Dosing of Atypical Antipsychotics in Children and Adolescents

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Atypical antipsychotic medications are increasingly used to treat children and adolescents with a variety of neuropsychiatric disorders. The most common symptom for which atypical antipsychotics are prescribed to young patients is pernicious, pervasive, persistent aggression in the context of disruptive behavior disorders. Unfortunately, the evidence base informing physicians about atypical antipsychotic dosing in young people is relatively small, and high rates of neuropsychiatric comorbidity in pediatric populations can increase the risk of overmedication. A growing body of evidence regarding some pediatric neuropsychiatric conditions suggests that focused combination pharmacotherapy, particularly in cases of comorbidity, may be a rational choice. Specifically, a targeted treatment approach that combines a psychostimulant and an atypical antipsychotic, each at the lowest effective dose, might be the most effective means of treating some patients with the common pediatric comorbidity of attention-deficit/hyperactivity disorder and aggressive disruptive behavior disorder. Available data, though few, seem to suggest that the combination of a psychostimulant with the atypical antipsychotic risperidone may be safe and well tolerated in this patient population.

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Due in part to the improved tolerability and efficacy profiles of the newer, atypical antipsychotics, antipsychotic medications are being prescribed with increasing frequency to children and adolescents with a variety of neuropsychiatric disorders. Unfortunately, the evidence base informing atypical antipsychotic treatment in young people is relatively meager. Further, high rates of neuropsychiatric comorbidity in pediatric populations can exacerbate the existing risk of overmedication. To avoid overmedication, cautious combination pharmacotherapy using the lowest possible dose of more than one medication might be a rational approach for treating some children and adolescents with comorbid disorders, particularly aggressive behavior disorders and attention-deficit/hyperactivity disorder (ADHD).

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ATYPICAL ANTIPSYCHOTICS IN PEDIATRIC POPULATIONS

Although antipsychotics are all indicated only for the treatment of psychosis in adults, they have been found in clinical practice to have many other applications as well. Conditions for which young people are often treated with antipsychotics include pervasive developmental disorders such as autistic disorder, movement disorders such as chronic tic and Tourette's disorders, mood and anxiety disorders, delirium, and eating disorders (Table 1).[1] The most common reason that antipsychotics are prescribed to young patients is pernicious, pervasive, persistent aggression in the context of disruptive behavior disorders.[2] These comprise conduct disorder, oppositional defiant disorder, and disruptive behavior disorder not otherwise specified; this list does not include ADHD, although a high proportion of young people with a disruptive behavior disorder also have ADHD.

Despite the growing use of atypical antipsychotics in the treatment of pediatric neuropsychiatric disorders, there is at present a paucity of data to definitively inform clinicians about dosing and safety in young patients. Children and adolescents are not, of course, simply smaller adults, and they do not always respond to treatment with psychotropic agents in the way that adults do. Pharmacodynamics, pharmacokinetics, and biodisposition may change across the life cycle, affecting therapeutic response and vulnerability to adverse events. As illustrated by poor or

Table 1. Common Pediatric Uses of Antipsychotics[a]

Psychosis
Pervasive developmental disorders
Movement disorders
Mood and anxiety disorders
Delirium
Eating disorders
Aggression

[a]Based on Findling et al.[1]

equivocal results of trials testing tricyclic antidepressants in the treatment of depressed young people,[3] a drug's safety and efficacy in adults does not imply that it will be safe and efficacious in children or even adolescents. Young people are at higher risk for many of the adverse events that are seen in adult patients and may have side effects that are particular to that age group. It appears that young people are at higher risk than adults of developing acute drug-induced movement disorders, such as extrapyramidal symptoms, early in the course of treatment and that the younger the patient, the more substantial that risk.[4] Motor side effects are not usually inherently dangerous in the short-term, but, along with other adverse effects like sedation and weight gain, they can negatively affect medication adherence and the therapeutic alliance between doctor and patient. Because young people are more vulnerable to some adverse effects, a more gradual titration schedule should generally be employed in children and adolescents than is usually necessary in adults. A slow rate of titration appears to be associated with reduced rates of side effects, particularly extrapyramidal symptoms.[1]

DOSING OF ATYPICAL ANTIPSYCHOTICS IN YOUNG PATIENTS

There have been few rigorous studies of antipsychotic dosing in pediatric populations. Generally speaking, psychotic symptoms require higher doses of antipsychotics than nonpsychotic conditions in both children and adolescents.[5] Experience indicates that optimally therapeutic doses of antipsychotics for the treatment of schizophrenia in adolescents and adults are similar, while what little is known about rare childhood schizophrenia indicates that these psychotic children respond to lower doses than are used in adolescents and adults.[5]

