EVIDENCE-BASED MEDICINE
Key Words: autism spectrum disorder, treatment, psychotherapy, psychopharmacology

Treatment of Autism Spectrum Disorder in Children and Adolescents

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ABSTRACT *~ Autism spectrum disorder is a diagnosis that includes significant social communication deficits/delays along with restricted patterns of interests and behaviors. The prevalence of this diagnosis has increased over the past few decades, and it is unclear whether this is solely attributable to the increased awareness of milder forms of the disorder among medical providers. The current treatment options for the core symptoms of autism are limited to psychosocial therapies, such as applied behavior analysis. Medications have been most effective in treating the associated behavioral symptoms of autism, though studies have examined potential benefits in some of the core symptoms of autism with certain medications, especially the repetitive behaviors often seen with this diagnosis. Risperidone and aripiprazole are currently the only medications FDA approved for symptoms associated with autism spectrum disorders, targeting the irritability often seen with this diagnosis. Children and adolescents with autism spectrum disorder appear to be more susceptible to adverse effects with medications; therefore, initiation with low doses and titrating very slowly is recommended. Some complementary alternative treatments have been researched as possible treatments in autism, though evidence supporting many of these is very limited.* Psychopharmacology Bulletin. *2016;46(2):18–41.*

Diagnosis and Prevalence

Changes to diagnostic criteria in the Diagnostic and Statistical Manual of Mental Disorders, 5th edition included eliminating several sub-diagnostic categories (i.e. Asperger syndrome, pervasive developmental disorder not otherwise specified, disintegrative disorder) and using one term to describe both the lower and higher functioning forms of autism: autism spectrum disorder (ASD). The requirements for this diagnosis also decreased from 3 criteria (social reciprocity, communicative intent, and restricted and repetitive behaviors in DSM IV-TR) to 2 criteria (social communication/interaction and restricted and repetitive behaviors in DSM 5).[1,2] Individuals must meet all the social communication/interaction criteria, which include: problems reciprocating social or emotional interaction; severe problems maintaining relationships; and nonverbal communication problems. They must also meet 2 of the 4 restricted and repetitive behaviors criteria, which include: stereotyped

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or repetitive speech, motor movements or use of objects; excessive adherence to routines, ritualized behavior, or excessive resistance to change; highly restricted interests, abnormal in intensity or focus; and hyper or hypo reactivity to sensory input or unusual interest in sensory aspects of environment. These symptoms must cause functional impairment for a diagnosis to be made. Associated symptoms may be seen with autism spectrum disorder, including, but not limited to, irritability, hyperactivity, aggressive behaviors, anxiety, mood symptoms, and insomnia.[3]

Current recommendations by both the American Academy of Child and Adolescent Psychiatry and the American Academy of Pediatrics include routine developmental screening for symptoms of ASD in young children.[4,5] The US Preventative Services Task Force recently reported there is insufficient evidence to assess the balance of benefits and harms of screening for ASD in young children for whom no concerns of ASD have been raised either by their parents or their clinicians.[6] Their recommendation is for clinicians to use clinical judgment to decide if screening for ASD in these children is appropriate.

The Center for Disease Control's Autism and Developmental Disabilities Monitoring Network estimated prevalence of ASD to be 1 in 68 individuals in their latest survey.[7] The prevalence of ASD has continuously increased in past decades, with a nearly fourfold increase in diagnosis (parent-reported) from 1997 to 2008. This is thought to be, at least partially, due to increased awareness of milder forms of the diagnosis among clinicians, meaning many cases are being identified which would have previously gone undiagnosed. The latest National Health Statistics Report by the US Department of Health and Human Services and the CDC showed school-aged children newly diagnosed with ASD in or after 2008 were more likely to have milder ASD and less likely to have severe ASD than those diagnosed in or before 2007.[8]

A recent systematic review of prognosis/outcome studies showed that intelligence quotient (IQ) and early language ability are the strongest predictors for a favorable prognosis in ASD. Studies also show with age (in general) the diagnosis of ASD remains stable, but adaptive functioning improves and co-morbid behavioral symptoms become less severe, whereas social functioning, cognitive ability and language skills have more variable outcomes.[9]

Treatment

Psychosocial Therapies

Many different psychosocial interventions have been developed targeting both the core symptoms and associated symptoms of ASD.

