Treatment of Aggression in Children and Adolescents With Autism and Conduct Disorder

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The optimal clinical management of aggression in children and adolescents involves both behavioral and pharmacologic intervention strategies. This article reviews medication treatments for youngsters with autistic disorder and conduct disorder, conditions for which the pharmacologic management of aggression is often necessary. Efficacy results and associated adverse effects from selected clinical trials of most classes of psychotropic medications are discussed. While preliminary progress has been made in the development of medication treatments for these serious disorders of youth, additional controlled research and longitudinal studies are needed to better understand the efficacy and tolerability of currently available compounds within each diagnostic group.

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Aggression is a common clinical manifestation of autistic disorder (autism) and conduct disorder. Although behavioral therapy can be an effective treatment modality for both conditions, pharmacotherapy is frequently indicated. This article reviews relevant studies on the pharmacologic treatment of aggression in children and adolescents with these disorders.

AUTISTIC DISORDER

Autism and other pervasive developmental disorders (PDDs) are characterized by severe and pervasive impairment in reciprocal social interaction, communication, and behavior.[1] PDDs are typically evident in the first few years of life and are frequently associated with mental retardation. Treatment is multimodal and largely based on educational and behavioral interventions. While speech therapy is essential for optimizing outcome, physical and occupational therapy are also often needed.

Despite the available nonpharmacologic interventions, many individuals with autism remain significantly impaired. Under these circumstances, pharmacologic treatment is often necessary. Medication can be useful for reducing interfering symptoms, thus allowing other treatment interventions to proceed more effectively.

A number of behavioral symptoms, including hyperactivity; inattention; impulsivity; aggression toward self, others, or property; and interfering repetitive thoughts and behavior, are often present in patients with PDDs. Different classes of psychotropic agents have been found to be helpful for particular domains of symptom impairment. The reader is referred to a recent, comprehensive review of drug treatment for this broad range of symptoms commonly observed in patients with autism and other PDDs.[2] Here, proceeding by class of drug, we describe efficacy and safety results from selected trials in autistic subjects for whom aggression was a primary target of pharmacotherapy (Table 1).

Typical Antipsychotics

Typical antipsychotics were among the first medications to be assessed systematically in autistic children. Indeed, they have often been prescribed to treat severe aggression in individuals with developmental disabilities in general. Most of the available typical antipsychotics, including many low-potency agents, were studied in heterogeneous samples of children that included autistic subjects. While these agents were often found to be helpful for reducing symptoms of aggression, their adverse effects

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Table 1. Selected Double-Blind Placebo-Controlled Studies Targeting Aggression in Autistic Disorder

Medication	Symptoms Improved	Significant Adverse Effects	Comments	Reference No.
Haloperidol	Affective lability, anger, temper outbursts	Acute dystonic reactions, withdrawal and tardive dyskinesias	No controlled studies in adults	3–7
Risperidone	Aggression, irritability	Mild transient sedation	Conducted in adults	10
Risperidone	Aggression, irritability	Weight gain, increased appetite, sedation, tremor, hypersalivation	Largest controlled study to date in children with autism	11
Clomipramine	Aggression, self-injury	QTc prolongation, tachycardia, seizure	Conducted in children and young adults	23
Fluvoxamine	Aggression, repetitive phenomena	Nausea, sedation	No controlled pediatric data; unpublished pediatric data unfavorable	25
Lamotrigine	No better than placebo	Insomnia, hyperactivity	Study did not specifically focus on aggression	35
Methylphenidate	Hyperactivity, irritability	Minimal	Modest improvement in hyperactivity; 2 of 10 required addition of haloperidol to manage aggression	37
Clonidine	Hyperactivity, irritability, oppositional behavior, aggression, self-injury	Hypotension, sedation, decreased activity	Small number of subjects	38

tended to outweigh any clinical benefit. The lower potency antipsychotics tended to cause sedation and cognitive impairment, particularly at higher doses, which interfered with educational and other programming attempts. Regarding the high-potency antipsychotics, Campbell and coworkers[3–5] conducted several well-designed controlled studies of haloperidol in autistic children. In doses of 1 to 2 mg/day, haloperidol was found to be more efficacious than placebo for affective lability, anger, and temper outbursts. However, acute dystonic reactions, along with withdrawal and tardive dyskinesias, were not infrequent.[6,7]

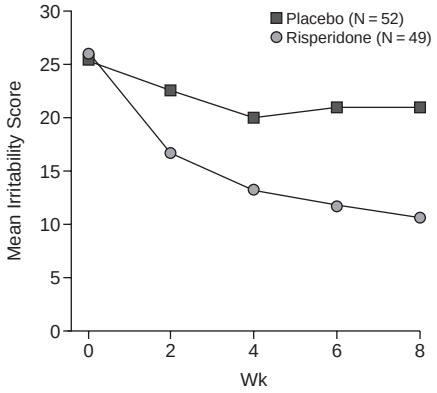
Atypical Antipsychotics

The atypical antipsychotics may have a reduced propensity toward motor side effects, including tardive dyskinesia secondary to their potent antagonism at both dopamine (DA) and serotonin (5-hydroxytryptamine, 5-HT) receptors. Clinically, they are among the most effective drugs for reducing aggression in individuals with autism.

Clozapine. Two case reports found clozapine, in doses of 200 to 450 mg/day, effective for reducing aggression in children and adolescents with autism.[8,9] The limited number of reports of clozapine treatment might reflect concern about the risks of seizures and agranulocytosis that are associated with the drug. Additionally, the need for frequent blood draws is not ideal for children with autism.

Risperidone. Among the available atypical antipsychotics, risperidone has received the most attention as a potential treatment for aggression associated with autism. In a double-blind, placebo-controlled trial of risperidone (mean ± SD dose = 2.9 ± 1.4 mg/day) involving 31 adults with autism, a significant reduction occurred in aggression toward self, others, and property.[10] Mild transient sedation was the most common adverse effect in this study. The National Institute of Mental Health–sponsored Research Units on Pediatric Psychopharmacology (RUPP) Autism Network recently completed the largest drug study to date in children with autism (N = 101).[11] In this 8-week double-blind, placebo-controlled, parallel-group study, risperidone (mean dose = 1.8 ± 0.7 mg/day) was found to be significantly more efficacious than placebo for the treatment of aggression and irritability (Figure 1). Weight gain, increased appetite, sedation, tremor, and hypersalivation were more common in the risperidone- versus the placebo-treated group.

