Treatment of Aggression in Children

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Many young people display aggressive behavior, for a variety of reasons. In the majority of cases, aggressive behavior is not pathologic and can be treated with nonpharmacologic interventions. A careful diagnostic assessment is crucial to identifying causes and potential treatments of aggression in children. Psychiatric conditions associated with aggression that can be identified in childhood include conduct disorder, oppositional defiant disorder, disruptive behavior disorder not otherwise specified, and attention-deficit/hyperactivity disorder. The majority of young patients with aggressive behavior are not appropriate candidates for pharmacotherapy. However, for a small number of young people with persistent, pernicious, pervasive aggression over a longitudinal course, pharmacotherapy may be a rational treatment approach. When chronic aggression goes untreated, repercussions are costly and likelihood of a poor outcome is high. Safe, effective interventions are needed. Studies reviewed in this article show the efficacy of the stimulant methylphenidate, the mood stabilizer lithium, typical antipsychotics, and the atypical antipsychotic risperidone in treating aggressive behavior in children and adolescents. Although there is a growing body of data about the treatment of youths with a primary diagnosis of conduct disorder and its related conditions, more research is needed into pharmacotherapeutic treatments for the small number of young people who are impaired by uncontrollable aggression within the context of these disorders.

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Many young people display aggressive behavior, for a variety of reasons. Often, young people participate in a small number of destructive acts or physical altercations en route to adulthood. In the majority of cases, such behavior is not pathologic and can be addressed with psychosocial interventions. However, a small number of markedly aggressive children and adolescents are unable to control their aggressive impulses. When a clinician encounters a young patient with pronounced aggressive behavior, a careful diagnostic assessment is crucial.

Psychiatric conditions associated with aggression that may be identified in childhood are conduct disorder, oppositional defiant disorder, disruptive behavior disorder not otherwise specified, and attention-deficit/hyperactivity disorder (ADHD).[1] Aggression may also be present in youths suffering from mood and anxiety disorders, or a young patient may repeatedly show aggression for situational reasons unassociated with any syndromal psychiatric disorder. For example, a schoolchild who is frequently bullied at recess may engage in disruptive or aggressive behavior specifically in order to be kept inside the classroom during recess. In all cases, the evaluating clinician must ask the question: Is this young person's aggression persistent, pernicious, and pervasive? Then, the clinician must carefully consider all the conditions and comorbidities that may be underpinning the aggressive behavior. In this population, recourse to medication should be limited to instances in which compelling evidence justifies such an intervention.

In childhood psychopathology, comorbidity is the rule rather than the exception.[2] Proper treatment of aggression relies on the correct identification of the patient's primary and secondary condition(s). The DSM-IV[1] delineates 3 major disruptive behavior disorders: conduct disorder, oppositional defiant disorder, and disruptive behavior disorder not otherwise specified. Conduct disorder is characterized by a repetitive, persistent pattern of behavior that violates the basic rights of others or violates major age-appropriate societal norms. It is not, however, antisocial personality disorder presenting in the young. Youngsters with conduct disorder are likely to struggle—at least initially—with the fact that their behavior impairs their relationships with peers and adults, but they seem unable to control their explosive, impulsive, aggressive actions. In order to meet diagnostic symptom criteria for conduct disorder, an individual has shown 3 of the following in the 12-month period prior to diagnosis: aggression toward

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Table 1. Selected Placebo-Controlled, Double-Blind Studies of Pharmacotherapy for Aggressive Conduct Disorder in Children

Drug and Study	Duration of Active Treatment, wk	N	Diagnosis	Dose, mg/d	Results and Comments
Methylphenidate					
Klein et al,[2] 1997	5	83	DSM-III CD ADHD not excluded	Mean = 41.3	All measures of conduct disorder, including aggression, improved except socialized aggression; effects on conduct disorder were independent of severity of and effects on ADHD; normalization was rare
Lithium vs haloperidol					
Campbell et al,[3] 1984	4	61	DSM-III CD	Lithium: 500–2000 Haloperidol: 1–6	Hospitalized sample; both active treatments were superior to placebo, but haloperidol was associated with more severe side effects
Risperidone					
Findling et al,[4] 2000	10	20	DSM-IV CD	Average range, 0.75–1.50	Risperidone was more effective than placebo in decreasing aggression on most measures; low doses of risperidone were used; no parkinsonian or dystonic reactions were reported
Aman et al,[5] 2002	6	118	DSM-IV CD, ODD, or DBD NOS and subaverage IQ	Mean = 1.16	Risperidone was more effective than placebo in decreasing disruptive behaviors

