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The Use of Complementary Alternative Medicine in Children and Adolescents with Autism Spectrum Disorder

By Melissa DeFilippis

ABSTRACT *~ Complementary alternative medicine (CAM) is used to a greater degree in children and adolescents with autism spectrum disorder (ASD), when compared to children and adolescents without this diagnosis. There is limited evidence supporting the use of many of these treatments in ASD, despite their popularity. Current FDA approved medications for ASD target associated behavioral symptoms of the diagnosis, not the core symptoms of social communication deficits and restricted/repetitive behaviors. These medications are also associated with concerning adverse effects. Evidence-based therapies for core symptoms, such as applied behavior analysis (ABA), are sometimes difficult for families to access for various reasons. Families are sometimes hesitant to discuss their interest in CAM with physicians. Physicians report knowledge gaps about CAM and their use in ASD and concerns about potential conflict with parents regarding differing beliefs of CAM's role in the management of ASD. It is important for physicians to know the current evidence which examines the use of CAM treatments in children and adolescents with autism so that they may have conversations with families which are informed and evidence-based.* Psychopharmacology Bulletin. *2018;48(1):40–63.*

Introduction

The prevalence of autism spectrum disorder (ASD) has increased significantly over the past few decades, now affecting 1 in 68 children in the United States, based on Centers for Disease Control data.[1] Causes for this increase are not fully known, but it is understood to be, at least partially, due to increased recognition and diagnosis of milder forms of the illness by clinicians. The National Health Statistics Report by the US Department of Health and Human Services and the CDC reported that school-aged children newly diagnosed with ASD

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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.[2] The presence of other factors (i.e., environmental influences) involved in the prevalence increase are currently unknown. Evidence based treatments for the core symptoms of ASD (social communication deficits and restricted/repetitive behaviors) include psychosocial interventions, such as applied behavior analysis (ABA) therapies. While these therapies can be very effective, high cost, limited coverage by insurance, and decreased availability of trained providers can make obtaining this treatment difficult or impossible for some families. Risperidone and aripiprazole have Food and Drug Administration (FDA) approval for treating associated symptoms of irritability and agitation in children with ASD, but no other medications have an indication for use specifically in this population. Additionally, no medications are approved for treating the core symptoms of ASD. Due to the limited treatment options and the associated fear of adverse effects with some traditional medications, parents and families of children with ASD are turning to complementary and alternative treatments for their children, including treatments with limited or no supporting evidence. This paper reviews the most popular complementary and alternative medicine (CAM) used in children with ASD, specifically examining the evidence that supports or fails to support the use of these treatments in this population. The focus will be on biomedical complementary treatment and dietary interventions.

Popularity of CAM for ASD

The use of CAM in children and adolescents in the United States was approximately 11.6% in 2012, a figure that did not change significantly from the last National Health Interview Survey in 2007 (12%).[3] Among children with ASD, use of CAM ranges from 28% to 51%, with lifetime use as high as 71%. Use of CAM is higher in Non-Hispanic white families, families with higher socio-economic status, and families with parents who have higher education status. Most parents who use CAM treatments report at least some improvement in ASD symptoms from CAM, but the monetary cost of treatment is reported as a concern by nearly half of parents.[4–6] The most commonly used CAM treatments used in children with ASD are modified/special diets (e.g., gluten-free, casein-free, sugar-free, lactose-free), vitamins/minerals (e.g., multivitamins, vitamin B6), and food supplements (e.g., omega-3 fatty acids, dimethylglycine). CAM treatments are used for a variety of symptoms in children with autism, including core symptoms of ASD, concentration, relaxation, gastrointestinal symptoms, sleep problems, communication, sensory issues,

seizures, and for general health. The most common reason parents give for choosing CAM treatments for their children with ASD is concern about side effects with conventional treatments/prescription medication. Sources of recommendation for CAM therapies are most likely to be friends and family, followed by health professionals, the internet, and books. Over half of the parents who choose to use CAM want to consult first with their physician for advice. Reasons parents may be hesitant to share their decision to use CAM treatments with physicians include the perceived lack of knowledge on the physician's part about CAM, the belief that it's not necessary, and because the physician doesn't ask about CAM treatments.[7,8] Pediatricians have reported knowledge gaps about CAM and uncertainty of their role in the management of ASD in their patients, and parents and pediatricians report possible conflict when discussing CAM treatments in clinic, which may lead parents to pursue CAM without discussing the safety and efficacy of these treatments first with their physicians.[9] Thus, it is important for physicians to review the available evidence examining the efficacy of CAM treatments in patients with autism, in order to feel comfortable discussing and providing guidance on using these treatments with their patients and families.

Melatonin

The efficacy of melatonin for sleep disturbances in children and adolescents with ASD has been examined in multiple double-blind, placebo-controlled studies, making it one of the best-studied CAM treatments used in ASD. Two studies have examined the efficacy of controlled-release melatonin for insomnia in children with autism. The largest of these compared placebo with cognitive behavioral therapy (CBT) alone and CBT plus controlled-release melatonin (3 mg) in 160 children (aged 4 to 10 years) with autistic disorder.[10] This 12-week study showed combination treatment (melatonin plus CBT) was 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. A double-blind, randomized, placebo-controlled study compared controlled-release melatonin (5 mg) to placebo in the treatment of insomnia in 51 children and adolescents (aged 2 to 18 years) with neurodevelopmental disabilities, including ASD.[11] This study was a crossover study, with 10 days on either placebo or controlled-release melatonin, a 3–5 day washout phase, and then 10 days on the alternate treatment. Significant improvement in sleep latency and total nighttime sleep duration was seen in the active treatment group, when compared to placebo, and there was no difference between the groups in reported adverse effects.