The majority of information regarding atypical antipsychotic dosing in young people pertains to risperidone, the first "front-line" atypical antipsychotic marketed in the United States. According to available data and clinical experience, risperidone may be initiated at 0.5 mg to 1 mg b.i.d. for adolescents with schizophrenia, then increased in 0.5-mg or 1-mg increments every 3 or 4 days until an effective dosage (usually less than 6 mg/day) is reached.[1] At present, risperidone is the only atypical antipsychotic with published placebo-controlled data for childhood and adolescent aggression in the context of disruptive behavior disorders. For this population, a considerably lower dose administered once daily is sufficient. Risperidone may be initiated at 0.25 mg/day for severely aggressive children and 0.5 mg/day for severely aggressive adolescents and slowly titrated to a maximum dose of 1.5 mg/day and 3 mg/day, respectively.[6]

Currently, information on olanzapine in children and adolescents is based mostly on case series and case reports but appears to suggest effectiveness in treating recalcitrant schizophrenia and other, nonpsychotic psychiatric disorders in young patients.[1] Compared with risperidone, olanzapine seems to be associated with a lower risk of motor side effects and elevated prolactin but a higher risk of sedation and weight gain. Few data exist regarding the other first-line atypical antipsychotics—quetiapine, ziprasidone, and aripiprazole—in the treatment of young patients.

Providers must be vigilant against unintentionally overmedicating young patients in an effort to achieve optimal therapeutic response. Higher than normal doses of antipsychotic are unlikely to yield enhanced or expanded therapeutic benefit but are quite likely to exacerbate the risk of adverse effects. A patient's target symptoms must be closely considered not only in terms of drug dosing but also in terms of drug effectiveness. For example, while impulsive forms of pernicious aggressive behavior respond well to antipsychotic treatment, socialized aggression generally may not respond to pharmacotherapy. Nor will using an antipsychotic to treat a markedly aggressive child with ADHD necessarily produce for the patient an improved attention span. The goal of treating a patient's entire symptom spectrum without overmedicating a vulnerable young person can be particularly challenging in the highly comorbid pediatric population.

COMBINATION PHARMACOTHERAPY IN THE TREATMENT OF CHILDREN AND ADOLESCENTS WITH AGGRESSION AND ADHD

To effectively treat a young patient who has comorbid disorders while minimizing the risk of adverse effects, a clinician may isolate the symptom cluster of each syndrome and prescribe pharmacotherapy with agents that target a particular symptom cluster. Such a targeted treatment approach can help avoid overmedication by using drugs at customary doses according to their spheres of greatest effect. In ADHD, the syndromal symptom cluster is restlessness, distractibility, and impulsivity. ADHD is frequently comorbid with aggressive disruptive behavior disorders, but considerable aggression may also be manifest in youths with uncomplicated ADHD. Even when a child with only ADHD is considerably impaired by aggressive symptoms, practitioners should not treat with antipsychotics to address the classic symptoms of ADHD,

which instead respond optimally to treatment with psychostimulants. When the aggressive symptoms of a young patient with a disruptive behavior disorder and comorbid ADHD have been successfully treated with an atypical antipsychotic, but clear core symptoms of comorbid ADHD persist, increasing the dose of antipsychotic may lead to increased side effects without necessarily improving the patient's restlessness, distractibility, and impulsivity. Likewise, attempting to resolve lingering aggression associated with ADHD with higher than normal doses of psychostimulants seems to lead to undesirable drug doses and little improvement in the target symptom of aggression.

A growing body of evidence regarding some pediatric neuropsychiatric conditions suggests that combination pharmacotherapy, particularly in cases of comorbidity, may be a rational choice. Specifically, combining a psychostimulant and an atypical antipsychotic, each at the lowest effective dose, might be the most efficient means of treating the common comorbidity of ADHD and an aggressive disruptive behavior disorder. Available data,[7] though few, seem to suggest that the combination in this population of a psychostimulant with the atypical antipsychotic risperidone may be safe and well tolerated.

Two 6-week, placebo-controlled studies[8,9] provided data on the safety and efficacy of risperidone in children aged 5 to 12 years with aggressive disruptive behavior disorders and subaverage IQ (36 to 84, inclusive). A subset of these study subjects had comorbid ADHD. Data on these subjects were analyzed separately as a function of risperidone treatment and whether or not a preexisting psychostimulant regimen was in place.[7] One hundred fifty-five children with subaverage IQ, an aggressive disruptive behavior disorder, and comorbid ADHD were treated with risperidone, risperidone + psychostimulant, placebo, or placebo + psychostimulant. The mean dose of risperidone used concomitantly with a psychostimulant was 1.07 mg/day, while the mean dose of risperidone used alone was slightly higher at 1.11 mg/day. Statistical analysis using last observation carried forward showed a lack of significant interaction between risperidone and a psychostimulant; the use of a psychostimulant for the symptoms of comorbid ADHD did not alter the mean daily dose or the efficacy of risperidone for the aggressive symptoms of disruptive behavior disorders.

