Aggressive Behavior in Patients With Attention-Deficit/Hyperactivity Disorder, Conduct Disorder, and Pervasive Developmental Disorders

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Aggressive behaviors are frequently observed in patients with attention-deficit/hyperactivity disorder, conduct disorder, and pervasive developmental disorders. Several theories have been postulated to explain the etiology of aggression in these disorders, but no one theory can account for all the different types of aggressive behaviors observed. Numerous uncontrolled studies with small sample sizes have produced mixed results of pharmacologic agents now being used to treat aggression. This article discusses the phenomenology, etiology, assessment, and pharmacologic treatment of aggressive behavior in patients who have attention-deficit/hyperactivity disorder, conduct disorder, and pervasive developmental disorders.
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Aggressive behavior is often associated with attention-deficit/hyperactivity disorder (ADHD), conduct disorder, and pervasive developmental disorders. The etiology of aggression in these disorders is unknown, and the results of studies of pharmacologic agents used for treatment have been mixed. This article will discuss the phenomenology, etiology, assessment, and pharmacologic treatment of aggressive behavior in patients who have attention-deficit/hyperactivity disorder, conduct disorder, and pervasive developmental disorders.

ATTENTION-DEFICIT/HYPERACTIVITY DISORDER

Phenomenology

Aggressive behavior, which is frequently observed in patients with ADHD, was described in the literature as early as 1977.[1–4] There is no aggressive subgroup in the ADHD population (using DSM-IV criteria) and aggressive and nonaggressive subtypes are typically not designated in ADHD studies. However, considerable data suggest that children who have aggressive behavior with ADHD differ from those who have ADHD without aggression. Aggressive behavior in children with ADHD is associated with greater psychological disturbance,[5,6] antisocial familial factors,[7,8] and subsequent development of antisocial personality and substance abuse.[9] In children, ADHD without aggression is associated with greater cognitive deficits,[5,6] cognitive problems at follow-up,[9] and learning difficulties in siblings.[7]

Frequency of aggression may change with the stage of development in children with ADHD.[10] Physical aggression may be typically seen in toddlers and preschool-age children. This early aggression usually decreases with age, but may cause unforeseen difficulties for the family, e.g., the child may be expelled from preschool. The more serious forms of aggression, with violence toward others, may increase with age. The prevalence of ADHD is estimated at 3% to 5% in school-age children; data on prevalence in adolescence and adulthood are limited.[11]

Etiology

Several theories have been explored on the etiology of aggression and the differences between aggressive and nonaggressive children with ADHD. These include neurotransmitter, hormonal, and developmental theories. A challenge procedure using the serotonergic (5-HT) agonist *d,l*-fenfluramine has been given to well-defined groups of aggressive versus nonaggressive ADHD children. The aggressive children were found to have a significantly larger prolactin response to fenfluramine than the nonaggressive children, which suggests differences in central 5-HT function.[12] Additionally, binding of [^{3}H]-imipramine on blood platelets was reduced in children

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with a diagnosis of mixed ADHD and conduct disorder[13] but not in children with ADHD without aggression.[14]

A study exploring the hormonal theory of aggression showed no differences between blood plasma cortisol levels in aggressive and nonaggressive prepubertal boys with ADHD.[15] ADHD is a risk factor for the development of aggression and other destructive behavioral disorders. The components of ADHD that confer this risk are unknown, but may include hyperactivity, impulsivity, learning disabilities, speech and/or language deficits, chronic parental and/or peer rejection, and low preschool IQ.[16]

Assessment

The reliability of measurable epidemiologic samples of aggression in children and adolescents is inadequate because aggressive behaviors of all types have extremely low base rates. Subcategories of aggression such as physical, nonphysical, and verbal aggression occur even less frequently, which results in even more problems in reliability of measurements. Traditionally, boys outnumber girls in physically aggressive acts. However, girls are more likely to exhibit relational aggression, i.e., threats of withholding friendships, exclusion of others from joining their groups, and nonconfrontational verbal devaluations, all of which are more difficult to assess than physical aggression. Comorbidity issues are also important in assessing aggression because ADHD children often have comorbid oppositional defiant disorder or conduct disorder. Rating scales used to evaluate aggression in children and adolescents are the Iowa Conners Teacher Questionnaire,[17] the Children's Aggression Scale (which is the scale used most frequently), and the parent and teacher versions of the Child Behavior Checklist.