Figure 1. Mean Score for Irritability in Risperidone- Vs. Placebo-Treated Children With Autism[a]



[a]Reprinted from Research Units on Pediatric Psychopharmacology Autism Network,[11] with permission. Higher Scores on the Irritability subscale of the Aberrant Behavior Checklist indicate greater irritability.

Olanzapine. Case reports, an open-label case series,[12] and a prospective, open-label comparison with haloperidol[13] have described reductions in aggression in patients with autism and other PDDs treated with olanzapine. In a recently published study using a parallel-group design, 12

children with autism were randomly assigned to 6 weeks of open-label treatment with olanzapine or haloperidol. Mean final daily dosages were 7.9 ± 2.5 mg for olanzapine and 1.4 ± 0.7 mg for haloperidol. Five of 6 subjects in the olanzapine group were rated as responders compared with 3 of 6 subjects treated with haloperidol. Weight gain from baseline to the end of the trial was significantly higher in the olanzapine group (mean = 9.0 ± 3.5 lb; range, 5.9 to 15.8 lb [4.1 ± 1.6 kg; range, 2.6 to 7.1 kg]) than in the haloperidol group (mean = 3.2 ± 4.9 lb; range, –5.5 to +8.8 lb [1.4 ± 2.2 kg; range, –2.5 to +3.9 kg]). One subject given haloperidol demonstrated mild rigidity, whereas no subject treated with olanzapine showed motor side effects.[13]

Quetiapine. There has been only 1 report describing quetiapine treatment in autism.[14] Of the 6 subjects who participated in the 16-week open-label trial, which was targeted toward aggression and irritability, only 1 showed sustained benefit. Side effects included sedation, increased appetite, weight gain (range, 2–18 lb [0.9–8.1 kg]), behavioral activation, and a possible seizure in 1 subject.

Ziprasidone. Ziprasidone is the fifth atypical antipsychotic to be marketed in the United States.[15] In controlled studies to date involving adults with schizophrenia[16,17] and children and adolescents with Tourette's disorder,[18] ziprasidone has not been associated with significant weight gain or other serious adverse effects. Our group recently found 6 of 12 youths with autism responsive to open-label ziprasidone (mean dose = 59.2 ± 34.8 mg/day).[19] The target symptoms included aggression, agitation, and irritability. Among the 8 patients who experienced side effects, transient sedation was most common. One patient with a history of tardive dyskinesia involving his hands developed an oral dyskinesia that resolved upon drug discontinuation. Otherwise, no serious adverse effects occurred, including cardiac side effects. The mean change in weight for the entire group was –5.8 ± 12.5 lb (–2.6 ± +5.6 kg) (range, –35 to +6 lb [–15.8 ± +2.7 kg]). The weight loss was likely due to the gradual decrease and discontinuation of a concurrently administered atypical antipsychotic agent.

Serotonin Reuptake Inhibitors

Many lines of evidence point to abnormalities in 5-HT function in autism.[20] Serotonin reuptake inhibitors (SRIs) were initially hypothesized to have efficacy based on the presumed 5-HT dysfunction and because of some of the similarities between obsessive-compulsive disorder and the repetitive phenomena seen in autism.[21] In addition, serotonergic drugs have been shown to have antiaggressive properties.[22]

Clomipramine. Clomipramine (mean dose = 152 ± 56 mg/day), a tricyclic antidepressant, was found to be superior to placebo and desipramine for the treatment of several symptoms, including anger/uncooperativeness and self-injury, in children and young adults with autism.[23] In a large, open-label trial in 35 adults with PDDs, clomipramine (mean dose = 139 ± 50 mg/day) was effective for reducing aggression, among other symptoms.[24] Despite its probable effects on treating aggression in autism, clomipramine is not frequently prescribed for this symptom cluster due to concerns about tolerability and the availability of the safer selective SRIs (SSRIs).

Fluvoxamine. To date, there is only 1 published placebo-controlled trial of an SSRI in autism. McDougle and colleagues[25] compared fluvoxamine (mean dose = 276.7 ± 41.7 mg/day) and placebo in 30 adults with autism for 12 weeks. Eight of 15 patients in the fluvoxamine group compared with none in the placebo group were categorized as "much improved" or "very much improved" on the Clinical Global Impressions (CGI) scale. Fluvoxamine was significantly more effective than placebo for reducing repetitive phenomena, maladaptive behavior, and aggression. Adverse effects of nausea and sedation were minimal and self-limited.

Results from studies of SSRIs in children and adolescents with autism have not been as encouraging. In a study involving pediatric patients with PDDs, McDougle and colleagues (C.J.M.; J. P. Holmes, R.N., M.S.N.; L. H. Price, M.D.; unpublished data, Sept. 1997) found that fluvoxamine (mean dose = 106.9 mg/day) was efficacious in only 1 of 18 fluvoxamine-treated subjects compared with none of 16 placebo-treated subjects. Fluvoxamine was poorly tolerated and caused increased aggression in 5 subjects. This difference in rates of improvement between children and adults suggests possible developmental differences in drug responsivity and tolerability in autism.

Other SSRIs. Case reports and open-label studies suggest that other SSRIs may reduce aggression in some persons with autism. In a retrospective case series of adults with PDDs and comorbid mental retardation, Branford and colleagues[26] found that 6 (24%) of 25 patients treated with fluoxetine and 3 (25%) of 12 patients given paroxetine were rated as "much improved" or "very much improved" on the CGI scale in terms of perseverative behaviors, aggression, and self-injury. However, in an open-label study of fluoxetine in 37 children with PDDs (age range, 2.2–7.8 years), aggression was a frequent cause for drug discontinuation.[27] McDougle and colleagues[28] examined the short-term effectiveness of sertraline in adults with PDDs and found it beneficial in 24 (57%) of 42 subjects, primarily for reducing repetitive and aggressive symptoms. In a 4-month, open-label study of 15 adults with severe and profound mental retardation (7 with PDD), paroxetine at doses of 20 to 50 mg daily was significantly effective for symptoms of aggression at 1 month, but not at 4-month follow-up.[29]

Mirtazapine. Because SSRIs are frequently associated with activating side effects in prepubertal children with autism, other serotonergic drugs that may cause less agitation have recently been studied. Posey and colleagues[30] found the serotonergic and noradrenergic antidepressant mirtazapine effective in a treatment-refractory group of subjects

with PDDs. Mirtazapine (mean dose = 30.3 ± 12.6 mg/day) was helpful in 9 (35%) of 26 subjects for symptoms that included aggression and self-injury. Thus, mirtazapine may represent an option for the treatment of irritability and aggression in autistic children unable to tolerate SSRIs.