Applied behavior analysis (ABA) is a treatment based on theories of learning and operant conditioning. It includes specific intervention targets, coupled with positive reinforcement (verbal praise, tokens, or edible rewards), with repetition of learning-trials a key component.[10] It was postulated that early, intensive ABA intervention might lead to remarkable outcomes, including almost half of the children receiving this treatment gaining significant IQ points and being mainstreamed into regular classes.[11] Many of the earlier studies lacked methodological rigor, and replication with randomized controlled trials was needed to support such claims. One proposed early intensive ABA therapy model, the Early Start Denver Model, showed significant cognitive and adaptive behavior gains over the course of 2 years in a randomized, controlled trial of 48 preschool-aged children.[12] A meta-analysis examining the efficacy of ABA interventions for young children with autism showed medium to large positive effects on intellectual functioning, language development, daily living skills acquisition, and social functioning, with the larger effect sizes observed on language-related outcomes.[13]

Limitations to this form of intervention include the length of time required to see improvements, questionable generalizability of learned skills, and lack of motivation at times from the patient to work on these skills.[14] Additional limitations to ABA interventions include the cost of these intensive therapies, which can be substantial, given the intensive nature of treatment (usually 20+ hours a week).

Another intervention that shows some promise in treating core symptoms of ASD is Pivotal Response Treatment (PRT) and includes a more naturalistic behavioral method that targets specific skills as well as motivations (i.e. pivotal areas).[15,16] The theory is that PRT leads to more widespread/generalizable gains in areas not specifically targeted by the therapy, such as joint attention. It is also less time-intensive than ABA therapies. A randomized, controlled trial found PRT to be helpful for functional and adaptive communication skills in 53 children (aged 2 to 6 years) with autism and significant language delay.[17] A randomized clinical trial comparing PRT and ABA interventions found PRT to be superior to ABA in improving verbal expressive communication with three months of treatment.[18] Children also were found to exhibit less disruptive behaviors during PRT when compared to ABA.[19]

One randomized controlled trial examined the addition of a supplemental social curriculum to treatment, which included aspects of ABA and PRT to assess whether the supplemental curriculum resulted in improved joint attention, shared positive affect and socially engaged imitation as compared to those without the supplemental curriculum.[20] The group with the supplemental curriculum showed a twofold increase

in socially engaged imitation, though the other two outcome variables showed similar gains in both treatment groups. Other psychosocial interventions include parent-mediated early interventions (teaching parents interventions that they can then apply in the home) and social skills interventions. Studies examining parent-mediated interventions have shown mixed results and most include small sample sizes, though one large randomized controlled trial showed parent training to be superior to parent education alone.[21–25] Other randomized controlled trials have found parent-training to be effective in improving social communication and adaptive behavior.[26,27]

Social skills interventions have also been studied, though usually as components of other types of therapies. They have been studied more extensively in individuals with medium to higher cognitive functioning levels and are often provided in a group format. Social skills interventions include peer-related mediation, social narratives, and video modeling. Goals of social skills training may include emotional regulation, basic conversation skills, nonverbal communication skills, perspective taking, initiating, responding, and maintaining social interactions.[28] Reviews of social skills interventions show them to be promising treatments, especially with targeted skills; however, the generalizability of skills is still unclear and more rigorous, high quality intervention studies are needed.[29,30] Cognitive behavior therapy (CBT) has been studied as a treatment for co-morbid anxiety disorders in children and adolescents with autism spectrum disorder. Randomized controlled trials have shown CBT to be an effective treatment for anxiety, but it may be more effective for higher functioning individuals.[31–34]

Pharmacology

Medications are primarily used for treating associated symptoms of autism spectrum disorder, as efficacy for use in treating the core symptoms of autism has not been established. Targeted associated symptoms may include, but are not limited to, irritability, aggression, self-injurious behaviors, anxiety, hyperactivity, impulsivity, inattention, and insomnia.

Atypical Antipsychotics

Risperidone and aripiprazole are approved by the Food and Drug Administration (FDA) for the treatment of irritability associated with the diagnosis of autism spectrum disorder. Risperidone is approved in children at least 5 years of age and aripiprazole is approved for children at least 6 years of age.

Risperidone

A double blind, placebo-controlled study by the Research Units on Pediatric Psychopharmacology (RUPP) Autism Network examined the efficacy of risperidone in treating irritability associated with autism in 101 individuals, aged 5–17 years.[35] This 8 week study compared risperidone (mean dose 1.8 mg/d) to placebo on measures of irritability (Abberant Behavior Checklist Irritability subscale) and global improvement (Clinical Global Impressions – Improvement scale).[36–37] Response was defined as ⩾ 25% decrease in the irritability score and a rating of much improved or very much improved on the CGI-I scale. Response rates were 69% in the risperidone treatment group and 12% in the placebo group, which was a significant difference. Significant side effects in the risperidone group were weight gain (2.7 kg versus 0.8 kg in the risperidone and placebo groups, respectively), increased appetite, fatigue, drowsiness, dizziness, and drooling. Of the responders in the risperidone group, 68% maintained this response at a 6 month follow up.

An 8-week, double-blind, placebo-controlled study examined the efficacy of risperidone on irritability in children with autism and other pervasive developmental disorders. The risperidone group (mean dose 1.17 mg/d) was superior to placebo in decreasing scores on the irritability subscale of the ABC.[38] Weight gain was significant in the risperidone group, with a mean increase of 2.7 kg versus 1 kg in the placebo group.

