Pharmacologic treatments for the behavioral symptoms associated with autism spectrum disorders across the lifespan

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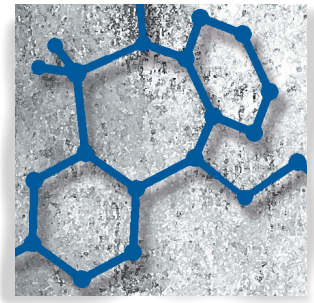

This review outlines pharmacologic treatments for the behavioral symptoms associated with autism spectrum disorders (ASDs) in children, adolescents, and adults. Symptom domains include repetitive and stereotyped behaviors, irritability and aggression, hyperactivity and inattention, and social impairment. Medications covered include serotonin reuptake inhibitors (SRIs), mirtazapine, antipsychotics, psychostimulants, atomoxetine, α-2 agonists, D-cycloserine, and memantine. Overall, SRIs are less efficacious and more poorly tolerated in children with ASDs than in adults. Antipsychotics are the most efficacious drugs for the treatment of irritability in ASDs, and may be useful in the treatment of other symptoms. Psychostimulants demonstrate some benefit for the treatment of hyperactivity and inattention in individuals with ASDs, but are less efficacious and associated with more adverse effects compared with individuals with ADHD. D-cycloserine and memantine appear helpful in the treatment of social impairment, although further research is needed.

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Introduction

Autistic disorder (autism), Asperger's disorder, and pervasive developmental disorder not otherwise specified (PDD-NOS) are diagnostic subtypes of Pervasive Developmental Disorders (PDDs) in the *Diagnostic and Statistical Manual of Mental Disorders, 4th Edition, Text Revision (DSM-IV-TR).* In this review, these three diagnostic subtypes will collectively be referred to as "autism spectrum disorders" (ASDs), given the widespread use of this terminology in the recent literature. The following is a comprehensive review of available pharmacotherapies for the behavioral symptoms associated with ASDs in children, adolescents, and adults.

Autism, as defined in *DSM-IV-TR*, is characterized by impaired reciprocal social interaction, aberrant language development or communication skills, and the presence of repetitive, stereotyped behavior, interests, or activities.[1] Delay in or dysfunction of social interaction, language, or symbolic or imaginative play must be present before age 3 years. Asperger's disorder also requires impairment in social interaction and a pattern of restricted or stereotyped behavior, but differs in that language and cognitive development are preserved. The prevalence of Asperger's disorder is not known, but it is diagnosed five

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times more frequently in males than females. PDD-NOS is diagnosed when there is a severe and pervasive social impairment associated with abnormal communication, or with the presence of stereotyped behaviors, but the criteria for autistic disorder or Asperger's disorder are not met. Other pervasive developmental disorders include Rett's disorder and childhood disintegrative disorder; subjects with these disorders are rarely included in pharmacotherapy studies of ASDs. These disorders are believed to be quite rare. Unless otherwise noted, they are not included in the present review.

Behavioral symptoms associated with ASDs that will be reviewed here include repetitive and stereotyped behaviors, irritability and aggression, hyperactivity and inattention, and social impairment. Repetitive behaviors may entail stereotyped motor mannerisms, such as hand-flapping, clapping, rocking, or spinning, or may include inflexible adherence to nonfunctional routines or rituals. These symptoms are often difficult to distinguish from those of obsessive-compulsive disorder (OCD), so treatment for both will be included in this review. Irritability in ASDs may include severe temper outbursts and/or impulsive aggression towards self or others. Moderate-to-severe irritability is known to occur in up to 30% of children and adolescents with ASDs.[2] Hyperactivity and inattention are common in individuals with ASDs, although a diagnosis of an ASD excludes a concurrent diagnosis of attention-deficit/hyperactivity disorder (ADHD) based on *DSM-IV-TR* criteria. An estimated 40% to 59% of children diagnosed with ASDs also meet criteria for ADHD.[3,4] Qualitative impairments in social interaction, such as lack of social or emotional reciprocity and impaired gestures used to regulate social interaction, are key diagnostic features of ASDs, although few medications are known to improve this domain.

The most common psychotropic medications used to treat the behavioral symptoms associated with ASDs include serotonin reuptake inhibitors (SRIs), antipsychotics, and medications used to treat ADHD. Overall, SRIs are less efficacious and more poorly tolerated in children with ASDs compared with adults. The antipsychotics are the most efficacious drugs for the treatment of irritability in ASDs, and may be useful in the treatment of other symptoms. Psychostimulants demonstrate some benefit for the treatment of hyperactivity and inattention in individuals with ASDs, but are less efficacious and associated with more adverse effects compared with individuals with ADHD. Other medications that may be useful in individuals with ASDs for various symptoms include mirtazapine, atomoxetine, α-2 agonists, D-cycloserine, and memantine, although further research is needed.

Articles for this review were located using Medline, under the keywords "autism," "pervasive developmental disorders," "treatment," and using the names of specific medications. Articles were limited to the English language and those published in 1982 or later.

Serotonin reuptake inhibitors and other drugs affecting serotonin neurotransmission

Table I summarizes published placebo-controlled studies of SRIs for interfering repetitive behaviors.

Serotonin abnormalities have been implicated in the pathophysiology of autism for more than 50 years.[5-9] This has prompted the study of SRIs in the treatment of ASDs. Studies examining the effectiveness of SRIs in ASDs have yielded mixed results. Overall, SRIs appear to be less efficacious and more poorly tolerated in children with ASDs than in adults.

Clomipramine

Clomipramine has been shown to be efficacious for the treatment of repetitive behaviors and stereotypies in some individuals with ASDs, and may be helpful for aggression and hyperactivity. However, many subjects, particularly children and adolescents, have significant adverse effects.

