

Novel and emerging treatments for autism spectrum disorders: A systematic review

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BACKGROUND: Currently, only one medication (risperidone) is FDA-approved for the treatment of autism spectrum disorders (ASD). Perhaps for this reason, the use of novel, unconventional, and off-label treatments for ASD is common, with up to 74% of children with ASD using these treatments; however, treating physicians are often unaware of this usage.

METHODS: A systematic literature search of electronic scientific databases was performed to identify studies of novel and emerging treatments for ASD, including nutritional supplements, diets, medications, and nonbiological treatments. A grade of recommendation ("Grade") was then assigned to each treatment using a validated evidence-based guideline as outlined in this review:

- A:** Supported by at least 2 prospective randomized controlled trials (RCTs) *or* 1 systematic review
- B:** Supported by at least 1 prospective RCT *or* 2 nonrandomized controlled trials
- C:** Supported by at least 1 nonrandomized controlled trial *or* 2 case series
- D:** Troublingly inconsistent or inconclusive studies *or* studies reporting no improvements

Potential adverse effects for each treatment were also reviewed.

RESULTS: Grade A treatments for ASD include melatonin, acetylcholinesterase inhibitors, naltrexone, and music therapy. Grade B treatments include carnitine, tetrahydrobiopterin, vitamin C, alpha-2 adrenergic agonists, hyperbaric oxygen treatment, immunomodulation and anti-inflammatory treatments, oxytocin, and vision therapy. Grade C treatments for ASD include carnosine, multivitamin/mineral complex, piracetam, polyunsaturated fatty acids, vitamin B₆/magnesium, elimination diets, chelation, cyproheptadine, famotidine, glutamate antagonists, acupuncture, auditory integration training, massage, and neurofeedback.

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CONCLUSIONS: The reviewed treatments for ASD are commonly used, and some are supported by prospective RCTs. Promising treatments include melatonin, antioxidants, acetylcholinesterase inhibitors, naltrexone, and music therapy. All of the reviewed treatments are currently considered off-label for ASD (ie, not FDA-approved) and some have adverse effects. Further studies exploring these treatments are needed. Physicians treating children with an ASD should make it standard practice to inquire about each child's possible use of these types of treatments.

KEYWORDS: autism, supplements, diets, novel treatments

INTRODUCTION

Autistic disorder (autism), Asperger's syndrome, Rett syndrome, and pervasive developmental disorder not otherwise specified (PDD-NOS) comprise a heterogeneous spectrum of neurodevelopmental disorders (often termed autism spectrum disorders or ASD) that are behaviorally defined and characterized by impairments in communication and social interaction, along with restrictive and repetitive behaviors.¹ The number of children diagnosed with an ASD has substantially increased over the last decade,²⁻⁴ and ASD currently affect an estimated 1 of 150 individuals in the United States.⁵ ASD are generally considered "static" neurodevelopmental disorders,⁶ without any known cure and with very few proven and effective treatments. The use of medication in children with ASD is common, and several studies report that more than 45% of children with an ASD are treated with psychotropic medication.⁷⁻¹⁰ Currently, only risperidone is FDA-approved for the treatment of autism (for the symptomatic treatment of irritability),¹¹ but this medication has the potential for serious adverse effects.^{12,13} Because the use of novel, unconventional, and/or off-label treatments for children with ASD is increasing and is now common,¹⁴ physicians treating children with an ASD are often asked to prescribe or give advice about these types of treatments.¹⁵

This purpose of this review article is to collate and critically evaluate published scientific data pertaining to novel and emerging treatments for ASD—disorders

with no clear or well-defined biological treatments. A systematic search of PubMed and Google Scholar from 1966 to April 2009 was conducted to identify pertinent studies in all languages using the search terms *autism* OR *autistic* OR *pervasive* OR *PDD* in all combinations with the treatments listed in this article. A list of potential treatments was generated from an inventory maintained by the Autism Research Institute (SEE TABLE 1), along with examination of review articles and the author's knowledge of the medical literature. The references cited in identified articles were also searched to locate additional studies. All pertinent studies that were identified (including case reports) are listed in this review. Due to the number of studies reviewed, an in-depth discussion of each is not possible. For some treatments, multiple supporting studies were identified; however, some treatments either had no studies or very few studies were identified. Each identified study was individually assessed to first determine the corresponding level of evidence ("evidence level"), ranging from 1a to 5, using a validated evidence-based guideline as described in TABLE 2.¹⁶ The use of such guidelines is essential, especially since some randomized double-blind, placebo-controlled (R-DBPC) studies in individuals with an ASD have reported a placebo response rate as high as 30% to 37%.^{17,18} The highest evidence level (level 1a or 1b) was assigned to a systematic review (SR) of randomized controlled trials (RCTs) with homogeneity (including Cochrane reviews) or a prospective high-quality RCT, whereas the lowest evidence level (level 4 or 5) was assigned to case reports or studies based on expert opinion without critical appraisal (SEE TABLE 2). After assessing all identified studies for each treatment, a grade of recommendation was then derived for each treatment, as outlined in TABLE 3,¹⁶ ranging from A (based on level 1 studies) to D (level 5 evidence, or troublingly inconsistent or inconclusive studies of any level or studies reporting no improvements). If no studies were identified for a treatment, a grade was assigned as category N (no studies). The assigned grades for each treatment are summarized in TABLES 4 TO 6. A summary of treatments and their effects on certain autistic behaviors is found in TABLE 7. All of the reviewed treatments in this article are currently considered off-label (ie, not FDA-approved) for ASD.

Many of the reviewed treatments fall into the category of complementary and alternative medicine (CAM). CAM has been defined as "a broad domain of

TABLE 1**The top 20 complementary and alternative medicine treatments for children with an ASD, excluding diets***

Ranking	Treatment	Better ^a (%)	No change ^b (%)	Worse ^c (%)	No. responses ^d	Grade
1	Chelation	74	23	3	803	C
2	MB12 injections	67	26	7	170	D
3	Melatonin	65	27	8	1105	A
4	B ₁₂ (oral)	61	32	7	98	D
5	HBOT	60	34	5	134	B
6	Digestive enzymes	58	39	3	1502	D
7	Fatty acids	56	41	2	1169	C
8	MB12 (nasal)	56	29	15	48	D
9	Cod liver oil	51	45	4	1681	C
10	Vitamin B ₆ (PLP)	51	37	12	529	C
11	Zinc	51	47	2	1989	N
12	B ₆ /magnesium	48	48	4	6634	C
13	Folic acid	43	53	4	1955	D
14	Vitamin B ₃	43	52	4	927	N
15	Vitamin C	43	55	2	2397	B
16	DMG	42	51	8	5807	D
17	TMG	42	43	15	803	D
18	Transfer factor	42	48	10	174	D
19	Vitamin A	41	57	2	1127	D
20	5-HTP	40	47	13	343	D

5-HTP: 5-hydroxytryptophan; DMG: dimethylglycine; HBOT: hyperbaric oxygen treatment; MB12: methylcobalamin; TMG: trimethylglycine.

*As ranked by approximately 26,000 parental reports (by percentage of children improved) and as compiled by the Autism Research Institute,²⁵ along with the grade of recommendation derived in this review.

^aPercentage of children that parents ranked as improved with treatment

^bPercentage of children that parents ranked as having no obvious changes with treatment

^cPercentage of children that parents ranked as worse with treatment

^dNumber of parents responding on questionnaire concerning treatment

Percentages may not add up to 100% due to rounding.

healing resources that encompasses all health systems, modalities, and practices and their accompanying theories and beliefs, other than those intrinsic to the politically dominant health system of a particular society or culture in a given historic period.¹⁹ Some CAM treatments are well supported by the medical literature and eventually become standard medical practices.¹⁵ The use of CAM is common even in typically developing children.²⁰ In one survey of 376 families with a special-needs child, the prevalence of CAM usage was high,

especially when the condition was thought to be “nonrepairable” (76% usage).²¹ The use of CAM in children with ASD is common in the United States, with some studies reporting that as many as 52% to 74% have received these treatments,^{22,23} compared with 24% to 28% of typically developing children.^{20,22} The use of CAM in children with ASD is also high in other areas of the world, such as Canada (52% usage) and Hong Kong (41% usage).²⁴ The Autism Research Institute tracks the effects of different treatment modalities in children with ASD, including nutritional supplements and medications, and has compiled and ranked data from more than 26,000 parental surveys; the top 20 CAM treatments (excluding diets) as ranked by parents (ranked by percentage of children improved) are listed in **TABLE 1**.²⁵ Most parents report that CAM treatments are either helpful or ineffective, but generally not harmful,²³ although one study reported that 9% of children with an ASD were using potentially harmful CAM treatments.²⁶ In many cases, the child’s treating physician is not aware of any CAM usage.¹⁵ Physicians who encourage CAM usage in children with ASD are most likely to recommend treatments such as multivitamins, essential fatty acids, melatonin, and probiotics.²⁷

In one survey, most parents with a developmentally disabled child ranked the child’s primary physician’s knowledge about CAM as “worse than neutral.”²⁸ A nationwide survey of 745 pediatricians reported that 87% had been asked by parents about CAM treatments, but less than 5% felt “very knowledgeable” about these treatments.²⁹ The American Academy of Pediatrics Committee on Children with Disabilities recommends that CAM interventions be discussed in a nonjudgmental manner and that the treating physician provide “balanced advice about therapeutic options” and information about potential

TABLE 2**Levels of evidence**

Level	Description
1a	SR or meta-analysis of RCTs with homogeneity or Cochrane review with favorable findings
1b	Prospective high-quality RCT
2a	SR of cohort (prospective, nonrandomized) studies with homogeneity
2b	Individual cohort (prospective, nonrandomized) study or low-quality RCT
3a	SR of case-control (retrospective) studies with homogeneity
3b	Individual case-control (retrospective) study
4	Case series or reports
5	Expert opinion without critical appraisal or based on physiology or bench research

RCT: randomized controlled trial; SR: systematic review.