A six month randomized controlled trial examined the efficacy of risperidone in children with autism spectrum disorder.[39] Targets included some core autism symptoms (social and emotional responsiveness and communication) and associated symptoms (aggressiveness, hyperactivity, and irritability). The primary outcome measures were the changes in the median Childhood Autism Rating Scale rating from baseline and the mean Children's Global Assessment Scale score from baseline.[40–41] The risperidone group was superior to the placebo group on both outcome measures. Risperidone also lessened hyperactivity and aggression and improved social responsiveness and nonverbal communication. Side effects in the risperidone group included mild sedation, increased appetite, weight gain (mean 2.8 kg), and mild, transient dyskinesias.

Several studies have examined the long-term benefits of risperidone in autism spectrum disorder. A blinded discontinuation study examined the long-term efficacy of risperidone in children, aged 5 to 17 years.[42] The 8 week, randomized, double-blinded discontinuation phase of this study included 32 individuals.[35] After 6 months of risperidone treatment, 62.5% of youth randomized to placebo relapsed compared to 12.5% of youth randomized to continue risperidone treatment, which was a significant finding. Relapse was defined as a 25% increase in the

ABC irritability subscale score and a CGI-I score of much worse or very much worse compared to the prediscontinuation baseline. A study examining the long term efficacy of risperidone in autism spectrum disorder in 36 youths (aged 5 to 17 years) included 6 months of risperidone treatment followed by an 8 week, randomized, double-blinded, placebo-controlled discontinuation phase.[43] Signifcantly more youth in the placebo group relapsed (67%) when compared to youth who continued risperidone treatment (25%) during the discontinuation phase of the study. Side effects in the risperidone group included increased weight and appetite, anxiety, and fatigue. A 21-month naturalistic study followed 84 children and adolescents over an average of 21 months and showed 2/3 of the participants remained on risperidone throughout the follow up period.[44] Though risperidone was associated with more adverse effects (weight gain, enuresis, increased appetite), the study concluded that these were balanced by the positive effects seen in those who continued treatment. These included improved social skills/socialization and decreased irritability, compared to baseline and compared to the group who discontinued treatment during the follow up phase.

The efficacy of risperidone and haloperidol was compared in 30 children and adolescents, aged 8 to 18 years in a 12-week randomized controlled trial.[45] The mean dose was 2.6 mg/d in both the risperidone and haloperidol groups. Risperidone was shown to be more effective in reducing behavioral symptoms and impulsivity than haloperidol. It was also more effective in improving language skills and social relations. When comparing adverse effects, the risperidone group had greater increases in prolactin and the haloperidol group had greater increases in alanine amino transferase (ALT). There was no significant difference between the two groups in weight gain.

Though no medication is approved for use in treating the core symptoms of autism, there is some evidence that risperidone may be effective in treating the repetitive and restricted patterns of behaviors in children with autism. An open-label continuation study of 63 children and adolescents (aged 5–17 years) examined the efficacy of risperidone in treating the core symptoms of autism spectrum disorder.[46] Measurements included the Ritvo-Freeman Real Life Rating Scale, the Children's Yale Brown Obsessive Compulsive Scale, and the maladaptive behavior domain of the Vineland Adaptive Behavior Scales.[47–49] Statistically significant improvements in restricted, repetitive, and sterotyped patterns of behavior, interest, or activities was observed over the 16 week continuation phase. No significant improvement was observed in the area of social interaction and communication.

The benefits of risperidone for adaptive behaviors in autism spectrum disorder was examined in 48 children and adolescents, aged 5 to

16 years.[50] Adaptive behaviors were assessed using the Vineland Adaptive Behavior Rating Scales over a 6 month period. Significant improvement was seen in adaptive behavior in the areas of communication, daily living skills, and socialization. This suggests possible direct positive effects on adaptive behavior with risperidone treatment, but more rigorous study is needed in this area.

Aripiprazole

The efficacy of aripiprazole in the acute treatment of irritability associated with autism spectrum disorder was examined in an 8 week, double-blind, randomized controlled trial in 218 children and adolescents, aged 6 to 17 years.[51] Subjects were randomized into four fixed dosing groups, 5 mg, 10 mg, 15 mg, or placebo. All doses of aripiprazole were superior to placebo on the primary outcome measure, the mean change on ABC irritability subscale score from baseline to endpoint. Weight gain was significantly higher in each aripiprazole dose group when compared to placebo, and sedation was the most common adverse effect reported. An 8 week trial examined the efficacy of aripiprazole in the treatment of irritability associated with autism spectrum disorder in 98 children and adolescents, aged 6–17 years, using a flexible dosing schedule.[52] Doses at 8 weeks were either 5 mg, 10 mg, 15 mg, or placebo. Aripiprazole was found to be superior to placebo on the primary outcome measure of mean change of the ABC irritability subscale score from baseline to endpoint. The most common side effects in the aripiprazole group were somnolence and fatigue. The rate of extrapyramidal symptoms was 14.9% in the aripiprazole group, versus 8% in the placebo group.