Pharmacologic Treatment

Methylphenidate, a dopaminergic agent, has been widely studied in the treatment of aggression in children with ADHD (Table 1), but results have been mixed and the samples have been small. A double-blind investigation by Casat et al.[18] showed that methylphenidate 0.6 mg/kg decreased aggression in 6 children with ADHD. Klorman et al.[19] gave methylphenidate 0.3 mg/kg in the a.m. and noon and 0.15 mg/kg in the afternoon to 44 children with attention deficit disorder (ADD) and 28 children with ADD and aggression/oppositionality. Behavior improved in both groups and aggression decreased in the aggressive group. In a review of the effects of cognitive-behavioral therapy and methylphenidate, Hinshaw et al.[20] found that methylphenidate 0.3 mg/kg produced no significant effects on anger or verbal or physical aggression in children with ADHD. However, in a later double-blind study of 25 boys with ADHD—who also received cognitive-behavioral anger management training—Hinshaw and colleagues[21] found that methylphenidate 0.6 mg/kg effectively reduced physical retaliation during group provocation. Kaplan et al.[22] reported significant reduction in aggression measures in 6 adolescents treated with methylphenidate 0.6 mg/kg. Gadow et al.[23] reported methylphenidate 0.6 mg/kg suppressed nonphysical, physical, and verbal aggression in 11 aggressive ADHD children. Similar responses were noted by Barkley et al.[24] when 2 doses of methylphenidate (0.3 and 0.5 mg/kg) were administered to 37 ADHD aggressive children and 37 ADHD nonaggressive children. Matier et al.[25] administered a single 5-mg dose to 3 groups of children (11 nonaggressive ADHD, 14 aggressive ADHD, and 13 controls). Both nonaggressive and aggressive ADHD groups had significant decreases in inattention whereas impulsivity remained unchanged. Activity levels decreased only in the nonaggressive ADHD group. Winsberg et al.[26] reported that aggression decreased in 18 hyperactive, aggressive children treated with methylphenidate 30 mg b.i.d. Perhaps the largest study (N = 84) is that of Klein et al.,[27] who assigned children with conduct disorder to receive methylphenidate up to 60 mg/day or placebo for 5 weeks. Two thirds of the children also met criteria for ADHD. Methylphenidate was effective in the treatment of aggression in children with conduct disorder with or without symptoms of ADHD.

Dextroamphetamine has also been used as pharmacologic treatment for aggression in children with ADHD. However, most of the information is anecdotal and sample

Table 1. Pharmacologic Treatment of Aggression in Patients With Attention-Deficit/Hyperactivity Disorder (ADHD)

Study	Drug	Number	Response
Casat et al[18]	Methylphenidate	6	Decreased aggression
Klorman et al[19]	Methylphenidate	28 aggressive 44 nonaggressive	Behavior improved in both groups, aggression decreased in aggressive group
Hinshaw et al[21]	Methylphenidate	25	Decreased physical and verbal aggression[a]
Kaplan et al[22]	Methylphenidate	6	Reduction in aggression
Gadow et al[23]	Methylphenidate	11	Suppression of nonphysical, physical, and verbal aggression
Barkley et al[24]	Methylphenidate	37 aggressive 37 nonaggressive	Similar response from both groups
Matier et al[25]	Methylphenidate	14 aggressive	Increased attention in both groups, impulsivity unchanged
		11 nonaggressive	Activity level decreased only in nonaggressive group
Winsberg et al[26]	Methylphenidate	18	Aggression decreased
	d-Amphetamine	18	Aggression decreased
Klein et al[27]	Methylphenidate	84	Aggression improved[b]
Amery et al[28]	*d*-Amphetamine	10	Aggressive behavior decreased

[a]Cognitive-behavioral anger management training included in study.
[b]Diagnosis of conduct disorder with and without ADHD.

sizes are small. Amery et al.[28] assessed aggressive behavior in 10 boys with conduct disorder treated with dextroamphetamine 15–30 mg/day and reported that the number of aggressive playroom behaviors decreased. Winsberg et al.[26] also found that aggression decreased in 18 hyperactive, aggressive children treated with dextroamphetamine 20 mg b.i.d. Additional controlled studies with larger samples are necessary to determine the benefits of current pharmacologic treatment for aggression associated with ADHD.