Source: Adapted from reference 16.

TABLE 3**Grade of recommendation**

Grade	Description
A	At least one level 1a study or two level 1b studies
B	At least one level 1b, 2a, or 3a study, or two level 2b or 3b studies
C	At least one level 2b or 3b study, or two level 4 studies
D	Level 5 evidence, or troublingly inconsistent or inconclusive studies of any level, or studies reporting no improvements
N	No studies identified

Source: Adapted from reference 16.

risks.¹⁵ Physicians should attempt to work with families who choose to use CAM treatments, even if there is some disagreement in treatment philosophy.^{27,30} Furthermore, physicians should make it standard practice to inquire about CAM usage in children with an ASD and to maintain an open dialogue concerning these treatments and the evidence supporting CAM usage.^{14,27} Since many physicians may not be aware of the type of novel, unconventional, and/or off-label treatments that some children with ASD are receiving, this article reviews the most common treatments currently used.

Some of the treatments in this review are nutrition based. Interest in nutritional treatments for certain

psychiatric disorders has increased in recent years, and some nutritional supplements, such as folic acid, polyunsaturated fatty acids,³¹ tyrosine, tryptophan, and cholinelecithin,³² have been reported to improve some psychiatric disorders, such as major depression, bipolar disorder, schizophrenia, and anxiety disorders.³³ Several DBPC studies in typically developing children have reported significant improvements in cognition with the use of certain nutritional supplements and with increased intake of fruits and vegetables, even in children who are well nourished.³⁴⁻³⁸ Both macronutrients (eg, amino acids and lipids) and micronutrients (eg, vitamins and minerals) have been proposed as treatments for ASD, especially since certain nutritional deficiencies in children with ASD appear to be relatively common. For instance, one study of 138 children with ASD and 298 typically developing children reported that the ASD group had significantly more feeding problems and ate less fruit, vegetables, and protein, although family food preferences appeared to influence food selection.³⁹ In another study of 46 children with ASD, many had inadequate daily intakes of fiber, calcium, iron, and vitamin D.⁴⁰

Many of the treatments reviewed in this article also decrease inflammation and/or oxidative stress. Recent evidence has implicated oxidative stress in many psychiatric disorders,^{41,42} including ASD.⁴³⁻⁴⁷ Furthermore, immunologic problems and inflammation appear to be common in certain psychiatric disorders.⁴⁸ Several recent studies in individuals with an ASD have reported evidence of cerebral inflammation⁴⁹⁻⁵³ and gastrointestinal (GI) inflammation.⁵⁴⁻⁵⁷ GI problems such as gastrointestinal reflux (GER) or esophagitis, chronic constipation or encopresis, lactose intolerance, and dietary limitations appear to be relatively common in children with ASD. For example, in one study of 36 children with autism referred to a gastroenterologist for GI problems, reflux esophagitis was present in 69%, chronic gastritis in 42%, chronic duodenitis in 67%, and low intestinal carbohydrate digestive enzyme activity in 58%.⁵⁸ Another study of 50 children with ASD and 50 typically developing children reported that 70% of the ASD group had a history of GI problems, compared with 28% of the control group ($P < .001$).⁵⁹ Common GI problems found in one study of 112 children with autism referred to a gastroenterologist included diarrhea (28%), gaseousness (60%), bloating (38%), abdominal pain (38%), and fecal impaction (19%); 80% of the children with autism had at least one GI-related problem, and these problems were sig-

nificantly more common in this group, compared with 44 typically developing siblings.⁶⁰ Several studies have also reported dysbiosis in children with ASD, including higher levels of *Clostridia* species⁶¹⁻⁶³ and yeast (*Candida albicans*)⁶⁴ in the GI tract. Some symptoms that are normally attributed to “autistic behavior” may actually be manifestations of these underlying medical problems. For instance, self-injurious behavior or aggression can be caused by GER-related pain in some children with an ASD, and treatment of this medical condition can alleviate this problem behavior.⁶⁵

Each treatment reviewed in this article is classified as either “biological” (eg, nutritional supplements, elimination diets, and medications) or “nonbiological” (eg, neurofeedback and massage).⁶⁶ The treatments are listed by classification (biological followed by nonbiological), then evidence level (A to D), followed by alphabetical order. This review does not examine Applied Behavioral Analysis (ABA), which is proven to be effective in children with ASD.^{23,30}

Biological treatments: Nutritional supplementation

Melatonin (Grade A). Abnormalities in the physiology of melatonin have been reported in some individuals with an ASD, including abnormal melatonin circadian patterns.^{67,68} In one study of 14 children with autism and 20 typically developing children, the autism group had significantly lower mean blood melatonin concentrations ($P < .001$).⁶⁸ In another study, the nighttime urinary excretion of 6-sulphatoxymelatonin (a main metabolite of melatonin) was significantly lower in 49 children with autism, compared with 88 typically developing children ($P = .0001$) and was correlated with impairments in verbal communication and play skills ($P < .05$ for both) in the autism group.⁶⁹ A more recent study reported that polymorphisms in the *ASMT* gene, which encodes for the last enzyme involved in melatonin synthesis, were more common in 250 children with ASD, compared with 255 typically developing children ($P = .0006$). These polymorphisms were associated with significantly decreased blood melatonin levels in the ASD group ($P < .00001$), and the investigators suggested that a low melatonin level might be a risk factor for developing an ASD.⁷⁰

The use of melatonin has been shown to improve sleep in some children with an ASD. For example, one retrospective study of 100 children with chronic sleep disorders and a neurologic or developmental disability

(including an unspecified number with autism) reported that fast-release melatonin (2.5 to 10 mg at bedtime) improved sleep in just over 80% of the children, without any adverse effects or tolerance observed.⁷¹ In one case report of a 14-year-old child with autism, 6 mg of melatonin given at 11 PM prolonged total night sleep and improved the sleep-wake rhythm.⁷² In an open-label study of 50 individuals with a sleep disorder and a developmental disorder, including 27 with autism, melatonin administered at bedtime led to improvements in sleep in 84%. Mild adverse effects, including morning drowsiness, nighttime awakening, and excitement before going to sleep, were noted in 34%.⁷³ In a 2-week open-label study of 15 children with Asperger’s syndrome, melatonin (3 mg at bedtime) was well tolerated and significantly improved sleep patterns and decreased sleep latency ($P = .002$).⁷⁴ In another open-label study of 25 children with autism and sleep problems, the use of controlled-release melatonin (3 mg at bedtime) improved sleep in all of the children without any adverse effects observed ($P < .001$).⁷⁵ When the melatonin was stopped, 16 of the children returned to their pretreatment sleep problems and improved again when melatonin was reintroduced. The improvements with melatonin were maintained at both 12- and 24-month follow-ups.⁷⁵ In a retrospective study of 107 children with ASD who received melatonin (0.75 to 6 mg at bedtime) for insomnia, 85% of the children had improvements in sleep. Only one child had worsening of sleep with melatonin and 3 other children had mild adverse effects, including morning sleepiness or increased enuresis. No increase in seizures was noted in the subset of children who also had epilepsy.⁷⁶ An R-DBPC crossover study of 51 children with a neurodevelopmental disorder (including 16 children with ASD) and sleep problems studied the use of melatonin (5 mg controlled-release) given at bedtime. Sleep improved in 47 of 51 children when treated with melatonin, including improvements in length of sleep ($P < .01$) and sleep latency ($P < .01$), compared with placebo.⁷⁷ Another 2-month R-DBPC crossover study of 11 children with ASD demonstrated that melatonin (5 mg at bedtime) significantly improved sleep latency by nearly 0.9 hours ($P < .05$), decreased nighttime awakenings ($P < .05$), and increased sleep duration by 1.1 hours ($P < .05$) when compared with placebo.⁷⁸ Finally, the use of melatonin (3 mg at bedtime) in another 4-week R-DBPC crossover study of 18 children with autism and/or fragile X syndrome reported that melatonin increased mean sleep

duration ($P = .02$), sleep latency ($P = .0001$), and sleep-onset time ($P = .02$), compared with placebo.⁷⁹

Carnitine (Grade B). In a retrospective study of 100 children with autism, free and total serum carnitine levels were significantly reduced ($P < .001$), suggesting mild mitochondrial dysfunction.⁸⁰ In a 6-month controlled study of 21 individuals with Rett syndrome, supplementation with L-carnitine (100 mg/kg/d) led to improvements in sleep efficiency ($P = .027$), energy level ($P < .005$), communication skills ($P = .004$), and expressive speech ($P = .011$), compared with 62 children with Rett syndrome who did not receive L-carnitine; adverse effects included diarrhea and fishy body odor.⁸¹ In a 4-month R-DBPC study of L-carnitine (100 mg/kg/d) in 35 individuals with Rett syndrome, improvements were found in overall well-being ($P < .02$) and in orofacial/respiratory motor behavior ($P < .02$), compared with placebo; adverse effects included loose stools and fishy body odor.⁸²