A double-blind, randomized, placebo-controlled trial examined the efficacy of aripiprazole in preventing relapse in long-term maintenance treatment.[53] The study included 85 youths, aged 6 to 17 years with autism, who were responders to acute treatment with aripiprazole for 12 weeks. They were randomized to receive either continued aripiprazole treatment or placebo and followed to relapse or 16 weeks. Time from randomization to relapse was the primary outcome measure, and there was no difference between the two groups on this measure. The hazard ratio (HR = 0.57) and number needed to treat (NNT = 6) suggested that some patients may benefit from maintenance treatment.

The long-term efficacy of aripiprazole for irritability in patients with autism spectrum was examined in a 52 week open-label study of 199 children and adolescents, aged 6–17 years.[54] The study included responders to acute treatment with aripiprazole (who continued treatment for the 52 weeks of this study) as well as individuals with no

prior treatment with aripiprazole (who began open-label treatment with this study, continuing for 52 weeks). Flexible dosing was used, with a mean daily dose of 10.6 mg by week 52. The group that continued treatment with aripiprazole maintained response, as measured by the ABC irritability subscale and the CGI improvement scores. The group of patients with no prior aripiprazole treatment showed significant improvement in both scores compared to baseline. The most common side effects included weight gain, vomiting, nasopharyngitis, appetite increase, pyrexia, upper respiratory tract infection, and insomnia.

A 2-month randomized, double-blind, placebo-controlled comparison trial examined the efficacy of aripiprazole versus risperidone in 59 children and adolescents with autism spectrum disorder and associated behavioral symptoms.[55] There was no difference between the groups on primary outcome measures (ABC scores) or on safety measures (including appetite increase and weight gain).

Olanzapine

The efficacy of olanzapine on global improvement was examined in an 8-week double-blind, randomized, placebo-controlled study of 11 children and adolescents (aged 6 to 14 years) with pervasive developmental disorders.[56] Response rates (CGI-I $\leqslant$ 2) were significantly higher in the olanzapine group compared to the placebo group (50% versus 20%, respectively). Weight gain was significant in the olanzapine treatment group (mean 7.5 pounds) compared to the placebo group (mean 1.5 lbs).

In a 3 month open-label study, the efficacy of olanzapine was examined in 25 children and adolescents (aged 6 to 16 years) with autistic disorder or pervasive developmental disorder not otherwise specified.[57] The mean daily dose of olanzapine in the study was 10.7 mg. The 23 who completed the study showed significant improvements on the ABC subscales of irritability, hyperactivity, and excessive speech; however, only 3 youth were deemed "responders" based on CGI Severity/Improvement scores. Significant weight gain was observed (mean 4.7 kg), along with appetite increase and loss of strength.

An open label study examining the efficacy of olanzapine in 40 male youth, aged 7 to 17 years, with autism showed significant decreases in the ABC subscales of irritability, stereotyped behaviors, hyperactivity, and inappropriate speech.[58] Only 30% of the study participants were considered much improved based on CGI severity scores when compared to baseline. Mean daily dose was 7.5 mg and no significant weight gain was observed in this study.

Lurasidone

A 6-week, double-blind, randomized, placebo-controlled study examined the efficacy of lurasidone for irritability associated with autism spectrum disorder in 150 children and adolescents, aged 6 to 17 years.[59] Study participants were randomized into three different fixed dosing groups: lurasidone 20 mg/day, lurasidone 60 mg/day, and placebo. Lurasidone was not found to be superior to placebo at either dose as measured by the change in ABC-I scores from baseline. Lurasidone was superior to placebo, as measured by change in the CGI-I scores from baseline to endpoint, in the 20 mg/day treatment group but not in the 60 mg/day treatment group. The most commonly observed side effects included vomiting and somnolence.

Quetiapine

Several small, open-label studies have examined the efficacy of quetiapine in children and adolescents with autism spectrum disorder. One 16-week trial included 6 male children with autism who also had intellectual disability.[60] No statistically significant improvement in symptoms were demonstrated. Side effects with quetiapine were sedation, a possible seizure, behavioral activation, increased appetite and weight gain. A 12-week trial with 9 adolescents with autism showed overall low response; only 2 study participants met criteria for response (CGI $\leqslant$ 2).[61] A study examined the efficacy of low dose quetiapine in 11 adolescents with autism spectrum disorder over the course of 8 weeks.[62] Mean dose of quetiapine was 122.7 mg/day at the end of the study. The study showed significant improvements in aggression and sleep, and quetiapine was generally well-tolerated at these lower doses.