Mood Stabilizers

Mood stabilizers, namely lithium and the anticonvulsants, have been used to treat aggression in a variety of neuropsychiatric disorders, including autism. Case reports have found lithium effective for maniclike symptoms, aggression, and self-injury.[31,32] There has also been 1 case report of lithium augmentation of fluvoxamine in the treatment of an adult with autism.[33] Hollander and colleagues[34] recently reported results of a retrospective review of divalproex sodium in PDDs. In this study, divalproex sodium (mean dose = 768 mg/day) was associated with improvement in 10 of 14 subjects (age range, 5–40 years). Improvement was seen in affective instability, aggression, and repetitive behavior. Most recently, Belsito and colleagues[35] conducted a double-blind, placebo-controlled trial of lamotrigine in 28 children with autism. In this investigation, lamotrigine (mean dose = 5.0 mg/kg/day) was no better than placebo on any of the outcome measures, although this study focused on the overall treatment of autism and not specifically on aggression.

Psychostimulants

Psychostimulant treatment is often associated with reductions in aggression in children with attention-deficit/hyperactivity disorder (ADHD).[36] However, studies in autism have not found stimulants to be consistently useful for the treatment of aggression. Quintana and colleagues[37] administered methylphenidate and placebo in a double-blind, crossover fashion to 10 autistic children (age range, 7–11 years) at doses of 10 or 20 mg twice daily for 2 weeks. Statistically significant improvement was seen in hyperactivity and irritability, and adverse effects were minimal. The authors' overall impression was that the effects of methylphenidate were modest. After completion of the study, haloperidol was added to the treatment regimen of 2 of the 10 children due to continued symptoms of aggression. Anecdotal reports from physicians in clinical practice often include the onset or exacerbation of irritability, insomnia, and aggression during stimulant treatment of children with autism. A large, controlled study of methylphenidate versus placebo is currently being conducted in children and adolescents with PDDs by the RUPP Autism Network. One goal of this study is to determine if PDD subtype, age, IQ, and dose of drug are associated with response to methylphenidate.

α_2-Adrenergic Agonists

Clonidine was shown to be effective for reducing hyperactivity and associated symptoms in 2 small, controlled studies of subjects with autism. In a double-blind, placebo-controlled crossover study of clonidine (0.15–0.2 mg/day) in 8 autistic children (age range, 5.0–13.4 years), improvement was seen in hyperactivity, irritability, stereotypies, inappropriate speech, and oppositional behavior.[38] The most significant treatment effect was a 33% decrease in the irritability subscale of the Aberrant Behavior Checklist, which encompasses tantrums, aggression, and self-injury. Recently, our group reported results of a retrospective review of the effectiveness of guanfacine in children and adolescents with PDDs (D.J.P.; J. I. Puntney, B.A.; T. M. Sasher, B.A.; et al., manuscript submitted, Oct. 2002). Eighty subjects (age range, 3–18 years) were treated with guanfacine (mean dose = 2.6 mg daily) for a mean duration of treatment of nearly 1 year. While guanfacine was modestly effective for tics, hyperactivity, and inattention, it was only effective in 14.5% of the subjects who had significant aggression at baseline.

β-Adrenergic Agonists

There have been no published controlled studies of β-blockers in persons with autism. In an uncontrolled study, 19 adults with severe-to-profound mental retardation (1 with autism) were treated with propranolol at doses of 40 to 240 mg daily.[39] Eleven patients had symptom improvement in the areas of aggression and self-injury. Hypotension and bradycardia were common dose-related adverse effects. In another uncontrolled study, propranolol (100–360 mg/day) or nadolol (120 mg/day) was effective in decreasing aggression and self-injury in 8 consecutively treated adults with autism.[40]

CONDUCT DISORDER

Conduct disorder is characterized by a repetitive and persistent pattern of disruptive behavior in which the basic rights of others or major age-appropriate societal norms or rules are violated.[1] The diverse behaviors observed with this disorder are subdivided into 4 categories: aggression toward people and animals, destruction of property, deceitfulness or theft, and serious violation of rules. Destructive symptoms commonly lead to a significant impairment in functioning across a variety of settings. Conduct disorder is one of the most frequently diagnosed conditions in children and adolescents. Prevalence rates are higher among males than females and vary from less than 1% to more than 10%,[1] according to the population sampled.

Children and adolescents with conduct disorder often manifest aggression. Because of its destructive influence, it is this behavior that is frequently brought to the attention of the clinician for evaluation and management. Vitiello and Stoff[41] suggest that the efficacy of a range of treatment interventions differs with regard to separate subtypes of aggression. On the basis of a review of the evidence concerning childhood aggression, the available data sup-

Table 2. Selected Double-Blind Placebo-Controlled Studies Targeting Aggression in Conduct Disorder

Medication	Symptoms Improved	Significant Adverse Effects	Comments	Reference No.
Molindone	Aggression, hostility	Dystonia	Molindone as effective as thioridazine	44
Thioridazine	Aggression, hostility	Sedation, dizziness, headache		44
Haloperidol	Aggression, explosiveness	Sedation, acute dystonia	Treatment-refractory symptoms	45
Risperidone	Aggression	Well tolerated	No motor side effects	47
Risperidone	Aggression, destructive behavior	Headache, somnolence, weight gain		48
Risperidone	Aggression, destructive behavior	Sedation, headache, increased appetite, motor side effects	Motor side effects (13%)	49
Paroxetine	Aggression, impulsivity	Delayed ejaculation	Decrease in aggression noted at end of 3-week trial	54
Lithium	Severe aggression, explosiveness	Weight gain	Treatment-refractory symptoms	45
Lithium	Severe aggression, explosiveness	Weight gain/loss, nausea, vomiting, tremor, headache, polyuria	Treatment-refractory symptoms	56
Lithium	Aggression	Nausea, vomiting, polyuria	Adverse effects in > 50% of subjects	57
Lithium	Not effective	Well tolerated	Trial duration of only 2 weeks	58
Carbamazepine	Not effective	Rash, transient moderate/marked leukopenia, dizziness, diplopia		60
Divalproex sodium	Aggression, anger	Increased appetite	Study replicated open-label findings	62
Methylphenidate	Aggression	Dizziness, decreased appetite, headache		63
Methylphenidate	Aggression toward others and property, antisocial behaviors	Decreased appetite, insomnia	Independent influence of drug on aggression	36
Methylphenidate	Aggression, symptoms of conduct disorder, impulsivity	Well tolerated		64
Clonidine	Aggression, symptoms of conduct disorder, impulsivity	Bradycardia	New-onset bradycardia in 6 of 16 children	64