Tetrahydrobiopterin (Grade B). In a controlled study of 20 children with autism and 10 typically developing children, cerebrospinal fluid (CSF) concentrations of tetrahydrobiopterin (BH4) were significantly lower in the autism group ($P < .01$).⁸³ Clinical improvements in language and social interaction were found in 7 of 14 children with autism in a 24-week open-label study using BH4 at 1 mg/kg/d; the treatment was well tolerated.⁸⁴ In another open-label study of 136 individuals with autism, BH4 (1 to 3 mg/kg/d) led to moderate or marked improvements in 49%.⁸⁵ BH4 (3 mg/kg/d) was also reported to improve social interaction, eye contact, and vocabulary, and led to increased CSF BH4 levels after treatment for 3 months in an open-label study of 6 children with autism who initially had low CSF levels of BH4.⁸⁶ An R-DBPC crossover study of 12 children with autism and low CSF levels of BH4 reported a significant improvement in social interaction ($P = .04$) after 6 months of treatment with BH4 (3 mg/kg/d), compared with placebo; adverse effects included agitation and sleep problems, which were similar in frequency to placebo.⁸⁷ In another DBPC study of 82 Japanese individuals with autism, supplementation with BH4 at 1 mg/kg/d led to moderate-to-marked improvements in 54%, compared with 31% who received placebo ($P < .05$).⁸⁸

Vitamin C (Grade B). Recently, 2 case reports of scurvy in children with autism were reported.^{89,90} A 30-week R-DBPC crossover study of vitamin C (approximately 114 mg/kg/d) in 18 children with autism

reported significant improvements in stereotypical behaviors ($P < .05$), including rocking, pacing, flapping, and whirling, compared with placebo; no adverse effects were noted.⁹¹

Carnosine (Grade C). In an 8-week R-DBPC study of 31 children with ASD, the use of 800 mg of L-carnosine per day was well tolerated and led to significant improvements in autistic behavior, socialization, communication, and vocabulary ($P < .05$ for each), compared with no significant improvements on placebo.⁹²

Multivitamin/mineral complex (Grade C). The use of a multivitamin/mineral supplement may be beneficial in children with ASD to help ensure adequate nutritional intake. In a 3-month R-DBPC study of 20 children with ASD, the use of a multivitamin/mineral supplement (containing moderate levels of B vitamins, folic acid, calcium, zinc, selenium, and vitamins A, D, and E) improved sleep ($P = .03$) and GI symptoms ($P = .03$) on a Clinical Global Impression (CGI) scale compared with placebo (although the overall CGI score did not improve); no adverse effects were observed.⁹³

Piracetam (Grade C). Some investigators have speculated that piracetam (a nootropic) may be beneficial in ASD.⁹⁴ In a 10-week R-DBPC study of 40 children with autism, piracetam (800 mg daily) combined with risperidone was well tolerated and led to significant improvements in autistic behavior ($P < .0001$), compared with risperidone combined with placebo.⁹⁵

Polyunsaturated fatty acids (Grade C). Polyunsaturated fatty acid (PUFA) deficiency has been associated with poor reading, spelling, and auditory working memory,⁹⁶ and has been implicated in several neurodevelopmental disorders, including attention-deficit/hyperactivity disorder (ADHD), ASD, dyslexia, dyspraxia, and developmental coordination disorder.^{97,98} In one study of 100 boys with behavioral and learning problems, those with lower plasma omega-3 fatty acid concentrations had significantly more behavioral problems, including hyperactivity ($P = .002$), temper tantrums ($P = .002$), sleep problems ($P = .02$), and learning problems ($P = .005$), including problems with math ($P = .05$), compared with those study participants with higher fatty acid levels.⁹⁹

Omega-3 fatty acid deficiency appears to play a role in the development of ASD. Lower levels of plasma omega-3 fatty acids were found in one study of 15 children with autism compared with 18 mentally retarded children ($P = .032$).¹⁰⁰ Another study of 94 children with autism and

10 with Asperger's syndrome reported that red blood cell membrane omega-3 fatty acid levels were lower ($P < .05$) and omega-6 fatty acids higher ($P < .05$) compared with 71 typically developing children.¹⁰¹ However, a smaller study of 16 children with autism and 22 typically developing children reported that plasma docosahexaenoic acid (DHA) levels were significantly higher in the autism group ($P = .02$).¹⁰² Finally, in a study of 861 children with autism and 123 typically developing children, a significantly higher risk of developing autism was observed in children who did not receive DHA and arachidonic acid supplementation through breastfeeding (odds ratio [OR] = 2.5; 95% confidence interval [CI], 1.4 to 4.4) or in infant formula (OR = 4.4; 95% CI, 1.2 to 15.7).¹⁰³

Supplementation with PUFA may improve symptoms in ASD. In one case report, the use of eicosapentaenoic acid (EPA) and other omega-3 fatty acids (totaling 3 g/d) led to "complete elimination" of anxiety and agitation in an 11-year-old child with autism.¹⁰⁴ In a 3-month open-label study of 18 children with autism, supplementation with omega-3 (247 mg/d) and omega-6 (40 mg/d) fatty acids led to significant improvements in language skills ($P < .01$) and in several other domains; however, this study was not peer reviewed.¹⁰⁵ The addition of 860 mg of EPA and 300 mg of DHA in 2 children with Asperger's syndrome and 7 children with autism led to improvements (as rated by parents) in general health, sleep, concentration, eye contact, aggression, and hyperactivity in an uncontrolled study; however, several children also had an increase in behavioral problems.¹⁰¹ In an open-label study of 19 adults with severe autism, the use of 930 mg of EPA and DHA over a 6-week period led to no obvious improvements.¹⁰⁶ However, some improvements in the posttreatment period were noted, suggesting the possibility of a delayed treatment effect.¹⁰⁶ In a 3-month open-label study of 30 children with autism and 30 typically developing children, blood omega-3 fatty acid levels were significantly lower in the autism group ($P < .0001$). Supplementation with PUFA (DHA 240 mg/d, EPA 52 mg/d, gamma-linolenic acid 48 mg/d, and arachidonic acid 20 mg/d) led to behavioral improvements in 66% of the children with autism ($P < .0001$), including better eye contact, language, concentration, and motor skills.¹⁰⁷ In a 6-week R-DBPC study of 13 children with autism, supplementation with approximately 1.5 g/d of omega-3 fatty acids (EPA 840 mg and DHA 700 mg) was well tolerated, and improvements in hyperactivity and stereotypy were

TABLE 4

Grade of recommendation for nutritional supplements and diets in ASD

Treatment	Grade
Nutritional supplements	
Melatonin	A
Carnitine	B
Tetrahydrobiopterin	B
Vitamin C	B
Carnosine	C
Multivitamin/mineral complex	C
Piracetam	C
Polyunsaturated fatty acids	C
Vitamin B ₆ and magnesium	C
Folic acid and vitamin B ₁₂	D
Ginkgo biloba	D
Inositol	D
Iron	D
Probiotics and digestive enzymes	D
St John's wort	D
TMG and DMG	D
Tryptophan and 5-HTP	D
Vitamins A and D and calcium	D
Selenium	N
Zinc	N
Diets	
Elimination diets	C

5-HTP: 5-hydroxytryptophan; ASD: autism spectrum disorders; DMG: dimethylglycine; TMG: trimethylglycine.

observed (with a large effect size for each) compared with placebo; however, the improvements were not statistically significant.¹⁰⁸ A recent systematic review found insufficient evidence to determine if treatment with omega-3 fatty acids is effective for ASD.¹⁰⁹

Vitamin B₆ and magnesium (Grade C). Some studies in children with ASD have reported that plasma vitamin B₆ levels are sometimes high,¹¹⁰ whereas concentrations of the active form of vitamin B₆ (pyridoxal-5'-phosphate or PLP) are often low, suggesting a problem with the conversion of vitamin B₆ to PLP.⁹³ Furthermore, lower plasma levels of magnesium were reported in

one study of 29 children with ASD compared with 14 typically developing children ($P = .02$).¹¹¹ Bonish first reported that pyridoxine (vitamin B₆) administration led to improvements in speech and language in some children with ASD.¹¹² Rimland noted that combining vitamin B6 with magnesium (B₆/Mg) lessened some of the adverse effects seen with B₆ alone, including enuresis, irritability, and sensitivity to sound, and led to additional improvements.¹¹³ A total of 7 open-label studies reported significant improvements in speech, social interaction, and other autistic behaviors in children with ASD using B₆/Mg.^{112,114-119} Most of these studies used high doses of vitamin B₆ (30 mg/kg/d) and magnesium (10 to 15 mg/kg/d). Furthermore, 7 double-blind, crossover trials also reported significant improvements in speech, social interaction, and other autistic behaviors using B₆/Mg in children with ASD.¹²⁰⁻¹²⁶ In some of these studies, urinary homovanillic acid levels decreased with B₆/Mg treatment, suggesting that dopamine metabolism improved.^{115,116,123} In other studies, average evoked potentials improved, suggesting improved sensory processing ability.^{116,118,123}

In addition, 3 small R-DBPC studies evaluated B₆/Mg treatment in ASD. In one R-DBPC study, 15 children with autism were treated over a 35-week period with 2.9 mg/kg/d of B₆ and 1.4 mg/kg/d of magnesium gluconate, with no change in autistic behaviors observed, compared with placebo¹²⁷; however, these doses were much lower than those used in other studies. In another 10-week R-DBPC study of 12 children with autism, the use of B₆ (30 mg/kg/d) and magnesium (10 mg/kg/d) was well tolerated, but no benefit was found, compared with placebo.¹²⁸ Finally, in a 4-week R-DBPC study of 15 children with ASD, the use of B₆ (100-200 mg/d) led to significant improvements in verbal IQ compared with placebo ($P = .01$); no adverse effects were observed.¹²⁹ A recent Cochrane review, which excluded all studies except the 3 R-DBPC studies,¹²⁷⁻¹²⁹ reported that these studies had methodological problems and small sample sizes, and that the use of B₆/Mg for improving autistic behavior could not be supported.¹³⁰ Since that review was published, a 6-month study of 33 children with pervasive developmental disorder (PDD) and 36 typically developing children reported that the mean intraerythrocyte magnesium level was significantly lower in the children with PDD compared with controls ($P < .05$). Furthermore, the use of B₆ (0.6 mg/kg/d) and magnesium (6 mg/kg/d) led to significant improvements in autistic symptoms in 70% of the PDD group ($P < .0001$),

including social interaction, communication, and stereotypy. No adverse effects were observed, and when the B₆/Mg treatment was discontinued, the undesired behavior returned within a few weeks.¹³¹ Caution should be exercised when using high doses of magnesium, as fatal hypermagnesemia was reported in one nonautistic child who received megadoses of vitamins and minerals.¹³²