A double-blind, randomized, placebo-controlled study examined the efficacy of melatonin for sleep difficulties not amenable to behavior management in 22 children and adolescents (aged 3–16 years) with ASD.[12] In this crossover trial, melatonin (mean dose 7 mg) was superior to placebo in improving sleep latency and in total amount of sleep, but there was no difference between the two groups in number of night awakenings. Melatonin was well-tolerated in this study. A 4-week randomized, placebo-controlled crossover trial found melatonin (3 mg) to be superior to placebo in treating sleep problems in children with autism and/or fragile X syndrome.[13] The study included 18 youth (aged 2 to 15 years), and the group treated with melatonin showed increased sleep duration, shorter sleep latency and earlier sleep onset when compared to the placebo group. The findings were statistically significant, and no adverse effects were reported. A 9-week randomized controlled crossover trial examined the efficacy of melatonin (5 mg) versus placebo for sleep difficulties in 7 children and adolescents (aged 4 to 16 years) with autism.[14] Melatonin significantly reduced sleep latency and number of awakenings and increased total time asleep when compared to placebo. A 14-week open label trial of melatonin in children with autism (ages 3–9 years) showed melatonin (mean dose 3 mg) decreased sleep latency, and parents reported improved behaviors and decreased parental stress.[15]

Melatonin was reported to be well-tolerated in all the above studies, and it appears to be a safe treatment option for sleep difficulties in children and adolescents with ASD.

Omega-3 Fatty Acids

Omega-3 fatty acids have been examined as potential treatments for ASD, specifically for the associated symptom of hyperactivity. A 6-week randomized, placebo-controlled trial examined the efficacy of omega-3 fatty acid supplementation in 57 children (aged 5 to 8 years) with ASD.[16] Omega-3 (1.3 g/day) decreased hyperactivity symptoms more than placebo, as measured by the Aberrant Behavior Checklist-hyperactivity subscale (ABC-H), but it did not reach statistical significance.[17] There was no difference between the two groups in reported adverse effects. A 12-week study examined the efficacy of omega-3 fatty acids (1.3 g/day) for hyperactivity in 27 children, aged 3–8 years, with ASD.[18] Though hyperactivity decreased in the active treatment group compared to placebo, this was not a statistically significant finding. Reported adverse effects did not differ between the two groups. A study of 13 children and adolescents with autism, aged 5 to 17 years, examined the efficacy of omega-3 supplementation on both core and associated symptoms of ASD.[19] This 6-week, randomized, placebo-controlled

study found no statistically significant difference between the active treatment (1.5 g/day) and placebo groups, as measured by the Aberrant Behavior Checklist, though the active treatment group showed a trend toward superiority over placebo in decreasing hyperactivity. Omega-3 supplementation was well-tolerated. A 6-month randomized controlled study examined the efficacy of omega-3 for core symptoms and externalizing behaviors in 38 young children (aged 2 to 5 years) with ASD.[20] Omega-3 fatty acid supplementation (1.5 g/day) failed to show significant improvement in either core symptoms or associated externalizing symptoms, as measured by the Pervasive Developmental Disorders Behavioral Inventory (PDDBI) and the Behavior Assessment System for Children (BASC-2).[21,22]

A 12-week open-label trial examined omega-3 supplementation in 41 children and adolescents (aged 7 to 18 years) with ASD.[23] Omega-3 fatty-acids supplementation (2 g/day) was associated with improvements on the parent-reported Social Responsiveness Scale (SRS) and on two components of the Child Behavior Checklist (CBCL): social problems and attention problems.[24,25] Supplementation appeared to be well-tolerated in this study.

Though most studies have failed to show statistical significance in either improvement of core symptoms of autism or symptoms of hyperactivity, omega-3 fatty acids were well-tolerated in the studies mentioned above. Larger clinical trials are needed to examine the potential benefit of this treatment for hyperactivity and core symptoms of ASD in children and adolescents.

Methyl B12, Folic Acid, and Folinic Acid

An area of interest in the pathophysiology of ASD is the possible involvement of oxidative stress and DNA methylation differences.[26] Several supplements have been examined as potential treatments for ASD, based on the roles they play in cellular methylation reactions. A 12-week, double-blind, placebo-controlled study examined the efficacy of methyl B12 in 30 children (aged 3–8 years) with autism.[27] There was no significant difference between Methyl B12 and placebo on behavioral assessments or on glutathione status. The dose of methyl B12 was 64.5 mcg/kg every 3 days (subcutaneous injection), and side effects included hyperactivity and increased mouthing of objects. A trial examining the efficacy of Methyl B12 in 57 children (aged 3–7 years) with autism showed significant improvement in clinician-rated measures of overall improvement[28] (change in Clinical Global Impressions – Improvement score)[29] when compared to placebo. In this 8-week, randomized, double-blind study, there was

no statistical significant difference when considering responders (much or very much improved on the CGI-I scale) or on the parent-rated Aberrant Behavior Checklist (ABC).[17] The dose of methyl B12 was 75 mcg/kg every 3 days (subcutaneous injection). There were no difference between the two groups in adverse events, and no serious side effects were observed. In both of the studies mentioned above, authors theorize that there may be a subset of patients who respond to Methyl B12 treatment.