port a dichotomy between an "impulsive-affective" and a "controlled-predatory" subtype. According to the authors, this distinction is important in that the controlled-predatory group may be more likely to respond to behavioral therapy, whereas the impulsive-affective group might be expected to be more responsive to pharmacologic and psychosocial interventions intended to decrease hostility, impulsivity, and arousal. Experts in the field concur that the affective subtype of aggression associated with conduct disorder is the feature expected to respond to pharmacologic intervention.[42,43] The following sections review the most relevant studies to date on the pharmacologic management of aggression in conduct disorder (Table 2).

Typical Antipsychotics

The typical antipsychotics are potent dopamine-2 receptor antagonists. Due to their increased propensity for tardive dyskinesia, these compounds are commonly reserved for persons suffering from severe, treatment-resistant symptoms. Their usefulness in decreasing aggression in individuals with conduct disorder has been evaluated in several studies.[44,45]

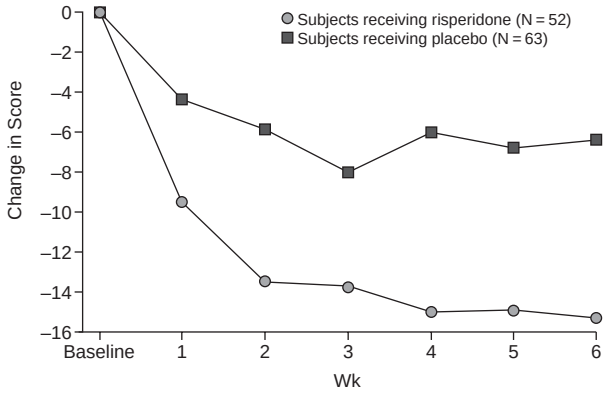
Greenhill et al.[44] conducted an 8-week, double-blind study of molindone (mean dose = 26.8 mg/day; 1.3 mg/kg/day) and thioridazine (mean dose = 169.9 mg/day; 4.6 mg/kg/day) in 31 hospitalized youngsters (age range, 6–11 years) with conduct disorder. The outcome measures utilized included the Connors Rating Scale, the Inpatient Aggression Scale, and the Children's Psychiatric Rating Scale (CPRS). Molindone was found to be as effective as thioridazine, as reflected by a significant improvement in all outcome measures. Dystonia and sedation, respectively, were commonly reported adverse effects.

The efficacy and tolerability of haloperidol (mean dose = 2.95 mg/day; range, 1–6 mg/day) and lithium (mean dose = 1166 mg/day; range, 500–2000 mg/day) were investigated in a 4-week, double-blind, placebo-controlled study of 61 hospitalized children (mean age = 8.97 years; age range, 5.2–12.9 years) with conduct disorder.[45] Haloperidol and lithium were superior to placebo for decreasing aggression, as measured by the CPRS and CGI scale. Lithium was better tolerated than haloperidol, with weight gain and sedation, respectively, being the most common adverse effect associated with each drug. Acute dystonia was the second most frequent adverse effect associated with haloperidol.

Atypical Antipsychotics

The atypical antipsychotics, with their profile of potent antagonism at 5-HT and DA receptors, have a lower inci-

Figure 2. Mean Change in Score on the Conduct Problem Subscale of the Nisonger Child Behavior Rating Form for Children With Subaverage Intelligence With Risperidone Vs. Placebo[a]



[a]Reprinted from Aman et al.,[48] with permission. Significant differences between groups at weeks 1 to 6.

dence for tardive dyskinesia. Although research is needed to further understand the role of this class of drugs in individuals with conduct disorder, 4 studies regarding risperidone warrant discussion.[46–49]

The efficacy and tolerability of risperidone were investigated via a retrospective chart review conducted in 106 patients presenting with various psychiatric disorders.[46] Thirteen (12.3%) of the 106 youngsters (mean age = 11.3 years) were diagnosed with conduct disorder. According to CGI-Improvement scale measures, 73% of patients overall were rated as having had a "marked" or "moderate" improvement at the final study assessment. It is important to note that most patients were also taking concomitant medications, including psychostimulants, antidepressants, and clonidine. The authors suggested that risperidone may be useful for managing behavioral disturbances, including aggression, in a variety of psychiatric conditions.

Findling and colleagues[47] published the first double-blind, placebo-controlled study of risperidone (mean dose = 0.028 mg/kg/day; range, 0.75–1.50 mg/kg/day) in 20 children and adolescents (mean age = 9.2 years; range, 6–14 years) with conduct disorder. According to its primary outcome measure, the Rating of Aggression Against People and/or Property (RAAPP) scale, the 10-week study found risperidone superior to placebo for decreasing aggression. Overall, the drug was well tolerated, with none of the risperidone-treated patients developing acute motor side effects.

In a set of parallel multicenter studies, the efficacy of risperidone was studied in youngsters diagnosed with subaverage intelligence and comorbid conduct or disruptive behavior disorder.[48] In the first 6-week, double-blind, placebo-controlled study, 118 children (age range, 5–12 years) (IQ range, 36–84) with severely disruptive behavior received risperidone (mean dose = 1.16 mg/kg/day; range, 0.02–0.06 mg/kg/day) or placebo. The risperidone group showed significantly greater improvement than did the placebo group on the conduct problem subscale of the Nisonger Child Behavior Rating Form (NCBRF) from week 1 through endpoint (Figure 2). The most common adverse effects reported with risperidone were headache and somnolence. Motor side effects were comparable between risperidone and placebo. A mean weight increase of 4.9 lb (2.2 kg) occurred in the risperidone group.[48] The second study involved 110 children (age range, 5–12 years) (mean IQ = 68) treated with risperidone (mean dose = 0.98 mg/day; range, 0.40–3.80 mg/day) or placebo for 6 weeks. Of the 41 subjects with conduct disorder, 31 had a comorbid diagnosis of ADHD. Risperidone resulted in a significant improvement of disruptive behaviors as measured by the NCBRF conduct problem subscale. The authors concluded that risperidone effectively reduced aggression and destructive behavior in this population. Sedation, headache, and increased appetite were among the more commonly reported adverse effects. Motor side effects were reported in 7 (13%) of 53 subjects in the risperidone group.[49]

Serotonergic Antidepressants

Several studies support an association between 5-HT and aggression.[50–52] These promising findings have led to additional investigations regarding the efficacy of serotonergic compounds in patients with conduct disorder.