An early case report of a 12-year-old male with autism treated with clomipramine 75 mg/day revealed worsening of self-mutilation, irritability, and sensitivity to loud noises.[10] A case series of five individuals with autism, aged 13 to 33 years, revealed improvements in obsessive-compulsive symptoms, aggression, and impulsive behavior with clomipramine.[11]

Open-label studies in children have shown mixed responses to clomipramine, often with limitations due to adverse effects. In a study of five children with autism and mental retardation (MR), aged 6 to 12 years, clomipramine resulted in reduced adventitious movements and compulsions.[12] However, in another trial, clomipramine was not therapeutic in managing stereotypies, aggression, and hyperactivity in eight hospitalized children with autism, aged 3 to 8 years, and adverse effects were common.[13] Five more children with autism, aged 7 to 12 years (mean age,

9 years), had a reduction in movement disorders and compulsions with clomipramine, although three subjects exhibited extreme agitation and aggression that required hospitalization.[14]

An open-label study in 33 adults with ASDs, aged 18 to 44 years (mean age, 30 years), revealed a 55% response rate with significant reduction of repetitive thoughts and behaviors as measured by the Yale-Brown Obsessive Compulsive Scale (Y-BOCS), as well as improvements in aggression and aspects of social relatedness.[15] Notably, there were differences in treatment response by diagnosis, with response noted in 63% (10 of 16) of those with autism, 33% (2 of 6) of those with Asperger's disorder, and 55% (6 of 11) of those with PDD-NOS. Clomipramine was well tolerated, although 13 subjects had clinically siginificant adverse effects.

Double-blind, placebo-controlled studies have revealed good efficacy with clomipramine, but adverse effects have also been limiting at times. Clomipramine was found to be superior to the potent norepinephrine reuptake inhibitor desipramine and placebo in the management of anger and repetitive and compulsive behaviors in seven subjects with autism, aged 6 to 18 years.[16] A study of 30 subjects with autism, aged 6 to 23 years (mean age, 10 years) demonstrated efficacy in the treatment of obsessive-compulsive symptoms and motor stereotypies, as well as diminished self-injurious behavior (SIB).[17] In a study of 36 individuals with autism, aged 10 to 36 years (mean age, 16 years), clomipramine was statistically comparable to haloperidol in improving irritability and stereotypy.[18] However, 62% of the clomipramine-treated group were unable to complete the study due to adverse effects, behavioral problems, or lack of efficacy.

Across these various studies, dosages ranged from 75 to 250 mg/day and were sometimes divided. Adverse effects, from minor to significant, included sleep disturbances, dry mouth, constipation, fatigue or lethargy, dystonia, depression, and behavioral problems. In one study of children, prolonged cardiac QT interval and severe tachycardia resolved after dose reduction. Seizures also occurred in some subjects.

Fluvoxamine

Fluvoxamine is minimally effective and poorly tolerated in children and adolescents with ASDs, although it has

Study	Drug	Subjects	Design	Results
Gordon et al, 1993[17]	Clomipramine	N=30 Age =6 – 23 Dx = AUT	5 weeks Crossover	Clomipramine > PLA Clomipramine > DMI 19/28 (68%) responders
Remington et al, 2001[18]	Clomipramine Haloperidol	N=36 Age =10 – 36 Dx = AUT	7 weeks Crossover	Clomipramine > PLA Clomipramine > Haloperidol
Sugie et al, 2005[21]	Fluvoxamine	N=18 Age =3 – 8 Dx = AUT	12 weeks Crossover	Fluvoxamine 5/18 (28%) responders
McDougle et al, 1996[24]	Fluvoxamine	N=30 Age =18 – 53 Dx = AUT	12 weeks Parallel groups	Fluvoxamine > PLA 8/15 (53%) responders
Hollander et al, 2005[26]	Fluoxetine	N=45 Age =5 – 16 Dx = AUT, ASP	8 weeks Crossover	Fluoxetine > PLA repetitive behavior
Hollander et al, 2012[34]	Fluoxetine	N=37 Age =18 – 60 Dx = AUT	12 weeks Parallel groups	Fluoxetine > PLA 7/20 (35%) responders
King et al, 2009[41]	Citalopram	N=149 Age =5 – 17 Dx = AUT	12 weeks Parallel groups	Citalopram = PLA

Table I. Published placebo-controlled studies of SRIs for interfering repetitive behaviors. SRIs, serotonin reuptake inhibitors; AUT, autistic disorder; ASP, Asperger's disorder; Dx, diagnosis; PLA, placebo; DMI, desipramine; all ages are in years

been found to be efficacious in the management of repetitive behaviors, maladaptive behaviors, and aggression in some adults with autism.

One case report of a 7-year-old female with PDD-NOS revealed reduced stereotypies and no adverse effects during treatment with fluvoxamine.[19] However, in a double-blind, placebo-controlled study of 34 children with ASDs, aged 5 to 18 years (mean age, 9.5 years), only 1 subject (5.5%) showed clinical improvement and 14 (78%) experienced adverse effects to blinded drug administration.[20] A crossover study of 18 children with autism, aged 3 to 8 years, showed only a 20% rate of response.[21]

Regarding adults, a 30-year-old male with autism and comorbid OCD experienced a marked reduction in obsessive-compulsive symptoms, improved social interaction, and decreased temper tantrums with fluvoxamine.[22] A 20-year-old female with autism demonstrated cessation of interfering repetitive behaviors and reduction of anxiety, and improved verbal communication.[23] A randomized, placebo-controlled trial in 30 adults with autism, aged 18 to 53 years (mean age, 30 years), revealed a 53% response rate with reductions in repetitive thoughts and behavior, maladaptive behavior, and aggression.[24]

In the above studies, doses in children ranged from 25 to 250 mg/day, with adverse effects that included insomnia, aggression, increased rituals, anxiety, anorexia, increased appetite, irritability, decreased concentration, and increased impulsivity. In adults, doses ranged from 50 to 300 mg/day and fluvoxamine was overall well-tolerated.

Fluoxetine

Larger studies of fluoxetine have not found it to be effective in the treatment of repetitive behaviors in children. The drug has proven to be more effective in adults and adolescents with autism. Adolescents appear to experience adverse effects more frequently than adults. The Study of Fluoxetine in Autism (SOFIA), the largest double-blind, placebo-controlled trial of an SRI in children with autism to date, concluded that fluoxetine is not effective for the treatment of repetitive behaviors in children.[25] Prior to this, a study found liquid fluoxetine superior to placebo in decreasing repetitive behaviors in children and adolescents, with minimal adverse effects.[26] Two males with Asperger's disorder, aged 9 and 10 years old, exhibited initial improvements in compulsive behaviors and reduced irritability, respectively, but later experienced episodes of hypomania with fluoxetine 20 mg/day.[27]

A retrospective review of 7 subjects with autism, aged 9 to 20 years (mean age, 16 years), revealed improvement in stereotypy, irritability, lethargy, and inappropriate speech during fluoxetine treatment.[28] An open-label study of individuals with autism, aged 7 to 28 years (mean age, 15 years), showed favorable responses in the treatment of perseverative and compulsive behaviors, although the presence of comorbid Axis I diagnoses in many subjects makes it difficult to generalize these results.[29] Twenty-three percent of subjects experienced significant adverse effects that interfered with drug continuation.

