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Treating Aggression in Adults with Autism

INTRODUCTION

Autism is a complex neurodevelopmental disorder that usually presents during early childhood. It is one of five disorders in the category of Pervasive Developmental Disorders (PDD) as outlined by the DSM-IV; the other ones are Asperger's Disorder, Childhood Disintegration Disorder (CDD), Rett's Disorder and PDD-Not Otherwise Specified (PDD-NOS). The criteria for diagnosis of autism in the DSM-IV include qualitative impairments in social interaction and communication as well as restricted, repetitive and stereotyped patterns of behavior, interests and activities.^{1,2}

Pathophysiology

While there is no known cause for autism, it appears to be associated with abnormalities in brain structure and function.³ It is hypothesized that the temporal lobe is the critical area involved, however decreased Purkinje cells in the cerebellum have also been found.¹ There are many theories as to which neurotransmitter abnormalities are involved in the etiology of autism. An imbalance in the serotonergic system may play a role as up to one-third of autistic patients have hyperserotonemia and one-third of patients also have antibodies that attack serotonin (5-HT) receptors. Some patients have decreased serotonergic response to receptor stimulation as shown by a lower prolactin rise in response. The dopaminergic system also seems to play a role as treating patients with dopamine agonists causes worsened behaviors, aggression and hyperactivity.⁴⁻⁷

Impact of Autism

Autism is the most common form of PDD with an estimated prevalence of 10 cases per 10,000 individuals.⁸ It is usually diagnosed by 1-2 years of age when communication impairments become

apparent. The incidence of autism is higher in boys than girls for unknown reasons, with a 4:1 ratio.³

Although usually considered a childhood disorder, studies indicate that most people with autism must deal with considerable functional impairment throughout their life and less than 5% become independent as adults and up to 60% remain severely impaired requiring institutionalized care.⁹ Approximately 70% children have low IQ (<70) and can be classified as having mild to moderate mental retardation. Some children may have unusual precocious abilities such as memorizing, calculation or musical talents and these are known as splinter functions. They excel in these particular areas but may have below average functioning in other cognitive or communication areas.

Approximately half of autistic patients will have nonspecific abnormalities on electroencephalography (EEG).¹⁰ Up to one-third of autistic children will also develop epilepsy, which is a much higher rate than the normal population.^{1,10} Mood and behavior disorders also seem to be common in autism. Case reviews and studies have reported the incidence of 35% for affective disorders, 36% for hyperactivity and 43% for self-injurious behaviors.^{11,12}

Features of Autism

There are many different presentations of the symptoms and characteristics of autism, and it is therefore known as a spectrum disorder. Features may include: difficulty initiating or maintaining a conversation; a markedly restricted variety of activities and interests; insistence on sameness; repetitive behaviors; difficulty in expressing needs; little or no eye contact; sustained odd play; inappropriate attachment to objects; difficulty mixing with others; and in some cases aggression and/or self-injurious behavior.^{1,3}

Treatment Approaches in Autism

Treatment is multifactorial and relies heavily on educational and behavioral interventions for the autistic child as well as family education. Physical, occupational and speech therapy are also often needed. Pharmacological therapy is used as adjunctive treatment for targeted symptoms that interfere with the autistic person's functioning. The most common targeted symptoms include hyperactivity, impulsivity, aggression toward self/others/property, and interfering repetitive thoughts/behaviors.¹³ No available drug treatment is curative in autistic disorder.

Pharmacological Treatment of Aggression in Autism

The following review summarizes available data on treating aggression in adult autistic patients. Studies conducted specifically in autistic patients are limited and therefore some data are extrapolated from pediatric populations or from other conduct disorders. The treatments are categorized by class of medications.

Traditional Antipsychotics

Antipsychotics have been used in the treatment of autism based on the potential dopamine excess theory of the disease etiology. Earlier trials in the 1960s and 1970s often directly compared two medications (combinations of chlorpromazine, trifluoperazine, thiothixene and fluphenazine) without placebo arms and involved heterogeneous patient populations due to less refined diagnostic methods.