The efficacy of folinic acid (5-formyltetrahydrofolate) in 48 children and adolescents with autism was studied in a 12-week, double-blind, placebo controlled trial.[30] The primary outcome measure was verbal communication, as measured by the Clinical Evaluation of Language Fundamentals (CELF)[31] and the Preschool Language Scales (PLS-5).[32] Folinic acid was dosed at 2 mg/kg/day. Verbal communication was improved in the folinic acid group when compared to the placebo group, and folate receptor-α autoantibody (FRAA) status was predictive of response to treatment (FRAA-positive individuals had significantly higher rates of response to treatment with folinic acid than the placebo group, with large effect sizes observed). Glutathione redox status was not associated with a significant difference between the active treatment and placebo groups. There was no significant difference between the two groups in adverse effects.

A 3-month, open-label trial examined the efficacy of combination treatment with methyl B12 and folinic acid on adaptive behavior in 37 children (mean age 5.1 years).[33] Primary outcome measures were change in the Vineland Adaptive Behavior Scale (VABS)[34] scores and improvement in glutathione redox status from baseline to endpoint. Doses used included 75 μg/kg of methyl B12 subcutaneously twice a week and 800 μg/day of folinic acid (orally). The study showed improvements in both outcome measures over the 3-month study period, with an average effect size on the VABS subscales of 0.59. Adverse effects included hyperactivity, decreased sleep and discomfort with injections, which prompted some participants to leave the study (5% of participants). The authors found a greater improvement in glutathione redox status was associated with a greater improvement in many of the behavioral measures.

A 3-month, open-label trial examined the efficacy of folic acid in combination with structured teaching (when compared to structured teaching alone) in 66 children (mean age 57 months) with ASD on both core and associated behavioral symptoms of ASD.[35] Folic acid was dosed at 800 μg/day. No significant difference was found between the two groups on either the Aberrant Behavior Checklist (ABC) or the Childhood Autism Rating Scale (CARS).[36] Significant improvements were observed in the

folic acid group on some subscales of the Autism Treatment Evaluation Checklist (ATEC)[37] and Psychoeducational Profile-third edition (PEP-3)[38,39] in the areas of sociability, cognitive verbal/preverbal, receptive language, affective expression and communication.

While methyl B12 is generally well-tolerated, the need for frequent injections may be a concern for some parents and patients, and larger, randomized-controlled trials studying this treatment in children and adolescents with ASD are needed. Folinic acid and folic acid also need more rigorous trials examining their efficacy in this population, but they seem to be safe treatments to consider in patients with ASD. There is some evidence to suggest there may be a subset of patients in which these supplements may be more effective, however, more evidence is needed.

Oxytocin

Intranasal oxytocin has been studied as a potential intervention in a small number of studies including children or adolescents, with mixed results. A 14-week randomized-crossover trial examined the efficacy of oxytocin in 31 children, aged 3 to 8 years, with autism.[40] The dose of intranasal oxytocin was 24 International Units (IU) daily. Several outcome measures were used, with the two primary outcome measures being the parent-rated Social Responsiveness Scale (SRS)[24] and Repetitive Behavior Scale-Revised (RBS-R).[41] There was significant improvement in the active treatment group on the SRS, but no difference between the groups on the RBS-R. There was no significant difference between the two groups on any of the other outcome measures, and the active treatment group reported side effects of thirst and increased urination.

A 3-month, randomized controlled trial examined the efficacy of oxytocin on core symptoms of ASD in 50 adolescent males (aged 12 to 18 years) with autism.[42] Oxytocin was dosed at 18 or 24 IU, depending on age (younger participants received the lower dose, older participants received the higher dose). Primary outcome measures included the parent-rated Social Responsiveness Scale (SRS) and the clinician-rated CGI-I scale. No significant difference was seen on the outcome measures between the two groups. Intranasal oxytocin was well-tolerated, with reported adverse effects not differing significantly between the two groups. A 3-month, double-blind, randomized controlled trial examined the efficacy of intranasal oxytocin in 38 males, aged 7 to 16 years, with autism.[43] Doses were either 12 or 24 IU, depending on weight. No significant difference was found between the two groups on social deficits or repetitive behaviors, measured by the parent-rated Social Responsiveness Scale (SRS)[24] and Social Skills Rating Scale (SSRS).[44]

The available research does not support the use of oxytocin for symptoms of ASD in children, and more research is needed examining its efficacy in this patient population.

Tetrahydrobiopterin

Tetrahydrobiopterin is an important cofactor in the biosynthesis of catecholamines and serotonin that has been studied as a potential treatment for children with ASD. In a 12-month randomized, double-blind, placebo controlled crossover trial, 12 children (aged 4–7 years) with autism and low cerebral spinal fluid (CSF) levels of tetrahydrobiopterin were treated with either synthetic tetrahydrobiopterin or placebo for 6 months, followed by a change to the other treatment with no washout period in between.[45] The dose of tetrahydrobiopterin was 3 mg/kg twice daily. The primary outcome measure in this study was the change in total score on the Childhood Autism Rating Scale (CARS)[36] from baseline to endpoint, and there was no significant difference between the two groups on this measure. Post hoc analysis showed significant improvement in the active treatment group on the social interaction subscale of the CARS.