Zubieta and Alessi[53] conducted an open trial of trazodone (mean dose = 241 mg/day; range, 100–800 mg/day), a weak inhibitor of 5-HT reuptake and potent antagonist of 5-HT_{2A} and 5-HT_{2C} receptors, on 22 hospitalized children (mean age = 9 years; age range, 5–12 years) with a disruptive behavior disorder. Thirteen (59%) of 22 children responded to the drug, based on parent interview after discharge from the hospital (mean duration = 8.8 months; range, 3–14 months). Overall, aggression and impulsivity were reported as most often showing improvement. Regarding symptoms more specific to conduct disorder, cruelty to people and animals, destruction of property, and involvement in physical fights were most frequently improved. Adverse effects were judged mild, with the exception of 2 subjects who discontinued the study due to orthostatic hypotension and painful erections, respectively.

Cherek and colleagues[54] investigated the role of the SSRI paroxetine (20 mg/day) in treating aggression and impulsivity in their 3-week, double-blind, placebo-controlled study in 12 adult males with a history of conduct disorder. Experimental sessions were designed to measure aggressive and impulsive responses. When compared with response in the placebo group, decreases in aggressive responses became apparent only by the end of the 3-week trial in the 6 patients receiving paroxetine. The drug was generally well tolerated, with 1 individual report-

ing delayed ejaculation. Another SSRI, citalopram (mean dose = 27 mg/day; range, 20–40 mg/day), was investigated in an open-label fashion in 12 children and adolescents (mean age = 10.2 years; range, 7–15 years) with an impulsive-affective profile of aggression.[55] All 11 completers of this 6-week trial were diagnosed with conduct disorder. Comorbid diagnoses included oppositional defiant disorder (ODD) and ADHD. Citalopram significantly reduced symptoms of aggression as measured by the modified Overt Aggression Scale (OAS), the Child Behavioral Checklist, and the CGI scale. Adverse effects were mild and included sedation, headache, and nightmares.

Lithium

The monovalent cation lithium, whose mechanism of action is uncertain, has been investigated for the treatment of aggression in patients with conduct disorder. Campbell and colleagues,[45] as previously discussed, found lithium, as well as haloperidol, to be more beneficial than placebo, with lithium being generally well tolerated.

A 6-week, double-blind, placebo-controlled study of lithium (mean dose = 1248 mg/day; range, 600–1800 mg/day) was conducted in 50 hospitalized aggressive youngsters with conduct disorder (mean age = 9.4 years; range, 5.1–12.0 years).[56] The authors reported that lithium was superior to placebo in the management of severe aggression in this population. Common adverse effects included weight gain or loss, nausea, vomiting, tremor, headache, and polyuria.

The effectiveness of lithium for targeting symptoms of aggression was also investigated by Malone et al.[57] in a double-blind, placebo-controlled study of 40 hospitalized children and adolescents (mean age = 12.5 years) with conduct disorder. A 4-week trial of lithium at doses ranging from 900–2100 mg/day (mean dose = 1425 mg/day) was more effective than placebo for reducing aggression as measured by the CGI scale, the Global Clinical Judgements (Consensus) Scale (GCJCS), and the OAS. More than half of the subjects receiving lithium reported nausea, vomiting, and urinary frequency.

In contrast to the above findings, one double-blind, placebo-controlled study failed to support the use of lithium in the management of aggression in subjects with conduct disorder.[58] In this study, 11 (79%) of 14 patients (mean age = 15.2 years; range, 12–17 years) were considered nonresponders to lithium (mean blood level = 0.79 mmol/L; range, 0.60–1.25 mmol/L). However, a major limitation of this study was its duration of only 2 weeks, a conceivably inadequate length of time to yield a beneficial response. Although lithium was associated with an increased incidence of adverse effects, all were considered mild.

Anticonvulsants

Kafantaris and colleagues[59] conducted an open-label study of carbamazepine (mean dose = 630 mg/day; range, 600–800 mg/day) in 10 patients (mean age = 8.27 years; range, 5.25–10.92 years) with conduct disorder. Overall, carbamazepine resulted in a significant improvement in aggression, with all but 1 subject rated as "much improved" or "very much improved" on the CGI scale. Adverse effects were transient and included fatigue, blurred vision, and dizziness.

The efficacy and tolerability of carbamazepine in the treatment of aggression in children within this diagnostic group were also considered by Cueva et al.[60] in a 6-week, double-blind, placebo-controlled study of 22 children (mean age = 8.97 years; range, 5.33–11.70 years). In contrast to the aforementioned open-label study, carbamazepine (mean dose = 683 mg/day; range, 400–800 mg/day) was not superior to placebo in reducing aggression, as measured by the GCJCS, OAS, CGI scale, and CPRS. Rash, transient moderate and marked leukopenia, dizziness, and diplopia were the most common adverse effects.

Donovan and colleagues,[61,62] in an attempt to replicate open-label findings in support of the efficacy of divalproex sodium in decreasing aggression in subjects with a disruptive behavior disorder (ODD or conduct disorder), investigated the drug in a double-blind, placebo-controlled crossover fashion. Twelve (80%) of 15 patients (mean age = 13.8 years; range, 10–18 years) with a disruptive behavior disorder who completed both 6-week phases of divalproex sodium (mean blood level = 82.2 mg/mL; dose range, 750–1500 mg/day) showed a significant improvement in aggression, as rated by the modified OAS and the Symptom Checklist-90 (SCL-90) anger-hostility items. Divalproex sodium was well tolerated, with increased appetite reported as the only significant adverse effect.

