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Using the Atypical Antipsychotic Agents in Children and Adolescents

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It has been estimated that six to nine million pediatric patients in the United States (US) have a serious psychiatric illness.[1,2] While some disorders, such as depression and attention deficit hyperactivity disorder, have been the focus of much clinical research, other illnesses have received less attention. Until recently, there was little information on therapies for childhood-onset schizophrenia, Tourette's syndrome, and severe behavior disorders. The availability of the atypical antipsychotic agents, with their more favorable adverse effect profile, is likely have a significant impact on these illnesses. Clozapine, the first atypical antipsychotic, was introduced in 1989. Since that time, four additional agents have been released: olanzapine, quetiapine, risperidone, and ziprasidone. This issue of *Pediatric Pharmacotherapy* will briefly review the growing number of cases and clinical trials supporting the use of these in pediatric patients.

Mechanism of Action

The mechanism by which antipsychotic agents act is not well understood. While they work primarily as antagonists at dopaminergic and serotonergic sites, activity at other receptors (muscarinic, alpha-adrenergic, and histaminergic) may play an important role in both their beneficial and adverse effects.

The atypical antipsychotic agents are divided into two groups based on chemical structure: the dibenzepines (clozapine, olanzapine, and quetiapine) and the benzisoxazoles (risperidone and ziprasidone). While there are significant pharmacodynamic differences within the group, the atypical antipsychotics can generally be said to have an increased affinity for serotonergic (5-HT_2) receptors over dopaminergic (D_2) receptors compared to traditional antipsychotics such as the phenothiazines. In addition, the blockade of dopaminergic receptors is more pronounced in the limbic system, compared to the basal ganglia. As a result, the atypical antipsychotics have significantly less extrapyramidal effects.[3,4]

Therapeutic Use

The use of the atypical antipsychotics in children began in 1992 with several small case series involving clozapine. Among those first papers, Birmaher and colleagues treated three schizophrenic adolescents who had failed standard antipsychotic therapy.[5] The improvement in symptoms observed at clozapine doses of 300 to 400 mg/day has been repeated in several other papers. Unfortunately, the adverse effect profile of clozapine, particularly its association with rare, but occasionally fatal, agranulocytosis, has limited its usefulness.

With the approval of risperidone by the Food and Drug Administration (FDA) in 1993, the first safer alternative became available. Among the atypical antipsychotics, risperidone remains the most widely studied in children and adolescents. In 1995, Lombroso and colleagues conducted an 11-week open-label pilot study of risperidone in children with chronic tic disorders.[6] Seven children, ranging in age from 11 to 16 years, received risperidone beginning with 0.5 mg at bedtime and titrated to a maximum of 2.5 mg/day. The authors found significant reductions in the Yale Global Tic Severity Scale (YGTSS) scores, ranging from 8 to 66%. Symptoms of obsessive compulsive disorder, present in three patients, did not improve. Four of the patients experienced sedation, one had a brief dystonic reaction on the third day, and one patient had muscle stiffness. Weight gain occurred in all patients, ranging from 3 to 6 kg.

Bruggeman and coworkers found similar improvement in their study comparing risperidone to standard therapy with pimozide in 50 children and adults with Tourette's syndrome.[7] In this double-blind parallel-group study, both drugs were found to be efficacious and well tolerated. Fewer patients in the risperidone group experienced extrapyramidal symptoms (4/26 versus 8/24 patients). The authors concluded that risperidone should be considered an alternative first-line therapy in patients with Tourette's syndrome.

In May 1997, a 6-week open-label risperidone pilot study was conducted in children with schizophrenia.[8] Ten patients between 11 and 18 years of age were enrolled. Doses used in the study ranged from 4 to 10 mg/day. In all patients, risperidone produced clinical improvement. All patients had reduction in their Brief Psychiatric Rating Scale (BPRS) as well as the Positive and Negative Syndrome Scale for Schizophrenia (PANSS) scores. Six of the patients had at least a 20% reduction in their PANSS score. Nine children also had improvement in Clinical Global Impression (CGI) scores.