Folic acid and vitamin B₁₂ (Grade D). In a controlled study of 12 children with ASD, urinary methylmalonic acid was measured in 8 children and was found to be significantly higher when compared with 14 typically developing children ($P = .003$); this finding is consistent with a functional vitamin B₁₂ deficiency.¹³³ In a study of 43 individuals with autism, levels of serum and red blood cell folate and serum B₁₂ concentrations were normal compared with 77 control children.¹³⁴ In a 6-month R-DBPC crossover study of oral folic acid (1.5 mg/kg/d) in 4 children with both autism and fragile X syndrome, the treatment was well tolerated, and 3 children had mild to moderate improvements in autistic behavior when on folic acid compared with placebo; one other child had no obvious change.¹³⁵ Another study of 20 children with autism and 33 typically developing children reported that oral folinic acid (800 mcg/d) and trimethylglycine (TMG, 1000 mg/d) for 3 months, along with the addition of subcutaneous injections of methylcobalamin (MB12; 75 mcg/kg twice a week) for 1 month, increased total plasma glutathione levels in the autism group ($P = .016$); no adverse effects were noted. Clinical improvements were also noted in speech and cognition by the treating physician but were not formally quantified.⁴⁵ An open-label study of 13 children with autism demonstrated that MB12 (25 to 30 mcg/kg/d) for up to 25 months was well tolerated and led to improvements in IQ ($P < .05$) and autistic behaviors ($P < .001$).¹³⁶ In another open-label study of 40 children with autism, the use of subcutaneous injections of MB12 (75 mcg/kg twice a week) and oral folinic acid (400 mcg twice a day) led to significant increases in cysteine and glutathione ($P < .001$ for both) as well as significant improvements in autistic behavior as measured on the Vineland Adaptive Behavior Scale (VABS).¹³⁷

Several recent studies have focused on cerebral folate deficiency (CFD) as a cause of autistic symptoms or ASD. For instance, in one study of 7 children with CFD, all had developmental regression, and 5 met the diagnostic criteria for an ASD.¹³⁸ In one case report, a 6-year-old girl with CFD and autistic features had low CSF levels of 5-

methyltetrahydrofolate (5-MTHE, the biologically active form of folate); blood folate and vitamin B₁₂ levels were normal. Treatment with folinic acid (0.5 to 1 mg/kg/d) reversed the CSF findings and led to improvements in motor skills.¹³⁹ In a larger study of 25 children with low-functioning autism, CSF levels of 5-MTHF were low in 23 children, and serum folate receptor autoantibodies were elevated in 19 children. Oral folinic acid supplementation (1 to 3 mg/kg/d) reversed the CSF findings and led to clinical recovery (partial or complete) after 12 months of treatment.¹⁴⁰ In another study of 24 children with CFD, removal of cow's milk from the diet in 12 children significantly decreased autoantibody production to the folate receptor ($P = .012$), and improvements in some of the children were observed in ataxia, seizure frequency, communication, and stereotypy; the autoantibody titers increased when milk was reintroduced ($P = .013$). In the control group of 12 children who did not eliminate cow's milk from their diets, the autoantibody titer significantly increased over a 10- to 24-month period ($P = .001$).¹⁴¹

Ginkgo biloba (Grade D). In one open-label study, 3 adults with autism were given 200 mg/d of ginkgo biloba for 4 weeks. Mild, nonsignificant improvements in irritability, hyperactivity, eye contact, and speech as rated by parents on the Aberrant Behavior Checklist (ABC) were observed; no significant improvements were observed by clinicians.¹⁴²

Inositol (Grade D). An 8-week DBPC crossover trial of inositol (200 mg/kg/d) in 9 children with autism found no benefit compared with placebo.¹⁴³

Iron (Grade D). Iron deficiency in infancy has been associated with poorer cognitive, motor, and social/emotional functioning in later childhood and adolescence.¹⁴⁴ In a study of 5398 typically developing children, iron deficiency was significantly associated with lower standardized math scores (OR = 2.3; 95% CI, 1.1 to 4.4).¹⁴⁵ Supplementation with ferrous sulfate in iron-deficient girls has been shown to significantly improve verbal learning and memory compared with placebo ($P < .02$).¹⁴⁶ Iron deficiency appears to be common in ASD, and serum ferritin is low in a number of children with ASD,^{147,148} which in most cases is due to inadequate dietary iron intake.¹⁴⁹ In an 8-week open-label study of 33 children with ASD, supplementation with iron (6 mg/kg/d) significantly improved sleep and increased mean ferritin levels; adverse effects included constipation, loose stools, and tooth staining. An inverse relationship was found between ferritin levels and communication

problems, as measured by the Autism Diagnostic Observation Schedule (ADOS) ($P = .009$); in other words, more severe communication problems were associated with lower ferritin levels. The investigators suggested that children with ASD should be routinely screened for iron deficiency.¹⁵⁰

Probiotics and digestive enzymes (Grade D). Because some children with ASD have decreased production of digestive enzymes^{58,60} and increased dysbiosis,¹⁵¹ some investigators have speculated that supplementation with probiotics and digestive enzymes might be beneficial.^{152,153} In one case report, a 6-year-old child with autism had improvements in autistic behavior with probiotics and worsening of behavior when the probiotics were removed.¹⁵⁴ In a 12-week open-label study of 46 individuals with ASD, supplementation with oral digestive enzymes led to significant improvements in multiple autistic behaviors ($P < .05$); adverse effects included hyperactivity and loose stools.¹⁵²

St John's wort (Hypericum perforatum) (Grade D). In one open-label study, 3 adults with autism were given St John's wort (20 mg/d for 4 weeks). Significant improvements in irritability, hyperactivity, eye contact, and speech ($P < .05$ for each) were observed, as rated by parents on the ABC; as rated by clinicians, no significant improvements were found.¹⁵⁵

Trimethylglycine and dimethylglycine (Grade D). A 14-week DBPC crossover study of 8 individuals with autism reported no significant benefit with a low dose of dimethylglycine (DMG; approximately 4 to 6 mg/kg/d) compared with placebo.¹⁵⁶ A larger 4-week R-DBPC study of 37 children with ASD demonstrated no significant improvements with a higher dose of DMG (approximately 6 to 10 mg/kg/d) compared with placebo.¹⁵⁷ As previously discussed, the use of TMG, along with folinic acid and MB12, increased glutathione levels in children with ASD and appeared to improve speech and cognition.⁴⁵

Tryptophan and 5-hydroxytryptophan (Grade D). In an R-DBPC crossover study of 20 adults with autism, depletion of tryptophan from the diet for 24 hours was associated with a significant decrease in plasma tryptophan levels ($P < .001$) and a significant increase in stereotypy ($P < .05$), including flapping, rocking, toe-walking, pacing, and self-abuse, compared with a sham diet containing tryptophan.¹⁵⁸ In a 20-week DBPC crossover study of 3 children with autism, L-5-hydroxytryptophan (5-HTP; 50 to 500 mg/

d) was given in combination with carbidopa (100 mg/d), and no discernible benefit was observed compared to when the children received placebo.¹⁵⁹

Vitamins A, D, and calcium (Grade D). In one study of 46 children with ASD and 31 typically developing children, the ASD group had a lower mean calcium intake ($P < .05$).⁴⁰ Because of limited dietary intake, vitamin A and D deficiencies have also been described in some children with ASD. Some investigators have speculated that vitamin D deficiency may play a role in autism.¹⁶⁰ For example, in one case report, a 15-year-old boy with an ASD who had hypocalcemia and undetectable vitamin D levels subsequently developed rickets.¹⁶¹ Another child with autism developed hypocalcemia, corneal erosions, and rickets after consuming only french fries and water for several years.¹⁶² The physical and biochemical abnormalities in this child were reversed with nutritional supplementation, including vitamins A and D.¹⁶² A 5-year-old boy with autism who ate only bacon and blueberry muffins and drank only Kool-Aid had a very low vitamin A level and subsequently developed a corneal ulcer and xerophthalmia.¹⁶³ These problems improved with vitamin A supplementation.¹⁶³ Another 8-year-old boy with autism who ate only fried potatoes over a 4-year period had an almost undetectable vitamin A level and developed xerophthalmia and loss of vision, both of which improved dramatically with vitamin A supplementation.¹⁶⁴ In one case series, 60 children with autism had “dramatic, immediate improvements” in eye contact, attention, socialization, and language with the use of vitamin A (3500 IU/d) and bethanechol (12.5 mg twice daily); no adverse effects were noted.¹⁶⁵ However, vitamin A intoxication has been described in a 4-year-old nonautistic child receiving megavitamin treatment,¹⁶⁶ and a 3-year-old child with autism who was taking 100,000 to 150,000 IU per day of vitamin A over a 6-month period developed vitamin A toxicity and hypercalcemia.¹⁶⁷ Therefore, in children with ASD, vitamin A intake should be carefully monitored. No studies on the use of calcium or vitamin D as a treatment for ASD were identified.

Selenium (Grade N). One study of 20 children with autism and 15 typically developing children reported a significantly lower mean red blood cell selenium level ($P < .0006$) in the autism group.¹⁶⁸ However, no studies were identified on the use of selenium as a treatment for ASD.

