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REVIEW ARTICLE

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 B_6/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.

[a]Percentage of children that parents ranked as improved with treatment
[b]Percentage of children that parents ranked as having no obvious changes with treatment
[c]Percentage of children that parents ranked as worse with treatment
[d]Number 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 choline-lecithin,[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 inflammation[49-53] 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* species[61-63] 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 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]

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.

Vitamin B_6 and magnesium (Grade C). Some studies in children with ASD have reported that plasma vitamin B_6 levels are sometimes high,[110] whereas concentrations of the active form of vitamin B_6 (pyridoxal-5´-phosphate or PLP) are often low, suggesting a problem with the conversion of vitamin B_6 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 B_6) administration led to improvements in speech and language in some children with ASD.[112] Rimland noted that combining vitamin B6 with magnesium (B_6/Mg) lessened some of the adverse effects seen with B_6 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 B_6/Mg.[112,114-119] Most of these studies used high doses of vitamin B_6 (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 B_6/Mg in children with ASD.[120-126] In some of these studies, urinary homovanillic acid levels decreased with B_6/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 B_6/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 B_6 and 1.4 mg/kg/d of magnesium gluconate, with no change in autistic behaviors observed, compared with placebo[127]; 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 B_6 (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 B_6 (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 B_6/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 B_6 (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 B_6/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 B_{12} (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 B_{12} deficiency.[133] In a study of 43 individuals with autism, levels of serum and red blood cell folate and serum B_{12} 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-MTHF, the biologically active form of folate); blood folate and vitamin B_{12} 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 developing 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 neuroimmune 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 child[238]; 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 period[240]; 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 ($CaNa_2$-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 children 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 $CaNa_2$-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 a 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 autistic behaviors

Speech/communication	Carnitine	Tetrahydrobiopterin
	Carnosine	B_6/magnesium
	GFCF diet	AI
	Alpha-2 adrenergic agonists	HBOT
	Cyproheptadine	Famotidine
	Glutamate antagonists	Music therapy
	AIT	Neurofeedback
Autistic behavior	Carnosine	Piracetam
	B_6/magnesium	Folic acid/B_{12}
	Probiotics	Digestive enzymes
	GFCF diet	AI
	Alpha-2 adrenergic agonists	HBOT
	Cyproheptadine	Music therapy
	Vision therapy	
Social interaction	Tetrahydrobiopterin	Carnosine
	B_6/magnesium	GFCF diet
	AI	Naltrexone
	HBOT	Oxytocin
	Famotidine	Glutamate antagonists
	Massage	Neurofeedback
Stereotypy	Vitamin C	Omega 3 fatty acids
	B_6/magnesium	Naltrexone
	Alpha-2 adrenergic agonists	Cyproheptadine
	Famotidine	Glutamate antagonists
	AIT	Massage
Hyperactivity	Omega 3 fatty acids	Magnesium
	AI	Naltrexone
	Alpha-2 adrenergic agonists	Chelation
	Glutamate antagonists	AIT
	Massage	
Eye contact	Tetrahydrobiopterin	Omega 3 fatty acids
	AI	HBOT
	Famotidine	Music therapy
Attention	Omega 3 fatty acids	AI
	Alpha-2 adrenergic agonists	Glutamate antagonists
	Music therapy	
Sleep	Melatonin	Carnitine
	Multivitamin	Iron
	Alpha-2 adrenergic agonists	

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 ≥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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REFERENCES

1. Diagnostic and statistical manual of mental disorders, 4th ed. Washington, DC: American Psychiatric Association; 1994.
2. Baird G, Charman T, Baron-Cohen S, et al. A screening instrument for autism at 18 months of age: a 6-year follow-up study. J Am Acad Child Adolesc Psychiatry. 2000;39:694-702.
3. Bertrand J, Mars A, Boyle C, et al. Prevalence of autism in a United States population: the Brick Township, New Jersey, investigation. Pediatrics. 2001;108:1155-1161.
4. Chakrabarti S, Fombonne E. Pervasive developmental disorders in preschool children. JAMA. 2001;285:3093-3099.
5. Rice C. Prevalence of autism spectrum disorders—autism and developmental disabilities monitoring network, 14 sites, United States, 2002. MMWR. 2007;56:12-28.