CONDUCT DISORDER

Phenomenology

According to DSM-IV criteria, the characteristic patterns of behavior in patients with conduct disorder fall into 4 main groups: aggression toward people or animals, destruction of property, deceitfulness or theft, and serious violations of rules. Since only 3 symptoms out of 4 characteristic patterns must have been present in a 12-month period, aggression is not mandatory for a diagnosis of conduct disorder. There were changes in the description of conduct disorder from DSM-II to DSM-IV. DSM-II segregated conduct disorder subtypes into socialized versus undersocialized, while the current DSM-IV segregates conduct disorder subtypes on the basis of age at onset, i.e., early (before age 10 years) versus adolescent (after age 10 years). Prevalence rates listed in DSM-IV vary depending on the population sampled and gender. Rates are 6% to 16% for males less than age 18 years, and 2% to 9% for females.[11] Affective aggression (impulsive, uncontrolled, unplanned, or overt) and/or predatory aggression (goal-oriented, controlled, planned, or hidden) may be observed in patients who have conduct disorder.

Etiology

As with ADHD, there are numerous theories concerning the etiology of aggression in patients who have conduct disorder. Neurotransmitter theories of increased aggression include lowered serotonin levels, increased turnover of norepinephrine, acetylcholine stimulation (of animal brain), and dopaminergic agents.[29] Genetic theories suggest XY chromosomal effects and hormonal theories implicate testosterone and multiple other hormones. Developmental theories attempt to explain the manifestations of aggression from childhood to early adulthood and between genders,[30] and the relationship between abusive parents and aggressive surroundings in incarcerated juveniles.[31]

Assessment

The frequency of aggression in conduct disorder is difficult to capture. Boys outnumber girls in aggressive acts, but it is questionable whether DSM-IV criteria adequately assess the diagnosis of conduct disorder in girls or their level of aggression. Comorbidity is again an important issue in the assessment of patients with conduct disorder.

Table 2. Pharmacologic Treatment of Aggression in Patients With Conduct Disorder

Study	Drug	Number	Response
Klein et al[27]	Methylphenidate	37	Effective for treating aggression
Gadow et al[23]	Methylphenidate	11	Effective for treating aggression
Kemph et al[32]	Clonidine	17	Decrease in aggression
Hunt et al[33]	Clonidine	…	Decrease in aggression
Kafantaris et al[34]	Carbamazepine	10	Effective for treating aggression
Cueva et al[35]	Carbamazepine	22	No difference from placebo
Platt et al[37]	Lithium, haloperidol	61	Both drugs superior to placebo in treating aggression
Campbell et al[38]	Lithium	50	Modest effect on aggression
Rifkin et al[39]	Lithium	33	Not effective against aggression in adolescents
Greenhill et al[41]	Molindone, thioridazine	31	Both drugs decreased aggression

Rating scales include the Overt Aggression Scale, the Aggression Questionnaire, and the conduct subscales and peer conflict subscales of the Comprehensive Teacher's Rating Scale and the Children's Psychiatric Rating Scale.

Pharmacologic Treatment

Pharmacologic treatment of aggression in patients with conduct disorder include stimulants, clonidine, anticonvulsants, lithium, and neuroleptics (Table 2).

In the placebo-controlled Klein et al. study,[27] methylphenidate was effective in treating aggression in children with conduct disorder, with or without ADHD (N = 37). Gadow et al.[23] reported that methylphenidate suppressed aggression and hyperactivity in 11 boys in a public school setting. Overall, stimulants have not been effective in the treatment of affective aggression or high-frequency aggression.

Kemph et al.[32] reported a decrease in aggression using clonidine in an open trial designed to correlate childhood aggression with plasma levels of gamma-aminobutyric acid (GABA) in 17 children. A decrease in aggression was associated with an increase in GABA, suggesting that plasma GABA levels may be a useful marker of drug compliance. Hunt et al.[33] also reported less aggression in hyperactive boys treated with clonidine.