Zinc (Grade N). Low zinc levels in typically devel-

oping children have been associated with learning problems, mental retardation, and hyperactivity.¹⁶⁹ In one study, significantly lower plasma zinc levels were reported in 21 children with oppositional defiant disorder, compared with 24 typically developing children ($P < .05$).¹⁷⁰ Two small controlled studies reported similar zinc levels in children with ASD compared with controls.^{168,171} However, a larger controlled study of 45 children with autism and 41 typically developing children reported that plasma and erythrocyte zinc levels were significantly lower in the autism group ($P < .05$).¹⁷² No studies were identified on the use of zinc as a treatment for individuals with an ASD.

Biological treatments: Elimination diets

Elimination diets (Grade C). In 1979, Panksepp first proposed that casein and gluten malabsorption may play a causal role in autism by altering neurotransmitter metabolism.¹⁷³ Since then, several studies have examined possible mechanisms of gluten and casein intolerance in children with ASD. In a study of 40 children with autism, antibodies to milk butyrophilin cross-reacted with 9 different neuron-specific antigens when compared with 40 typically developing children ($P < .001$), and the investigators suggested this cross-reaction could contribute to autoimmunity in the autism group.¹⁷⁴ In another study of 50 children with autism, 44% produced IgG antibodies against gliadin and casein, compared with 12% of typically developing children ($P < .0001$); this antibody production was associated with significant autoimmune reactions in the autism group.¹⁷⁵ One study of 50 children with autism and 50 typically developing children reported that 42% of the autism group produced IgG antibodies to gliadin peptides, compared with 16% of controls ($P < .0001$), and these antibodies also cross-reacted with cerebellar peptides and Purkinje cells ($P < .003$).¹⁷⁶ Gliadin peptide reacted with certain peptidases and induced the formation of autoantibodies in another study of 50 children with autism ($P < .001$), which the investigators suggested “may result in neuro-immune dysregulation and autoimmunity.”¹⁷⁷ In a study of 72 children with ASD and 41 typically developing children, exposure to dietary peptides from gliadin and cow’s milk was independently associated with increased production of proinflammatory cytokines, including interferon- γ and tumor necrosis factor- α (TNF- α), from peripheral blood mononuclear cells in the ASD group compared with the control group ($P < .02$); this exposure

was thought to contribute to increased GI inflammation in the ASD group.¹⁷⁸ In another study of 109 children with ASD, those with GI symptoms (75 children) produced significantly more TNF- α from peripheral blood mononuclear cells after exposure to cow's milk protein ($P < .005$) and gliadin ($P < .02$), compared with 19 typically developing children; this reaction to gliadin in the ASD children was most frequently observed in children who also had loose stools.⁶⁴ In a study of 21 children with ASD, those on a gluten-free and casein-free (GFCF) diet had less TNF- α -producing cells in the colonic mucosa compared with children with no dietary exclusions ($P < .05$).¹⁷⁹ In one retrospective study of 103 children with ASD and 29 typically developing children, consumption of cow's milk was significantly correlated with constipation ($P < .01$) in the ASD group.¹⁸⁰ Finally, it should be noted that a retrospective study of 150 children with ASD found a 3-fold higher prevalence of celiac disease than in the general pediatric population; the investigators suggested that all ASD children should be screened for celiac disease, regardless of whether or not GI symptoms are present.¹⁸¹ Since the proper testing for celiac disease requires ongoing exposure to gluten, laboratory testing for celiac disease should be considered before placing a child on dietary restrictions.

Several studies have investigated the effects of dietary restrictions on certain behaviors in children with ASD. In an 8-week study of 36 children with autism, the elimination of allergic foods (as determined by a positive skin test) led to significant improvements in autistic behaviors ($P < .05$) and worsening of these behaviors when the allergic foods were reintroduced.¹⁸² One open-label study of a ketogenic diet in 30 children with autistic behavior reported that 18 children (60%) had various improvements ($P < .001$), including social interaction, stereotypy, hyperactivity, cooperation, and learning over a 6-month period.¹⁸³ A case report of an 8-year-old child with autism, who was continually monitored in a treatment room for 31 consecutive days, found that the reintroduction of certain foods (including wheat, corn, and dairy products) after all food had been eliminated for 6 days (the child only drank water during these 6 days) led to significant worsening of autistic behavior, including hyperactivity, uncontrolled laughter, and disruptive behavior (such as screaming, biting, and throwing objects).¹⁸⁴ In another case report of a 6-year-old child with autism, improvements in behavior were observed with the elimination of gluten and casein from

the diet.¹⁵⁴ In one study of 7 children with autism, no significant benefits were observed with the introduction of a gluten-free diet over a 6-month period.¹⁸⁵ However, 6 open-label studies (each enrolling 15 to 70 children with ASD) that eliminated gluten and/or casein from the child's diet (over a 2-month to 1-year period) reported significant clinical improvements in behavior, including expressive speech, attention, coordination, hyperactivity, and sleep.^{182,186-190} However, other investigators have noted that some of these studies have methodologic flaws.¹⁹¹ In a recent medical survey of 479 parents of a child with autism, 155 children had tried a GFCF diet; 51% of parents reported that their child experienced behavioral improvements with the use of this diet; 10% had worsening behavior on this diet.¹⁹² In a randomized, single-blind, controlled study of 20 children with ASD, 10 of the children were placed on a GFCF diet and the other 10 ate a normal diet. The children on the GFCF diet had significant improvements over a 12-month period in attention, socialization, communication, and cognition ($P < .05$ for each) compared with the children who ate a normal diet.¹⁹³ A double-blind, crossover study of 15 children with ASD reported no significant improvements while the children were on a GFCF diet for 6 weeks, compared with a normal diet for 6 weeks,¹⁹⁴ but this time period may have been too short to observe significant changes, and the study sample was relatively small. A recent Cochrane review examining the GFCF diet in ASD could not perform a meta-analysis but was able to pool study data. The review reported improvements in overall autistic traits ($P = .001$), social isolation ($P = .002$), and overall communication and interaction ($P = .006$) in children with ASD who received the GFCF diet compared with a control diet. No harmful outcomes were identified, and the investigators recommended larger controlled trials,¹⁹⁵ which are currently in progress.¹⁹¹ Diet studies in children can be difficult to perform, but a recent study of 52 children with autism examined the feasibility of the GFCF diet and reported that most children were willing to eat foods that did not contain gluten and casein.¹⁹⁶ Additional studies are needed to evaluate the efficacy of restricted diets (including GFCF diets) in children with ASD and to determine which children respond to these diets.

Children with ASD who are placed on a restricted diet need close supervision to ensure adequate nutritional intake. For example, in one retrospective study of 36 children with ASD, there was a trend for children on

TABLE 5**Grade of recommendation for novel and emerging medications in ASD**

Treatment	Grade
Acetylcholinesterase inhibitors	A
Naltrexone	A
Alpha-2 adrenergic agonists	B
HBOT	B
Immunomodulation/anti-inflammatory treatments	B
Oxytocin	B
Chelation	C
Cyproheptadine	C
Famotidine	C
Glutamate antagonists	C
Antibiotics	D
Secretin	D

ASD: autism spectrum disorders; HBOT: hyperbaric oxygen treatment.

a GFCF diet (10 children) to have lower plasma essential amino acid levels, including tryptophan and tyrosine, compared with children on an unrestricted diet (26 children) and with 24 developmentally delayed control children.¹⁹⁷ In another prospective uncontrolled study of 75 children with ASD, reduced cortical bone thickness was reported, compared with a standard reference range; this finding was most pronounced in children who were on a casein-restricted diet, which is usually associated with lower calcium intake.¹⁹⁸

Biological treatments: Medications

Acetylcholinesterase inhibitors (Grade A). Deficits in brain cholinergic function have been described in some individuals with autism.¹⁹⁹ Several studies have examined the use of acetylcholinesterase inhibitors, including rivastigmine, donepezil, and galantamine in children with ASD. In a 12-week open-label study of 32 children with autism, the use of rivastigmine (0.4 to 0.8 mg twice daily) led to significant improvements in expressive speech and overall autistic behavior ($P = .001$); adverse effects included nausea, diarrhea, irritability, and hyperactivity.²⁰⁰

A retrospective study of donepezil in 8 children with autism reported improvements in irritability and hyperactivity in 4 of the children.²⁰¹ In a 12-week open-label

study of donepezil (2.5 to 5 mg/d) in 25 children with ASD, improvements were found in expressive speech ($P = .032$), with a mean gain in speech of 8 months.²⁰² In a 6-week R-DBPC study of 43 children with ASD, the use of donepezil (1.25 to 2.5 mg/d) led to improvements in expressive ($P = .044$) and receptive language ($P = .002$) and a decrease in overall autistic behavior ($P = .004$) compared with placebo; the most common adverse effect was mood lability.²⁰³

The use of galantamine (4 mg/d) enhanced expressive language in an open-label study of 3 adults with autism.²⁰⁴ In another 12-week, open-label study of 13 children with autism, galantamine (4 to 24 mg/d) was well tolerated and led to significant improvements in irritability ($P = .03$), social withdrawal ($P = .01$), and inattention ($P = .02$) as rated by parents; a reduction in anger ($P = .03$) and autistic behavior ($P = .001$) was also observed by clinicians.²⁰⁵ In an R-DBPC crossover study of 20 children with autism, treatment with galantamine was well tolerated and led to improvements in irritability ($P = .039$), hyperactivity ($P = .038$), eye contact ($P = .049$), and inappropriate speech ($P = .045$) compared with placebo.²⁰⁶

Naltrexone (Grade A). Numerous DBPC studies have reported significant clinical improvements with the use of naltrexone in children with ASD.²⁰⁷⁻²¹² A systematic review of 3 case reports, 8 case series, and 14 prospective clinical trials reported that naltrexone, at doses ranging from 0.5 to 2 mg/kg/d, led to significant improvements in self-injurious behavior, hyperactivity, social withdrawal, stereotypy, agitation, and irritability in children with ASD. Transient sedation was the most common adverse effect noted.²¹³

