Pharmacotherapy for Aggression in Children and Adolescents

Adelaide S. Robb, MD

Aggression is a behavior that is hardwired in individuals as part of the fight or flight response to a perceived threat. Aggression can be a normal reaction to a severe stress or threat, or it can be maladaptive. Children and adolescents can be aggressive because they perceive things as threatening or violent, whether they are truly violent or not. For some, they have learned to perceive even benign stimuli in their environment as threatening and react to those threats with aggression. Maladaptive aggression accounts for one of the most frequent referrals to child psychiatric clinics.1 Aggression can be maladaptive based on duration of symptoms, frequency, intensity, or severity of the aggression in response to the level of the precipitant. It may even occur without any notable cause in the environment, as in a child who explodes for “no reason.” These children may not cease the aggression, even with intervention by adults, and often misread social cues in the environment from peers and adults. Aggressive children may see negative emotions, while non-aggressive peers perceive positive emotions, as demonstrated by McClure et al, when presented with “neutral” sample facial expressions.2

Recent scientific understanding of aggression has split the aggression seen in children and adolescents into two main subcategories: impulsive (reactive) ag-
assultion (IA) and proactive aggression (PA). In IA, the person displaying aggression becomes aggressive in response to a situation. This type of aggression is usually based in fear and impulsive in nature, not preplanned, and easily observed by those in the child's life. In PA, the person premeditates aggressive behavior in a "cold and calculating" fashion. Such aggression is seen in some bullies and may be used to gain rewards or impose the child’s will on others. The IA is frequently accompanied by negative emotions, including guilt and remorse after the event, as is often seen in clinic populations, while PA is more often seen in delinquent groups. Children with IA have early difficulties with peers and problem-solving skills, and up to 21% have a history of physical abuse. As these IA children progress through school, they have more severe psychopathology, including varying Axis I disorders. In several studies of large cohorts, children with IA account for 18% of all child and adolescent psychiatry visits, and up to 40% receive two or more medications. The most severe form of aggression is violence, and 18- to 24-year-old men tend to have the highest crime and murder rates as the most severe expression of aggressive behavior.

This review of the pharmacologic treatment of aggression will focus on the treatment of IA. It will begin with evaluation of aggression and the use of rating scales. The next section will briefly examine non-pharmacologic interventions, which should be done as part of a multi-modal treatment plan for the child with IA. IA is frequently seen as a manifestation of an Axis I disorder, and this review covers the treatment of IA associated with the most common Axis I diagnoses. The article will also cover two important consensus documents that propose guidelines for treatment of IA in hospitalized youth and the future of pharmacologic studies for IA across diagnoses.

**EVALUATION AND RATING SCALES**

The first step in evaluating a child or teenager who presents with aggression is to obtain a detailed psychiatric evaluation, including psychiatric and medical history, previous psychiatric treatment, family history, and psychosocial stressors, including abuse, bullying, and other traumatic events. A good description of the aggressive event and the time course is crucial. Was this the first time the child acted in this way? Has the child been aggressive before this time? Was the aggression verbal, physical, against people or property? How long did the event last? Was there any build up before the event? After the child calmed down, how did he act, including expressions of guilt and remorse? It is important to interview the parents and child, and obtain collateral information (after obtaining a release of information) from school and other settings where the child has exhibited aggression. When interviewing the child, it may take more than one visit to secure the child’s trust, so he or she can tell you what it feels like when self-control slips. If you can help the child identify the early signs of impending aggression, you may subsequently be able to intervene with psychotherapeutic modalities to prevent future potential aggressive events.

In an article that presented an overview of IA in various child psychiatric disorders, Jensen and colleagues developed a consensus report calling for accurate descriptions, rating scales, and new treatment trials. Rating scales used in the evaluation of aggression can help to characterize and quantify the IA, as well as provide a baseline of symptoms before treatment. General psychometric instruments that capture aggression as one of the symptoms on the broader scale include the Young Mania Rating Scale (YMRS), General Behavior Inventory Parent Version (P-GBI), Child Behavior Checklist (CBCL), Aberrant Behavior Checklist (ABC), and Nisonger Child Behavior Rating Form (NCBRF). Each of these instruments has an irritability, aggression, or conduct subscale as part of the overall rating scale. Other instruments are designed specifically to capture aggression as the main focus of the instrument, including the Modified Overt Aggression Scale (MOAS) and the Rating of Aggression Against People and/or Property (RAAPPS). In psychopharmacologic trials for the treatment of aggression in youth with IA, some or all of these rating scales may be used to evaluate the severity of aggression and as the primary outcome measure to quantify change with an intervention. The initial interventions, before pharmacologic management, are psychotherapy and psychoeducation as described in the next section.