Phenytoin and phenobarbital have not proven effective in treating aggression in patients with conduct disorder. Kafantaris et al.[34] reported that carbamazepine treatment was effective in treating aggression in conduct disorder in an open trial of 10 aggressive and explosive children with a diagnosis of conduct disorder. However, in a double-blind, placebo-controlled study by Cueva et al.,[35] carbamazepine demonstrated no superiority over placebo in reducing aggressive behavior in 22 children. Donovan et

al.[36] used divalproex in an open trial in 10 adolescents with chronic temper outbursts and mood lability. All subjects showed clear improvement at the end of the 5-week study and during follow-up while taking medication.

Successful treatment of adolescent conduct disorder is rare. Platt et al.[37] reported that the effects of lithium and haloperidol were equally superior to placebo in 61 children with a profile of highly explosive and aggressive behavior. However, in a later study that attempted to replicate earlier findings, Campbell et al.[38] noted that the effects of lithium on aggression, although superior to placebo, were more modest than previously reported (N = 50). A 2-week trial by Rifkin et al.[39] in an adolescent population with conduct disorder (N = 33) found neither lithium nor placebo effective in treating aggression. The most common side effects of lithium include enuresis, fatigue, ataxia,[40] weight gain, and cognitive dulling. Enuresis, a fairly common finding in aggressive children with conduct disorder, may be aggravated by lithium administration.

Chlorpromazine and thioridazine are approved by the Food and Drug Administration for treatment of aggression in young children, but the side effects of tardive dyskinesia are worrisome. Similarly, although haloperidol is effective against aggression,[37] the side effects included excessive sedation and acute dystonia. In an 8-week double-blind parallel study by Greenhill et al.[41] comparing molindone and thioridazine in 31 aggressive children, both drugs significantly decreased aggression, but side effects included sedation—an unwelcome side effect in school-age children—and acute dystonia. Controlled studies are lacking on the use of atypical neuroleptics in children and adolescents with conduct disorder. Although frequently effective in treating explosive aggression in patients with conduct disorder, typical and possibly atypical neuroleptic agents may lead to undesirable extrapyramidal effects. Thus, all children treated with neuroleptics for aggression should be periodically assessed by the Abnormal Involuntary Movement Scale (AIMS).

PERVASIVE DEVELOPMENTAL DISORDERS

Phenomenology

Pervasive developmental disorders include autistic disorder, Rett's disorder, childhood disintegrative disorder, Asperger's disorder, and pervasive developmental disorder, not otherwise specified. DSM-IV criteria for pervasive developmental disorders include qualitative impairments in social interaction and communication (verbal and nonverbal) and restricted and stereotyped patterns of behavior, interests, and activities. Additionally, there must be an onset of abnormal functioning before age 3 years in at least 1 of the following areas: social interaction, language used in social communication, and symbolic or imaginative play. Aggressive behavior associated with pervasive developmental disorders can be directed toward other persons or may be self-injurious. Pervasive developmental disorders are more common in males than females by a ratio of 4:1, but whether aggression is more common in males is unknown. Epidemiologic studies suggest prevalence rates of autistic disorder to be 2–5/10,000.[11] Children with these disorders are usually referred for psychiatric evaluation when they demonstrate aggression, outbursts of self-injurious behavior, hyperactivity, severe stereotypies, or difficulties with focusing or concentration.

Etiology

No one etiologic theory accounts for all the aggressive behaviors exhibited in pervasive developmental disorders. Among theories postulated are neuroanatomical theories, genetic mechanisms, and a neurotoxin theory (lead poisoning). Deviance in parenting skills, an earlier developmental theory of aggression, is no longer accepted as an etiology.[42] Abnormal biochemical findings include elevated serotonin levels, elevated dopamine levels, alteration of hypothalamic dopamine receptor sensitivity, hypothalamic dysregulation (with an abnormal response to thyrotropin-releasing hormone), elevated triiodothyronine levels, and abnormalities of the endogenous opiate system—including reduction of urinary free catecholamines and MHPG (3-methoxy-4-hydroxyphenylglycol), reduction of β-endorphin in plasma, and elevated endorphin fraction II levels in CSF.[43]