Abbreviations: ADHD = attention-deficit/hyperactivity disorder; CD = conduct disorder; DBD NOS = disruptive behavior disorder not otherwise specified; DSM = Diagnostic and Statistical Manual of Mental Disorders; ODD = oppositional defiant disorder.

people or animals, property destruction, deceitfulness or theft, and serious violation of rules. Aggressive acts include persistent bullying or threatening, initiating fights, using a weapon that can cause serious harm, stealing while confronting the victim, forcing someone into sexual activity, and showing physical cruelty. However, it is only those young people who have persistent, pernicious, and pervasive conduct problems over a longitudinal course for whom pharmacotherapy may be appropriate treatment. Patients with a primary diagnosis of conduct disorder may fail to respond to psychosocial treatment, and left untreated, the associated behaviors may interfere with school functioning or with deportment at home. The potential outcomes of untreated conduct disorder are unfavorable and far-reaching: academic underachievement, underemployment or unemployment, criminality, relationship dysfunction, drug and alcohol abuse, and mood disorders.

Oppositional defiant disorder presents as a recurrent pattern of negativistic, defiant, disobedient, and hostile behavior directed toward authority figures.[1] In oppositional defiant disorder, aggression is usually verbal rather than physical. The child loses his or her temper, argues with adults, does not comply with requests made by adults, deliberately annoys others and is in turn easily annoyed, blames others, and is often angry, resentful, spiteful, or vindictive. Some patients with problem behaviors that do not meet full symptom criteria for conduct or oppositional defiant disorders may be most appropriately given the primary diagnosis of disruptive behavior disorder not otherwise specified.

Treatment options for these behavior disorders include group or individual behavior therapies based at school or at home and psychotropic medication. Again, many children may appear to be problematically aggressive, but only a small number of young patients are appropriate candidates for pharmacotherapy. A young person with few if any behavioral problems in grade school who becomes irritable, disruptive, and aggressive in junior high school, even if he or she meets DSM-IV criteria for conduct disorder, is unlikely to be among the pervasively impaired, aggressive youths who may require medication treatment. A youth who develops behavioral problems unexpectedly may be suffering from a mood disorder or a substance abuse disorder. A careful assessment of the longitudinal course of a youth's aggressive behavior is in some regards more important diagnostically than a current cross-sectional symptom assessment. For those young patients whose longitudinal course indicates that pharmacotherapy may be a rational consideration, there are a number of treatment options supported by research.

PHARMACOTHERAPY FOR CHILDHOOD AGGRESSION

Agents in several drug classes have been studied as treatments for aggressive children with conduct disorder (Table 1).[2–5]

Methylphenidate

One of the most common psychopharmacologic agents with which primary care physicians are familiar is the stimulant methylphenidate. This drug is highly effective in treating ADHD. Stimulants have historically not been considered as treatment for conduct disorders per se, but they have been seen as means to possibly reduce aggressive behavior in children with a primary diagnosis of ADHD. In a

1997 study by Klein et al.[2] focusing on behavioral problems associated with conduct disorder, methylphenidate was administered to 83 subjects, aged 6 to 15 years, all of whom had conduct disorder and 69% of whom had comorbid ADHD. (Study design originally called for subjects with conduct disorder alone, but the incidence of comorbidity in this population affected both the feasibility and the clinical relevance of the original plan.) Subjects were randomly assigned to receive up to 60 mg/day of methylphenidate or placebo for 5 weeks. Contrary to expectation, behavioral problems specific to conduct disorder, including less overt behaviors such as cheating and stealing, were significantly reduced by treatment with the active drug. Results showed that patients treated with methylphenidate (average dose = 41.3 mg/day) showed a significantly lower rate of physical aggression; however, reductions in uncommon, severe delinquent behavior were not statistically significant. Of note, clinical normalization almost never occurred for these subjects.

Mood Stabilizers and Typical Antipsychotics

Some mood stabilizers and typical antipsychotics are effective treatments for childhood aggression.

The mood stabilizer carbamazepine appeared to show clinically and statistically significant effectiveness in an open-label pilot study[6] treating 10 children hospitalized for aggressive conduct disorder, but when tested in a double-blind, placebo-controlled study[7] carbamazepine was not superior to placebo in reducing aggressive behavior among similar subjects, highlighting the need for methodologically rigorous studies in this patient group.