The frequently observed anorectic effect of psychostimulants did not appear to reduce the tendency of atypical antipsychotics to cause weight gain. Subjects receiving risperidone + psychostimulant gained a mean of 2.2 kg (approximately 4.9 lb), while subjects receiving risperidone gained a mean of 2.1 kg (approximately 4.7 lb).[7] While weight gain is of concern with risperidone treatment, it is uncommon that risperidone-related weight gain leads to frank obesity or to discontinuation of the associated drug due to intolerability.[1] Most of the subjects in the pooled analysis[7] experienced some adverse event, including somnolence, headache, and indigestion. Nosebleed, weight gain of at least 1 kg (2.2 lb), and hyperprolactinemia occurred only in subjects receiving risperidone with or without a psychostimulant. There were no group differences from baseline to endpoint on the Extrapyramidal Symptom Rating Scale.

Overall, this interim analysis of pooled data[7] suggests that minimal additional risk is associated with the combination of low doses of the atypical antipsychotic risperidone and a psychostimulant in pediatric populations with aggressive disruptive behavior disorders and comorbid ADHD, although further study is needed. It should be remembered that risperidone, though it has shown beneficial effects in children with a disruptive behavior disorder and comorbid ADHD, is not itself an appropriate treatment for patients with uncomplicated ADHD.

CONCLUSION

Atypical antipsychotics may be prescribed in pediatric populations for many reasons, persistent aggression the leading among them. The risk of overmedication is high among children and adolescents, and the lowest effective drug doses should be used for most pediatric patients. However, neuropsychiatric comorbidity is so common among young patients that this advisory may at times seem almost incompatible with effective treatment. A growing body of evidence in some pediatric neuropsychiatric conditions suggests that combination pharmacotherapy using the lowest possible dose of each medication may be a rational choice for clinicians faced with difficult youngsters who have pernicious, persistent, pervasive aggression and comorbid ADHD. Although treatment with customary amounts of a psychostimulant can lead to diminutions of aggressive behavior in children with ADHD and/or conduct disorder, unusually high doses of psychostimulants do not appear advisable when residual aggressive symptoms associated with a disruptive behavior do not respond to standard psychostimulant doses. Similarly, antipsychotic doses higher than those described in the medical literature are not recommended in order to control the restlessness, distractibility, impulsivity, or residual hyperactivity of ADHD. However, if the 2 medications are combined to treat the target symptoms for which each is intended, lower doses of each seem able to be used to beneficial effect. Focused combination therapy may help avoid overmedication of severely impaired young patients. The atypical antipsychotic risperidone used with a concomitant psychostimulant appears to be effective and reasonably safe in pediatric populations with aggression in the context of a disruptive behavior disorder and comorbid ADHD. At present, the clinical use of atypical antipsychotics in pediatric populations has outpaced published data to guide it. Atypical antipsychotics have shown many

applications in pediatric psychiatry, and further study is needed to refine their use in children and adolescents, particularly within the context of combination pharmacotherapy.

Drug names: aripiprazole (Abilify), olanzapine (Zyprexa), quetiapine (Seroquel), risperidone (Risperdal), ziprasidone (Geodon).

Disclosure of off-label usage: The author of this article has determined that, to the best of his knowledge, aripiprazole, olanzapine, quetiapine, risperidone, and ziprasidone are not approved by the U.S. Food and Drug Administration for the treatment of aggression in young people.

REFERENCES

1. Findling RL, McNamara NK, Gracious BL. Paediatric uses of atypical antipsychotics. Exp Opin Pharmacother 2000;1:935–945
2. Kaplan SL, Simms RM, Busner J. Prescribing practices of outpatient child psychiatrists. J Am Acad Child Adolesc Psychiatry 1994;33:35–44
3. Hazell P, O'Connell D, Heathcote D, et al. Tricyclic drugs for depression in children and adolescents. Cochrane Database Syst Rev 2002: CD002317
4. Findling RL. Paediatric psychopharmacology: closing the gap between science and practice. Expert Opin Pharmacother 2001;2:523–525
5. Findling RL, Schulz SC, Reed MD, et al. The antipsychotics: a pediatric perspective. Pediatr Clin North Am 1998;45:1205–1232
6. Findling RL, McNamara NK, Branicky LA, et al. A double-blind pilot study of risperidone in the treatment of conduct disorder. J Am Acad Child Adolesc Psychiatry 2000;39:509–516
7. Snyder R, Turgay A, Aman M, et al. Risperidone in Children With Oppositional Defiant Disorder, Conduct Disorder, Subaverage IQ, and Comorbid ADHD. Presented at the APA Institute of Psychiatric Services; October 10–14, 2001; Orlando, Fla
8. Aman MG, De Smedt G, Derivan A, et al. Double-blind, placebo-controlled study of risperidone for the treatment of disruptive behaviors in children with subaverage intelligence. Am J Psychiatry 2002;159: 1337–1346
9. Snyder R, Turgay A, Aman M, et al. Effects of risperidone on conduct and disruptive behavior disorders in children with subaverage IQs. J Am Acad Child Adolesc Psychiatry 2002;41:1026–1036