Ziprasidone

A 6-week, open-label pilot study of ziprasidone examined the efficacy and safety of this medication in 12 adolescents with autism.[63] Seventy-five percent of participants were deemed responders (CGI-I $\leqslant$ 2), and ziprasidone was well-tolerated, with no weight gain and mean QTc increase of 14.7 msec. Two study participants experienced acute dystonic reactions. An open-label trial examined the efficacy of ziprasidone in 12 patients, aged 8–20 years with autism or pervasive developmental disorder not otherwise specified for at least 6 weeks.[64] Fifty percent of study participants were considered responders (CGI-I $\leqslant$ 2), with transient sedation as the most commonly observed side effect. There was no observed weight gain and no observed cardiovascular side effects.

Paliperidone

An 8-week, open-label trial examined the efficacy of paliperidone in the treatment of irritability in 25 adolescents and young adults (aged 12–21 years) with autism.[65] The mean daily dose of paliperidone was 7.1 mg. Eighty-four percent of study participants were considered "responders" (CGI-I $\leqslant$ 2 and $\geqslant$ 25% improvement in ABC-I score). Mild to moderate extrapyramidal symptoms were reported in 4 study participants and mean weight gain was 2.2 kg over the course of the study.

Typical Antipsychotics

Haloperidol

Haloperidol was one of the first medications studied for use in autism spectrum disorder. Studies of acute treatment with haloperidol have shown benefits in the areas of hyperactivity, temper tantrums, withdrawal, stereotypical behaviors, and facilitating learning on discrimination tasks.[66–68] Doses used in these studies ranged from 0.25 mg to 4 mg per day. The most commonly observed side effects included sedation, irritability, and acute dystonic reactions. A 6-month study examining the long-term efficacy of haloperidol in 60 children (aged 2–8 years) with autism showed maintenance of efficacy over the course of the study.[69] It was most helpful for children with irritability, angry/labile affect, and uncooperative behaviors. Side effects included haloperidol-related dyskinesias, including withdrawal dyskinesias.

The risk of extrapyramidal symptoms with haloperidol is a concern. A prospective, longitudinal study followed 118 children, aged 2 to 8 years, with autism treated with haloperidol for associated behavioral symptoms for a mean length of 708 days.[70] Thirty-four percent of children developed either withdrawal or tardive dyskinesia during the course of the study. The risk of dyskinesia increased with length of treatment, making long-term use of this medication especially concerning. For this reason, haloperidol should be considered after the atypical antipsychotics in children and adolescents with autism spectrum disorder.

Antidepressants

Antidepressants have been considered for use in autism spectrum disorder due to the observed symptoms of repetitive, ritualistic behaviors and insistence on restricted patterns of routines. Selective serotonin reuptake inhibitors (SSRIs), tricyclic antidepressants, and other antidepressants have been studied in patients with autism spectrum disorders.

Selective Serotonin Reuptake Inhibitors (SSRIs)

Studies examining the efficacy of SSRIs in autism spectrum disorder have had mixed results. Some studies show potential benefits in the treatment of repetitive movements and irritability, while others show no improvement and significant adverse effects when these medications are used in this patient population.

Two double blind, placebo-controlled studies examining the efficacy of fluoxetine showed conflicting results. In one study of 45 children and adolescents (aged 5 to 17 years), the efficacy of liquid fluoxetine was compared to placebo for repetitive behaviors associated with autism spectrum disorder.[71] This cross-over study included 8 weeks of treatment with fluoxetine and 8 weeks of treatment with placebo, separated by a 4-week washout phase. Fluoxetine (mean dose 10 mg/day) was found to be superior to placebo in the treatment of repetitive behaviors, as measured by the Children's Yale-Brown Obsessive-Compulsion Scale, compulsions subscale (CY-BOCS).[72] Fluoxetine appeared to be well-tolerated. A 14-week double-blind, placebo-controlled trial examined the efficacy of low dose fluoxetine for repetitive behaviors associated with a diagnosis of autistic disorder in 158 children and adolescents (aged 5 to 17 years).[73] Fluoxetine was not found to be superior to placebo in this study. An open trial examined the efficacy of fluoxetine in 23 children and adults with autistic disorder and found significant improvement in CGI ratings of clinical severity in 15 of 23 subjects.[74] Observed side effects were restlessness, hyperactivity, agitation, decreased appetite or insomnia.

Citalopram was not superior to placebo in a randomized, placebo-controlled trial of 149 children and adolescents (aged 5 to 17 years) with autism spectrum disorder.[75] The primary outcome measures were the CGI, Improvement subscale and CY-BOCS (repetitive movements), and the mean daily dose of citalopram was 16.5 mg. 97% of those in the citalopram group experienced adverse effects, including increased energy, impulsivity, decreased concentration, hyperactivity, stereotypy, diarrhea, insomnia, and dry skin or pruritus.

Fluvoxamine was studied in a double-blind, placebo-controlled study in 34 children with autistic disorder.[76] No significant clinical improvement was seen with the medication when compared to placebo. The efficacy of low dose fluvoxamine (mean 67 mg/day) was examined in an open study of 18 children and adolescents with pervasive developmental disorders.[77] No statistically significant improvement was seen during the 10-week study. Adverse effects were experienced in 72% of the participants, with agitation/behavioral activation and insomnia the most commonly reported symptoms.