Some case reports of adults describe reductions in repetitive behaviors, obsessive-compulsive symptoms, and temper outbursts with fluoxetine.[30,31] However, a case series that included adults and adolescents together observed poor responses in treating repetitive symptoms but improvements in depressive symptoms.[32] The adolescent subjects exhibited anxiety and agitation above 20 mg/day of fluoxetine, so therapeutic doses in these studies remained near that level. Another case report of a 25-year-old male with Asperger's disorder, OCD, major depression and 45,X/46,XY mosaicism described poor response to fluoxeine in the treatment of OCD.[33]

A recent double-blind, placebo-controlled study in 37 adults with autism, aged 18 to 60 years (mean age, 34 years), showed moderate efficacy in the management of repetitive behaviors, with a 50% response rate compared to 8% in the placebo-treated group.[34] Unless otherwise noted, fluoxetine was dosed 20 to 80 mg/day in the studies above and adverse effects were generally milder in adults than children.

Sertraline

Sertraline is moderately effective and relatively well-tolerated in the management of repetitive behaviors and aggression in adults with ASDs. There is minimal data in children to draw definitive conclusions, although adverse effects may be greater with the use of sertraline in this population.

One case series of nine children, aged 6 to 12 years, described improvements in transitioned-induced behaviors, such as panic, anxiety, irritability, or agitation, although 33% had a loss of initial response after a few months.[35] Another case report of an 11-year-old female with Asperger's disorder and separation anxiety disorder described relief of these symptoms with sertraline 150 mg/day.[36]

A 25-year-old male with Asperger's disorder, OCD, major depression, and 45,X/46,XY mosaicism experienced adverse effects and poor response to sertraline in the management of depression.[33] An open-label trial of sertraline in nine adults with MR, five of whom had autism, aged 20 to 47 years (mean age, 31 years), led to improvement of aggression and SIB in 89% of subjects (8 of 9).[37] Open-label sertraline in 42 adults with ASDs, aged 18 to 39 years (mean age, 26 years), resulted in significant improvement in repetitive and aggressive symptoms in 57% of subjects.[38] Approximately two thirds of patients with autistic disorder and PDD-NOS were deemed clinical responders compared with none with Asperger's disorder, suggesting differences in response by diagnosis.

In the above studies, dosages in children ranged from 25 to 50 mg/day with worsening of behavior above 75 mg/day. Adults tolerated 25 to 200 mg/day. Discontinuation of sertraline occurred due to increased anxiety or agitation, worsening of self-picking, a syncopal episode of undetermined cause, and noncompliance. Adverse effects were minimal, with the most common being weight gain and anxiety or agitation.

Citalopram

Citalopram has limited efficacy in the management of repetitive behaviors in children and adolescents with ASDs, and is more likely to be associated with adverse effects. Some studies have suggested, however, that it may be beneficial in the treatment of other associated symptoms. There are currently no published studies of citalopram in adults with ASDs.

Two retrospective reviews in children and adolescents found favorable responses to citalopram for a range of symptoms, including repetitive behaviors and preoccupations, aggression, anxiety, and disturbed mood.[39,40] Adverse effects were mild and minimal in both studies, with dosages ranging from 5 to 40 mg/day.

However, a multisite, double-blind, placebo-controlled study of 149 children and adolescents with autism (mean age, 9 years) revealed no significant differences between citalopram and placebo in the management of repetitive behaviors.[41] Citalopram was significantly more likely to be associated with adverse events such as increased energy, impulsiveness, decreased concentration, hyperactivity, stereotypy, diarrhea, insomnia, or dry skin or pruritis.

Escitalopram

Preliminary studies of escitalopram have found some benefit in children and adolescents with ASDs, although dose-related adverse effects may limit its use. There are currently no published studies of escitalopram in adults with ASDs.

An open-label study in 28 children and adolescents, aged 6 to 17 years (mean age, 10 years), revealed significant improvement in the Aberrant Behavior Checklist (ABC) subscale scores of Irritability, Lethargy, Stereotypy, Hyperactivity, and Inappropriate Speech.[42] Dose-related adverse effects, notably irritability and/or hyperactivity, occurred at doses above 10 mg/day in 78% of the subjects able to complete the study. Dosages ranged from 10 to 20 mg/day.

Venlafaxine

Venlafaxine, a combined serotonin and norepinephrine reuptake inhibitor, has been found somewhat effective in children, adolescents, and adults with ASDs, although the current research is limited to small, open-label reports.

A retrospective review of 10 individuals with ASDs, aged 3 to 21 years (mean age, 10 years), revealed a 60% response rate with improvements in repetitive behaviors and interests, social deficits, communication, inattention, and hyperactivity.[43] Adverse effects included behavioral activation, inattention, polyuria, and nausea. A case series of two adolescents, both aged 17 years, and one adult, aged 23 years, reported a beneficial response to venlafaxine for the management of SIB and hyperactivity.[44]

Dosages of venlafaxine ranged from 6.25 to 50 mg/day in the above trials.

Trazodone

This heterocyclic antidepressant resulted in reduced aggression and SIB in a 17-year-old male with autism and severe MR whose symptoms had not been well-managed with other psychotropic medications.[45] The most effective dose was 150 mg/day in divided doses. Another case study described a 13-year-old male with autism and moderate MR who experienced priapism after taking trazodone 100 mg at bedtime for 5 months.[46] The priapism resolved after trazodone was discontinued.

Mirtazapine

This tetracyclic antidepressant, which antagonizes both α-2 adrenergic and serotonin receptors, is somewhat effective in managing some symptoms associated with autism, including inappropriate sexual behaviors.
One open-label trial in 26 subjects with ASDs (including 1 with Rett's disorder), aged 3 to 23 years (mean age, 10 years), found a 35% response rate with improvements in aggression, SIB, irritability, hyperactivity, anxiety, depression, and insomnia.[47] Adverse effects were minimal and included increased appetite, irritability, and transient sedation. Dosages ranged from 7.5 to 45 mg/day.
Case reports of one 5-year-old and two 13-year-old males with autism revealed successful management of excessive masturbation and other inappropriate sexual behaviors with mirtazapine.[48-50] An open-label study of 10 subjects with autism, aged 5 to 16 years, revealed an 80% response rate for such behaviors.[51] Dosages ranged from 5 to 30 mg/day with common adverse effects including increased appetite, weight gain, and sedation. In one subject, heightened activity and agitation were experienced at higher doses.