Risperidone has also been found to improve symptoms in patients with aggressive symptoms.[9-11] In a 10-week double-blind, placebo-controlled study, Findling and colleagues studied the effects of risperidone in 20 adolescents with conduct disorder (severe explosive behaviors).[9] Dosing in the treatment arm was initiated at 0.25 mg in children < 50 kg and 0.5 mg in children $\geq$ 50 kg. Doses were titrated by clinical response, with an average final dose of 0.028 ± 0.004 mg/kg/day (range 0.75 to 1.5 mg/day). Subjects who received risperidone were significantly less aggressive during the final 4 weeks of the study when compared to controls or to their own baseline, as measured by CGI scores and the Rating of Aggression Against People and/or Property (RAAPP) scale.

Buitelaar and colleagues reported similar findings in 38 hospitalized adolescents with aggression.[11] In this randomized controlled trial, patients received up to 2.9 mg/day risperidone or placebo. Treatment was associated with significant improvement in three different rating scales, including CGI scores. Risperidone has also been shown to benefit patients with autism and other pervasive developmental disorders, bipolar mania, and anorexia nervosa.

Olanzapine was approved by the FDA in September 1996. At this time, there is little information available on its use in pediatrics. Sholevar and coworkers described using olanzapine in 15 hospitalized children with schizophrenia.[12] The patients ranged in age from 6 to 13 years. In the authors' estimation, the majority of the patients improved. Sedation was the most frequently observed adverse effect, but was transient in most of the children. Olanzapine has also been found to improve symptoms in pediatric patients with pervasive developmental disorders and Tourette's syndrome using doses of 5 to 10 mg/day.[13-15]

Quetiapine was the next agent to become available, with its introduction in September 1997. Like olanzapine, little information is available in children and adolescents. Results from initial reports are mixed. In 1999, Martin and colleagues published the results of a 16-week open-label study of six patients (ages 7-14 years) with autism. Only two of the six patients were felt to have had a positive response and completed the entire study. Doses used were 100 to 350 mg/day. The primary reasons for withdrawal were sedation, agitation, and weight gain.[16] In April 2001, Parraga and Woodward described two children with Tourette's syndrome who responded favorably to quetiapine using doses up to 150 mg/day.[17]

In February 2001, the newest of the atypical antipsychotics, ziprasidone, was approved. Unlike earlier agents, it was studied in pediatric patients prior to its release. In the March 2000 issues of the *Journal of the American Academy of Child and Adolescent Psychiatry*, Sallee and colleagues reported the results of a pilot study using ziprasidone in 28 children with Tourette's syndrome.[18] The patients, ranging from 7 to 17 years, were randomized to receive either ziprasidone, initiated at 5 mg/day and titrated up to a maximum of 40 mg/day, or placebo. Ziprasidone-treated patients had significantly lower YGTSS scores. The average effective treatment dose was 28.2 ± 9.6 mg/day. Mild somnolence was the most frequent adverse effect noted. One ziprasidone-treated patient developed akathisia. No weight gain or other extrapyramidal symptoms were observed.

These studies, while all small in scale, provide a valuable background for the use of the atypical antipsychotic agents in children and adolescents. Additional studies, particularly longitudinal studies focusing on compliance and adverse effects, are needed to complement the work done to date in the pediatric population.

Pharmacokinetics

The absorption of oral doses of the atypical antipsychotic agents is often erratic, but peak serum concentrations typically occur 2 to 4 hours following a dose. They are widely distributed, with concentrations in the central nervous system exceeding those of the plasma. Because of their high degree of lipophilicity, these agents tend to accumulate in tissues. All undergo hepatic metabolism, with half-lives ranging from 20 to 40 hours in adults.[3] Pharmacokinetic parameters of olanzapine and quetiapine in children and adolescents appear to be similar to those in adults.[19,20]

Adverse Effects

Because of their predominant effect at serotonergic receptors, the atypical antipsychotics have a significantly different adverse effect profile than the traditional agents. While sedation and other anticholinergic adverse effects are still common, the risk of neuroleptic malignant syndrome and extrapyramidal symptoms is quite low (2% risk of akathisia). The most frequently reported adverse effects with these agents include: agitation or anxiety (up to 25% of patients), dizziness or drowsiness (4-20%), headache and insomnia (2-20%), tachycardia (3-7%), constipation (7-14%), dry mouth (6-7%), orthostatic hypotension (5-7%), and rash (2-5%). Weight gain, an antiserotonergic effect, has been observed in 2 to 6% of patients. The wide ranges of these adverse effects reflect differences within the class. Selection of an agent should be based, in part, on specific adverse effect profiles.[3]