Psychostimulants

The efficacy of methylphenidate (mean dose = 0.47 mg/kg/day; range, 0.36–0.56 mg/kg/day) on aggression was considered by Kaplan et al.[63] in 9 adolescents (mean age = 14.4 years; range, 13–16 years) with conduct disorder and ADHD. After 3 open trials, a 3-week, double-blind, placebo-controlled crossover design was utilized. The results obtained from the 6 double-blind subjects revealed a significant reduction of aggression as measured by the Adolescent Antisocial Behavior Checklist. Regarding adverse effects, 3 of 9 subjects reported dizziness, appetite loss, and headache.

Klein and colleagues[36] published a 5-week, double-blind, placebo-controlled study of methylphenidate (mean dose = 41.3 mg/kg/day; 1.0 mg/kg/day) in 74 youngsters (mean age = 10.2 years; range, 6–15 years) with conduct disorder. Two thirds of the children also met criteria for ADHD. The authors found that methylphenidate improved key aspects of antisocial adjustment that were independent of the severity of the subjects' initial ADHD symptoms. In particular, they found an independent influence of the drug

on aggressive behaviors. Commonly reported adverse effects included decreased appetite and delayed sleep onset.

Another double-blind study compared the efficacy and tolerability of methylphenidate monotherapy (mean dose = 32.5 mg/day), methylphenidate (mean dose = 35.0 mg/day) and clonidine (mean dose = 0.21 mg/day), and clonidine monotherapy (mean dose = 0.17 mg/day) over 3 months in 24 patients (mean age = 9.4 years; range, 6–16 years) diagnosed with ADHD and comorbid ODD or conduct disorder.[64] All treatment groups demonstrated significant improvement in symptoms of conduct disorder. Although the 3 treatments were not found to differ significantly from each other over time on most measures, they could not be judged to be equally efficacious due to the small sample size. Overall, the authors suggested that symptoms of disruptive behavior disorders, such as aggression, may be responsive to methylphenidate, clonidine, or the combination, particularly when comorbid with ADHD.

α_2-Adrenergic Agonists

The effectiveness of clonidine for symptoms of aggression was investigated by Kemph and colleagues,[65] in an open-pilot study of 17 children (mean age = 10.1 years; range, 5–15 years), 15 of whom were diagnosed with conduct disorder. Fifteen (88.2%) of 17 patients demonstrated a significant decrease in aggressive behavior during the administration of clonidine (mean dose = 0.24 mg/day; range, 0.15–0.4 mg/day) over a mean duration of 5.2 months (range, 1–18 months), as measured by the RAAPP scale. Plasma levels of γ-aminobutyric acid increased significantly during treatment and correlated with the reduction of aggression. The most commonly reported adverse effect was sedation at the onset of treatment.

β-Adrenergic Agonists

Although research has demonstrated a therapeutic effect of propranolol in some patients with aggressive behavior,[66,67] there is little information available regarding its utility in individuals with conduct disorder. Several open-label studies have suggested that the drug may improve aggression associated with this disorder; however, the subjects often also had considerable central nervous system pathology.[68–70]

Benzodiazepines

The authors suggest utilizing benzodiazepines with caution due to their potential for abuse and dependence, as well as worsened aggression in this population.[71]

CONCLUSION

Autism and conduct disorder are representative disorders of childhood and adolescence in which the pharmacologic management of aggression is often necessary. Available research suggests that several classes of medication may effectively target aggression in individuals with these conditions. In patients with autism, potentially helpful medications include the atypical antipsychotics, SSRIs, mirtazapine, mood stabilizers, and α_2-adrenergic agonists. Studies completed in patients with conduct disorder support a role for the atypical antipsychotics, SSRIs, mood stabilizers, psychostimulants, and α_2-adrenergic agonists. Controlled research and longitudinal studies are needed to better understand the efficacy and tolerability of currently available compounds within each diagnostic group. In addition to well-designed trials, future investigations should attempt to understand the impact of age and other developmental factors on clinical response. Improvements in the treatment of aggression will increasingly allow affected individuals to benefit from behavioral and educational interventions, thus improving the quality of life for those afflicted with these serious disorders.

Drug names: carbamazepine (Tegretol, Epitol, and others), citalopram (Celexa), clomipramine (Anafranil and others), clonidine (Catapres and others), clozapine (Clozaril and others), desipramine (Norpramin and others), divalproex sodium (Depakote), fluoxetine (Prozac and others), fluvoxamine (Luvox and others), guanfacine (Tenex and others), haloperidol (Haldol and others), lamotrigine (Lamictal), methylphenidate (Ritalin, Concerta, and others), mirtazapine (Remeron), molindone (Moban), nadolol (Corgard and others), olanzapine (Zyprexa), paroxetine (Paxil), propranolol (Inderal and others), quetiapine (Seroquel), risperidone (Risperdal), sertraline (Zoloft), thioridazine (Mellaril and others), trazodone (Desyrel and others), ziprasidone (Geodon).

Disclosure of off-label usage: The authors of this article have determined that, to the best of their knowledge, carbamazepine, citalopram, molindone, and thioridazine are not approved by the U.S. Food and Drug Administration for the treatment of conduct disorder; clomipramine, clozapine, desipramine, fluvoxamine, guanfacine, lamotrigine, mirtazapine, nadolol, olanzapine, quetiapine, sertraline, and ziprasidone are not approved for the treatment of autistic disorder; clonidine, haloperidol, lithium, methylphenidate, paroxetine, propranolol, and risperidone are not approved for the treatment of autistic disorder and conduct disorder; divalproex sodium is not approved for the treatment of pervasive developmental disorder, conduct disorder, and oppositional defiant disorder; fluoxetine is not approved for the treatment of pervasive developmental disorder; and trazodone is not approved for the treatment of disruptive behavior disorder.