Alpha-2 adrenergic agonists (Grade B). Several studies have examined the use of alpha-2 adrenergic agonists, including clonidine and guanfacine, in children with ASD. In one case report of an adult with autism and violent behavior, transdermal clonidine (0.6 mg/d) led to a large reduction in violent behavior.²¹⁴ In a retrospective study of 19 children with ASD, the use of clonidine (0.05 to 0.1 mg at bedtime) improved sleep, nighttime awakenings, attention, hyperactivity, aggression, and mood.²¹⁵ A 12-week DBPC study of 9 children with autism reported that transdermal clonidine (0.005 mg/kg/d) led to significant improvements in sensory problems ($P = .049$) and global symptoms ($P < .0001$), as rated by a psychiatrist or a psychologist, compared with placebo; adverse effects included

fatigue and sedation during the first 2 weeks of treatment.²¹⁶ In a 14-week R-DBPC crossover study of 8 children with autism who also had either inattention, impulsivity, or hyperactivity, the use of oral clonidine (4 to 10 mcg/kg/d) led to significant improvements in irritability ($P = .01$), stereotypy ($P = .05$), hyperactivity ($P = .03$), inappropriate speech ($P = .05$), and oppositional behavior ($P = .05$) compared with placebo; adverse effects included drowsiness ($P = .01$) and decreased activity ($P = .03$).²¹⁷

In a retrospective study of 80 children with ASD, the use of guanfacine (mean dose 2.6 mg/d) was associated with improvements in attention, hyperactivity, insomnia, and tics; treatment was considered effective in 24% of the children, and the investigators called for additional studies.²¹⁸ In another 8-week open-label study of 25 children with PDD and hyperactivity, guanfacine (1 to 3 mg/d) led to significant improvements in hyperactivity ($P < .01$) as rated by parents and teachers.²¹⁹ A recent R-DBPC crossover study of 11 children with autism who also had hyperactivity and inattention reported that guanfacine (maximum dose of 3 mg/d) led to significant improvements in hyperactivity on the ABC and the CGI scale ($P < .05$ for each), as rated both by parents and teachers, compared with placebo; adverse effects included drowsiness and irritability.²²⁰ The most common adverse effects observed with guanfacine in one study were insomnia, fatigue, blurred vision, headache, and mood alteration, but it had no significant effect on blood pressure or pulse rate.²²¹

Hyperbaric oxygen treatment (Grade B). Hyperbaric oxygen treatment (HBOT) may be beneficial in some individuals with an ASD because it has been shown to significantly lower inflammation and improve cerebral hypoperfusion, both reported as problems in some individuals with an ASD.²²² One case series of 6 children with autism reported improvements in overall autistic behavior ($P < .02$) with the use of hyperbaric treatment at 1.3 atmosphere (atm) for 40 hourly treatments.²²³ An open-label study in 18 children with autism reported significant improvements with HBOT (40 treatments at 45 minutes each; 12 children received 1.3 atm and the other 6 received 1.5 atm) in motivation, speech, and cognitive awareness ($P < .05$ for each) and a significant decrease in an inflammatory marker (C-reactive protein, $P = .021$) when children were grouped.²²⁴ Similar clinical improvements were observed when comparing the 2 pressure groups, although the number of

children in each group was small, making comparisons of the 2 pressures difficult.²²⁴ Another open-label study of 7 children with autism from Thailand using HBOT at 1.3 atm for 10 hourly treatments reported significant improvements in social development, language, coordination, and self-help skills ($P < .001$ for each).²²⁵ A more recent randomized, double-blind, controlled study in 62 children with autism studied the effects of hyperbaric treatment at 1.3 atm and 24% oxygen compared with near-placebo (1.03 atm and 21% oxygen). The children receiving 1.3 atm had significant improvements as rated by parents and physicians in several areas, including overall functioning, receptive language, social interaction, and eye contact ($P < .05$ for each), compared with the near-placebo group; the treatment was safe and well tolerated.²²⁶

Immunomodulation/anti-inflammatory treatments (Grade B). Because cerebral and GI inflammation have been described in ASD,⁴⁹⁻⁵⁷ some investigators have studied the use of anti-inflammatory treatments in individuals with an ASD. In a case report of a child with autism and an autoimmune disorder, the use of oral prednisone (2 mg/kg/d) led to large improvements in speech and developmental milestones.²²⁷ In another case report, a child with PDD was treated with oral prednisone (2 mg/kg/d), and considerable improvements in speech and social interaction were observed.²²⁸ One prospective open-label study of 44 children with ASD (who had previously experienced language regression and also had an abnormal EEG) reported that the addition of a weekly bolus of high-dose prednisone or methylprednisolone (10 mg/kg/wk) to valproic acid led to additional EEG improvements in 60% of the children, compared with the results observed with valproic acid alone.²²⁹ The combination of valproic acid and either prednisone or methylprednisolone also improved speech in 82%; adverse effects, including cushingoid complications, were “unremarkable,” even after 18 months of treatment.²²⁹ In 3 R-DBPC crossover trials that included a total of 48 children with ASD, an adrenocorticotrophic hormone (ACTH) analog (the peptide Org 2766; 20 to 40 mg/d orally for 4 to 8 wk) significantly improved social interaction, play behavior, and stereotypy ($P < .05$ for each) compared with placebo; adverse effects were minimal.²³⁰⁻²³² In one open-label study of 25 children with ASD, the use of pioglitazone (30 to 60 mg/d), which has anti-inflammatory properties, was well tolerated and led to significant improvements in hyper-

activity, stereotypy, irritability, and lethargy ($P < .05$ for each) over 3 to 4 months of use.²³³ Spironolactone has been shown to be a potent anti-inflammatory, and one case report described improvements in behavior, including irritability, hyperactivity, stereotypy, and speech in a 12-year-old child with autism receiving 2 mg/kg/d for 4 weeks.²³⁴ Pentoxifylline has immunomodulatory effects and inhibits TNF- α secretion. A review of 5 uncontrolled Japanese studies (ranging from 18 to 50 children with ASD) reported improvements with pentoxifylline (150 to 600 mg/d), including language and attention; further studies were recommended.²³⁵

Several studies have investigated the use of oral or intravenous immunoglobulin (IVIG) in children with ASD. One recent controlled study reported that plasma immunoglobulin levels in 116 children with autism were significantly lower than those of 96 typically developing children ($P < .001$) and that children with the lowest levels had the highest autism severity as rated on the ABC ($P < .0001$).²³⁶ In an open-label study of 10 children with autism who also had abnormal serum immunoglobulin levels, IVIG (400 mg/kg) was given monthly for at least 6 months. No adverse effects were noted, and improvements were observed in social interaction, eye contact, speech, and response to commands; in 2 children, the improvements in speech were large, and one child "almost completely recovered speech."²³⁷ In another open-label study of 10 children with autism, the use of IVIG (154 to 375 mg/kg) administered every 6 weeks for up to 4 doses led to mild improvements in attention and hyperactivity in 4 of the children, no improvements in 5 children, and "almost total amelioration of autistic symptoms" in 1 child²³⁸; however, the children in this study had normal immune function and received lower, more infrequent doses of IVIG compared with other studies.²³⁹ In an uncontrolled study of 7 children with autism, no improvements were observed with the use of monthly IVIG (400 mg/kg) over a 6-month period²⁴⁰; however, a limitation of this study was that none of the children had any known immunologic problems or abnormal immune tests.²⁴¹ In an open-label study of 26 children with autism and immunologic problems, IVIG (400 mg/kg) was administered monthly over a 6-month period and was well tolerated. Significant improvements were observed in hyperactivity, speech, irritability, lethargy, and stereotypy ($P < .01$ for each); however, when the treatment was stopped, 22 of the children regressed to their pre-IVIG level within 2 to 4 months.²⁴²

In an open-label study of 12 children with autism and chronic GI problems, the use of oral human immunoglobulin (420 mg/d) over an 8-week period led to improvements both in behavior and GI problems in 50% of the children; adverse effects included vomiting, fever, and rash.²⁴³ However, a recent R-DBPC of oral human immunoglobulin (140 to 840 mg/d) in 125 children with autism who also had persistent GI symptoms reported no significant differences in autistic behaviors or GI symptoms compared with placebo.²⁴⁴ In one case report of a child with autism who also had congenital cytomegalovirus, the use of injected transfer factor (from human donors) led to improvements in motor development over an 18-month period.²⁴⁵ In an open-label study of 22 children with autism, the use of injected transfer factor led to improvements in autistic behavior in 21 children, including 10 who improved significantly.²⁴⁶

Oxytocin (Grade B). Oxytocin functions as a neurotransmitter and is involved in regulating repetitive behaviors and social interaction; as such, it may play a role in modulating ASD behavior.²⁴⁷ Certain polymorphisms in the oxytocin receptor gene have been associated with autism.²⁴⁸⁻²⁵⁰ In one prospective study of 29 children with autism and 30 typically developing children, significantly lower plasma oxytocin levels were found in the autism group ($P < .004$).²⁵¹ In a DBPC study of 30 healthy males without autism, the use of intranasal oxytocin (24 IU/d) significantly improved the ability to determine the affective mental state of other people, compared with placebo ($P < .02$).²⁵² In one R-DBPC study of 15 adults with ASD, the intravenous infusion of oxytocin was well tolerated and caused a significant reduction in repetitive behaviors compared with placebo ($P = .027$).²⁵³ In another R-DBPC crossover study of 15 adults with ASD, the infusion of oxytocin led to improvements in the comprehension of affective speech compared with placebo ($P = .033$).²⁵⁴