Antipsychotics

Table II summarizes published placebo-controlled studies of antipsychotics for irritability.
Antipsychotics are the most efficacious medications for the treatment of irritability in individuals with ASDs. Typical antipsychotics are more potent antagonists of dopamine-2 receptors. Atypical antipsychotics, which antagonize both dopamine and serotonin receptors, may have a decreased risk of extrapyramidal symptoms (EPS). Reports on the use of the typical antipsychotics, haloperidol and pimozide, as well as the atypical antipsychotics, clozapine, risperidone, olanzapine, quetiapine, ziprasidone, aripiprazole, and paliperidone, in ASDs are reviewed in this section.

Haloperidol

In children and adolescents, haloperidol has been demonstrated to be efficacious in the short- and long-term treatment of symptoms associated with autism. In adults, haloperidol is superior to clomipramine in the management of irritability.
Studies in children have shown that haloperidol is superior to placebo in reducing stereotypies and social withdrawal in children older than 4 years.[52] Haloperidol has resulted in reduced rates of stereotypy and improved orientation,[53] as well as decreased maladaptive behaviors.[54] Older children respond more favorably to haloperidol compared with younger children, higher IQ is more predictive of a greater reduction in behavioral symptoms, and there was a greater reduction of symptoms when the severity of illness was greater.[55] Adverse effects have included dose-related sedation and rare dyskinesias. Development of long-term dyskinesias has not been found to be related to symptom reduction during short-term treatment.[55]
Haloperidol has also been shown to be efficacious in the long-term treatment (at least 6 months) of maladaptive behaviors in children, with the greatest response occurring in those with irritability, labile and angry affect, and uncooperativeness.[56] However, 34% of subjects developed dyskinesias in another study of long-term treatment.[57] Female gender, treatment length, and higher doses increased the risk of developing dyskinesias.
In comparison studies, haloperidol was more effective than fluphenazine at reducing withdrawal, aggression and stereotypies in children with autism, although adverse effects included acute dystonic reactions, akathisia, and sedation.[58] Haloperidol was favored over clomipramine in the treatment of individuals with autism, aged 10 to 36 years, in the treatment of hyperactivity, irritability, and global symptom severity.[18] However, haloperidol has been less effective than the atypical antipsychotic risperidone in the short- and long-term treatment of behavioral symptoms, impulsivity, and impaired language skills and social relations.[59,60] Both haloperidol and olanzapine have shown comparable symptom reduction in children.[61]
In all of the abovementioned studies, haloperidol was dosed between 0.5 to 4.0 mg per day.

Pimozide

Pimozide is another typical antipsychotic that may be helpful in the management of sleep and excretion disorders in children with autism, but there are very few reports describing its use in the treatment of ASDs. There are no published reports of pimozide in adults with ASDs. A case report of a 6-year-old male with autism describes

repeated episodes of acute dystonic reactions with pimozide treatment.[62] One double-blinded, placebo-controlled study compared pimozide with haloperidol in 87 children (39% of whom had autism), aged 3 to 16 years, for the management of behavioral disturbances.[63] Pimozide was superior to placebo in the cluster group "abnormal symptoms," particularly sleep disturbance and excretion disorders, but not significantly different from haloperidol or placebo in the management of behavioral disturbances.

Dosages of pimozide ranged from 1 to 9 mg/day and adverse events included sleepiness.

Clozapine

Clozapine is the first atypical antipsychotic to be released in the US. Clozapine carries an increased risk of agranulocytosis and has the potential to lower the seizure threshold, making its use limited in ASDs. Studies in children, adolescents, and adults with autism suggest good tolerability and effective management of severe aggression and irritability, although controlled trials are lacking.

A case series described two 8-year-old boys and one 12-year-old girl who responded to clozapine with marked

Study	Drug	Subjects	Design	Results
Campbell et al, 1978[52]	Haloperidol	N=40 Age =2 – 7 Dx = AUT	10 weeks Parallel groups	Haloperidol > PLA
Cohen et al, 1980[53]	Haloperidol	N=10 Age =2 – 7 Dx = AUT	2 weeks Crossover	Haloperidol > PLA
Anderson et al, 1984[54]	Haloperidol	N=40 Age =2 – 7 Dx = AUT	4 weeks Crossover	Haloperidol > PLA
Naruse et al, 1982[63]	Pimozide Haloperidol	N=87 Age =3 – 16 Dx = AUT, PDD	8 weeks Crossover	Pimozide > PLA Haloperidol > PLA Pimozide = Haloperidol
McCracken et al, 2002[69]	Risperidone	N=101 Age =5 – 17 Dx = AUT	8 weeks Parallel groups	Risperidone > PLA 34/49 (69%) responders; (57%) improvement on ABC-I
Shea et al, 2004[70]	Risperidone	N=79 Age =5 – 12 Dx = AUT, PDD	8 weeks Parallel groups	Risperidone (64%) > PLA (31%) improvement on ABC-I
McDougle et al, 1998[78]	Risperidone	N=31 Age =18 – 43 Dx = AUT, PDD	12 weeks Parallel groups	Risperidone > PLA 8/14 (57%) responders
Hollander et al, 2006[87]	Olanzapine	N=11 Age =6 – 17 Dx = AUT, ASP, PDD	8 weeks Parallel groups	Olanzapine > PLA 6/11 (55%) responders
Marcus et al, 2009[97]	Aripiprazole	N=218 Age =6 – 17 Dx = AUT	8 weeks Parallel groups	Aripiprazole > PLA on ABC-I
Owen et al, 2009[98]	Aripiprazole	N=98 Age =6 – 17 Dx = AUT	8 weeks Parallel groups	Aripiprazole > PLA (52%) responders

Table II. Published placebo-controlled studies of antipsychotics for irritability. Dx, diagnosis; AUT, autistic disorder; PDD, pervasive developmental disorder not otherwise specified; PLA, placebo; RUPP, Research Units on Pediatric Psychopharmacology; ABC-I, Aberrant Behavior Checklist Irritability subscale; all ages are in years

improvement on the Children's Psychiatric Rating Scale (CPRS).[64] Another report featured a 17-year-old Hispanic male with autism and severe MR who was successfully treated with clozapine for worsening aggression towards others.[65] A 15-year-old girl with autism who was hospitalized for recurrent and sudden outbursts of aggression demonstrated dramatically improved behavior after treatment with clozapine.[66] In another case report, a 27-year-old male with autism, profound MR, and a history of hospitalizations due to maladaptive behaviors exhibited marked improvements in destructive behavior, aggression towards others, and SIB, as well as reduced ritualistic behavior and improved social engagement with clozapine treatment.[67] Dosages for these subjects ranged from 200 to 475 mg/day and adverse effects were minimal.