REFERENCES

1. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision. Washington, DC: American Psychiatric Association; 2000
2. Posey DJ, McDougle CJ. The pharmacotherapy of target symptoms associated with autistic disorder and other pervasive developmental disorders. Harv Rev Psychiatry 2000;8:45–63
3. Campbell M, Anderson LT, Meier M, et al. A comparison of haloperidol and behavior therapy and their interaction in autistic children. J Am Acad Child Psychiatry 1978;17:640–655
4. Cohen IL, Campbell M, Posner D, et al. Behavioral effects of haloperidol in young autistic children: an objective analysis using a within-subjects reversal design. J Am Acad Child Adolesc Psychiatry 1980;19:665–677
5. Anderson LT, Campbell M, Grega DM, et al. Haloperidol in the treatment of infantile autism: effects on learning and behavioral symptoms. Am J Psychiatry 1984;141:1195–1202
6. Anderson LT, Campbell M, Adams P, et al. The effects of haloperidol on discrimination learning and behavioral symptoms in autistic children. J Autism Dev Disord 1989;19:227–239
7. Perry R, Campbell M, Adams P, et al. Long-term efficacy of haloperidol

in autistic children: continuous versus discontinuous drug administration. J Am Acad Child Adolesc Psychiatry 1989;28:87–92
8. Zuddas A, Ledda MG, Fratta A, et al. Clinical effects of clozapine on autistic disorder [letter]. Am J Psychiatry 1996;153:738
9. Chen NC, Bedair HS, McKay B, et al. Clozapine in the treatment of aggression in an adolescent with autistic disorder [letter]. J Clin Psychiatry 2001;62:479–480
10. McDougle CJ, Holmes JP, Carlson DC, et al. A double-blind placebo-controlled study of risperidone in adults with autistic disorder and other pervasive developmental disorders. Arch Gen Psychiatry 1998;55: 633–641
11. Research Units on Pediatric Psychopharmacology (RUPP) Autism Network. Risperidone in children with autism and serious behavioral problems. N Engl J Med 2002;347:314–321
12. Potenza MN, Holmes JP, Kanes SJ, 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. Malone RP, Cater J, Sheikh R, et al. Olanzapine versus haloperidol in children with autistic disorder: an open pilot study. J Am Acad Child Adolesc Psychiatry 2001;40:887–894
14. Martin A, Koenig K, Scahill L, et al. Open-label quetiapine in the treatment of children and adolescents with autistic disorder. J Child Adolesc Psychopharmacol 1999;9:99–107
15. Tandon R, Harrigan E, Zorn SH. Ziprasidone: a novel antipsychotic with unique pharmacology and therapeutic potential. J Serotonin Res 1997;4: 159–177
16. Keck P Jr, Buffenstein A, Ferguson J, et al. Ziprasidone 40 and 120 mg/day in the acute exacerbation of schizophrenia and schizoaffective disorder: a 4-week placebo-controlled trial. Psychopharmacology 1998;140:173–184
17. Daniel DG, Zimbroff DL, Potkin SG, et al. Ziprasidone 80 mg/day and 160 mg/day in the acute exacerbation of schizophrenia and schizoaffective disorder: a 6-week placebo-controlled trial. Neuropsychopharmacology 1999;20:491–505
18. Sallee FR, Kurlan R, Goetz CG, et al. Ziprasidone treatment of children and adolescents with Tourette's syndrome: a pilot study. J Am Acad Child Adolesc Psychiatry 2000;39:292–299
19. McDougle CJ, Kem DL, Posey DJ. Case series: use of ziprasidone for maladaptive symptoms in youths with autism. J Am Acad Child Adolesc Psychiatry 2002;41:921–927
20. McDougle CJ, Naylor ST, Cohen DJ, et al. Effects of tryptophan depletion in drug-free adults with autistic disorder. Arch Gen Psychiatry 1996;53: 993–1000
21. McDougle CJ, Kresch LE, Goodman WK, et al. A case-controlled study of repetitive thoughts and behavior in adults with autistic disorder and obsessive-compulsive disorder. Am J Psychiatry 1995;152:772–777
22. Coccaro EF, Kavoussi RJ. Fluoxetine and impulsive aggressive behavior in personality-disordered subjects. Arch Gen Psychiatry 1997;54: 1081–1088
23. Gordon CT, State RC, Nelson JE, et al. A double-blind comparison of clomipramine, desipramine, and placebo in the treatment of autistic disorder. Arch Gen Psychiatry 1993;50:441–447
24. Brodkin ES, McDougle CJ, Naylor ST, et al. Clomipramine in adults with pervasive developmental disorders: a prospective open-label investigation. J Child Adolesc Psychopharmacol 1997;7:109–121
25. McDougle CJ, Naylor ST, Cohen DJ. A double-blind, placebo-controlled study of fluvoxamine in adults with autistic disorder. Arch Gen Psychiatry 1996;53:1001–1008
26. Branford D, Bhaumik S, Naik B. Selective serotonin reuptake inhibitors for the treatment of perseverative and maladaptive behaviors of people with intellectual disability. J Intellect Disabil Res 1998;42:301–306
27. DeLong GR, Teague LA, McSwain KM. Effects of fluoxetine treatment in young children with idiopathic autism. Dev Med Child Neurol 1998;40: 551–562
28. McDougle CJ, Brodkin ES, Naylor ST, et al. Sertraline in adults with pervasive developmental disorders: a prospective open-label investigation. J Clin Psychopharmacol 1998;18:62–66
29. Davanzo PA, Belin TR, Widawski MH, et al. Paroxetine treatment of aggression and self-injury in persons with mental retardation. Am J Ment Retard 1998;102:427–437
30. Posey DJ, Guenin KD, Kohburn AE, et al. A naturalistic open-label study of mirtazapine in autistic and other pervasive developmental disorders. J Child Adolesc Psychopharmacol 2001;11:267–277
31. Kerbeshian J, Burd L, Fisher W. Lithium carbonate in the treatment of two patients with infantile autism and atypical bipolar symptomatology. J Clin Psychopharmacol 1987;7:401–405
32. Steingard R, Biederman J. Lithium-responsive manic-like symptoms in two individuals with autism and mental retardation. J Am Acad Child Adolesc Psychiatry 1987;26:932–935
33. Epperson CN, McDougle CJ, Anand A, et al. Lithium augmentation of fluvoxamine in autistic disorder: a case report. J Child Adolesc Psychopharmacol 1994;4:201–207
34. Hollander E, Dolgoff-Kaspar R, Cartwright C, et al. An open trial of divalproex sodium in autism spectrum disorders. J Clin Psychiatry 2001;62: 530–534
35. Belsito KM, Law PA, Kirk KS, et al. Lamotrigine therapy for autistic disorder: a randomized, double-blind, placebo-controlled trial. J Autism Dev Disord 2001;31:175–181
36. Klein RG, Abikoff H, Klass E, et al. Clinical efficacy of methylphenidate in conduct disorder with and without attention deficit hyperactivity disorder. Arch Gen Psychiatry 1997;54:1073–1080
37. Quintana H, Birmaher B, Stedge D, et al. Use of methylphenidate in the treatment of children with autistic disorder. J Autism Dev Disord 1995;25: 283–294
38. Jaselskis CA, Cook EH Jr, Fletcher KE, et al. Clonidine treatment of hyperactive and impulsive children with autistic disorder. J Clin Psychopharmacol 1992;12:322–327
39. Ratey JJ, Mikkelsen E, Sorgi P, et al. β-blockers in the severely and profoundly mentally retarded. J Clin Psychopharmacol 1986;6:103–107
40. Ratey JJ, Mikkelsen E, Sorgi P, et al. Autism: the treatment of aggressive behaviors. Am J Psychiatry 1987;144:341–344
41. Vitiello B, Stoff DM. Subtypes of aggression and their relevance to child psychiatry. J Am Acad Child Adolesc Psychiatry 1997;36:307–315
42. Reis D. Central neurotransmitters in aggression. Res Publ Assoc Res Nerv Ment Dis 1974;52:119–148
43. Vitiello B, Behar D, Hunt J, et al. Subtyping aggression in children and adolescents. J Neuropsychiatry Clin Neurosci 1990;2:189–192
44. Greenhill LL, Solomon M, Pleak R, et al. Molindone hydrochloride treatment of hospitalized children with conduct disorder. J Clin Psychiatry 1985;46(8, sec 2):20–25
45. Campbell M, Small AM, Green WH, et al. Behavioral efficacy of haloperidol and lithium carbonate. Arch Gen Psychiatry 1984;41:650–656
46. Simeon J, Milin R, Walker S. A retrospective chart review of risperidone use in treatment-resistant children and adolescents with psychiatric disorders. Prog Neuropsychopharmacol Biol Psychiatry 2002;26:267–275
47. 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
48. 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
49. 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
50. Cleare AJ, Bond AJ. The effect of tryptophan depletion and enhancement on subjective and behavioral aggression in normal male subjects. Psychopharmacology 1995;118:72–81
51. Higley JD, Mehlman PT, Poland RE, et al. CSF testosterone and 5-HIAA correlate with different types of aggressive behaviors. Biol Psychiatry 1996;40:1067–1082
52. Bjork JM, Dougherty DM, Moeller FG, et al. The effects of tryptophan depletion and loading on laboratory aggression in men: time course and a food restricted control. Psychopharmacology (Berl) 1999;142:24–30
53. Zubieta J, Alessi N. Acute and chronic administration of trazodone in the treatment of disruptive behavior disorders in children. J Clin Psychopharmacol 1992;12:346–351
54. Cherek DR, Lane SD, Pietras CJ, et al. Effects of chronic paroxetine administration on measures of aggressive and impulsive responses of adult males with a history of conduct disorder. Psychopharmacology (Berl) 2002;159:266–274
55. Armenteros JL, Lewis JE. Citalopram treatment for impulsive aggression in children and adolescents: an open pilot study. J Am Acad Child Adolesc Psychiatry 2002;41:522–529
56. Campbell M, Adams PB, Small AM, et al. Lithium in hospitalized aggressive children with conduct disorder: a double-blind and placebo-controlled study. J Am Acad Child Adolesc Psychiatry 1995;34:445–453