Chelation (Grade C). Multiple studies were identified that suggest some individuals with an ASD manifest clinical and behavioral improvements with chelation (removal of heavy metals with medication). In one case report of 3 children with autism, pica, and lead toxicity (blood lead concentrations ranging from 63 to 80 mcg/dL), injection with calcium disodium edetate (CaNa₂-EDTA) significantly reduced blood lead concentrations and was associated with various clinical improvements in behavior, attention, mood, and school performance.²⁵⁵ In a case series of 6 children with autism and concomi-

tant lead toxicity (blood lead concentrations ranged from 40 to >100 mcg/dL), following chelation treatment (type unspecified), one child had mild improvements in behavior; 4 other children received chelation treatment without any reported behavioral improvements (it was not noted if the last child received chelation).²⁵⁶ Eppright et al reported on one child with autism and ADHD who also had an elevated blood lead level of 42 mcg/dL. The child was treated with oral meso-2,3-dimercaptosuccinic acid (DMSA) over an 18-day period and demonstrated both a reduction in blood lead concentration and improvements in hyperactivity and repetitive, self-stimulatory behavior; when the chelator was stopped, these undesired behaviors returned.²⁵⁷ In another report, 2 children with lead toxicity (blood lead concentrations >45 mcg/dL in both) experienced significant deteriorations in acquired skills (including speech and cognition) and were subsequently diagnosed with an ASD. These deteriorations occurred contemporaneously to the lead exposure; one child had a vocabulary of approximately 10 words at age 16 to 20 months and then “lost the ability to speak around the time that lead poisoning was detected.” Both children received chelation (type unspecified), which lowered blood lead concentrations; follow-up evaluations determined that the children no longer met the criteria for an ASD, although it is unclear if chelation led to the improvements described.²⁵⁸ An open-label study of 152 children with ASD treated with oral DMSA found clinical improvements in 83% (126 of 152) of the children, with children under age 6 more likely to show an improvement; however, transient worsening of behavior before improvement was noted in some cases and this study was not published in a peer-reviewed journal.²⁵⁹ The Autism Research Institute tracks the effects of different treatment modalities in children with ASD, including nutritional supplements and medications, and when assessing the use of chelation, 74% of parents reported some form of behavioral improvement in their child; this is the highest percentage improvement reported for any of the 93 interventions tracked.²⁵ Three percent of parents rated their child’s behavior as worse with chelation (SEE TABLE 1).²⁵ In one study that surveyed 479 parents of a child with autism, 32 children had tried chelation and 50% of parents reported their child experienced behavioral improvements with chelation; 6% had worsening behavior.¹⁹²

One prospective uncontrolled study of 10 chil-

dren with ASD reported that thiamine tetrahydrofurfuryl disulfide (TTFD), a mild chelator of heavy metals, increased urinary excretion of cadmium, lead, and nickel in some of the children, and led to clinical improvements in speech and behavior on the Autism Treatment Evaluation Checklist (ATEC) in 8 of the 10 children; an unusual odor with TTFD administration was noted in 9 of the 10 children.²⁶⁰ Another prospective uncontrolled study of 11 children with ASD reported significant increases in the urinary excretion of arsenic, lead, and mercury ($P < .05$ for each), and improvements in behavior ($P < .05$), cognition ($P < .005$), and sociability ($P < .05$) on the ATEC by using a combination of oral DMSA and injected leuprolide acetate.²⁶¹ A 6-month uncontrolled prospective study of 10 children with ASD who also had ADHD and elevated urinary lead concentrations reported that nutritional supplementation, dietary changes, and chelation treatment, including intravenous $\text{CaNa}_2\text{-EDTA}$ and 2,3-dimercapto-1-propanesulfonic acid (DMPS), led to a significant decline in urinary lead excretion ($P < .001$) and improvements in behavior, including social interaction, concentration, stereotypical movements, and play skills. The investigators reported that 4 of the children had substantial improvements and left special education curricula to enter regular classroom settings.²⁶² Several other studies were identified that examined chelation in children with ASD, but none reported on clinical effects,²⁶³⁻²⁶⁸ although one reported a significant mean reduction ($P < .002$) in a biochemical marker (urinary coproporphyrin) of heavy metal toxicity in children with autism after the use of oral DMSA.²⁶³

No significant adverse effects of chelation were reported in these studies, although one child developed diarrhea after oral DMSA and had to stop treatment.²⁶⁵ However, Stevens-Johnson syndrome was described in one case report of a typically developing child after receiving oral DMPS; the rash resolved after stopping the medication.²⁶⁹ Furthermore, mineral depletion and redistribution of heavy metals from one area of the body to another are potential adverse effects of chelation, although none of the reviewed studies reported evidence of these effects. In addition, it should be noted that 2 children (one with autism) in the United States who received intravenous *disodium* edetate died from cardiac arrest secondary to hypocalcemia. However, these deaths were caused by medication errors, as this form of edetate should not be used in children; instead, *calcium disodium* edetate

should have been used because this medication has not been associated with hypocalcemia during intravenous infusion.²⁷⁰ The reviewed studies of chelation in children with an ASD suggest that when properly administered, side effects of chelation are rare, idiosyncratic, and reversible.

Overall, the collective strength of these studies investigating the use of chelation in individuals with an ASD is limited, as some are case reports and none included a control group. In some of these studies, it is unclear if the children had elevated heavy metal levels prior to initiating chelation or if this treatment directly caused the clinical improvements described. It is also possible that any improvements observed with chelation in these children could have been due to some chelator effect other than the removal of heavy metals because some chelators also remove pesticides,²⁷¹ raise glutathione levels,²⁷² and reduce oxidative stress.²⁷³ In placebo-controlled studies of typically developing children with elevated blood lead levels (20 to 44 mcg/dL), treatment with oral DMSA for up to 3 months was not associated with long-term neurodevelopmental benefits,^{274,275} although it did improve postural balance and gait ($P < .05$ for both) in one R-DBPC study of 161 children.²⁷⁶ It should be noted that placebo-controlled studies of chelation in individuals with an ASD have not been performed; a large planned placebo-controlled study of chelation in children with autism was recently cancelled by the National Institute of Mental Health.²⁷⁷ However, despite the obvious limitations of the reviewed studies, their cumulative findings suggest that chelation might be a viable form of treatment in some individuals with an ASD who have elevated heavy metal burden, or as suggested by several studies,^{263,267,268} biochemical changes suggestive of metal toxicity. Further research investigating this possibility should thus be considered, including carefully designed controlled studies of chelation that include appropriate clinical monitoring as well as objective prescreening to identify children with ASD who have concomitant elevated heavy metal burden.

Cyproheptadine (Grade C). In a case report of 2 children with ASD, the use of cyproheptadine (12 to 24 mg/d) led to a decrease in stereotypical behaviors in one child and improved expressive speech in the other child.²⁷⁸ In an 8-week R-DBPC study of 40 children with autism, the use of oral cyproheptadine (0.2 mg/kg/d) was well tolerated and led to significant improvements in autistic behavior on the ABC when combined with haloperidol (P

$< .001$), compared with a group receiving haloperidol and placebo; side effects were similar to placebo and included increased appetite and constipation.²⁷⁹

Famotidine (Grade C). Some investigators have speculated that famotidine might be helpful for certain ASD symptoms because it is a histamine-2 receptor blocker and has been shown to improve certain symptoms in schizophrenia.²⁸⁰ In a single-subject research design, oral famotidine (2 mg/kg/d) was administered in a 10-week R-DBPC crossover manner to 9 children with ASD who had no history of GI problems; 4 children (44%) were considered “responders” and had various behavioral improvements, including improvements in eye contact, communication, repetitive behaviors, and social interaction compared with placebo.²⁸¹

Glutamate antagonists (Grade C). Postmortem brain samples indicate evidence of excessive glutamatergic activity in some individuals with autism.²⁸² In a study of 14 children with autism, 57% had an elevated plasma glutamate level.²⁸³ Several studies in children with ASD were identified that investigated the use of drugs that are glutamate antagonists, including amantadine, memantine, and lamotrigine. In a 4-week R-DBPC study of 39 children with autism, the use of amantadine (2.5 mg/kg/d) was well tolerated and led to improvements in hyperactivity ($P = .046$) and inappropriate speech ($P = .008$) compared with placebo.¹⁸

In one case report, an adult with autism and disruptive behavior leading to the loss of 2 jobs was treated with memantine (5 to 10 mg/d) and had significant improvements in behavior.²⁸⁴ In a retrospective study of memantine (2.5 to 20 mg/d) in 18 children with ASD, 61% were “much improved” or “very much improved” in attention and social interaction, and a significant improvement was observed in hyperactivity ($P = .03$).²⁸⁵ In an open-label study of 14 children with ASD, the use of 0.4 mg/kg/d of memantine over an 8-week period led to improvements in memory, hyperactivity, and irritability.²⁸⁶ In another open-label study of 151 individuals with an ASD, the use of memantine (2.5 to 30 mg/d) for up to 20 months was associated with improvements in language, social behavior, and self-stimulatory behavior as rated by the treating physician; 11% of the patients experienced an adverse effect, including worsening of autistic behavior, but none of the adverse effects were considered serious.²⁸⁷

Elevated glutamate levels have been observed in the CSF of some children with Rett syndrome, and in one

open-label study of 4 children, improvements in seizures and “well-being” were observed with lamotrigine.²⁸⁸ One case report of a child with Rett syndrome reported large improvements in stereotypy, self-injurious behavior, and hyperactivity with use of lamotrigine.²⁸⁹ In another report of 2 children with Rett syndrome and seizures, the use of lamotrigine improved seizure activity and “markedly decreased” stereotypical hand movements and other autistic behaviors.²⁹⁰ In an open-label study of 12 children with Rett syndrome, lamotrigine led to improvements in concentration, alertness, and happiness in 4 of the children.²⁹¹ In a study of 50 children with epilepsy, including 13 children who also had autism, lamotrigine led to a reduction in autistic symptoms in 8 of the 13 children with autism.²⁹² Improvements in attention, stereotypy, and activity level in 6 children with autism with the use of lamotrigine were found by one group of investigators.²⁹³ However, an R-DBPC study of 28 children with autism (who apparently did *not* have seizures) reported no significant differences in autistic behavior with lamotrigine (titrated up to 5 mg/kg/d) given over an 18-week period compared with placebo.²⁹³