Clozapine is associated with one of the most significant adverse effects within the group, agranulocytosis, in up to 1% of patients. Since its initial release in the US, clozapine has been closely regulated in an effort to identify affected patients. During clinical testing, 17 cases were reported in 1,743 patients. Since the drug's release, an additional 149 cases have been reported; 32% of those were fatal. At this time, patients receiving clozapine are required to have a blood sample evaluated prior to starting therapy, every week during therapy, and weekly for a month after discontinuation.[3,4]

Risperidone and ziprasidone are known to prolong the QT interval, producing a risk for arrhythmias or sudden cardiac death. These agents should not be used in patients with underlying QT prolongation or concurrently with other agents known to prolong the QT interval.[3]

In animal models, quetiapine has been associated with the development of cataracts. Lens changes have also been reported in humans, but a relationship to quetiapine has not been clearly established. It is recommended that patients have periodic ophthalmic examinations, prior to and every 6 months during treatment. In addition, elevations in liver function tests have been reported in up to 6% of patients receiving quetiapine, compared to 1% with the other agents in this class. This effect typically occurs within the first month of treatment and subsides even when treatment is continued.[3]

The atypical antipsychotics, particularly olanzapine and risperidone, can also cause increased prolactin release. All patients should be monitored for the development of galactorrhea, amenorrhea, gynecomastia, or impotence.[3] The development or worsening of diabetes has also been reported.[21]

Drug Interactions

The atypical antipsychotics are involved in several significant drug interactions. Quetiapine is the most frequently affected, as a result of metabolism through the hepatic cytochrome P450 3A pathway. Clinically significant interactions are listed in the table below.[3]

Table. Atypical Antipsychotic Drug Interactions[a]

Antipsychotic	Interacting Drug	Result
All	Dopamine (DA) Agonists	Decr. effect of DA agonist
Quetiapine	Lorazepam	Incr. CL of lorazepam
Quetiapine	Thioridazine	Incr. CL of quetiapine
Olanzapine Risperidone Ziprasidone	Carbamazepine	Incr. CL of antipsychotic
Quetiapine	Cimetidine	Decr. CL of quetiapine
Quetiapine	Phenytoin	Incr. CL of quetiapine
Quetiapine Ziprasidone	CYP3A4 inhibitors (eg, ketoconazole)	Decr. CL of antipsychotic
Risperidone	Clozapine	Decr. CL of risperidone

[a] CL = clearance; Decr. = decreased; Incr. = increased

Dosing Recommendations and Availability

Treatment with clozapine (Clozaril®; Novartis or generic) should begin at 25 mg once or twice daily in adults. Dosage titration may be continued with 25 to 50 mg increments daily to a maximum of 450 to 500 mg/day within the first 2 weeks of treatment. Further dosage adjustments should be made at weekly intervals, to a maximum of 900 mg/day. Treatment in children should begin at 6.25 mg twice daily, with weekly increases of 6.25 mg, as needed. The typical

pediatric dose ranges from 50 to 300 mg/day. Clozapine is available in 25 and 100 mg tablets.[3,4]

Olanzapine dosing should begin at 2.5 to 5 mg once daily in children and adolescents, with weekly titration by 2.5 or 5 mg increments to a target of 15 to 20 mg/day. Olanzapine is marketed as Zyprexa® by Lilly. It is available in 2.5, 5, 7.5, 10, 15, and 20 mg tablets, as well as 5 and 10 mg orally disintegrating tablets. An intramuscular (IM) formulation is currently under investigation.[3,4]

Treatment with quetiapine (Seroquel®; AstraZeneca) should begin at 12.5 mg twice daily in children and 25 mg twice daily in adolescents and adults. The dose may be increased in 25 to 50 mg daily increments to a target range of 300 to 400 mg/day. Further increases, up to 800 mg/day, should be based on patient response. Tablets are available in 25, 100, 200, and 300 mg strengths.[3,4]

Unlike the other agents, risperidone (Risperdal®; Janssen) is available in both oral tablet and liquid dosage forms. Tablets come in 0.25, 0.5, 1, 2, 3, and 4 mg strengths; the concentration of the liquid is 1 mg/ml. Dosing is typically initiated at 1 mg twice daily in adolescents and adults, increasing to a target of 3 mg twice daily. Further increases may be made to 6 mg/day, as needed. In younger children, dosing may be initiated with 0.25 mg twice daily, and increased based on clinical response.[3,4]

Ziprasidone treatment should be initiated at a dose of 20 mg twice daily in adults and adjusted, as needed, up to 80 mg twice daily. It is recommended that dosage titration should be done at intervals $\geq$ 48 hours. In children, a slower dose titration is recommended, starting at 5 mg/day. Ziprasidone is available as Geodon® by Pfizer, in 20, 40, 60, and 80 mg capsules. An IM formulation is under investigation.[3]

Summary

The atypical antipsychotics have the potential to provide significant benefits in pediatric patients with psychiatric illnesses. These agents appear to be as effective as traditional therapy, while having fewer adverse effects. More research is needed to define ideal dosing strategies and to assure the long-term safety of these agents in younger patients.