More recently, controlled-studies have looked at **haloperidol** in doses of 1-2 mg/day in autistic children and found it to be superior to placebo for affective lability, anger and temper outbursts. However, these benefits are offset by the occurrence of acute dystonic reactions, and drug-related dyskinesias with long-term therapy.^{13,14,15} There are no controlled studies with traditional agents in adults with autism and they would not be an agent of first choice.

Atypical Antipsychotics

The exact mechanism of the efficacy for atypical

antipsychotics in treating aggression in autism is unknown but thought to be due to modulation of both serotonergic and dopaminergic neurotransmitter systems. Since the atypical agents have a lower propensity to cause extrapyramidal side effects and tardive dyskinesias than the traditional agents they are better tolerated and preferable choices in the setting of autism.

Risperidone is the most widely studied medication in autism from this drug class. In a 12-week, double-blind, placebo-controlled trial of risperidone (mean dose 2.9 mg) in 31 adults with autism or PDD-NOS, 57% of patients treated with risperidone were responders compared to none in the placebo group based on Clinical Global Impression (CGI) Scale.¹⁴ Risperidone was also superior to placebo in the treatment of interfering repetitive behavior (Yale-Brown Obsessive Compulsive Scale) and reducing aggressive behavior (Self-Injurious Behavior Questionnaire). The most common side effect was mild transient sedation during drug therapy initiation. A large double-blind, placebo-controlled trial of risperidone was conducted in 101 autistic children (mean age 9 yrs) with serious behavioral problems of tantrums, aggression or self-injurious behavior.¹⁶ They were treated with risperidone (mean dose 1.8 mg/day) for 8 weeks and the risperidone group had a 57% decrease in the mean irritability score on the Aberrant Behavior Checklist (ABC) compared to 14% in the placebo group. Side effects included weight gain and fatigue.

A small open-label pilot 12-week study with **olanzapine** (mean dose 7.8 mg/day) in four children and four adults with autism and PDD-NOS reported improvements in CGI scores at 4 weeks and continued through to 12 weeks.¹⁷ Side effects noted were weight gain (mean 8 kg) and sedation. It is possible that the sedative and mood stabilizing effects of olanzapine are beneficial in the treatment of aggressive behavior problems.

There are a few case reports in the literature using **clozapine** in autism with aggression or hyperactivity (4 children and adolescents). Doses used were 100-200 mg/d in children and 275 mg/d in the adolescent.^{18,19} One child relapsed at 5 months despite increased dosing to 450 mg/d. There is also a case report in an adult male with autism treated with clozapine 300 mg/d for 5 yrs with significant

improvements in aggressiveness, elimination of temper tantrums and improved social skills.²⁰ Clozapine is usually not a first choice in purely autistic patients due to need for blood count monitoring and increased risk for seizures, but would be a consideration for managing a patient with both autism-associated aggression and treatment-resistant schizophrenia. Clozapine also causes significant sedation and weight gain and in cases of refractory aggression, the sedation may be a helpful side effect.

Serotonin Reuptake Inhibitors

Serotonin reuptake inhibitors are thought to facilitate serotonin transmission and thereby reduce target symptoms in autism. Their efficacy is based on case reports in autism and is also extrapolated from the obsessive-compulsive patient population since there are similar overlapping characteristics of the two disorders.

