Behavioral and Pharmacologic Treatment of Aggression in Children With Autism

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This article will provide an overview of treatment modalities, with emphasis on the future direction of interventions targeting aggression in children with autism.

Autistic disorder (autism) is a childhood-onset disorder characterized by marked impairments in social interaction, communication and behavior. Aggression is a frequent reason for psychiatric referral in this population. As such, the clinician needs to be knowledgeable regarding aggression assessment and treatment. This article will provide an overview of treatment modalities, with emphasis on the future direction of interventions targeting aggression in children with autism.

Assessment
Behavioral and pharmacologic interventions cannot begin until the patient has been thoroughly assessed in terms of diagnosis, cognitive abilities and other factors related to the complaint of aggression. In identifying these factors, it is important to begin with a detailed inquiry as to the duration, frequency and severity of the aggression, as well as precipitating or exacerbating factors. Evaluation for comorbid psychiatric disorders (e.g., major depression) and symptoms (e.g., impulsivity), as well as medical conditions (e.g., epilepsy), is also important in guiding interventions. An initial behavioral assessment, called a functional analysis, is performed prior to behavioral therapy. Functional analyses are controlled observational sessions that are conducted to objectively determine the primary motivating factor for the child's misbehavior. Primary motivational factors or functions of behavior are typically to seek attention, access a preferred item or escape a task. Another function may be that the child engages in a behavior that is inherently pleasurable. As such, determination of any appropriate and beneficial treatment approach would be selected on the basis of the empirically determined motivational factor, rather than on arbitrary selection (Hagopian et al., 2001).

Behavioral Interventions
Behavioral interventions, particularly those based upon applied behavior analysis (ABA), have long had empirical support for addressing problematic behavior (for a review, see Schreibman, 2000). These methods have been utilized for a wide range of disorders and myriad behavioral difficulties (Heflin and Simpson, 1998) and have not been exclusively utilized for the treatment of autism. However, intervention with roots in ABA has been regarded as one of the primary forms of treatment, given its stability in the literature and practice over decades, as well as the fact that it lends itself to objective evaluation.

In general, ABA refers to methodologies based in operant conditioning theory and presumes that antecedent stimuli and consequences influence acquisition and continuation of behaviors. Objective assessment of observable and measurable behaviors and ongoing evaluation of the behavior change is inherent in treatment success. Particularly in the field of autism, terminology has often become muddled over the years. Many particular methodologies are equated to the whole of ABA, as opposed to being one tool or method within this rubric.

Specific methodologies enveloped within the field of ABA include Lovaas therapy or discrete trial teaching (Lovaas, 1987) and incidental teaching (McGee et al., 1999). Although based on the principles of ABA, these specific methodologies should be viewed as distinct interventions within the general framework of ABA.

Several behavioral strategies have been shown to be effective in decreasing severe aggression and self-injury (Kahng et al., 2001). Since intervention methods are best employed on a consistent and daily basis, parental involvement is very important (Briesmeister and Schaefer, 1998). In fact, parents and other caregivers are often a primary focus of training in ABA methods. There are many challenges in providing this training, as well as ensuring consistent implementation of treatment intervention, particularly for behaviors such as aggression.
Follow-up visits to coach the caregivers and ensure protocol fidelity are often infrequent. In addition, caregivers working in naturalistic settings with these children face inherent multiple challenges and competing time pressures on a daily basis. Providing prevention techniques that will prevent or limit the development of maladaptive behavior is more realistic in these settings (McClannahan and Krantz, 2004).

In addition, there has been documented success of parent and staff training interventions based in ABA to improve the caregiver's abilities to provide all levels of prevention, treatment intervention and skills acquisition. In particular, Harris et al. (in press) have completed a comprehensive review of the methods and strategies considered most useful for consistent and effective treatment implementation. Included are instructions, modeling/role-playing and corrective feedback, as well as ongoing consultation.

While much single-case research supports ABA intervention, randomized control trials have not thoroughly evaluated the efficacy of a standardized behavioral intervention program. The difficulty in doing so is inherent in the particular strength of behavioral analytic techniques to individualize the treatment to the characteristics and interests of the particular child. The National Institute of Mental Health recently funded three Research Units on Pediatric Psychopharmacology (RUPP) that are focused on autism and related pervasive developmental disorders (PDDs). The RUPP Autism Network has begun a controlled investigation into the use of a standardized behavioral intervention, targeting severe behaviors such as aggression and self-injury. Although the behavioral programming is not specific to the principles of ABA and will not prove the particular success of such an intervention with this population, the investigation will provide some input as to the benefit of incorporating general behavioral methods along with psychopharmacological intervention. Furthermore, it will provide a basis for manualizing a behavioral intervention so therapists without extensive experience with children with autism will have some guide to appropriate intervention strategies.

Pharmacotherapy

Several drug classes, including antipsychotics, serotonin reuptake inhibitors, mood stabilizers, psychostimulants and adrenergic agonists, have been evaluated in studies where aggression was a primary target in children with autism.