The efficacy of escitalopram was examined in a 10-week open-label trial of 28 children and adolescents (aged 6 to 17 years) with pervasive developmental disorders.[78] Significant improvement was seen on irritability and global improvement measures, and the study highlighted the need to start with very low doses and titrate slowly. Twenty-five percent of the participants responded at doses < 10 mg and did not tolerate doses at or above 10 mg. The most commonly reported adverse effects were irritability and hyperactivity, which appeared dose-related.

Other Antidepressants

Low dose venlafaxine was found to be effective for repetitive behaviors and restricted interests, social deficits, communication and language function, inattention, and hyperactivity in an open, retrospective clinical report of 10 individuals (aged 3 to 21 years) with autism spectrum disorder.[79] Over an average length of 5 months, 60% of participants responded to venlafaxine (mean dose 24.4 mg/day). Response was based on CGI, improvement scores, and adverse effects included behavioral activation, nausea, inattention and polyuria.

Mirtazepine was studied in a naturalistic open-label study of 26 children and adults (aged 3 to 23 years) with pervasive developmental disorders.[80] The mean daily dose was 30 mg/day, and 34.6% of participants were deemed responders (much improved or very much improved on CGI scale). The medication was not effective for the core symptoms of social or communication impairment. Adverse effects included increased appetite, irritability, and sedation.

A 6-week, open-label, pilot study of 8 children with autistic disorder showed clomipramine was not effective for symptoms, with 7 of the 8 children showing worsening symptoms.[81] Side effects were also concerning, including one incidence of acute urinary retention, requiring catheterization. Five children with autistic disorder and severe intellectual disability showed improvement in adventitious movements and compulsions in a small, open-label study of clomipramine.[82]

A double-blind, placebo-controlled trial examined the efficacy of clomipramine and desipramine in the treatment of autistic disorder.[83] This 12 week study included 24 participants, aged 6 to 23 years, with autistic disorder and included a clomipramine versus placebo group (n = 12) and a clomipramine and desipramine crossover comparison group (n = 12). Clomipramine was superior to both placebo and desipramine on measures of stereotypical behaviors, anger, and compulsive, ritualized behaviors. Both clomipramine and desipramine were helpful for reducing hyperactive behaviors. Adverse effects were high in the desipramine group, with 8 of the 12 subjects experiencing increased

irritability, temper outbursts, and uncharacteristic aggression while receiving desipramine. Clomipramine was relatively well-tolerated, with no significant adverse effects when compared to placebo.

Mood Stabilizers

There have been two small double-blind, placebo-controlled studies of divalproex sodium for the treatment of autism spectrum disorder in children and adolescents, aged 5 to 17 years. A 12-week study examined the efficacy of this drug in treating irritability in 27 children and adolescents with autism spectrum disorder.[84] Response was defined using scores from the ABC, irritability subscale and the CGI-I scale, with 62.5% in the divalproex sodium treatment group responders versus 9% in the placebo group, which was statistically significant. The trend was for responders to have higher valproate blood levels than the non-responders. Divalproex sodium was generally well-tolerated, with one case of extreme agitation in the treatment group. An 8-week study examined the efficacy of divalproex sodium in improving repetitive behaviors associated with autism spectrum disorder in 13 children and adolescents.[85] There was significant improvement in repetitive behaviors among the group treated with divalproex sodium when compared to placebo, as measured by the CY-BOCS. The most common adverse effect in the divalproex sodium group was irritability.

A randomized, double-blind, placebo-controlled trial examined the efficacy of lamotrigine in 28 children (aged 3–11 years) with autistic disorder.[86] This 18 week study showed no significant difference between lamotrigine and placebo on any of the outcome measures. Reported adverse effects also did not differ significantly between the groups.

Stimulants/Atomoxetine/Alpha-2 Agonists

Symptoms of attention-deficit/hyperactivity disorder (ADHD) are commonly observed with a diagnosis of autism spectrum disorder, which has led to research examining the efficacy and tolerability of ADHD treatments in this patient population. Several studies have examined the efficacy of methylphenidate for symptoms of inattention, hyperactivity, and impulsivity among patients with a diagnosis of autism spectrum disorder. The largest of these, a double-blind, placebo-controlled, crossover study,[87] included 72 children and adolescents, aged 5–14 years, with pervasive developmental disorders and hyperactivity. Methylphenidate was found to be superior to placebo in treating hyperactive symptoms using the ABC, hyperactivity subscale.