Fluvoxamine was studied in 30 autistic adults that excluded those with schizophrenia. Patients were randomized to placebo or fluvoxamine and treated for 12 weeks (mean dose 276 mg/day). Fluvoxamine was superior to placebo on (1) CGI scores, (2) in the treatment of repetitive behaviours and thoughts (Yale-Brown Obsessive Compulsive Scale), and (3) in improving maladaptive behaviours and aggressive symptoms (Vineland scale and Brown Aggression Scale).⁵ Case reports and open-label studies also suggest that **fluoxetine, sertraline and paroxetine** may also reduce aggression in autistic persons; however no controlled studies have been performed on these SSRIs thus far.^{13,21,22}

Clomipramine (mean dose 152 mg/day) has been compared to placebo and desipramine (mean dose 127 mg/day) in 24 autistic children and adolescents in a 10-week double-blind crossover study. This study found clomipramine to be superior to the two comparators as measured by the autism subscale of the Children's Psychiatric Rating Scale (CPRS) and also superior for obsessive-compulsive symptomatology. Clomipramine dosage had to be reduced in 2 patients due to prolongation of QTc-interval and tachycardia, and one other patient had a grand mal seizure and withdrew from the study.²³ Clomipramine causes significant weight gain and anticholinergic side effects which also must be taken into consideration.

Mood Stabilizers

Mood stabilizers have been shown to reduce impulsivity, aggression and affective instability across many different disorders. Some data is available in autistic patients however their usage is also based on efficacy demonstrated in other conduct disorders.

A retrospective study looked at 14 patients (5-40 yrs) with autistic disorder treated with **divalproex** (mean dose 768 mg/day) for 10 months. Concomitant medications included SSRIs, benzodiazepines, atypical antipsychotics and alpha-1 agonists. Seventy-one percent of patients were rated as sustained responders on CGI.¹⁰ A double-blind placebo-controlled study in 20 children and teens (10-18 yrs) with conduct disorders were randomized divalproex to 10 mg/lb/day with a final dose range of 750-1500 mg/day or placebo for 6 weeks then crossover treatment for 6 weeks. During the 1st phase, 80% of divalproex patients and no placebo patients were responders according to the Modified Overt Aggression Scale. During the crossover phase, 86% divalproex patients and 25% placebo patients responded.²⁴

Lithium has also been studied in children and adolescents with conduct disorders. The first one looked at 40 adolescent inpatients with conduct disorders and aggression (excluded patients with pervasive developmental disorders). These subjects were randomized to lithium (mean dose 1425 mg/day) or placebo for 4 weeks.²⁵ Based on the Global Clinical Judgements (Consensus) Scale (GCJCS), 80% in the lithium group were responders compared to 30% in the placebo group. In the CGI scale, 70% in the lithium group were responders compared to 20% in placebo. Another study in 26 adolescent inpatients with conduct disorders failed to see a difference between lithium therapy and placebo after 2 weeks on the Overt Aggression Scale although this trial was limited by its short duration.²⁶ Pooled data from other double-blind placebo-controlled studies using lithium in mentally handicapped patients with histories of aggression found lithium to have a 70% response rate compared to approximately a 30% response rate with placebo.²⁷ An open trial of **carbamazepine** (mean dose 630 mg/day) in 10 aggressive hospitalized children for 3-5 weeks led to improved CGI and CPRS scores.²⁸ Other open trials

in patients with dementia or Alzheimer's disease showed reduced assaultiveness and agitation after 4-6 weeks treatment.²⁷ However, a 7 month double-blind, placebo-controlled crossover trial in severe mentally-retarded patients with refractory behavior problems did not show a clinically significant benefit of carbamazepine over placebo based on nursing assessments.²⁷

There is no specific data on the use of *topiramate*, *lamotrigine* or *gabapentin* in autism. However it would be reasonable to attempt an adequate trial of therapy with them and monitor for reduced aggression if other mood stabilizers have been unsuccessful.