A 16-week open label study examined the efficacy of sapropterin (synthetic tetrahydrobiopterin) in 10 children, aged 2–6 years, with ASD and low spinal tetrahydrobiopterin levels.[46] The dose of sapropterin was 20 mg/kg/day. Significant improvement was seen in the primary outcome measure, the Preschool Language Scale (PLS) and measurements of several biomarkers suggested observed improvements may be related to nitric oxide metabolism.

L-Carnosine

L-Carnosine is a dipeptide known for its antioxidant properties and proposed enhancement of γ-aminobutyric acid (GABA) function in the brain, with possible anti-convulsive effects. An 8-week, double-blind, placebo-controlled trial examined the efficacy of L-carnosine supplementation in children aged 3 to 12 years with ASD.[47] The dose used in this study was 800 mg/day. There was no primary outcome measure identified, but changes from baseline to endpoint in several scales were followed, including the CARS,[36] the CGI scale,[29] the Expressive One-Word Picture Vocabulary Test (EOWPVT),[48] the Receptive One-Word Picture Vocabulary Test (ROWPVT),[49] and the Gilliam Autism Rating Scale (GARS).[50] There was no significant difference in the placebo group on any of the outcome measures. In the active treatment group, results failed to reach significance on the CARS, CGI scale, or

the EOWPVT. Significant improvement was seen on the ROWPVT and the GARS scores in the active treatment group from baseline to endpoint. The only adverse effect reported was increased hyperactivity in the active treatment group, which was alleviated by lowering the dose of l-carnosine. Though l-carnosine appears to be a safe treatment to consider in children with ASD, more studies are needed showing efficacy in this patient population.

N-Acetylcysteine

N-acetylcysteine (NAC) is an antioxidant with involvement in extracellular glutamate modulation. Glutamate is a prevalent excitatory neurotransmitter, and increased excitatory neurotransmission has been proposed as an underlying mechanism for at least some forms of ASD.[51] A randomized controlled pilot study examined the efficacy of NAC on irritability in 33 children, aged 3 to 10 years old, with autism.[52] In this 12-week study, children received either placebo or NAC 900 mg daily for 4 weeks, then twice daily for 4 weeks, then three times daily for 4 weeks. 14 children were on concomitant psychotropic medication during the study. The NAC was found to be superior to placebo on the primary outcome measure, the ABC-Irritability subscale.[17] It was well-tolerated, with no significant difference between groups on reported side effects.

NAC was studied in a 12-week, randomized controlled trial for core symptoms of ASD in 31 children, aged 4 to 12 years.[53] The dose of NAC in this trial was 60 mg/kg/day and concomitant medications were permitted at stable doses. The primary outcome measure in this study was the CGI-I score,[29] and no difference was found between the two treatment groups on this measure. Treatment with NAC also failed to show significant improvement on the secondary outcome measures, which included measurements of core symptoms and associated symptoms, including hyperactivity and irritability. NAC was well tolerated, with no significant difference between the two groups in reported adverse effects.

NAC has been studied in combination treatment with risperidone for irritability in children with autism. A randomized controlled trial examined this in 41 children and adolescents, aged 3 to 16 years old, with ASD.[54] The dose of NAC was 1200 mg/day and the dose of risperidone started at 0.5 mg/day and was titrated up to 3 mg/day, with flexible dosing based on symptoms and adverse effects. Study participants received either risperidone plus placebo or risperidone plus NAC for the 8 weeks of this study. The NAC plus risperidone group showed significant improvement on ABC scores[17] (primary outcome measure) when compared to the placebo plus risperidone group. There was no

difference between the two groups in core symptoms or on hyperactivity and noncompliance. The most common adverse effects in the NAC group included constipation, increased appetite, fatigue, nervousness, and daytime drowsiness.

A 10-week, randomized controlled trial examined the efficacy of combination NAC and risperidone in 40 youths, aged 4 to 20 years old, with ASD.[55] The dose of NAC used was between 600 mg/day to 900 mg/day, and risperidone was dosed up to 2 mg/day. NAC plus risperidone was superior to placebo plus risperidone on the primary outcome measure, the ABC–irritability[17] subscale score from baseline to endpoint. The NAC group was also superior on measures of hyperactivity and noncompliance. There was no difference between the two groups on core symptoms of autism. Side effects did not significantly differ between the two groups.

NAC seems to be well-tolerated, and it may have some benefit in treating the associated symptom of irritability in children with ASD, whether used as monotherapy or in combination with risperidone. There is no evidence to support its use for treating the core symptoms of autism.

Dimethylglycine

Dimethylglycine (DMG) is the N,N-dimethylated derivative of the amino acid glycine, and it has been studied as a dietary supplement in children with autism. A 4-week, double-blind, randomized controlled trial examined the efficacy of DMG in 37 children, aged 3 to 11 years old, with autism or pervasive developmental disorder.[56] The dose of DMG ranged from 125 mg/day to 625 mg/day, based on weight. Primary outcome measures included the Aberrant Behavior Checklist[17] and Vineland Maladaptive Behavior Domain, a section of the Vineland Adaptive Behavior Scale.[34] Significant improvement on outcome measures were seen in both the active treatment and placebo groups, with no significant difference between the two groups. Adverse effects did not differ significantly between the two groups. A small, 3.5 month, randomized, placebo-controlled, crossover study examined the efficacy of DMG in 8 males with autism (aged 4 to 30 years old).[57] There was no significant difference between the two groups on any of the outcome measures. Adverse effects were not reported in the study. There is currently no evidence to support the use of DMG in children with autism.