**PSYCHOTHERAPEUTIC MODALITIES**

Psychotherapeutic interventions, such as hospitalization and milieu treatment alone, can markedly reduce aggressive behavior in as many as 50% of youth. Other psychosocial interventions found to be helpful include token economies, training in anger management, problem solving and social skills, and parent train-
ing (with good communication between the school and home). Several excellent reviews cover psychosocial interventions for aggression and for conduct disorder in more detail.13,14

**PHARMACOLOGIC MANAGEMENT OF AGGRESSION**

Because IA is usually seen as a symptom of an underlying Axis I disorder, this review examines the pharmacologic interventions by major diagnostic categories in the *Diagnostic and Statistical Manual of Mental Disorders*, fourth edition. In an analysis of youth with IA, a consensus group found that between 50% and 90% of youth with attention-deficit/hyperactivity disorder (ADHD), unipolar depression, and bipolar disorder had medium to high levels of impulsive aggression, compared with 10% of youth without an Axis I diagnosis, demonstrating that aggression is seen across categories of Axis I disorders.8 A variety of psychotropic agents have been described in the literature as useful in the treatment of IA in youth with psychiatric disorders, including typical and atypical antipsychotics, anticonvulsants, anxiolytics, alpha-agonists, beta-blockers, sedatives, selective serotonin reuptake inhibitors, and stimulants.1,15

**Disruptive Behavioral Disorders**

Disruptive behavioral disorders include ADHD, oppositional defiant disorder (ODD), and conduct disorder (CD). These disorders can occur separately or in combination with each other and are frequently associated with aggressive behavior. In the Multimodal Treatment Study of Children with ADHD (MTA), 44% of children who had aggression at baseline in the medication or medication plus therapy groups remained significantly symptomatic after 14 months of treatment. Although this number seems high, it also indicates that 56% of those with aggression at baseline were not significantly symptomatic with aggression after the study interventions; this comprised 26% of all children in the MTA trial.16 One trial showed that children with ADHD and IA who are already being treated with a stimulant may respond to augmentation pharmacotherapy with risperidone.17 Other trials of children with ADHD and comorbid ODD/CD have shown that children may need higher doses of stimulants or atomoxetine to achieve remission of their ADHD and ODD/CD symptoms.18-20 In successful studies of conduct disorder, investigators have used clonidine, lithium, haloperidol versus lithium (both were effective), molindone, and aripiprazole.21-24 An open-label trial of ADHD and conduct disorder using clonidine at a dose of 0.4 mg/day showed improvement with reductions on the RAAPP and mild side effects.10 Other, more recent trials, include a successful study of quetiapine in the treatment of conduct disorder and guanfacine extended-release in the treatment of conduct disorder.25,26 The practice parameters for the treatment of conduct disorder and aggression in inpatients have a variety of recommendations that address behavioral and pharmacologic recommendations to treat the aggression seen with conduct disorder in outpatient and inpatient settings.27,28

**Autism and Pervasive Developmental Disorders**

Aggression in autism and patients with subaverage IQ is a serious problem that can disrupt life at home and jeopardize placement in the child’s educational setting. It is this aggression that frequently precipitates psychiatric hospitalization for children with these developmental disabilities. Medication trials for aggression in autism have included typical and atypical antipsychotic drugs, serotonergic drugs, naltrexone, alpha-agonists, beta-blockers, lithium, and anticonvulsants.29 Many of these trials have been positive and provide empiric support for the treatment of ag-
doses of 2 to 15 mg to treat the irritability associated with autism in children 6 to 17 years. This approval was based on a flexible-dose study of aripiprazole versus placebo in 98 children with autism and a larger fixed-dose study of 218 children with autism. The two medications have the only FDA approvals for the treatment of aggression in any psychiatric disorder in childhood.