Effect sizes ranged from 0.20 to 0.54, lower than what is seen in typically developing children and adolescents with ADHD treated with methylphenidate. Adverse effects were also observed more frequently than are seen in typically developing patients with ADHD, and included appetite decrease, insomnia, irritability and emotional outbursts. A placebo-controlled study examining the use of extended-release preparations of methylphenidate in 24 elementary school-aged children with autism spectrum disorder showed it was beneficial for hyperactivity, impulsivity and inattention with no evidence of an increased risk of adverse effects in this patient population.[88] This study included children who were relatively high functioning, and the investigators point this out as a potential limitation of the study.

Smaller placebo-controlled studies have shown benefits of methylphenidate for hyperactivity in children with autism spectrum disorder, but effects have been modest and side effects are concerning, especially at higher doses.[89–91] More studies examining the effects of this medication on core symptoms of autism are needed. The findings from the existing studies suggests a need to start these medications at low doses and increase slowly.

Atomoxetine has been studied in several double-blind, placebo-controlled trials in children and adolescents with autism spectrum disorder and ADHD symptoms.[92–94] Modest improvements in hyperactive and impulsive symptoms were seen in these studies, and atomoxetine was generally well-tolerated, with no indication of increased adverse effects in this population versus that of typically developing children and adolescents with ADHD. One study found atomoxetine to be effective in some core autism symptoms (decreasing restricted and stereotyped behaviors and communication) but showed no effect on social functioning.[94]

Due to concerns about a possible increased risk of side effects when using stimulants in children with autism spectrum disorder, alpha-2 agonists have been studied as possible alternatives to stimulants for managing hyperactivity and impulsivity in this patient population. A recent randomized, double-blind, placebo-controlled trial examined the efficacy of extended-release guanfacine in children and adolescents (aged 5 to 14 years) with autistic disorder, asperger's disorder, or pervasive developmental disorder, not otherwise specified.[95] This 8 week trial showed extended-release guanfacine to be superior to placebo in lowering scores on the ABC-hyperactivity subscale as well as on global improvement measures (CGI-I scores). Adverse effects included drowsiness, fatigue and decreased appetite. Blood pressure decreased slightly early in the study, but returned to baseline by study endpoint. These findings were similar to another trial in which guanfacine was compared

to placebo in children (aged 5 to 9 years) with autism, intellectual disability, and comorbid ADHD.[96] Guanfacine was superior to placebo on measures of hyperactivity and global improvement. Adverse effects included drowsiness and irritability, with no significant difference in blood pressure or pulse in the guanfacine group.

Two small double-blind, placebo-controlled studies and one retrospective open-label study have examined clonidine for the treatment of hyperactivity and impulsivity in children and adolescents with autism spectrum disorders.[97–99] All three studies found clonidine to be at least modestly effective for symptoms of hyperactivity. Some of the studies found it to be helpful for other symptoms, such as social relationships, sensory responses, irritability, sleep and aggression. Adverse effects common to all three studies were sedation or drowsiness, but the medication was otherwise well-tolerated.

Other Medications

Several randomized, placebo-controlled trials have examined the efficacy of naltrexone for core symptoms of autism, associated symptoms of hyperactivity and irritability, and for discrimination learning. Overall, it appears naltrexone may have some benefits in reducing hyperactivity and impulsivity in children and adolescents with autism spectrum disorder, but core symptoms did not appear to improve with this medication.[100–103] Naltrexone also had no effect on discrimination learning.[104–105] The efficacy of oxytocin has been examined in several randomized, placebo-controlled trials in children and adolescents with autism spectrum disorder and results have been mixed. One small study showed oxytocin to improve emotion recognition significantly when compared to placebo.[106] Two other studies showed no separation from placebo on social behaviors, emotion recognition, or general behavioral symptoms.[107,108]

Medications that have shown some promise in improving the core symptoms of autism in children and adolescents in randomized, placebo-controlled trials include donepezil hydrochloride, levocarnitine (l-carnitine), and the GABA-ergic drug, bumetanide.[109–111] Galantamine may be beneficial for irritability, hyperactivity and social withdrawal associated with autism spectrum.[112] More studies replicating these findings are needed to support the use of these medications in the management of autism spectrum disorders.

Medications that have shown mixed results in randomized, placebo-controlled trials of children and adolescents with autism spectrum disorders include amantadine and arbaclofen. Amantadine showed no improvement on parent-ratings of hyperactivity and irritability, but clinicians reported significant improvements in behavioral ratings.[113]

Arbacolfen showed no significant improvement on social withdrawal compared to placebo, but it did separate from placebo on improved global functioning scales.[114] Medications that have shown no benefits in treating symptoms of autism in children and adolescents in randomized, placebo-controlled studies include mecamylamine, memantine, and levetiracetam.[115–117]

Several medications have been studied as potential augmenting agents in combination studies with risperidone or haloperidol. Agents studied as augmenting agents to risperidone include pentoxifylline, N-acetylcysteine, riluzole, memantine, amantadine, celecoxib, pioglitazone, and buspirone.[118–126] All medications except buspirone were superior to risperidone plus placebo on various measures, including irritability, hyperactivity, social withdrawal, or inappropriate speech. Cyproheptadine was studied in combination with haloperidol and was found to be superior to haloperidol plus placebo on the primary outcome measure, change in scores on the Aberrant Behavior Checklist from baseline to endpoint.[127] More studies are needed examining medication augmentation strategies in children and adolescents with autism spectrum disorder.