Antibiotics (Grade D). In an 8-week single-blind study of 12 individuals with autism, improvements were found in social withdrawal ($P = .02$) with the use of D-cycloserine (up to 2.8 mg/kg/d), an antibiotic and a partial agonist at the glutamate receptor; adverse effects included a transient tic in one child.²⁹⁴ In one open-label study of 11 children with regressive autism, the use of oral vancomycin (which is minimally absorbed) over an 8-week period led to significant improvements in autistic behavior ($P = .003$) and communication ($P = .003$). The vancomycin was thought to improve behavior by killing neurotoxin-producing bacteria such as *Clostridia*. No adverse effects were noted, and 80% of the children had improvements, as rated by a blinded child psychologist who examined paired videotapes in random order; however, when the medication was stopped, the improvements largely disappeared in most children.¹⁵¹

Secretin (Grade D). More than a dozen DBPC studies involving more than 700 children with ASD have reported that intravenous secretin demonstrates no significant benefit compared with placebo.²⁹⁵⁻²⁹⁷ However, one recent R-DBPC crossover study in 15 children with ASD reported a significant improvement in speech ($P = .0479$) with *transdermal* secretin compared with placebo (this improvement was observed only in the children not using any other medications).²⁹⁸

TABLE 6

Grade of recommendation for nonbiological treatments in ASD

Treatment	Grade
Music therapy	A
Vision therapy	B
Acupuncture	C
Auditory integration training	C
Massage and yoga	C
Neurofeedback	C
Homeopathy	D
Vagus nerve stimulator	D

ASD: autism spectrum disorders.

Nonbiological treatments

Music therapy (Grade A). In an open-label study of 8 adults with autism, 60 minutes of weekly music therapy (including singing, drumming, and piano playing) led to significant improvements in autistic symptoms over a 52-week period.²⁹⁹ In another open-label study of 4 children with autism, the use of music therapy led to improvements in play skills.³⁰⁰ In a randomized, controlled study of 15 children with autism, the use of improvisational music therapy led to greater improvements in joint attention behavior ($P = .01$) and eye contact duration ($P < .0001$), compared with play sessions with toys.³⁰¹ In a recent DBPC trial of Tomatis (a form of music therapy) in 11 children with autism, improvements were similar to placebo.³⁰² In a meta-analysis of 9 studies examining the use of music therapy in children with ASD, significant improvements were found ($P < .01$) with a large effect size (0.77), compared with those receiving no music therapy.³⁰³ In a recent Cochrane review, music therapy was superior to “placebo” therapy, standard care, or no music therapy in improving communicative skills in children with ASD but had no significant effect on autistic behavior.³⁰⁴

Vision therapy (Grade B). In a randomized, controlled study of 14 children with autism, the use of ambient prism lenses improved posture and visual-motor coordination ($P < .001$ for both) compared with either wearing incorrect ambient lenses or no lenses.³⁰⁵ In a follow-up R-DBPC crossover study of 18 children with autism, improvements in autistic behaviors were observed with the use of ambient transitional prism lenses compared with placebo lenses ($P < .05$).³⁰⁶

TABLE 7

Summary of treatments leading to improvements in certain autistic behaviors

Speech/communication	Carnitine Carnosine GFCF diet Alpha-2 adrenergic agonists Cyproheptadine Glutamate antagonists AIT	Tetrahydrobiopterin B ₆ /magnesium AI HBOT Famotidine Music therapy Neurofeedback
Autistic behavior	Carnosine B ₆ /magnesium Probiotics GFCF diet Alpha-2 adrenergic agonists Cyproheptadine Vision therapy	Piracetam Folic acid/B ₁₂ Digestive enzymes AI HBOT Music therapy
Social interaction	Tetrahydrobiopterin B ₆ /magnesium AI HBOT Famotidine Massage	Carnosine GFCF diet Naltrexone Oxytocin Glutamate antagonists Neurofeedback
Stereotypy	Vitamin C B ₆ /magnesium Alpha-2 adrenergic agonists Famotidine AIT	Omega 3 fatty acids Naltrexone Cyproheptadine Glutamate antagonists Massage
Hyperactivity	Omega 3 fatty acids AI Alpha-2 adrenergic agonists Glutamate antagonists Massage	Magnesium Naltrexone Chelation AIT
Eye contact	Tetrahydrobiopterin AI Famotidine	Omega 3 fatty acids HBOT Music therapy
Attention	Omega 3 fatty acids Alpha-2 adrenergic agonists Music therapy	AI Glutamate antagonists
Sleep	Melatonin Multivitamin Alpha-2 adrenergic agonists	Carnitine Iron

AI: acetylcholinesterase inhibitors; AIT: auditory integration training;
GFCF: gluten-free, casein-free diet; HBOT: hyperbaric oxygen treatment.

Acupuncture (Grade C). An open-label study of 2 children with ASD who received electroacupuncture for 24 treatments over 2 months reported improvements in sensory problems.³⁰⁷ A 9-month randomized, controlled study of 20 children with autism (who all received language therapy twice a week) reported that 10 of the children who also received scalp acupuncture twice a week had significant improvements in attention ($P = .008$) and receptive semantics ($P = .034$), as rated

by a blinded language therapist, compared with the 10 children who received only language therapy.³⁰⁸

Auditory integration training (Grade C). Up to 40% of children with ASD may have some degree of sound sensitivity.³⁰⁹ Auditory integration training (AIT) involves listening to certain music filtered through a set of headphones to help reduce sound sensitivities. In one 3-month double-blind controlled study of 17 individuals with autism, those who received AIT had significant improvements in irritability ($P < .05$), stereotypy ($P < .01$), hyperactivity ($P < .05$), and expressive speech ($P < .01$) compared with a control group who received the same music that was unfiltered; these improvements persisted for 3 months.³⁰⁹ In a recent systematic review of AIT for ASD, 6 RCTs were identified, comprising a total of 171 children. A meta-analysis was not possible, but 3 of the studies reported improvements in overall autistic behavior in the AIT group; 3 studies reported no significant benefits.³¹⁰

Massage and yoga (Grade C). Massage in children with autism may enhance the emotional bond between the parent(s) and child.³¹¹ In an open-label study of 12 children with autism and learning difficulties, the use of aromatherapy massage with lavender oil showed no significant beneficial effect on sleep when compared with no treatment.³¹² In a 1-month randomized controlled study

of 20 children with autism, children receiving massage therapy for 15 minutes at bedtime exhibited improvements in hyperactivity, stereotypy, and social interaction ($P < .05$ for each) compared with children who were read stories for 15 minutes at bedtime.³¹³ In a 9-month open-label study of 8 children with autism, the use of a medical Qigong massage led to a decrease in autistic behavior and an increase in language.³¹⁴ In another open-label study of Qigong massage in 26 children with autism, significant

improvements were observed in autistic behaviors.³¹⁵ In a controlled study of 15 children with autism, the use of Qigong massage over a 5-month period in 8 children led to improvements in sensory impairments ($P < .01$), social skills ($P < .04$), and basic living skills ($P < .02$) as rated by blinded evaluators, compared with the 7 children who were untreated.³¹⁶

Neurofeedback (Grade C). In a study of 24 children with autism, 12 received neurofeedback, which led to improvements in speech ($P < .001$), social interaction ($P < .01$), and cognition ($P < .001$), compared with the 12 control children who received no treatment.³¹⁷

Homeopathy (Grade D). One study of homeopathy in 12 adults with autism reported that homeopathic secretin given weekly for 12 weeks demonstrated some worsening of behavior during treatment.³¹⁸

Vagus nerve stimulator (Grade D). An adult with Asperger's syndrome and intractable seizures had improvements in both seizure activity and behaviors when treated with a vagus nerve stimulator (VNS).³¹⁹ In one open-label study of 6 children with Landau-Kleffner syndrome and 59 individuals with autism, the use of a VNS for intractable seizures caused a $\geq 50\%$ reduction in seizures in 58% of the autism group at 12 months. Improvements in quality of life were also observed in the autism group at 12 months, including alertness in 76%, mood in 61%, and achievement in 53%.³²⁰ However, in another open-label study of 8 children with ASD and drug-resistant epilepsy, the use of a VNS did not reduce seizure activity, and only minor improvements in functioning were noted over a 2-year period.³²¹

CONCLUSIONS

This article critically reviews the use of novel and emerging treatments for individuals with an ASD. Many of these treatments, especially nutritional supplements, are well tolerated and generally regarded as safe. Several treatments are supported by prospective RCTs. Some of the more promising treatments include melatonin, antioxidants, acetylcholinesterase inhibitors, naltrexone, and music therapy. All of the treatments reviewed in this article are currently off-label (ie, not FDA-approved) and some have adverse effects. Further studies exploring these treatments are needed. Physicians treating children with ASD should make it standard practice to inquire about the child's possible use of these types of treatments. ■

DISCLOSURES: The author has 2 children with ASD and is a practicing primary care physician who treats ASD children with standard and integrative treatments, including some of the treatments reviewed in this article. The author has received funding from the International Hyperbarics Association for 2 studies on the use of hyperbaric treatment in children with autism.^{224,226} He was also a coauthor of a case report of spironolactone use in a child with autism.²³⁴ The author has no additional competing interests, and he alone is responsible for the content and writing of this paper.

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