Alpha₂-Adrenergic Agonists

A centrally acting alpha₂-receptor agonist causes a reduction in norepinephrine activity at the locus ceruleus. This is thought to be the mechanism for treating aggression as norepinephrine is a modulator of arousal states and directly affects dopamine and serotonin activity.²⁹

Clonidine has been studied in small double-blind placebo-controlled trials in autism. In one trial, oral clonidine was used in 8 autistic children in doses of 0.15-0.2 mg/day for 6 weeks. This resulted in a 33% decrease in the irritability subscale of the ABC, but no significant difference on clinician ratings of videotaped observations.³⁰ An open pilot study in 17 children and adolescents with conduct disorders used oral clonidine 0.24 mg/day (dose range 0.15-0.4 mg/d) over 5 months. The results in this trial showed significant decreases in aggressive behavior as measured by RAAPP scale.³¹ Transdermal clonidine has been studied in autistic males (age 5-33 yrs) at doses 0.1-0.3 mg/day (0.005 mg/kg/d) for 4 weeks with significant improvements in CGI scales and 3 of 5 subscales of Ritvo-Freeman Real-Life Rating Scale (RLRS).²⁹ One review paper has suggested that the behavioral effects of clonidine tablets last between 3 and 6 hours therefore requiring shorter and more frequent dosing intervals.³² Clonidine can cause some transient sedation during dose titration and monitoring of blood pressure and pulse rates are also necessary during therapy. Slow dose titration makes the hypotensive and sedative effects more tolerable.

Beta-Adrenergic Antagonists

Some investigators have hypothesized that non-selective beta-blockers decrease aggression and impulsivity by treating a chronic state of hyperarousal in autism. Case reports in patients with autism and others with chronic brain syndromes have demonstrated improvements in aggressive and self-abusive behaviors during the first 6 weeks to 3 months of treatment with *propranolol* (100-420 mg/day) or *nadolol* (120 mg/day) for total treatment durations of 4-23 months.^{33,34} Two small randomized, double-blind, placebo-controlled, crossover trials in 22 adult patients with severe dementia and organic brain syndrome reported benefits from treatment with propranolol SR and pindolol. **Propranolol SR** was titrated to 200-520 mg/day for 3 months and 7/9 patients showed moderate to marked improvements on a subjective 5-point scale for behaviour. *Pindolol* was titrated to 60-100 mg/day for 3 months and 9/11 patients had reduced hostility and improved communication on the same 5-point scale.²⁷ Beta-blockers cause hypotension, bradycardia and fatigue, therefore a slow dose titration as well as monitoring of vital signs is necessary during therapy.

Summary

Although large, well-designed studies are lacking in the adult autistic patient population, there are many small trials that suggest benefits of various treatment options for managing aggression in autistic patients. The ultimate treatment decision will be based on the person's co-morbid conditions, concurrent medications, tolerance of side effects and clinical response to an adequate trial of the medication. The ideal treatment choice would be one that has a simple dosing schedule (once or twice daily) to maximize compliance with minimal side effects from therapy. It would be ideal to be able to objectively track response to therapy such as occurrence of aggressive outbursts or other target symptoms to allow for ongoing assessment of efficacy for consideration in treatment decisions.