Assessment

To assess aggression in patients with pervasive developmental disorders, specific and realistic goals for target symptoms and their frequency and severity must be determined. Rating scales used to assess drug response of symptoms (including aggression) are the Childhood Autism Rating Scale, the Fish Scale, the Ritvo-Freeman Real Life Rating Scale for Autism, the Timed Behavioral Rating Scale, the Children's Psychiatric Rating Scale (14 items appropriate for symptoms of autism including aggression), the Clinical Global Impressions (CGI) scale, the Nurses Global Impression Scale, and the Conners Parent and Teacher Questionnaires. As stated above, initial and periodic AIMS assessments are recommended throughout treatment because of the increased frequency of movement disorders.

Pharmacologic Treatment

Pharmacologic treatment of aggression in patients with pervasive developmental disorders includes naltrexone, haloperidol, risperidone, clomipramine, clonidine, methylphenidate, and other psychotropic drugs (Table 3).

There is evidence, although inconclusive, for abnormalities in endogenous opioids in some autistic children, and naltrexone is a potent long-lasting opiate antagonist. A double-blind, placebo-controlled study by Campbell et al.[44] found naltrexone effects on behavioral symptoms and learning superior to placebo in 18 autistic children.

Table 3. Pharmacologic Treatment of Aggression in Patients With Pervasive Developmental Disorders

Study	Drug	Number	Response
Campbell et al[44]	Naltrexone	18	Superior to placebo
Bouvard et al[45]	Naltrexone	10	Benefited a subgroup of autistic children
Willemsen-Swinkels et al[46]	Naltrexone	23	Teachers reported superiority to placebo, parents saw no difference
Perry et al[49]	Haloperidol	60	Decrease in aggression
Anderson et al[47]	Haloperidol	45	Decrease in aggression
Naruse et al[48]	Haloperidol	87	Decrease in aggression
McDougle et al[50]	Risperidone	31	More effective than placebo in adults
McDougle et al[51]	Risperidone	18	Decreased aggression in children and adolescents
Gordon et al[52]	Clomipramine, desipramine	24	Clomipramine superior to desipramine
Sanchez et al[53]	Clomipramine	8	Not effective
Jaselskis et al[54]	Clonidine	8	Modestly effective
Fankhauser et al[55]	Clonidine	9	Effective in reducing several hyperarousal behaviors
Birmaher et al[56]	Methylphenidate	9	Improvement in hyperactivity
Quintana et al[57]	Methylphenidate	10	Improvement in attention and hyperactivity
Buitelaar et al[58]	Buspirone	22	Effective in treatment of irritability
Yarbrough et al[59]	Fenfluramine[a]	20	Not effective
Ritvo et al[60]	Fenfluramine[a]	14	Effective against aggression
Ekman et al[61]	Fenfluramine[a]	20	Minimally effective
Campbell et al[62]	Fenfluramine[a]	28	Not effective

[a]Withdrawn from market.

A double-blind, placebo-controlled study (N = 10) by Bouvard et al.[45] suggests that naltrexone only benefits a subgroup of autistic children with plasma abnormalities. In a double-blind, placebo-controlled crossover trial by Willemsen-Swinkels et al.,[46] teachers reported naltrexone superior to placebo on hyperactivity and irritability in 23 children; parents observed no difference.

Multiple studies[47–49] show the ability of haloperidol, a dopamine antagonist, to effectively decrease aggression in patients with pervasive developmental disorders, but the side effects of the drug—including withdrawal dyskinesias, tardive dyskinesia, acute dystonia, sedation, and weight gain—are distressing.

Risperidone is an atypical neuroleptic agent with potent D_2/5-HT_{2A} antagonism that may improve aggression in pervasive developmental disorders. Side effects include sedation (which hinders learning), the potential for abnormal movements, and weight gain. In a double-blind, placebo-controlled study of autism in adults (N = 31) by McDougle et al.,[50] risperidone was more effective than placebo in the short-term treatment of symptoms of autism, including aggression. In a 12-week open-label trial of risperidone in 18 children and adolescents with pervasive developmental disorders, McDougle and colleagues[51] reported that risperidone may be effective for improving behavioral symptoms in some patients.