Complementary Alternative Medicine

The efficacy of melatonin for sleep disturbances in children and adolescents with autism spectrum disorder has been examined in multiple double-blind, placebo-controlled studies, making it one of the best-studied complementary alternative treatments used in autism spectrum disorder. The largest of these examined controlled-release melatonin alone and in combination with cognitive-behavioral therapy (CBT) versus CBT alone and placebo in 160 children (aged 4 to 10 years) with autistic disorder.[128] This 12-week study showed combination treatment (melatonin plus CBT) to be the most effective intervention for sleep-related difficulties, but all active treatment groups outperformed placebo. No difference was observed between the groups in reported adverse effects. Other randomized, placebo-controlled trials and one open trial have shown similar improvements in sleep with melatonin, and none showed treatment-emergent adverse effects with this medication.[129–133] Melatonin was well-tolerated in all the above studies and appears to be a safe treatment option for sleep in children with autism spectrum disorder.

Omega-3 fatty acids have been examined as potential treatments for autism spectrum disorder, specifically for the associated symptom of hyperactivity. Randomized, placebo-controlled trials have shown possible improvements in hyperactivity in children and adolescents with

autism spectrum disorder, but the findings have failed to achieve statistical significance in this population.[134–136] Omega-3 supplementation has been relatively well-tolerated, and seems to be a safe intervention to consider in children with ASD.

Methyl B12 has been studied in two randomized, placebo-controlled trials as a treatment for both behavioral symptoms and core symptoms of autism spectrum disorder in children. One study found no significant difference between the placebo group and the active treatment group,[137] and the other study found significant improvement in clinician-ratings of global improvement but no difference in parent-ratings of behavioral or core symptoms when compared to placebo.[138] Though it was considered to be safe and was well-tolerated in these studies, the need for frequent injections make this treatment less desirable for many patients and their families. N-acetylcysteine may improve irritability in children with autism and appears to be well tolerated, but more studies are needed examining its efficacy in this patient population before this treatment can be recommended.[139] Vitamin supplementation has been studied as a possible treatment for autism spectrum disorder, and results from two randomized controlled trials have been mixed. One study found significant improvements only in gastrointestinal symptoms and sleep compared to placebo, but no significant improvements in core symptoms or associated behavioral symptoms of ASD.[140] The other study found significant global improvement on parent rating scales, along with improved receptive language and decreased hyperactivity and tantrums.[141]

Digestive enzymes and special diets have been examined as potential treatments in autism spectrum disorder, due to the increased rate of gastrointestinal symptoms found in these patients. The evidence does not support any improvement in core symptoms or associated behavioral symptoms of autism with digestive enzyme supplementation, though it may improve food variety scores in these patients.[142] A small randomized, placebo-controlled study examining the possible effects of a gluten-free/casein-free diet suggested no change in core symptoms or associated behavioral symptoms in children with autism in a double-blind challenge trial.[143]

Intravenous immunoglobulin therapy has been suggested as a potential treatment for autism spectrum disorder, however there are no randomized-controlled trials examining this treatment in children and adolescents with autism. The several open-label trials have been mixed, and there is significant risk associated with this treatment, therefore, available evidence does not support this treatment for ASD.[144–147]

Chelation is another suggested treatment for symptoms of autism spectrum disorder which is associated with significant risks and has limited evidence supporting its use in this patient population. Two studies

conducted by the same group reported possible benefits from chelation therapy for symptoms of autism spectrum disorder; however, the studies were not randomized controlled trials, and only served to compare one round versus multiple rounds of chelation therapy for autism symptoms. A small group of study participants showed worsening of symptoms, which is concerning. No difference was found between the two groups on any of the measures of core symptoms or associated behavioral symptoms.[148–149] Post-chelation urine metal reference ranges have not been validated, and comparing them with validated non-chelated urine specimens may be misleading.[150] There are risks associated with unnecessary chelation, some of which are severe (hypocalcemia, renal impairment, and reported death), and there is evidence that some patients may experience worsening symptoms after treatment, therefore, this treatment is not currently recommended for children and adolescents with autism spectrum disorder.[147] The FDA released a warning for parents regarding several possibly harmful treatments for autism spectrum disorder that do not have evidence supporting their use, including chelation therapies, hyperbaric oxygen therapy, miracle mineral solution, detoxifying clay baths, and coconut kefir and other probiotic products.[151] It is important for clinicians to be aware of the various proposed complementary and alternative treatments so they can answer questions parents and families may have and provide evidence-based treatment recommendations. ✤

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