The mood stabilizer lithium has repeatedly been shown to have efficacy in treating childhood aggression. In a double-blind, placebo-controlled trial reported in 1984,[3] 61 subjects aged 5 to 12 years who were hospitalized with treatment-resistant, aggressive conduct disorder were randomly assigned to receive lithium, the typical antipsychotic haloperidol, or placebo. (The typical antipsychotics haloperidol, thioridazine, and chlorpromazine are indicated for pediatric severe explosive behaviors.[8] Molindone has also been shown to have efficacy in treating aggression associated with conduct disorder.[9]) For subjects receiving lithium, optimal doses ranged from 500 mg/day to 2000 mg/day. Optimal doses of haloperidol ranged from 1 mg/day to 6 mg/day. Both lithium and haloperidol were superior to placebo in reducing target behaviors, but lithium offered overall greater improvements than haloperidol. When asked to characterize the actions of the 2 drugs, hospital staff agreed that lithium evoked positive changes while haloperidol simply rendered the child more manageable.[3] At therapeutic doses, haloperidol was associated with more adverse effects than lithium, although there was noticeable weight gain in the lithium group. Sixteen of the 20 subjects who received haloperidol experienced excessive sedation, which in this population can inhibit learning. Ten subjects taking haloperidol experienced acute dystonic reactions—a frightening event, especially for a child—and 6 had drooling.

The effectiveness of lithium in curbing childhood aggression was reiterated in 2 later studies.[10] In one double-blind, placebo-controlled trial,[11] inpatients aged 10 to 17 years with aggressive conduct disorder received lithium or placebo over 4 weeks. Final mean dosage of lithium was 1425 mg/day. Compared with placebo, lithium significantly reduced subjects' aggression according to specific and global measures, and hospital staff agreed that clinical improvement had occurred. However, due to the risks of lithium treatment and the adverse effects of the typical antipsychotics, the atypical antipsychotics may present an attractive alternative in the treatment of severe aggression.

Atypical Antipsychotics: Risperidone

Though published data remain few, evidence indicates that some atypical antipsychotics may provide relief from aggressive symptoms associated with disruptive behavior disorders. In a small clinical case series, Soderstrom et al.[12] found that 5 out of 6 aggressive teenaged subjects with neuropsychiatric disorders responded rapidly to treatment with the atypical antipsychotic olanzapine. Findling and colleagues[4] conducted a small, double-blind study of 10 weeks' duration to test the atypical antipsychotic risperidone in the treatment of youths with conduct disorder and average intelligence. Subjects had Child Behavior Checklist (CBCL)[13] aggression subscale scores at least 2 standard deviations above the mean and were aged 5 to 15 years. Children were excluded from the study if they had ADHD of moderate or greater severity, any meaningful psychiatric comorbidity or organic mental syndrome, an IQ of less than 70, or a positive toxicity screen. Ten subjects received risperidone at low doses, and 10 subjects received placebo. Subjects weighing less than 50 kg (approximately 111 lb) started risperidone at 0.25 mg/day and increased up to 1.5 mg/day, while subjects weighing more than 50 kg started risperidone at 0.50 mg/day and increased up to 3 mg/day. Dosage increases were limited to the first 6 weeks of treatment. Primary outcome measure was the clinician-rated Rating of Aggression Against People and/or Property (RAAPP) scale,[14] for which a score of 1 = no aggression and a score of 5 = intolerable behavior. The RAAPP scores indicated that subjects who received risperidone were significantly less aggressive during the last 4 weeks of the study and showed greater reductions in symptoms from baseline than those who received placebo. The risperidone group also had greater reductions in Conduct Problem t scores on the Conners Parent Rating Scale[15] and Delinquency t scores on the CBCL. Risperidone was generally well tolerated although associated with weight gain. The most common adverse effects were sedation and increased appetite. No subject experienced parkinsonian symptoms, acute dystonic reactions, or abnormal involuntary movements.

Difficulties with aggressive behavior within the context of disruptive behavior disorders may commonly occur among children with below-average IQ.[5] The costs of caring for an intellectually disabled person who is aggressive or destructive are substantial, and the co-occurrence of these factors compounds impairment. Aman et al.[5] tested the effectiveness of risperidone among 118 children aged 5 to 12 years with an IQ of 36 to 84 inclusive (mean = 68), who met a diagnosis of conduct disorder, oppositional defiant disorder, or disruptive behavior disorder not otherwise specified. All subjects had a Nisonger Child Behavior Rating Form (NCBRF)[16] score of ≥ 24, indicating that the child engaged in fights or cruel behavior, attacked or threatened people, destroyed property, or argued. Children were excluded from the study if they had autism or another pervasive developmental disorder, psychosis, causal head injury, or seizure disorder requiring medication. Following a 1-week, single-blind placebo lead-in, 55 subjects received risperidone and 63 received placebo for 6 weeks. For those receiving active treatment, risperidone solution was administered at 0.01 mg/kg/day on days 1 and 2, doubled on day 3, and thereafter increased as needed to a maximum of 0.06 mg/kg/day. Only established, consistent psychostimulant or behavioral therapy and sleep aids were allowed concurrent with the study regimen. The mean dose of risperidone at endpoint was 1.16 mg/day.