6. Muhle R, Trentacoste SV, Rapin I. The genetics of autism. Pediatrics. 2004;113:e472-e486.
7. Green VA, Pituch KA, Itchon J, et al. Internet survey of treatments used by parents of children with autism. Res Dev Disabil. 2006;27:70-84.
8. Aman MG, Lam KS, Collier-Crespin A. Prevalence and patterns of use of psychoactive medicines among individuals with autism in the Autism Society of Ohio. J Autism Dev Disord. 2003;33:527-534.
9. Witwer A, Lecavalier L. Treatment incidence and patterns in children and adolescents with autism spectrum disorders. J Child Adolesc Psychopharmacol. 2005;15:671-681.
10. Langworthy-Lam KS, Aman MG, Van Bourgondien ME. Prevalence and patterns of use of psychoactive medicines in individuals with autism in the Autism Society of North Carolina. J Child Adolesc Psychopharmacol. 2002;12:311-321.
11. US Food and Drug Administration. FDA approves the first drug to treat irritability associated with autism, risperdal 2006. Available at: http://www.fda.gov/bbs/topics/news/2006/new01485.html. Accessed May 6, 2009.
12. Scott LJ, Dhillon S. Risperidone: a review of its use in the treatment of irritability associated with autistic disorder in children and adolescents. Paediatr Drugs. 2007;9:343-354.
13. Rosebush PI, Mazurek MF. Neurologic side effects in neuroleptic-naive patients treated with haloperidol or risperidone. Neurology. 1999;52:782-785.
14. Hyman SL, Levy SE. Introduction: novel therapies in developmental disabilities—hope, reason, and evidence. Ment Retard Dev Disabil Res Rev. 2005;11:107-109.
15. American Academy of Pediatrics. Counseling families who choose complementary and alternative medicine for their child with chronic illness or disability. Committee on Children With Disabilities. Pediatrics. 2001;107:598-601.
16. Phillips B, Ball C, Sackett D, et al. Oxford Centre for Evidence-based Medicine Levels of Evidence. 2001. Available at: http://www.cebm.net/levels_of_evidence.asp. Accessed May 6, 2009.
17. Sandler AD, Bodfish JW. Placebo effects in autism: lessons from secretin. J Dev Behav Pediatr. 2000;21:347-350.
18. King BH, Wright DM, Handen BL, et al. Double-blind, placebo-controlled study of amantadine hydrochloride in the treatment of children with autistic disorder. J Am Acad

Child Adolesc Psychiatry. 2001;40:658-665.
19. Defining and describing complementary and alternative medicine. Panel on Definition and Description, CAM Research Methodology Conference, April 1995. Altern Ther Health Med. 1997;3:49-57.
20. Loman DG. The use of complementary and alternative health care practices among children. J Pediatr Health Care. 2003;17:58-63.
21. Sanders H, Davis MF, Duncan B, et al. Use of complementary and alternative medical therapies among children with special health care needs in southern Arizona. Pediatrics. 2003;111:584-587.
22. Wong HH, Smith RG. Patterns of complementary and alternative medical therapy use in children diagnosed with autism spectrum disorders. J Autism Dev Disord. 2006;36:901-909.
23. Hanson E, Kalish LA, Bunce E, et al. Use of complementary and alternative medicine among children diagnosed with autism spectrum disorder. J Autism Dev Disord. 2007;37:628-636.
24. Wong VC. Use of complementary and alternative medicine (CAM) in autism spectrum disorder (ASD): comparison of Chinese and Western culture (part A). J Autism Dev Disord. 2009;39:454-463.
25. Autism Research Institute. Parent ratings of behavorial effects of biomedical interventions. ARI Publ 34; February 2008. http://www.autism.com/treatable/form34qr.htm. Accessed May 6, 2009.
26. Levy SE, Mandell DS, Merhar S, et al. Use of complementary and alternative medicine among children recently diagnosed with autistic spectrum disorder. J Dev Behav Pediatr. 2003;24:418-423.
27. Golnik AE, Ireland M. Complementary alternative medicine for children with autism: a physician survey. J Autism Dev Disord. 2009;39:996-1005.
28. Liptak GS, Orlando M, Yingling JT, et al. Satisfaction with primary health care received by families of children with developmental disabilities. J Pediatr Health Care. 2006;20:245-252.