A retrospective analysis of six adolescents and adults with ASDs, aged 14 to 34 years (mean age, 23 years), found that treatment with clozapine led to decreased aggression, a reduction in the number of psychotropic drugs needed to manage behavior, and a decrease in the dose of concomitantly administered antipsychotic drugs.[68] Clozapine was welltolerated, with no significant reductions in white blood cell count or EPS, although common adverse effects included constipation and weight gain. One subject experienced metabolic syndrome and another had tachycardia.

Risperidone

Risperidone has been demonstrated to be efficacious in the treatment of irritability in children, adolescents, and adults with ASDs in a number of controlled studies.

One of the multisite, double-blind, placebo-controlled trials that led to the FDA approval of risperidone for the treatment of irritability in children and adolescents with autism revealed a 69% response rate with a 57% decrease in irritability as measured by the ABC Irritability subscale.[69] Similar results were observed in another randomized study of children and adolescents with ASDs.[70] Other investigations have also found increased relapse rates upon blinded risperidone discontinuation in children and adolescents with ASDs.[71,72] Risperidone treatment coupled with parent management training was also found to reduce irritability, stereotypic behavior, and hyperactivity/noncompliance more effectively than risperidone monotherapy in children with ASDs, aged 4 to 13 years.[73]

In controlled studies of risperidone in children with ASDs younger than 5 years, results have been mixed. One study of 24 children, aged 2 to 6 years, found minimally greater improvement in target symptoms but with insufficient findings to direct treatment.[74] Another study from India in children aged 2 to 9 years revealed a 63% response rate as measured by a 20% or greater improvement from baseline in the Childhood Autism Rating Scale (CARS), with no responders in the placebo group.[75]

Dosages in the studies above ranged from 0.5 to 3.5 mg/day, with the combination risperidone/parent management training group requiring a lower mean dose compared with the risperidone monotherapy group (1.98 versus 2.26 mg/day, respectively). Adverse effects included increased appetite, weight gain, fatigue, somnolence, drowsiness, dizziness, anxiety, hypersalivation, upper respiratory tract infections, and rhinitis. Transient dyskinesias occurred in 15% of the risperidone-treated group from the India study. Risperidone was also associated with a 2- to 4-fold mean increase in serum prolactin in children and adolescents with autism, although increases diminished with time.[76]

The first study to include adults was an open-label trial of risperidone in 11 individuals with autism, aged 6 to 34 years (mean age, 18 years), which revealed improvements in explosive aggression, SIB, and sleep hygiene.[77] A 12-week, double-blind, placebo-controlled trial in 31 adults with ASDs, aged 18 to 44 years (mean age, 28 years), found risperidone superior to placebo in reducing aggression, irritability, repetitive behaviors, anxiety or nervousness, and depression, with a 57% response rate compared with none in the placebo group.[78] Long-term efficacy with risperidone in the treatment of irritability was demonstrated in a cohort of individuals with MR and autism, aged 8 to 56 years (mean age, 22 years), revealing a 60% response rate with a 50% decrease in the ABC Irritability subscale score.[79]

Dosages in the above studies in adults ranged from 1 to 10 mg/day, sometimes in divided doses. Adverse effects included mild, transient sedation, increased appetite, and weight gain.

The adverse effect of weight gain from risperidone was assessed in a double-blind, placebo-controlled crossover study of 19 individuals with autism and MR, aged 6 to 65 years (mean age, 21 years).[80] Mean weight gain in children was 8.2 kg, in adolescents was 8.4 kg, and in adults was 5.4 kg. Diminished weight gain occurred when the drug was tapered and discontinued. Changes in serum

leptin levels have not reliably predicted risperidone-associated weight gain in children and adolescents.[81]

Olanzapine

Olanzapine is moderately efficacious in children with ASDs and has demonstrated some effectiveness in adults, but the adverse effects of increased appetite, weight gain, and sedation are common.

A case series examining two children with ASDs, aged 8 and 11 years, and five adults, aged 20 to 52 years, revealed response in 6 of the 7 subjects after long-term treatment with olanzapine (52 weeks).[82] Notably, most subjects had a comorbid psychiatric and/or neurodevelopmental disorder, making it difficult to meaningfully generalize the results.

Two open-label studies in children with ASDs with ages ranging from 6 to 17 years revealed improvements in irritability, lethargy, stereotyped behavior, hyperactivity, and inappropriate or excessive speech.[83,84] Another open-label study in eight individuals with ASDs, aged 5 to 42 years, revealed a 75% response rate with significant improvements in motor restlessness or hyperactivity, social relatedness, affectual reactions, sensory responses, language usage, SIB, aggression, irritability or anger, anxiety, and depression, but no changes in repetitive behaviors.[85] Open-label olanzapine was given to 10 males with Asperger's disorder, aged 10 to 15 years, with significant differences observed between baseline and completion scores of internalizing and externalizing behaviors on the Child Behavior Checklist, and a 90% response rate.[86]

In the only double-blind, placebo-controlled study of olanzapine in children and young adolescents with ASDs, 50% were considered clinical responders, although there were no significant changes in the measures of repetitive behaviors or aggression.[87]

In the above studies, dosages ranged from 2.5 to 20 mg/day and the most common adverse effects were weight gain, increased appetite, and loss of strength. Subjects in the case series received concurrent dietary management and/or behavioral intervention, which likely contributed to the weight stability in these participants.

Quetiapine

Quetiapine has been minimally effective in individuals with ASDs, with adverse effects of weight gain and sedation limiting its use in many subjects. There are no published controlled trials.