Antipsychotics. Typical antipsychotics were among the first agents assessed in an organized manner. Haloperidol (Haldol) decreased emotional outbursts and anger in placebo-controlled studies including young children with autism (Anderson et al., 1984). However, its role is limited due to concerns about dystonic reactions and dyskinesias (Campbell et al., 1997).

Atypical antipsychotic drugs have a reduced propensity to cause motor side effects and have largely replaced haloperidol in the clinical treatment of autism. Clozapine (Clozaril), quetiapine (Seroquel), olanzapine (Zyprexa) and ziprasidone (Geodon) have been evaluated in small or uncontrolled studies and case reports (Erickson et al., in press). Each of these drugs, with the exception of ziprasidone, is associated with frequent weight gain. Clozapine has additional liabilities, given its propensity to decrease the seizure threshold and requirement for frequent venipuncture. Among the atypical antipsychotics, risperidone (Risperdal) has received the most attention in treating maladaptive behaviors in patients with autism. This drug has been the subject of controlled trials in both adults (McDougle et al., 1998) and children (McCracken et al., 2002; Shea et al., 2004). McCracken et al. (2002) compared risperidone (mean dose=1.8 mg/day) to placebo in an eight-week, randomized, double-blind trial in 101 children with autism. Risperidone was markedly efficacious in reducing aggression and irritability. Side effects included weight gain, increased appetite, sedation, tremor and hypersalivation. Shea and colleagues (2004) also reported that risperidone (mean dose=0.04 mg/kg/day) was efficacious in reducing irritability, conduct problems, anxiety and hyperactivity in an eight-week, double-blind, placebo-controlled study of risperidone in a sample of 79 children. They also found significant weight gain, as well as increased pulse and systolic blood pressure in the risperidone-treated group.

Our group recently reported that aripiprazole (Abilify) (mean dose=12 mg/day) was effective for reducing aggression, agitation and self-injury in five youth with PDD (Stigler et al., 2004). During open-label aripiprazole treatment (mean duration=12 weeks), two patients experienced mild somnolence, but no changes in vital signs occurred. Weight loss was also noted. This weight loss may have been associated with patients discontinuing other medications that had caused excess weight gain. We are currently conducting a large placebo-controlled trial of aripiprazole for children and adolescents with autism and aggression.

Other psychotropic agents. Clonidine (Catapres), an α2-adrenergic agonist, was efficacious in two short-term, placebo-controlled trials, but its long-term efficacy has been questioned (McDougle et al., 2003). Guanfacine, a longer-acting α2-adrenergic agonist, was only effective in 19 of 80 (24%)
patients with PDD at mean treatment duration of one year (Posey et al., 2004b). Out of 69 patients with significant aggression, it was only effective in 10 (14%) patients.

Case reports and a retrospective review have reported on the use of lithium (Eskalith, Lithobid) or divalproex (Depakote) for aggressive behaviors in youth with autism (McDougle et al., 2003). While we expect more reports on the use of mood stabilizers in the future, our clinical experience, combined with available evidence, suggests that mood stabilizers will not be as effective as atypical antipsychotics in treating aggression.

The tricyclic antidepressant clomipramine (Anafranil) has shown some promise in treating aggression in one placebo-controlled trial (Gordon et al., 1993). Secondary to concerns over tolerability and the availability of safer selective serotonin reuptake inhibitors, the use of clomipramine has been limited. Fluvoxamine (Luvox) (mean dose=277 mg/day) was evaluated in a 12-week, randomized, placebo-controlled trial in 30 adults with autism (McDougle et al., 1996). Fluvoxamine was associated with significant global symptom improvement, as well as a reduction in maladaptive behavior and aggression. The same group conducted a similar study in 34 children with PDD but noted increased aggression without overall improvement (McDougle et al., unpublished data).

Hollander and colleagues (2005) reported on an eight-week, double-blind, placebo-controlled crossover trial of liquid fluoxetine (Prozac) in 45 children and adolescents with PDD. There was a reduction in repetitive behaviors but less reduction of global symptoms. Overall, SSRIs as first-line agents in targeting aggressive behaviors in children with autism is not currently supported by the available literature.

While psychostimulant treatment has been associated with reductions in aggression in children with attention-deficit/hyperactivity disorder, results in autism have been equivocal. Posey et al. (2004a) reported on a randomized, placebo-controlled, crossover study of methylphenidate (Ritalin, Concerta, Metadate) in children with PDD. Methylphenidate treatment was associated with small-to-medium improvements in hyperactivity but caused irritability in some patients. There was no improvement in aggression.

**Conclusion**

A comprehensive treatment plan for treating aggressive behaviors in children with autism begins with a precise and thorough assessment, followed by implementation of a comprehensive treatment plan. This treatment plan must incorporate ongoing behavioral assessment and intervention with continuous evaluation for areas in which pharmacotherapy could potentially curtail maladaptive and dangerous behaviors.

From a pharmacotherapy perspective, atypical antipsychotics, particularly risperidone, have shown the most promise in reducing aggressive behavior. Future directions in treating aggression in children with autism include further investigation of atypical antipsychotics that may not cause significant weight gain and testing the efficacy of manualized behavioral treatments.

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**References**


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