29. Kemper KJ, O'Connor KG. Pediatricians' recommendations for complementary and alternative medical (CAM) therapies. Ambul Pediatr. 2004;4:482-487.
30. Myers SM, Johnson CP. Management of children with autism spectrum disorders. Pediatrics. 2007;120:1162-1182.
31. Muskiet FA, Kemperman RF. Folate and long-chain polyunsaturated fatty acids in psychiatric disease. J Nutr Biochem. 2006;17:717-727.
32. Fernstrom JD. Can nutrient supplements modify brain function? Am J Clin Nutr. 2000;71:1669S-1675S.
33. Lakhan SE, Vieira KF. Nutritional therapies for mental health disorders. Nutr J. 2008;7:2.
34. Carlton RM, Ente G, Blum L, et al. Rational dosages of nutrients have a prolonged effect on learning disabilities. Altern Ther Health Med. 2000;6:85-91.
35. Benton D, Roberts G. Effect of vitamin and mineral supplementation on intelligence of a sample of schoolchildren. Lancet. 1988;1:140-143.
36. Osendarp SJ, Baghurst KI, Bryan J, et al. Effect of a 12-mo micronutrient intervention on learning and memory in well-nourished and marginally nourished school-aged children: 2 parallel, randomized, placebo-controlled studies in Australia and Indonesia. Am J Clin Nutr. 2007;86:1082-1093.
37. Haskell CF, Scholey AB, Jackson PA, et al. Cognitive and mood effects in healthy children during 12 weeks' supplementation with multi-vitamin/minerals. Br J Nutr. 2008;100:1086-1096.
38. MacLellan D, Taylor J, Wood K. Food intake and academic performance among adolescents. Can J Diet Pract Res. 2008;69:141-144.
39. Schreck KA, Williams K, Smith AF. A comparison of eating behaviors between children with and without autism. J Autism Dev Disord. 2004;34:433-438.
40. Herndon AC, DiGuiseppi C, Johnson SL, et al. Does nutritional intake differ between children with autism spectrum disorders and children with typical development? J Autism Dev Disord. 2009;39:212-222.
41. Ng F, Berk M, Dean O, et al. Oxidative stress in psychiatric disorders: evidence base and therapeutic implications. Int J Neuropsychopharmacol. 2008;11:851-876.
42. Tsaluchidu S, Cocchi M, Tonello L, et al. Fatty acids and oxidative stress in psychiatric disorders. BMC Psychiatry. 2008;8(suppl 1):S5.
43. Yorbik O, Sayal A, Akay C, et al. Investigation of antioxidant enzymes in children with autistic disorder. Prostaglandins Leukot Essent Fatty Acids. 2002;67:341-343.
44. James SJ, Melnyk S, Jernigan S, et al. Metabolic endophenotype and related genotypes are associated with oxidative stress in children with autism. Am J Med Genet B Neuropsychiatr Genet. 2006;141:947-956.
45. James SJ, Cutler P, Melnyk S, et al. Metabolic biomarkers of increased oxidative stress and impaired methylation capacity in children with autism. Am J Clin Nutr. 2004;80:1611-1617.
46. Chauhan A, Chauhan V, Brown WT, et al. Oxidative stress in autism: increased lipid peroxidation and reduced serum levels of ceruloplasmin and transferrin—the antioxidant proteins. Life Sci. 2004;75:2539-2549.
47. Chauhan A, Chauhan V. Oxidative stress in autism. Pathophysiology. 2006;13:171-181.
48. Sperner-Unterweger B. Immunological aetiology of major psychiatric disorders: evidence and therapeutic implications. Drugs. 2005;65:1493-1520.
49. Pardo CA, Vargas DL, Zimmerman AW. Immunity, neuroglia and neuroinflammation in autism. Int Rev Psychiatry. 2005;17:485-495.
50. Vargas DL, Nascimbene C, Krishnan C, et al. Neuroglial activation and neuroinflammation in the brain of patients with autism. Ann Neurol. 2005;57:67-81.
51. Chez MG, Dowling T, Patel PB, et al. Elevation of tumor necrosis factor-alpha in cerebrospinal fluid of autistic children. Pediatr Neurol. 2007;36:361-365.
52. Connolly AM, Chez MG, Pestronk A, et al. Serum autoantibodies to brain in Landau-Kleffner variant, autism, and other neurologic disorders. J Pediatr. 1999;134:607-613.