A retrospective review of 20 subjects with ASDs, aged 5 to 28 years (mean age, 12 years), revealed a 40% response rate,[88] while another review of 10 individuals with ASDs, aged 5 to 19 years (mean age, 12 years), revealed improvements in conduct, inattention, and hyperactivity in 60% of subjects.[89] Two open-label studies treated a total of fifteen children with autism (aged 6 to 15 years) with quetiapine; only four subjects were deemed clinical responders.[90,91]

Dosages ranged from 25 to 800 mg/day. Adverse effects included sedation, weight gain, behavioral activation, akathisia, and a probable seizure.

Ziprasidone

Ziprasidone is moderately effective in individuals with ASDs, although there are no published controlled trials.

A case report of a 7-year-old child treated with ziprasidone revealed improved agitation, impulsivity, mood, cognitive performance, and language.[92] Another report of a 15-year-old who was concurrently treated with methylphenidate showed improvements in maladaptive behaviors, attention to tasks, hyperactivity, impulsivity, and listening.[93]

A retrospective chart review of 10 adults with autism (mean age, 43 years) examined the effect on maladaptive behaviors after switching to ziprasidone from another atypical antipsychotic.[94] Six subjects (60%) showed improved behavior, while one (10%) had no change and 3 (30%) showed decompensated behavior. Weight loss occurred in 80% with a mean change of -5.9 kg. Four subjects had reduced total cholesterol levels, and 3 of 5 had reduced triglyceride levels.

An open-label study in 12 individuals with ASDs, aged 8 to 20 years (mean age, 11 years), revealed a 50% clinical response rate, although two patients with comorbid bipolar disorder were rated "much worse." [95]

Another open-label study in 12 adolescents, aged 12 to 18 years (mean age, 14 years), revealed a 75% response rate with statistically significant decreases observed in the ABC subscale scores of Irritability and Hyperactivity.[96]

In the studies above, dosages ranged from 10 to 160 mg per day, with the most common adverse event being transient sedation.

Aripiprazole

Aripiprazole is efficacious for the treatment of irritability in children and adolescents with autism, as evidenced by two large, double-blind, placebo-controlled trials.[97,98] Long-term treatment (up to 1 year) is also considered safe and well-tolerated in children and adolescents.[99,100] Studies in adults are limited to case reports.

Prior to these studies, open-label trials in children and adolescents with ASDs revealed favorable responses in the treatment of significant irritability.[101,102] A retrospective chart review, however, revealed poorer responses in the management of aggression, hyperactivity, impulsivity, and SIB.[103]

Dosages ranged from 2.5 to 15 mg/day. Adverse events that led to discontinuation included sedation, hypersalivation, aggression, and weight increase. EPS-like tremor, hyperactivity, akathisia, and dyskinesia have also been reported.[97,99]

Two case reports in adults have demonstrated mixed results. One report describes a 38-year-old Afro-Caribbean man with autism and severe intellectual disability who demonstrated significantly decreased aggression with aripiprazole 10 mg/day.[104] A second case report described the adverse effect of waxing-and-waning catatonia in a 26-year old man with autism and comorbid bipolar I disorder, who was treated with intermittent aripiprazole and concurrent oxcarbazepine.[105]

Paliperidone

Paliperidone appears effective in children, adolescents, and adults with ASDs, although studies are limited. One of these reports highlights successful treatment with paliperidone palmitate, an intramuscular (IM), sustained-release formulation of the drug.

A 16-year-old female and 20-year-old male with autism and comorbid MR demonstrated significant improvements in irritability and aggression while treated with oral paliperidone.[106] Dosages ranged from 6 to 12 mg/day, both patients experienced weight loss, and no adverse effects were observed.

A 5-year-old child exhibited significantly decreased irritability and aggression after 3 months of treatment with paliperidone palmitate.[107] Paliperidone palmitate was chosen after all efforts to control the subject's extreme irritability with oral antipsychotics were unsuccessful; there was also an overwhelming refusal of oral medications. Paliperidone palmitate was well-tolerated, and the only notable adverse effect was increased appetite.

An open-label trial conducted in 25 adolescents and young adults with autism, aged 12 to 21 years (mean age, 15 years), demonstrated an 84% response rate in the treatment of irritability.[108] Doses ranged from 3 to 12 mg/day, and mild-to-moderate EPS were recorded in four subjects. Mean weight gain was 2.2 kg and mean prolactin level increased from 5.3 to 41.4 ng/mL.

Medications for symptoms of hyperactivity and inattention

Table III summarizes published placebo-controlled studies of drugs for motor hyperactivity and inattention.

Psychostimulants are the pharmacologic treatments of choice in children with ADHD, with a response rate of 70% to 80%.[109,110] However, these medications are less efficacious and result in more frequent adverse effects in children with ASDs. In addition to studies of stimulants in ASDs, the non-stimulant atomoxetine and α-2 adrenergic receptor blockers clonidine and guanfacine, are also reviewed in this section.

Methylphenidate

Methylphenidate (MPH) is a psychostimulant that is moderately efficacious in the treatment of hyperactivity in children with ASDs, but its use may be limited by adverse effects. Studies in adults are limited to one case report, which was favorable.

Most research on MPH treatment in ASDs has been in children.[111-121] The largest double-blind, placebo-controlled trial in 72 children with ASDs, aged 5 to 14 years, revealed a 49% response rate and deemed MPH efficacious in the treatment of hyperactivity.[116] However, the magnitude of response was less than in children with ADHD and study discontinuation occurred in 18% of subjects due to adverse effects, mostly irritability. Other double-blind, placebo-controlled trials in children have revealed similar findings.[114,115] Preschool aged children (aged 3 to 5 years) with developmental disorders, most with ASDs, have also shown a 50% response rate to MPH, although over half the subjects experienced adverse effects.[120] A retrospective chart review of 195 subjects with ASDs, aged 2 to 19 years (mean age, 7 years) found that subjects

with autism or PDD-NOS were less likely to respond to stimulants compared with those with Asperger's disorder.[122]

In children, dosages ranged from 7.5 to 50 mg/day, sometimes divided and often dosed by weight (0.3 to 0.6 mg/kg/day). Preschool children received 5 to 20 mg/day in divided doses.

In adults, one case report described a 26-year-old male with Asperger's disorder who reported improved attention and reduced impulsive aggression and impatience after treatment with MPH.[123] MPH was dosed at 40 mg/day, split into three doses (15 mg, 15 mg, and 10 mg).