Vitamin Supplementation

Vitamin supplementation has been studied as a possible treatment option in children with ASD. The efficacy of multivitamin

supplementation in 20 children with ASD, aged 3 to 8 years, was examined in a 3 month, randomized, double-blind, placebo-controlled pilot study.[58] The primary outcome measure was a parent questionnaire developed by the authors of the study, measuring improvement in various symptoms, including core and associated symptoms of autism. This assessment tool had not been previously used or validated prior to its use in this study. The multivitamin group showed significant improvement in GI symptoms and sleep, according to the parent questionnaire, but had no effect on core symptoms or other symptoms measured. The multivitamin was well tolerated, overall, with the exception of nausea and vomiting in two children who took it on an empty stomach.

A 3-month, randomized, placebo-controlled trial examined the efficacy of multivitamin supplementation in 141 children, teens, and adults with ASD.[59] Concomitant psychotropic medications were allowed, as were other supplements (with the exception of multivitamins), and dietary restrictions (for example, gluten-free or dairy-free diets). Outcome measures used in the study included the PDDBI, the ATEC, the Severity of Autism Scale (SAS),[60] and the Parent Global Impressions-Revised scale (PGI-R) (the latter two researcher-created, non-validated assessment tools).[58] The study showed no significant difference between the two treatment groups in the PDDBI, the ATEC or the SAS. On the PGI-R, there was significant improvement in the multivitamin group on the overall score, as well as the subscales of receptive language, hyperactivity, and tantrumming. Adverse effects were generally mild, and included behavior problems and diarrhea/nausea in a small percentage of the participants. Significance or absence of significance in these symptoms between the two groups was not reported.

Vitamin D has no randomized, placebo-controlled trials in children with ASD. A 6-month, randomized, case-control study examined the efficacy of cholecalciferol (D3) supplementation in 21 children, aged 2 to 12 years with ASD.[61] Cholecalciferol was dosed at 2000 IU/day. There was no significant difference between the D3 group and the group receiving no supplementation on outcome measures, which included the CARS, VABS, and ATEC.[37] A 3-month, open label study found 81% improvement on CARS and ABC scores in children, aged 3–9 years with ASD.[62] The study included 106 children, but was limited by a 22% drop-out rate. Side effects reported in this study included mild skin rashes, itching, and diarrhea. A 3-month, open label trial found significant improvement on outcome measures (CARS and ABC) in 37 children with ASD.[63] The improvements measured were more pronounced in younger children (under 3 years old) than older children.

The efficacy of ascorbic acid (Vitamin C) was studied in a 30-week randomized, placebo-controlled trial in 18 children and adolescents,

aged 6 to 19 years, with autism.[64] Half of the youth were on neuroleptics during the study. The dose of ascorbic acid was 8 g/70 kg/day. The trial was a crossover study and showed significant improvements in the Ritvo-Freeman Real Life Rating Scale (R-F),[65] on the sensory-motor subscale. No difference was found on the other subscales (social, affective, sensory, or language). Side effects were not reported in the study.

A 2005 Cochrane systematic review examined the evidence of vitamin B6-magnesium use in children with ASD.[66] The studies included were all very small, with study participants totaling 33 for all studies combined. The Cochrane review concluded that no recommendation could be made for vitamin B6-magnesium as a treatment for autism. An update in 2010 came to the same conclusion.[67] Currently, the available evidence does not support the use of vitamin B6-magnesium as a treatment for ASD symptoms.

A cross-sectional study examined the effect of multivitamins and micronutrient intake in 288 children, aged 2 to 11 years, with ASD, focusing on dietary reference intakes (DRI) and using information about both vitamin supplementation and intake from diet in these children.[68] The study found that few children with ASD need the micronutrients commonly given in the form of supplements, which can lead to excessive intake and potential side effects. Additionally, calcium and vitamin D intake may not be sufficient, even with supplementation. This should be considered when discussing vitamin supplementation with patients and their families.

Ginkgo Biloba

Ginkgo biloba is an herbal remedy with proposed anti-inflammatory effects which has long-been used in China for a variety of conditions. A 10-week, double-blind, placebo-controlled trial, examined the efficacy of ginkgo biloba as an adjunctive treatment to risperidone for children, aged 4–12 years, with autism.[69] The dose of risperidone ranged from 1–3 mg/day. The dose of ginkgo biloba was 80 mg/day in children weighing less than 30 kg and 120 mg/day in children weighing over 30 kg. There was no significant difference between the two groups on the outcome measure, the Aberrant Behavior Checklist-Community,[17] or on reported side effects. Though well-tolerated, ginkgo biloba does not have supporting evidence for its use in children with ASD.