53. Connolly AM, Chez M, Streif EM, et al. Brain-derived neurotrophic factor and autoantibodies to neural antigens in sera of children with autistic spectrum disorders, Landau-Kleffner syndrome, and epilepsy. Biol Psychiatry. 2006;59:354-363.
54. Torrente F, Ashwood P, Day R, et al. Small intestinal enteropathy with epithelial IgG and complement deposition in children with regressive autism. Mol Psychiatry. 2002;7:375-382, 334.
55. Furlano RI, Anthony A, Day R, et al. Colonic CD8 and gamma delta T-cell infiltration with epithelial damage in children with autism. J Pediatr. 2001;138:366-372.
56. Ashwood P, Anthony A, Pellicer AA, et al. Intestinal lymphocyte populations in children with regressive autism: evidence for extensive mucosal immunopathology. J Clin Immunol. 2003;23:504-517.
57. Balzola F, Daniela C, Repici A, et al. Autistic enterocolitis: confirmation of a new inflammatory bowel disease in an Italian cohort of patients. Gastroenterology. 2005;128:A303.
58. Horvath K, Papadimitriou JC, Rabsztyn A, et al. Gastrointestinal abnormalities in children with autistic disorder. J Pediatr. 1999;135:559-563.
59. Valicenti-McDermott M, McVicar K, Rapin I, et al. Frequency of gastrointestinal symptoms in children with autistic spectrum disorders and association with family history of autoimmune disease. J Dev Behav Pediatr. 2006;27:S128-S136.
60. Horvath K, Perman JA. Autism and gastrointestinal symptoms. Curr Gastroenterol Rep. 2002;4:251-258.
61. Finegold SM, Molitoris D, Song Y, et al. Gastrointestinal microflora studies in late-onset autism. Clin Infect Dis. 2002;35:S6-S16.
62. Song Y, Liu C, Finegold SM. Real-time PCR quantitation of clostridia in feces of autistic children. Appl Environ Microbiol. 2004;70:6459-6465.
63. Parracho HM, Bingham MO, Gibson GR, et al. Differences between the gut microflora of children with autistic spectrum disorders and that of healthy children. J Med Microbiol. 2005;54:987-991.
64. Jyonouchi H, Geng L, Ruby A, et al. Evaluation of an association between gastrointestinal symptoms and cytokine production against common dietary proteins in children with autism spectrum disorders. J Pediatr. 2005;146:605-610.
65. Buie TM. Gastroesophageal reflux in children with autism: how do children present and can one test these children? J Pediatr Gastroenterol Nutr. 2005;41:505.
66. Levy SE, Hyman SL. Novel treatments for autistic spectrum disorders. Ment Retard Dev Disabil Res Rev. 2005;11:131-142.
67. Nir I, Meir D, Zilber N, et al. Brief report: circadian melatonin, thyroid-stimulating hormone, prolactin, and cortisol levels in serum of young adults with autism. J Autism Dev Disord. 1995;25:641-654.
68. Kulman G, Lissoni P, Rovelli F, et al. Evidence of pineal endocrine hypofunction in autistic children. Neuro Endocrinol Lett. 2000;21:31-34.
69. Tordjman S, Anderson GM, Pichard N, et al. Nocturnal excretion of 6-sulphatoxymelatonin in children and adolescents with autistic disorder. Biol Psychiatry. 2005;57:134-138.
70. Melke J, Goubran Botros H, Chaste P, et al. Abnormal melatonin synthesis in autism spectrum disorders. Mol Psychiatry. 2008;13:90-98.
71. Jan JE, O'Donnell ME. Use of melatonin in the treatment of paediatric sleep disorders. J Pineal Res. 1996;21:193-199.
72. Hayashi E. Effect of melatonin on sleep-wake rhythm: the sleep diary of an autistic male. Psychiatry Clin Neurosci. 2000;54:383-384.
73. Ishizaki A, Sugama M, Takeuchi N. [Usefulness of melatonin for developmental sleep and emotional/behavior disorders—studies of melatonin trial on 50 patients with developmental disorders] [In Japanese]. No To Hattatsu. 1999;31:428-437.
74. Paavonen EJ, Nieminen-von Wendt T, Vanhala R, et al. Effectiveness of melatonin in the treatment of sleep disturbances in children with Asperger disorder. J Child Adolesc Psychopharmacol. 2003;13:83-95.