The outcome measures used were change from baseline on the NCBRF, the Aberrant Behavior Checklist,[17] the Clinical Global Impressions-Severity and Improvement scales,[18] and a visual analogue scale used to rate an individual target symptom for each patient.[5] Seven percent of risperidone patients and 24% of placebo patients withdrew from the study, most frequently for lack of response to treatment. Most patients taking risperidone experienced rapid therapeutic effect. The risperidone group had a significantly greater decrease in NCBRF scores and on all other outcome measures than the placebo group. In general, subjects receiving risperidone demonstrated enhanced prosocial behaviors and diminished problem behaviors. Furthermore, the behavioral benefits of risperidone were shown to be independent of its sedative effects, which were generally mild and transient. Sedation was the most common side effect, occurring in 28 patients taking risperidone and in 6 patients taking placebo. Additionally, 2 patients taking risperidone developed extrapyramidal symptoms that resolved without treatment.

An open-label follow-up[19] of the double-blind study by Aman et al.[5] employed many of the same outcome measures but lasted 48 weeks. In this 48-week trial,[19] the mean dose of risperidone administered to children with subaverage IQ and primary disruptive behavior disorders was 1.5 mg/day. Results indicated that therapeutic effect was obtained for patients previously treated with placebo in the double-blind study and maintained for patients who had received risperidone in the double-blind study. The most common adverse effects were somnolence and headache; 16% of subjects experienced an extrapyramidal symptom–like event. Other adverse effects in decreasing order of frequency were rhinitis, weight gain, upper respiratory tract illness, and dyspepsia. In another study of risperidone for conduct disorder,[20] which included data from several studies including the ones noted above, mean serum prolactin levels initially rose but then began to decrease by week 8 of treatment and were within normal limits but above baseline values at the end of 1 year of treatment.

The side effect of weight gain is proportionately greater among children than among adults taking antipsychotics. Attempts to minimize weight gain that seem to be effective include using the lowest effective dose of antipsychotic and employing an anticipatory guidance model. In this model, young patients and their parents are forewarned about the high likelihood of increased appetite and advised how to proactively manage potential weight gain. For a child who gains an unacceptable amount of weight, the clinician must certainly re-evaluate whether continued treatment with the offending agent is justified. However, in many instances, the risk:benefit ratio justifies some weight gain.

CONCLUSION

Many young people display aggressive behavior. In the majority of cases, such behavior is not pathologic. However, a careful diagnostic assessment may reveal the presence of one or more psychiatric conditions associated with aggression, such as conduct disorder, oppositional defiant disorder, disruptive behavior disorder not otherwise specified, and ADHD. These disorders may be especially prevalent among children with intellectual limitations. In a limited number of young patients who fit the diagnostic criteria for conduct disorders, uncontrollable aggression may warrant the use of pharmacotherapy. When chronic aggression goes untreated, likelihood of a poor outcome is high; safe, effective interventions are needed. Studies discussed in this review showed the efficacy of the stimulant methylphenidate, the mood stabilizer lithium, the typical antipsychotic haloperidol, and the atypical antipsychotic risperidone in treating severe childhood aggression. While the majority of youngsters with aggressive behavior are not appropriate candidates for pharmacotherapy, more research is needed to identify treatments for those persistently, perniciously, and pervasively aggressive young patients who might benefit from medication.

Drug names: carbamazepine (Tegretol, Epitol, and others), chlorpromazine (Thorazine and others), haloperidol (Haldol and others), methylphenidate (Concerta, Ritalin, and others), molindone (Moban), olanzapine (Zyprexa), risperidone (Risperdal).

Disclosure of off-label usage: The author of this article has determined that, to the best of his knowledge, carbamazepine, chlorpromazine, haloperidol, lithium, methylphenidate, molindone, olanzapine,

risperidone, and thioridazine are not approved by the U.S. Food and Drug Administration for the treatment of aggression in children.

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