Digestive Enzymes and Probiotics

Digestive enzymes and probiotics have been examined as potential treatments in ASD, due to the increased rate of gastrointestinal

symptoms found in these patients. Studies have shown a possible link between the severity of autism symptoms and gastrointestinal symptoms, and have also shown changes in gut flora with probiotic use.[70,71]

Studies examining the efficacy of treatment with probiotics on either core or associated behavioral symptoms of ASD are limited. A 12-week randomized controlled trial examined the efficacy of Lactobacillus plantarum for both modulation of gut microbiota and behavioral symptoms in 62 children with ASD.[72] Probiotics were found to improve gut flora (increased lactobacilli and enterococci group and decreased clostridium cluster XIVa) and behavioral symptoms (disruptive antisocial behavior, anxiety problems, and communication disturbances), though the specific tools used to measure behavioral outcomes were not specified in the paper. Authors described the use of questionnaires to assess behavioral outcomes without further detail. Other limitations of the study included a very high dropout rate and high inter-individual variability. The authors did not report any adverse effects. A cohort study of 22 children with autism showed Lactobacillus acidophilus to be helpful in improving gut flora.[73] The authors also reported improvements in concentration and following directions, however, the specific tool used to measure these symptoms was not reported. Adverse effects were not reported in the study. Probiotic supplements may be helpful for gastrointestinal symptoms in patients with ASD, but the current evidence does not support the use of probiotics for core symptoms of ASD or for associated behavioral symptoms.

Studies examining the efficacy of digestive enzymes on symptom severity in children with ASD have been mixed. A 3-month, randomized controlled trial examined the efficacy of Neo-Digestin in 101 children, aged 3 to 9 years, with ASD.[74] Neo-Digestin is a digestive enzyme syrup containing papain 1.6 g/100 mL of solution and pepsin 0.8 g/100 mL. The dose of Neo-Digestin was 15 mL/day. The active treatment group showed significant improvement on 2 of the 15 parameters of the Child Autism Rating Scale,[36] emotional response and general impression. Gastrointestinal symptoms were also improved in the group receiving the digestive enzyme. There was no significant difference in reported adverse effects between the active treatment and placebo group. The authors concluded that the digestive enzyme supplement in this study was mildly beneficial and well-tolerated.

A 6-month, double-blind, randomized, placebo-controlled crossover study examined the use of Peptizyde™ (combination of peptidase, protease 4.5 and papain) in 43 children, aged 3 to 8 years, with ASD.[75] The primary outcome measure was the Global Behavior Rating Scale, which measures general behavior, sleep, gastrointestinal symptoms, and enuresis

in children with ASD.[76] There was no significant difference between the two groups on core or associated behavioral symptoms of autism, but there was a small, but significant improvement seen in food variety scores associated with enzyme supplementation. Digestive enzymes appear to be safe interventions, though efficacy for symptoms of autism is not clear. Digestive enzymes may be a treatment to consider in children with ASD who have significant gastrointestinal symptoms, but evidence does not support using this treatment for core symptoms of ASD.

Secretin is a polypeptide which helps aide pancreatic digestive enzymes, and has been studied extensively in children with ASD. A Cochrane Systematic Review examined 16 randomized, placebo-controlled trials examining the efficacy of secretin in over 900 children diagnosed with ASD.[77] Secretin, given as a single dose or multiple doses, was not shown to be effective for treating core symptoms of autism in children. The evidence does not support using or recommending secretin as a treatment for ASD.

Dietary Interventions

Dietary restrictions are a popular intervention chosen by parents of children with ASD. The gluten-free/casein-free (GFCF) diet is, perhaps, the most popular diet tried by families and has the most research studying the effects in children with ASD. There have been several randomized controlled trials, three which were double-blind studies, examining the efficacy of the CFCF diet in children with autism.

In a small, 30-week double-blind, randomized, placebo-controlled trial, 14 children, aged 3–5 years, with autism, were placed on a GFCF diet for 4 to 6 weeks before being randomized into four groups.[78] Each group then received weekly snacks, or "challenges", which contained either gluten, casein, gluten and casein, or placebo for 12 weeks, followed by a 12-week follow up period, where parents could choose to continue the GFCF diet or resume the child's regular diet. Gastrointestinal symptoms and behavioral symptoms were monitored throughout. The groups did not differ significantly on any of the outcome measures, including the Ritvo-Freeman Real Life Rating Scales, which measure ASD-associated behaviors.[65] No serious adverse events were observed in the study, and all of the families chose to continue the GFCF diet for the 12-week follow up period.

A double-blind, randomized controlled trial examined the effects of a gluten and casein challenge in 74 children (aged 2 to 10 years) with ASD and severe maladaptive behaviors, who were already on a GFCF diet.[79] The children in the study also had increased urinary intestinal fatty acids binding protein (I-FABP), a marker of enterocyte damage

found in a previous study to be associated with more severe behavioral disturbances in children with ASD (Pusponegoro HD et al, unpublished data). The study included two groups, one receiving a week of daily gluten/casein snacks and the other receiving a week of daily placebo snacks. There was no difference between the two groups on behavioral measures (approach withdrawal problem composite subtest of the PDDBI) or on gastrointestinal symptoms at endpoint.

A 12-week double-blind, placebo-controlled trial examined the efficacy of a GFCF diet on core and associated behavioral symptoms of ASD in 15 youth (aged 2 to 15 years), as measured by the CARS.[80] The study used a crossover design, with the two groups receiving either a GFCF diet or a placebo diet for 6 weeks, then switching to the alternate diet for the remaining 6 weeks with no washout period. The CARS was administered at baseline, week 6 and week 12. There were no significant differences between the two groups on the CARS, though parents reported anecdotal reports of improvement, and 9 of the 15 chose to continue a GFCF diet at study's end.

