and adolescents with aggression.[110] No published data are available for quetiapine or ziprasidone. A pharmacokinetic study has evaluated the use of aripiprazole in children and adolescents with conduct disorder; preliminary data suggest clinical effectiveness in this patient population.[127]

CONCLUSIONS

Although the literature on the use of atypical antipsychotics in pediatric patients is limited, these agents appear to be beneficial not only in the treatment of psychotic disorders but also in mood disorders, tic disorders, disruptive behavior disorders, and severe behavioral problems that may be associated with these neuropsychiatric conditions. In children, as in adults, the main advantage of atypical antipsychotics over conventional antipsychotics may prove to be superior safety, especially with the lower risk of EPS with the atypical antipsychotics. When reviewing the available data pertaining to the use of the atypical antipsychotics in young people, it should be remembered that the individual agents are not interchangeable; in terms of potential therapeutic benefits and adverse events, each agent has a unique pharmacologic profile. At this time, the most urgent need is for large-scale, well-designed, controlled clinical trials of atypical antipsychotics in pediatric patients with the disorders described in this review. Additionally, the focus of future research with the atypical antipsychotics should include head-to-head comparative trials and evaluation of long-term safety of these agents in pediatric patients.

Drug names: aripiprazole (Abilify), benztropine (Cogentin and others), carbamazepine (Carbatrol, Tegretol, and others), clomipramine (Anafranil and others), clonidine (Catapres and others), clozapine (Clozaril and others), divalproex sodium (Depakote), fluoxetine (Prozac and others), guanfacine (Tenex and others), haloperidol (Haldol and others), lorazepam (Ativan and others), methylphenidate (Ritalin and others), olanzapine (Zyprexa), pimozide (Orap), quetiapine (Seroquel), risperidone (Risperdal), ziprasidone (Geodon).

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