Atomoxetine

Atomoxetine is a selective norepinephrine reuptake inhibitor that is approved for the treatment of ADHD in children, adolescents, and adults. The drug is moderately efficacious in the treatment of hyperactivity and possibly inattention in children and adolescents with ASDs, although adverse effects may limit its use at times. Studies in adults are limited to one case report, which was favorable.

A retrospective chart review of 20 children and adolescents, aged 6 to 20 years (mean age, 11 years) revealed a 60% response rate to atomoxetine with improvements in conduct, hyperactivity, inattention, and learning.[124] Two open-label studies in children with ASDs, aged 6 to 14 years, found significant improvements in ADHD symptoms.[125,126] One study revealed a 75% response rate with additional improvements in irritability, social withdrawal, stereotypy, and repetitive speech.[125] A double-blind, placebo-controlled, crossover study in 16 children with ASDs, aged 5 to 15 years, revealed a 56% response rate to atomoxetine, which was superior to placebo in the treatment of hyperactivity.[127]

Dosages ranged from 1.2 to 1.4 mg/kg/day. Adverse effects were overall mild to moderate and included gastrointestinal symptoms, decreased appetite, irritability, ear ringing, mood swings, sleep problems, and sedation. One study, however, showed a 42% discontinuation rate due to adverse effects.[126]

One case report described a 22-year-old male with autism who demonstrated improvements in hyperactivity, irritability, inadequate eye contact, and inappropriate speech, although clinician ratings did not show any improvements.[128] Atomoxetine was dosed at 40 mg/day and adverse effects included drowsiness and decreased activity.

Clonidine

Oral and/or transdermal clonidine is moderately efficacious in treating hyperactivity and irritability in children with ASDs. Published studies have included small numbers of subjects. Studies in adults are limited to one case report.

An open-label study in 20 children with ASDs, aged 4 to 16 years, found clonidine helpful for sleep initiation and

Study	Drug	Subjects	Design	Results
GQuintana et al, 1995[114]	Methylphenidate	N=10 Age =7 – 11	2 weeks Crossover	Methylphenidate > PLA
Handen et al, 2000[115]	Methylphenidate	N=13 Age =5 – 11	1 week Crossover	Methylphenidate > PLA 8/13 (62%) responders
RUPP Autism Network, 2005[116]	Methylphenidate	N=72 Age =5 – 14	1 week Crossover	Methylphenidate > PLA
Arnold et al, 2006[127]	Atomoxetine	N=16 Age =5 – 15	6 weeks Crossover	Atomoxetine > PLA
Jaselskis et al, 1992[130]	Clonidine	N=8 Age =5 – 13	6 weeks Crossover	Clonidine > PLA by teacher and parent, but not clinician 6/8 (75%) responders at 1-year follow-up
Fankhauser et al, 1992[131]	Clonidine (transdermal)	N=9 Age =5 – 33	4 weeks Crossover	Clonidine > PLA 6/9 (67%) responders

Table III. Published placebo-controlled studies of drugs for motor hyperactivity and inattention. PLA, placebo; each study included subjects with autism; RUPP Autism Network, 2005 and Arnold et al, 2006 included subjects with autism and other pervasive developmental disorders; all ages are in years

maintenance, specifically for reducing sleep initiation latency and night awakening.[129] One double-blind, placebo-controlled study of oral clonidine in children with autism, aged 5 to 13 years (mean age, 8 years), revealed modest efficacy in the treatment of hyperactivity and irritability.[130] Another placebo-controlled study in individuals with autism, aged 5 to 33 years (mean age, 12 years), showed improvements in hyperarousal behaviors with transdermal clonidine.[131]
Dosages ranged from 0.1 to 0.2 mg/day, while adverse effects included drowsiness, sedation, and decreased activity.
One case report highlights a 26-year-old female with autism and intermittent explosive disorder who exhibited reduced aggression and increased alertness with the addition of transdermal clonidine dosed at 0.6 mg/day (two 0.3-mg patches/week).[132]

Guanfacine

A retrospective chart review of 80 children with ASDs who received guanfacine IR (immediate release), aged 3 to 18 years, revealed a response rate of 24% with improvements in hyperactivity, inattention, insomnia, and tics.[133] Greater response was observed in subjects with PDD-NOS and Asperger's disorder compared with those with autism, as well as those without comorbid MR compared with those with MR. The patients in this study had been poorly responsive to numerous prior medication treatment trials. An open-label trial in 25 children with ASDs (mean age, 9 years) revealed a 48% response rate with guanfacine IR.[134] This trial was conducted in subjects that did not respond to or could not tolerate MPH in the controlled study described earlier.[116]
The only double-blind, placebo-controlled trial in 11 children with developmental disabilities, seven of whom had ASDs, revealed a 57% response rate with guanfacine IR, with statistically significant drug-placebo differences in hyperactivity.[135]
In the studies above, dosages ranged from 0.25 to 9 mg/day, often in divided doses. Guanfacine was overall well-tolerated but common adverse effects included irritability, sedation, sleep disturbance, constipation, headache, and nocturnal enuresis.
Treatment with guanfacine XR was highlighted in case reports of two children with ASDs, a 4-year-old girl and a 9-year-old boy, who showed significant improvement in irritability and symptoms of ADHD.[136]

Social impairment

Pharmacologic treatments for the social impairments observed in ASDs are lacking. Although some trials of SSRIs and antipsychotics have suggested improvements in social relatedness, this has not yet been demonstrated in placebo-controlled studies.[137] Some drugs with mechanisms affecting the glutamate neurotransmitter system have been studied in the context of social impairment, including D-cycloserine and memantine.

D-cycloserine

D-cycloserine is an NMDA-receptor partial agonist that was studied in a prospective, single-blinded trial looking for short-term clinical benefits on social impairment in twelve individuals with autism, aged 5 to 27 years (mean age, 10 years).[137] Statistically significant improvements were observed in the CGI rating scale and the ABC subscale of Social Withdrawal. The other subscales did not show significant improvements. D-cycloserine was administered at 30, 50, and 85 mg/day for 2 weeks each, with the highest dose leading to a 60% decrease in symptom severity. Adverse effects occurred in 2 subjects and included a transient motor tic and increased echolalia.