Several single-blinded studies have examined the efficacy of a GFCF diet in children with autism with mixed results.[81–83] Parents in these studies knew the diet their child was receiving, but behavioral assessments were done by examiners blinded to the group assignments. An important finding in all the GFCF diet studies was the high level of parental belief in the diet's efficacy for ASD symptoms, even in studies where the evidence contradicted this. The GFCF diet was relatively well-tolerated in all the studies mentioned above, but some studies showed more difficulty with adherence to the GFCF diet. The current evidence does not support universal use of the GFCF diet in children with ASD.

The ketogenic diet is an intervention used in the management of epilepsy, and it has been studied as a possible treatment for ASD, though there are no randomized, controlled trials examining its efficacy. Some smaller open-label studies have examined its efficacy in children with ASD.[84,85] Adherence to the diet was a problem in both studies, and significant improvements in ASD symptoms were only seen in a small percentage of children involved in these studies. More research is needed before recommending this diet for youth with ASD.

Camel Milk

Camel milk has been promoted by some as a treatment for a variety of conditions, including autism. A 2-week randomized controlled trial examined the efficacy of camel milk in 45 children, aged 2 to 12 years, with autism. The study showed significant improvements in

the Childhood Autism Rating Scale (CARS) scores in the raw camel milk group, compared to non-significant changes in the boiled camel milk and placebo (cow milk) groups.[86] Irritability and stomach discomfort were mentioned as adverse effects, though there was no mention of whether there was a significant difference observed between treatment groups in reported adverse effects. A 2-week randomized controlled trial including 60 children (aged 2 to 12 years) with autism showed significant improvement in CARS scores in the camel milk groups (both raw and boiled) versus placebo.[87] A 2-week study examined the efficacy of camel milk in 65 children (aged 2–12) with autism, and showed significant improvement in CARS scores and Social Responsiveness Scale (SRS) scores in the camel milk group, but no significant difference in the Autism Treatment Evaluation Checklist (ATEC) scores between the camel milk and placebo groups.[88] In each of the studies mentioned above, children were continued on any prior treatments or supplements. Though the studies examining the efficacy of camel milk report on the similarity of appearance of the milk between the three groups, there was no report on the flavor of the milk and if it was indistinguishable between the groups, which affects the efficacy of the blinding. The cost of camel milk may be prohibitive for some families. Camel milk may be considered as a complementary treatment, but more research examining its safety and efficacy in children with ASD is needed, including some studies examining potential long-term benefits and risks. Additionally, the current studies were done by the same group, and findings have yet to be replicated by other researchers.

Acupuncture

Acupuncture has been studied as a potential complementary and alternative treatment in children with autism. The studies vary in methodology, and only two studies have included sham acupuncture in the control groups to produce a true blinded condition for the study participants. A 4-week, randomized controlled trial examined the efficacy of electro-acupuncture in 55 youth, aged 3 to 18 years, with ASD.[89] Both groups received conventional interventions or educational programs throughout the study. They received 12 sessions of either active treatment or sham acupuncture (using points that are a few millimeters off of the recognized therapeutic acupoints). Primary outcome measures included the Functional Independence Measure for Children (WeeFIM®),[90] the Pediatric Evaluation of Disability Inventory (PEDI),[91] the Leiter International Performance Scale-Revised (Leiter-R),[92] and the Clinical Global

Impression-Improvement (CGI-I) scale.[29] Improvement was seen in both groups, with a relatively high placebo response rate. Significant improvements were seen in language comprehension (WeeFIM®), self-care caregiver assistant (PEDI), and the CGI-I in the active treatment group when compared to the sham acupuncture group. Eight percent of study participants had poor compliance with acupuncture and mild side effects included bleeding, irritability and tearfulness during the procedure, though more specific information regarding side effects was not reported.

A 9-week, randomized controlled trial examined the efficacy of tongue acupuncture in 50 children, aged 3 to 11 years, with ASD.[93] All children continued in their conventional autism program while receiving 40 sessions of either active treatment or sham acupuncture. Primary outcome measures included the Griffiths Mental Developmental Scale (GMDS),[94] the Ritvo-Freeman Real Life Scale (R-F),[65] the Reynell Language Developmental Scale (RLDS),[95] the Symbolic Play Test,[96] and the WeeFIM®.[90] Both groups showed improvement on all the scales (high placebo response rate), with the only significant difference in the active treatment group seen on the self-care and cognition domains of the WeeFIM®. It was reported that most children adapted to the acupuncture easily, but this was not quantified. The study reported no adverse effects, but says children did experience some pain and crying during the procedure. No other specifics regarding adverse effects were mentioned.

Hyperbaric Oxygen Therapy

Several randomized controlled trials have examined the efficacy of hyperbaric oxygen therapy in children with ASD. The studies differed in the choice of pressure and oxygen levels, with one using true hyperbaric pressure (1.5 atmospheric pressure/atm) and 100% oxygen supplementation in the active treatment group.[97] In this study, 60 children, aged 3 to 9 years, with autism received 20 1-hour sessions of either hyperbaric oxygen therapy or sham therapy (1.15 atm and 21% oxygen). Primary outcome measures included the change from baseline to endpoint clinician and parent-rated Autism Treatment Evaluation Checklist (ATEC)[37] scores and CGI scores.[29] Both the active treatment and the control group showed significant improvements on the ATEC scores, but there was no significant difference between the two groups on either total ATEC or subscale scores. CGI scores were inconsistent between parents and clinicians. Adverse effects included minor-grade ear barotrauma events, which occurred more frequently in the active treatment group (a significant finding).