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References

1. Kaplan HI, Sadock BJ and Grebb JA. Synopsis of Psychiatry. 7th ed. Williams & Wilkins. 1994
2. Posey DJ and McDougle CJ. The pharmacotherapy of target symptoms associated with autistic disorder and other pervasive developmental disorders. *Harvard Rev Psychiatry* 2000;8:45-63.
3. Autism Society of American website. URL <http://www.autism-society.org> (accessed on September 7, 2003)
4. Purdon SE, Lit W, Labelle A and Jones BDW. Risperidone in the treatment of pervasive developmental disorder. *Can J Psychiatry* 1994;39:400-405.
5. McDougle CJ, Naylor ST, Cohen DJ et al. A double-blind, placebo-controlled study of fluvoxamine in adults with autistic disorder. *Arch Gen Psychiatry* 1996;53:1001-1008.
6. McDougle CJ and Posey D. Genetics of childhood disorders: XLIV. Autism, part 3: psychopharmacology of autism. *J Am Acad Child Adolesc Psychiatry* 2002; 41:1380-1383.
7. Tsai LY. Psychopharmacology in autism. *Psychosom Med* 1999;61:651-665.
8. Fombonne E. Epidemiological surveys of autism and other pervasive developmental disorders: an update. *J Autism Dev Disord* 2003;33:365-383.
9. Wing L. *Diagnosis and Treatment of Autism*. New York, NY: Plenum Publishing Corp; 1989.
10. 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.
11. Lainhart JE, Folstein SE. Affective disorders in people with autism: a review of published cases. *J Autism Dev Disord* 1994;24:587-601.
12. Ando H and Yoshimura I. Effects of age on communication skill levels and prevalence of maladaptive behaviors in autistic and mentally retarded children. *J Autism Dev Disord* 1979;9:83-93.
13. McDougle CJ, Stigler KA and Posey D. Treatment of aggression in children and adolescents with autism and conduct disorder. *J Clin Psychiatry* 2003;64[suppl 4]:16-25.
14. 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.
15. Campbell M, Armenteros JL, Malone RP et al. Neuroleptic-related dyskinesias in autistic children: a prospective, longitudinal study. *J Am Acad Child Adolesc Psychiatry* 1997;36:835-843.
16. Research Units on Pediatric Psychopharmacology Autism Network. Risperidone in children with autism and serious behavioral problems. *NEJM* 2002;347:314-321.
17. Potenza MN, Holmes JP, Kanesh SJ and McDougle CJ. Olanzapine treatment of children, adolescents, and adults with pervasive developmental disorders: an open-label pilot study. *J Clin Psychopharmacol* 1999;19:37-43.
18. Zuddas A, Ledda MG, Fratta A et al. Clinical effects of clozapine on autistic disorder [Letter]. *Am J Psychiatry* 1996;153:738.
19. Chen NC, Bedair HS, McKay B et al. Clozapine in the treatment of aggression in an adolescent with autistic disorder. *J Clin Psychiatry* 2001;62:479-480.
20. Gobbi G and Pulvirenti L. Long-term treatment with clozapine in an adult with autistic disorder accompanied by aggressive behaviour. *J Psychiatry Neurosci* 2001;26:340-341.
21. Hellings JA, Kelley LA, Gabrielli WF et al. Sertraline response in adults with mental retardation and autistic disorder. *J Clin Psychiatry* 1996;57:333-336.
22. McDougle CJ, Kresch LE and Posey DJ. Repetitive thoughts and behavior in pervasive developmental disorders: treatment with serotonin reuptake inhibitors. *J Autism Dev Disord* 2000;30:427-435.
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. 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.

25. 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.
26. Rifkin A, Karajgi B, Dicker R et al. Lithium treatment of conduct disorders in adolescents. *Am J Psychiatry* 1997;154:554-555.
27. Smith DA and Perry PJ. Nonneuroleptic treatment of disruptive behavior in organic mental syndromes. *Ann Pharmacother* 1992;26:1400-1408.
28. Kanfantaris 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.
29. Fankhauser MP, Karumanchi VC, German ML et al. A double-blind, placebo-controlled study of the efficacy of transdermal clonidine in autism. *J Clin Psychiatry* 1992;53:77-82.
30. Jaselskis CA, Cook EH, Fletcher KE and Leventhal BL. Clonidine treatment of hyperactive and impulsive children with autistic disorder. *J Clin Psychopharmacol* 1992;12:322-327.
31. Kempf 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.
32. Sweeney DP, Forness SR and Levitt JG. An overview of medications commonly used to treat behavioral disorders associated with autism, tourette syndrome, and pervasive developmental disorders. *Focus Autism Dev Disab* 1998;13:144-150.
33. Ratey JJ, Mikkelsen E, Sorgi P et al. Autism: the treatment of aggressive behaviors. *J Clin Psychopharmacol* 1987;7:35-41.
34. Yudofsky S, Williams D and Gorman J. Propranolol in the treatment of rage and violent behavior in patients with chronic brain syndromes. *Am J Psychiatry* 1981;138:218-220.