75. Giannotti F, Cortesi F, Cerquiglini A, et al. An open-label study of controlled-release melatonin in treatment of sleep disorders in children with autism. J Autism Dev Disord. 2006;36:741-752.
76. Andersen IM, Kaczmarska J, McGrew SG, et al. Melatonin for insomnia in children with autism spectrum disorders. J Child Neurol. 2008;23:482-485.
77. Wasdell MB, Jan JE, Bomben MM, et al. A randomized, placebo-controlled trial of controlled release melatonin treatment of delayed sleep phase syndrome and impaired sleep maintenance in children with neurodevelopmental disabilities. J Pineal Res. 2008;44:57-64.
78. Garstang J, Wallis M. Randomized controlled trial of melatonin for children with autistic spectrum disorders and sleep problems. Child Care Health Dev. 2006;32:585-589.
79. Wirojanan J, Jacquemont S, Diaz R, et al. The efficacy of melatonin for sleep problems in children with autism, fragile X syndrome, or autism and fragile X syndrome. J Clin Sleep Med. 2009;5:145-150.
80. Filipek PA, Juranek J, Nguyen MT, et al. Relative carnitine deficiency in autism. J Autism Dev Disord. 2004;34:615-623.
81. Ellaway CJ, Peat J, Williams K, et al. Medium-term open label trial of L-carnitine in Rett syndrome. Brain Dev. 2001;23 suppl 1:S85-S89.
82. Ellaway C, Williams K, Leonard H, et al. Rett syndrome: randomized controlled trial of L-carnitine. J Child Neurol. 1999;14:162-167.
83. Tani Y, Fernell E, Watanabe Y, et al. Decrease in 6R-5,6,7,8-tetrahydrobiopterin content in cerebrospinal fluid of autistic patients. Neurosci Lett. 1994;181:169-172.
84. Komori H, Matsuishi T, Yamada S, et al. Cerebrospinal fluid biopterin and biogenic amine metabolites during oral R-THBP therapy for infantile autism. J Autism Dev Disord. 1995;25:183-193.
85. Nagahata M, Kazamaturi H, Nuruse H, et al. Clini-

cal evaluation of apropterin hydrochloride (R-THBP) on infantile autism: a multicenter cooperative study. In: Naruse H, Ornitz EM, eds. Neurobiology of infantile autism. Proceedings of the International Symposium on Neurobiology of Infantile Autism; Nov 10-11, 1990; Tokyo, Japan. Amsterdam: Elsevier Science Ltd; 1992: 351-354.
86. Fernell E, Watanabe Y, Adolfsson I, et al. Possible effects of tetrahydrobiopterin treatment in six children with autism—clinical and positron emission tomography data: a pilot study. Dev Med Child Neurol. 1997;39:313-318.
87. Danfors T, von Knorring AL, Hartvig P, et al. Tetrahydrobiopterin in the treatment of children with autistic disorder: a double-blind placebo-controlled crossover study. J Clin Psychopharmacol. 2005;25:485-489.
88. Nakane Y, Naruse H, Takesada M, et al. Clinical effect of R-THBP on infantile autism. In: Naruse H, Ornitz EM, eds. Neurobiology of infantile autism. Proceedings of the International Symposium on Neurobiology of Infantile Autism; Nov 10-11, 1990; Tokyo, Japan. Amsterdam: Elsevier Science Ltd; 1992: 337-350.
89. Monks G, Juracek L, Weigand D, et al. A case of scurvy in an autistic boy. J Drugs Dermatol. 2002;1:67-69.
90. Duggan CP, Westra SJ, Rosenberg AE. Case records of the Massachusetts General Hospital. Case 23-2007. A 9-year-old boy with bone pain, rash, and gingival hypertrophy. N Engl J Med. 2007;357:392-400.
91. Dolske MC, Spollen J, McKay S, et al. A preliminary trial of ascorbic acid as supplemental therapy for autism. Prog Neuropsychopharmacol Biol Psychiatry. 1993;17:765-774.
92. Chez MG, Buchanan CP, Aimonovitch MC, et al. Double-blind, placebo-controlled study of L-carnosine supplementation in children with autistic spectrum disorders. J Child Neurol. 2002;17:833-837.