A double-blind, randomized controlled trial examined the efficacy of hyperbaric oxygen therapy in 62 children, aged 2 to 7 years, with autism, using lower pressures and lower oxygen concentrations than the previous study (1.3 atm and 24% oxygen).[98] The control group received sham therapy with 1.03 atm and 21% oxygen. Both groups received 40 sessions. Significant improvements were seen on CGI scores[29] in the active treatment group versus control group and on the sensory/cognitive awareness subscale of the ATEC.[37] Change in total ATEC scores and Aberrant Behavior Checklist (ABC)[17] scores did not differ significantly between the two groups. There were no significant adverse effects reported. A randomized controlled trial examined the efficacy of 80 sessions of hyperbaric oxygen therapy at 1.3 atm and 24% oxygen in 34 youth (aged 2 to 14 years) with autism.[99] The control group received sham treatments with free airflow (about 21% oxygen) at ambient air pressure. There were no significant differences between the two groups on primary outcome measures (change in Social Responsiveness Scale[24] and Autism Diagnostic Observation Schedule scores from baseline to endpoint).[100] There were no adverse effects related to barotrauma reported.

At this time, the evidence does not support the use of hyperbaric oxygen therapy as a treatment for autism, and more research is needed examining its efficacy and safety in this population.

Intravenous Immunoglobulin

Intravenous immunoglobulin (IVIG) therapy has been suggested as a potential treatment for ASD, however there are no randomized-controlled trials examining this treatment in children and adolescents with autism. Three case-series have examined the efficacy of IVIG in children with autism. A 6-month study in 10 children, aged 3 to 12 years, with autism and abnormal immune parameters showed remarkable improvement in symptoms of autism in 50% of the children with monthly treatments of IVIG.[101] A 24-week case series examined the efficacy of IVIG in 10 children with autism and abnormal immune parameters. Only one child showed notable improvement in symptoms, and symptoms returned 2 months after the last infusion.[102] A 6-month case series including 7 children, aged 3 to 6 years, with autism and untested immune parameters failed to show significant improvement in any of the participants with monthly IVIG infusions.[103] Serious adverse events have been reported after IVIG infusions, including renal failure, vascular thromboses, and aseptic meningitis.[104] It is recommended that new clinical uses of IVIG be subject to well-controlled trials prior to being widely used in medical practice due to safety concerns and the

relatively expensive cost of this treatment. At this time, the available evidence does not support the use of IVIG as a treatment for ASD.

Chelation

Chelation therapy (CT) has been proposed as a treatment for ASD based on a theory that autism is caused by heavy metal toxicity. This theory is not supported by the evidence, however, chelation continues to be a treatment that some parents seek for their children, with estimates of 7% of individuals with ASD receiving CT.[105] CT has potential serious adverse effects associated with its use, including hypertension, hypotension, cardiac arrhythmias, and hypocalcemia, the latter of which can be fatal. Hypocalcemia from CT has led to at least one death in a 5-year old child with autism.[106] There are no placebo-controlled, randomized clinical trials examining the efficacy or safety of CT in children with autism. One study compared multiple rounds of CT to one round of CT in 49 children, aged 3–8 years, with autism, in a randomized, double-blind trial.[107,108] Both groups showed improvement in symptoms of autism, with no significant difference seen between the two groups on the outcome measures, change in scores from baseline to endpoint on the ATEC, ADOS, PDD-BI, SAS or PGI (the latter two scales being researcher-developed, non-standardized scales). About 11% of children in the study experienced worsening of their scores.

Both a systematic review and a Cochrane review of CT concluded that this treatment is not recommended for individuals with ASD, and that risks associated with CT outweigh any potential benefits.[109,110] Additionally, the Cochrane review recommended no further trials examining CT in children with autism be conducted, until there is evidence supporting a causal link between heavy metals and autism.

Conclusion

The use of CAM treatments in children and adolescents with ASD is high, with more than half of parents trying at least one of these treatments at some time after their child receives the diagnosis. While the evidence is limited regarding the safety and efficacy of these treatments, it is important that physicians are up to date on the studies that have examined these treatments so far. Parents sometimes withhold information regarding their use of CAM in their children with their physicians because either they believe the physician is not knowledgeable about these treatments, the physician doesn't ask about these treatments, or because they are concerned their decision to use CAM

treatments in their children will cause conflict with their physician. The American Academy of Pediatrics (AAP) Committee on Children with Disabilities has put forth helpful guidelines for physicians discussing the use of CAM treatments with their patients and families. They include: seeking information and being prepared to share it with families, evaluating the evidence of specific treatments, identifying potential harmful effects/risks, providing information to families on a range of treatment options, educating families on how to evaluate studies (e.g., explaining the placebo effect, pointing out what makes a study weak or strong, methodologically), avoiding outright dismissal of CAM and defensiveness, assisting in monitoring response to and safety of chosen CAM treatments, and actively listening to the patient and family.[111] It is imperative that physicians remain open to the possibility of therapeutic benefits from CAM therapies, while simultaneously encouraging more rigorous studies to examine the efficacy and safety of these treatments in children and adolescents with autism. ✤

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