References

1. Stephenson J. Children with mental problems not getting the care they need. JAMA 2000;284:2043-4.
2. Kelleher KJ, McInerny TK, et al. Increasing identification of psychosocial problems: 1979-1996. Pediatrics 2000;105:1313-21.
3. Olin BR. Drug Facts and Comparisons. 2001. St. Louis: Facts and Comparisons, Inc., 933-50a.
4. Gracious BL, Findling RL. Antipsychotic medications for children and adolescents. Pediatr Ann 2001;30:138-45.
5. Birmaher B, Baker R, et al. Clozapine for the treatment of adolescents with schizophrenia. J Am Acad Child Adolesc Psychiatry 1992;31:160-4.
6. Lombroso PJ, Scahill L, et al. Risperidone treatment of children and adolescents with chronic tic disorders: a preliminary report. J Am Acad Child Adolesc Psychiatry 1995;34:1147-52.
7. Bruggeman R, van der Linden C, et al. Risperidone versus pimozide in Tourette's disorder: a comparative double-blind parallel-group study. J Clin Psychiatry 2001;62:50-6.
8. Armenteros JL, Whitaker AH, et al. Risperidone in adolescents with schizophrenia: an open pilot study. J Am Acad Child Adolesc Psychiatry 1997;36:694-700.
9. Findling RL, McNamara NK, et al. A double-blind study of risperidone in the treatment of conduct disorder. J Am Acad Child Adolesc Psychiatry 2000;39:509-16.
10. Sandor P, Stephens RJ. Risperidone treatment of aggressive behavior in children with Tourette syndrome. J Clin Psychopharmacol 2000;20:710-2.
11. Buitelaar JK, van der Gaag RJ, et al. A randomized controlled trial of risperidone in the treatment of aggression in hospitalized adolescents with subaverage cognitive abilities. J Clin Psychiatry 2001;62:239-48.
12. Potenza MN, Holmes JP, et al. Olanzapine treatment of children, adolescents, and adults with pervasive developmental disorders: an open-label pilot study. J Clin Psychopharmacol 1999;19:37-44.
13. Sholevar EH, Baron DA, Hardie TL. Treatment of childhood-onset schizophrenia with olanzapine. J Child Adolesc Psychopharmacol 2000;10:69-78.
14. Karam-Hage M, Ghaziuddin N. Olanzapine in Tourette's syndrome [letter]. J Am Acad Child Adolesc Psychiatry 2000;39:139.
15. Semerei ZB. Olanzapine in Tourette's disorder [letter]. J Am Acad Child Adolesc Psychiatry 2000;39:140.
16. Martin A, Koenig K, et al. Open-label quetiapine in the treatment of children and adolescents with autistic disorder. J Child Adolesc Psychopharmacol 1999;9:999-107.
17. Parraga HC, Woodward RL. Quetiapine for Tourette's syndrome [letter]. J Am Acad Child Adolesc Psychiatry 2001;40:389-91.
18. Sallee FR, Kurlan R, et al. Ziprasidone treatment of children and adolescents with Tourette's syndrome: a pilot study. J Am Acad Child Adolesc Psychiatry 2000;39:292-9.
19. Grothe DR, Calis KA, et al. Olanzapine pharmacokinetics in pediatric and adolescent inpatients with childhood-onset schizophrenia. J Clin Psychopharmacol 2000;20:220-5.
20. McConville B, Arvanitis L, et al. Pharmacokinetics, tolerability and clinical effectiveness of quetiapine fumarate in adolescents with selected psychotic disorders. J Clin Psychiatry 2000;61:252-60.
21. Selva KA, Scott SM. Diabetic ketoacidosis associated with olanzapine in an adolescent patient. J Pediatr 2001;138:936-8.

Formulary Update

The Pharmacy and Therapeutics Committee did not meet during July.

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