Memantine

Memantine is an NMDA-receptor antagonist is that FDA-approved for the treatment of Alzheimer's dementia, but has been shown in preliminary studies to be effective in the treatment of social impairment and other symptoms in individuals with ASDs. Research is limited to case reports, a retrospective review, and open-label trials.
A case report of a 15-year-old male with OCD, Tourette's disorder, and Asperger's disorder demonstrated improved OCD symptoms and social interaction with memantine added to fluoxetine and aripiprazole.[138] The subject became more amenable to social interactions, had improved eye contact, and participated more in school activities. Memantine was dosed 10 mg/day and adverse effects included increased appetite and weight gain (believed to be attributed to aripiprazole). One case report in an adult described a 23-year-old male with autism who demonstrated improved disruptive behavior, as well as decreased social withdrawal and impul-

sivity, after treatment with memantine 10 mg at bedtime.[139] The patient felt calmer at work and reported no further work-related conflicts, which had become problematic for him.

A retrospective review of 18 children and adolescents with ASDs, aged 6 to 19 years, treated with open-label memantine, revealed a response rate of 61%, with improvements noted in social withdrawal and inattention.[140] One open-label trial of memantine in 14 male subjects with ASDs, aged 3 to 12 years (mean age, 7 years), demonstrated significant improvements on the ABC subscales of Hyperactivity, Lethargy, and Irritability, as well as on a memory test.[141] However, there was no significant difference from baseline on measures of expressive or receptive language or nonverbal IQ. Another open-label trial of 151 individuals with autism, aged 2 to 26 years (mean age, 9 years), revealed significant improvements in language function, social behavior, and self-stimulatory stereotypic behaviors.[142] Eighty-two percent of the subjects continued on memantine, although 14.5% exhibited worsened behavior.

In the studies above, memantine was dosed 2.5 to 30 mg/day. Adverse effects in one study included irritability, rash, emesis, increased seizure frequency, and excessive sedation, although another study did not note any adverse effects.

Conclusion

Currently available research, with an emphasis on randomized, controlled studies, demonstrates that SRIs are more efficacious in adults and older adolescents compared with children for the treatment of repetitive behaviors, and children may exhibit more behavioral activation with an SRI. Atypical antipsychotics are efficacious for the treatment of irritability in children, adolescents, and adults with ASDs. For hyperactivity and inattention, psychostimulants may be beneficial but are less efficacious and associated with more adverse effects compared to individuals with ADHD. α-2 Adrenergic agonists and the non-stimulant atomoxetine may be effective where psychostimulants are not, although subjects should be monitored for adverse effects. Mirtazapine has shown benefit in the management of a wide range of symptoms in ASDs, including anxiety, irritability, SIB, repetitive behaviors, and inappropriate sexual behaviors, although further research is needed. D-cycloserine and memantine appear helpful in the treatment of social impairment, although again, further research is needed.

In the past quarter century, significant progress has been made in the psychopharmacology of ASDs. Target symptom domains associated with ASDs have been identified that are amenable to pharmacotherapy. Drugs that are efficacious interventions for other neuropsychiatric disorders have been evaluated in subjects with ASDs for the treatment of symptoms that appear similar phenotypically (eg, the repetitive behavior of OCD vs the repetitive behavior of ASDs; the motor hyperactivity of ADHD vs the motor hyperactivity of ASDs). Importantly, these drug treatments have largely been ineffective or less effective in subjects with ASDs than in those with the prototypical disorders. In addition, the tolerability of these drugs has been reduced in the subjects with ASDs. These results suggest that fundamental biological mechanisms may be quite different between disorders despite similarities in aspects of clinical presentation. Differences in response to drugs have also been identified across development in subjects with ASDs; the same has been observed with regard to drug tolerability. As in most areas of research, the more we have learned the more we have realized how much more we need to know. Clearly, additional randomized double-blind, placebo-controlled trials are needed, particularly in adults with ASDs. An ultimate goal is to develop a "rational pharmacology" that targets fundamental biological mechanisms underlying these complex disorders. ❑

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Tratamientos farmacológicos para los síntomas conductuales de los trastornos del espectro autista a través de la vida

Esta revisión describe los tratamientos farmacológicos para los síntomas conductuales asociados con los trastornos del espectro autista (TEA) en niños, adolescentes y adultos. Los síntomas incluyen conductas estereotipadas repetitivas, irritabilidad y agresividad, hiperactividad e inatención, y deterioro social. Los fármacos incluyen inhibidores de la recaptura de serotonina (IRSs), mirtazapina, antipsicóticos, psicoestimulantes, atomoxetina, agonistas α-2, D-cicloserina y memantina. Los IRSs como grupo son menos eficaces y peor tolerados en niños que en adultos con TEA. Los antipsicóticos son los fármacos más eficaces para el tratamiento de la irritabilidad en los TEA y pueden ser útiles para el tratamiento de otros síntomas. Los psicoestimulantes muestran algún beneficio para el tratamiento de la hiperactividad y la inatención en sujetos con TEA, pero son menos efectivos y se asocian con más efectos adversos en comparación con sujetos con ADHD. La D-cicloserina y la memantina parecen útiles para el tratamiento del aislamiento social, pero se requiere de más investigación.

Traitements pharmacologiques des symptômes comportementaux associés aux troubles autistiques au cours de la vie

Cet article présente les traitements pharmacologiques des symptômes comportementaux associés aux troubles autistiques (TA) chez les enfants, les adolescents et les adultes. Ces symptômes incluent des comportements répétitifs et stéréotypés, une irritabilité et une agressivité, une hyperactivité et un manque d'attention ainsi qu'un handicap social. Les traitements utilisés incluent les inhibiteurs de la recapture de la sérotonine (IRS), la mirtazapine, les antipsychotiques, les psychostimulants, l'atomoxétine, les α-2 agonistes, la D-cyclosérine et la mémantine. Globalement les IRS sont moins efficaces et moins bien tolérés chez les enfants que chez les adultes. Les antipsychotiques sont les produits les plus efficaces pour le traitement de l'irritabilité dans les TA et peuvent être utiles dans le traitement d'autres symptômes. Les psychostimulants font preuve de quelques avantages dans le traitement de l'hyperactivité et de l'inattention chez ceux ayant un TA, mais ils sont moins efficaces et associés à plus d'effets indésirables comparés à ceux ayant un TDAH (trouble déficitaire de l'attention avec hyperactivité). Si la D-cyclosérine et la mémantine sont utiles dans le traitement du dysfonctionnement social, de plus amples recherches sont nécessaires.

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