A series of additional studies used risperidone to treat aggression with and without ADHD/ODD/CD in children with subaverage IQ in short-term double-blind studies and long-term open-label studies. Risperidone was effective in the treatment of aggression in these very large trials. Dosing of risperidone in these studies ranged from 0.02 to 0.06 mg/kg/d and average daily doses were 1.5 mg/d. Common side effects included somnolence in approximately one-third of youth and weight gain beyond that attributable to normal growth. Based on the extensive trials in this population, risperidone is the first option for treating aggression in the developmentally delayed population, followed by aripiprazole. Other atypical antipsychotics (olanzapine, quetiapine, and ziprasidone) have also been evaluated for aggression in this population but are not currently FDA approved for this indication. These positive studies have been small open-label trials, and none has been a larger placebo-controlled trial.

**Bipolar Disorder**

Bipolar disorder frequently has irritability and aggression as part of its symptom cluster. A large pediatric trial of lithium and valproic acid measured IA with the YMRS and P-GBI. The trial demonstrated that IA was present in a subset of youth. It also found a tendency to respond less well to treatment with the three mood stabilizers than those without IA. In all of the registration trials for pediatric bipolar disorder using atypical antipsychotic medications, compared with placebo, the antipsychotic medications led to a significant reduction in aggressive symptoms on the YMRS. However, these medications are indicated for the treatment of bipolar disorder mixed or manic episodes, not the “treatment of aggression” in bipolar disorder. The Table (see page 233) provides a summary of the different disorders and types of effective medication.

**RECOMMENDATIONS FROM CONSENSUS GROUPS**

Two different groups approached the concept of IA in the field of child psychiatry and gave consensus recommendations about medication and treatment options and future research directions. The authors of the Treatment Recommendations for the use of Antipsychotics for Aggressive Youth (TRAAY) reviewed the literature, to date, on the pharmacologic treatment of aggression in youth and discussed agents commonly used to treat aggression in youth. The authors note haloperidol, pimozide, clozapine, olanzapine, quetiapine, and risperidone are all effective in the treatment of aggression. The studies were conducted with patients diagnosed with disorders ranging from conduct disorder and explosive aggression to tic disorders. Primary side effect concerns included weight gain, lipid, glucose, and insulin issues, as well as medication-specific side effects, such as agranulocytosis and seizures with clozapine, and QTc prolongation with ziprasidone. Their review noted that stimulants could improve the ADHD-associated aggression and the core symptoms of ADHD. Lithium and divalproex sodium were successful in treating aggression in conduct disorder, while carbamazepine was not successful in reducing aggression in conduct disorder. A review of 3 beta-blocker studies revealed they were effective in reducing aggression in a variety of psychiatric disorders in children with and without developmental disabilities, most frequently as an adjunctive...
medication. Side effects on beta-blockers can include sedation, hypotension, dizziness, bradycardia, bronchoconstriction, hypoglycemia, and possible alterations in growth hormone levels.

In a second article on the TRAAY consensus meeting, the experts set a series of recommendations on when to use atypical antipsychotics for aggression in youth. They had a series of 14 recommendations for treatment of individuals with antipsychotics for aggression (see Sidebar, page 234). They can serve as a solid set of guidelines to inform clinicians before instituting treatment of aggression with antipsychotics or other medications. Clinicians are encouraged to move sequentially through the steps, rather than going immediately to medication. Using such a measured approach helps clinicians avoid overmedicating and polypharmacy in children with aggression.

THE NEXT STEP

The second consensus group was involved in assessing the state of the science in studying IA across the diagnostic categories in child psychiatry. They stated that the field was ready to study IA as a primary target of pharmacotherapy rather than a symptom of the primary Axis I disorder. They based their recommendations on the previous trials in the field and the need for better studies of IA. An extensive series of open-label and double-blind trials of various psychotropic agents for the treatment of aggression over the past 15 years has led to the approval of only two medications by the FDA to treat aggression, which include aripiprazole and risperidone for the treatment of irritability in autism. This lack of approved treatment of aggression outside the diagnosis of autism. Treatment of aggression could allow children to remain in their homes and schools and not in more restrictive settings. As we advance in the field of pediatric psychopharmacology, being able to optimally treat the primary diagnosis and the comorbid aggressive symptoms will allow clinicians to provide more patients a chance to achieve remission, rather than just a reduction in symptoms. That change would be an important advance in the treatment of children with psychiatric illness.

REFERENCES