Clomipramine is a tricyclic antidepressant with potent serotonin reuptake blocking properties. Side effects include sedation, insomnia, anticholinergic effects, and behavioral toxicity that is characterized by irritability and dysphoria. Studies of the effectiveness of clomipramine against symptoms of pervasive developmental disorders yield mixed results. In a double-blind, placebo-controlled comparison of clomipramine, desipramine, and placebo by Gordon et al.,[52] clomipramine was superior to both placebo and desipramine on ratings of autistic symptoms (including stereotypies), anger, and compulsive ritualized behavior in 24 patients. However, in an open-label trial of clomipramine in 8 young autistic children reported by Sanchez et al.,[53] 6 children were rated as worse on the Clinical Global Consensus Ratings scale, and 1 child improved moderately. One child was excluded during the third week of treatment because of urinary retention.

Clonidine is an α_2-adrenergic receptor agonist. Side effects include sedation, changes in blood pressure, dizziness, depression, and rebound hypertension on withdrawal. Two double-blind studies have shown some evidence for effectiveness in pervasive developmental disorders although sample sizes have been small. Jaselskis et al.[54] reported that clonidine was modestly effective in the short-term treatment of irritability and hyperactivity in 8 children with autism. A double-blind, placebo-controlled study of the efficacy of transdermal clonidine in 9 autistic males by Fankhauser et al.[55] found clonidine effective in reducing several hyperarousal behaviors. The CGI scale indicated that clonidine produced a significant improvement on severity of illness, global improvement, and efficacy index for therapeutic effect of the drug.

Studies indicate some improvement in attention and hyperactivity when methylphenidate is given to patients with pervasive developmental disorders, but the samples are small.[56,57] In an open trial, Birmaher et al.[56] noted improvement of hyperactivity in 9 autistic children. In a double-blind crossover study of 10 autistic children using placebo and 2 methylphenidate doses (10 mg or 20 mg b.i.d.), Quintana et al.[57] reported modest but significant improvement of symptoms in patients taking methylphenidate. In this population, methylphenidate is associated with a substantial risk of side effects that include development and/or worsening of stereotypies, tics, sleep disturbances, loss of appetite, weight loss, and behavioral toxicity characterized by irritability and dysphoria.

Selective serotonin reuptake inhibitors are frequently administered to children with developmental disabilities by developmental pediatricians. However, double-blind, placebo-controlled studies are lacking. Side effects include restlessness, increased irritability, and decreased appetite. In an open trial of the efficacy and safety of buspirone in 22 children with pervasive developmental disorders, Buitelaar et al.[58] suggested that buspirone may be useful in the management of anxiety and irritability in this population.

Fenfluramine, a drug that has had mixed results in treating aggression in patients with pervasive developmental disorders,[59–62] has been withdrawn from the market.

CONCLUSION

Aggressive behavior in children and adolescents is often associated with ADHD, conduct disorder, and pervasive developmental disorders. Numerous pharmacologic agents, some with significant side effects, have been used to treat aggressive behaviors in this population. Anecdotal experience and drug studies have yielded mixed results. Controlled studies with adequate sample sizes are necessary to determine the best pharmacologic agents to effectively treat aggression in young patients with these disorders.

Drug names: buspirone (BuSpar), carbamazepine (Atretol, Tegretol, and others), chlorpromazine (Thorazine and others), clomipramine (Anafranil and others), clonidine (Catapres, Combipres, and others), desipramine (Norpramin and others), dextroamphetamine (Adderall, Dexedrine, and others), haloperidol (Haldol and others), methylphenidate (Ritalin), molindone (Moban), naltrexone (Revia), phenytoin (Dilantin), risperidone (Risperdal), thioridazine (Mellaril and others).

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DISCLOSURE OF OFF-LABEL USAGE

The authors of this article have determined that, to the best of their knowledge, the following agents mentioned herein are *not* indicated for treatment of aggression: buspirone, carbamazepine, clomipramine, clonidine, desipramine, and naltrexone.