57. Malone RP, Delaney MA, Luebbert JF, et al. A double-blind placebo-controlled study of lithium in hospitalized aggressive children and adolescents with conduct disorder. Arch Gen Psychiatry 2000;57:649–654
58. Rifkin A, Karajgi B, Dicker R, et al. Lithium treatment of conduct disorders in adolescents. Am J Psychiatry 1997;154:554–555
59. Kafantaris V, Campbell M, Padron-Gayol MV, et al. Carbamazepine in hospitalized aggressive conduct disorder children: an open pilot study. Psychopharmacol Bull 1992;28:193–199
60. Cueva JE, Overall JE, Small AM, et al. Carbamazepine in aggressive children with conduct disorder: a double-blind and placebo-controlled study. J Am Acad Child Adolesc Psychiatry 1996;35:480–490
61. Donovan SJ, Susser ES, Nunes EV, et al. Divalproex treatment of disruptive adolescents: a report of 10 cases. J Clin Psychiatry 1997;58:12–15
62. Donovan SJ, Stewart JW, Nunes EV, et al. Divalproex treatment for youth with explosive temper and mood lability: a double-blind, placebo-controlled crossover design. Am J Psychiatry 2000;157:818–820
63. Kaplan SL, Busner J, Kupietz S, et al. Effects of methylphenidate on adolescents with aggressive conduct disorder and ADHD: a preliminary report. J Am Acad Child Adolesc Psychiatry 1990;29:719–723
64. Connor DF, Barkley RA, Davis HT. A pilot study of methylphenidate, clonidine, or the combination in ADHD comorbid with aggressive oppositional defiant or conduct disorder. Clin Pediatr 2000;39:15–25
65. Kemph J, DeVane C, Levin G, et al. Treatment of aggressive children with clonidine: results of an open pilot study. J Am Acad Child Adolesc Psychiatry 1993;32:577–581
66. Yudofsky S, Williams D, Gorman J. Propranolol in the treatment of rage and violent behavior in patients with chronic brain syndromes. Am J Psychiatry 1981;138:218–220
67. Silver JM, Yudofsky SC, Slater JA, et al. Propranolol treatment of chronically hospitalized aggressive patients. J Neuropsychiatry Clin Neurosci 1999;11:328–335
68. Williams DT, Mehl R, Yudofsky S, et al. The effect of propranolol on uncontrolled rage outbursts in children and adolescents with organic brain dysfunction. J Am Acad Child Adolesc Psychiatry 1982;21:129–135
69. Kuperman S, Stewart MA. Use of propranolol to decrease aggressive outbursts in younger patients. Psychosomatics 1987;28:315–319
70. Sims J, Galvin MR. Pediatric psychopharmacologic uses of propranolol. J Child Adolesc Psychiatr Ment Health Nurs 1990;3:18–24
71. Petti TA, Fish B, Shapiro T, et al. Effects of chlordiazepoxide in disturbed children: a pilot study. J Clin Psychopharmacol 1982;2:270–273