93. Adams JB, Holloway C. Pilot study of a moderate dose multivitamin/mineral supplement for children with autistic spectrum disorder. J Altern Complement Med. 2004;10:1033-1039.
94. Paczynski M. Piracetam: a novel therapy for autism? J Autism Dev Disord. 1997;27:628-630.
95. Akhondzadeh S, Tajdar H, Mohammadi MR, et al. A double-blind placebo controlled trial of piracetam added to risperidone in patients with autistic disorder. Child Psychiatry Hum Dev. 2008;39:237-245.
96. Richardson AJ, Calvin CM, Clisby C, et al. Fatty acid deficiency signs predict the severity of reading and related difficulties in dyslexic children. Prostaglandins Leukot Essent Fatty Acids. 2000;63:69-74.
97. Richardson AJ. Omega-3 fatty acids in ADHD and related neurodevelopmental disorders. Int Rev Psychiatry. 2006;18:155-172.
98. Richardson AJ. Long-chain polyunsaturated fatty acids in childhood developmental and psychiatric disorders. Lipids. 2004;39:1215-1222.
99. Stevens LJ, Zentall SS, Abate ML, et al. Omega-3 fatty acids in boys with behavior, learning, and health problems. Physiol Behav. 1996;59:915-920.
100. Vancassel S, Durand G, Barthelemy C, et al. Plasma fatty acid levels in autistic children. Prostaglandins Leukot Essent Fatty Acids. 2001;65:1-7.
101. Bell JG, MacKinlay EE, Dick JR, et al. Essential fatty acids and phospholipase A2 in autistic spectrum disorders. Prostaglandins Leukot Essent Fatty Acids. 2004;71:201-204.
102. Sliwinski S, Croonenberghs J, Christophe A, et al. Polyunsaturated fatty acids: do they have a role in the pathophysiology of autism? Neuro Endocrinol Lett. 2006;27:465-471.
103. Schultz ST, Klonoff-Cohen HS, Wingard DL, et al. Breastfeeding, infant formula supplementation, and autistic disorder: the results of a parent survey. Int Breastfeed J. 2006;1:16.
104. Johnson SM, Hollander E. Evidence that eicosapentaenoic acid is effective in treating autism. J Clin Psychiatry. 2003;64:848-849.
105. Patrick L, Salik R. The effect of essential fatty acid supplementation on language development and learning skills in autism and Asperger's syndrome. Autism Asperger's Digest. 2005;Jan/Feb:36-37.
106. Politi P, Cena H, Comelli M, et al. Behavioral effects of omega-3 fatty acid supplementation in young adults with severe autism: an open label study. Arch Med Res. 2008;39:682-685.
107. Meguid NA, Atta HM, Gouda AS, et al. Role of polyunsaturated fatty acids in the management of Egyptian children with autism. Clin Biochem. 2008;41:1044-1048.
108. Amminger GP, Berger GE, Schafer MR, et al. Omega-3 fatty acids supplementation in children with autism: a double-blind randomized, placebo-controlled pilot study. Biol Psychiatry. 2007;61:551-553.
109. Bent S, Bertoglio K, Hendren RL. Omega-3 fatty acids for autistic spectrum disorder: a systematic review. J Autism Dev Disord. 2009; 39:1145-1154.
110. Adams JB, George F, Audhya T. Abnormally high plasma levels of vitamin B6 in children with autism not taking supplements compared to controls not taking supplements. J Altern Complement Med. 2006;12:59-63.
111. Strambi M, Longini M, Hayek J, et al. Magnesium profile in autism. Biol Trace Elem Res. 2006;109:97-104.
112. Bonish VE. Experiences with vitamin B6 with brain-damaged children with autistic syndrome. Proxis der Kinderpsychologie. 1968;8:308-310.
113. Rimland B. An orthomolecular study of psychotic children. Orthomolecular Psychiatry. 1974;3:371-377.
114. Barthelemy C, Martineau J, Bruneau N, et al. [Clinical (behavior scale items), electrophysiologic (conditioned evoked potentials) and biochemical (urinary homovanillic acid) markers in infantile autism] [In French]. Encephale. 1985;11:101-106.
115. Lelord G, Callaway E, Muh JP, et al. [Modifications in urinary homovanillic acid after ingestion of vitamin B6; functional study in autistic children (author's transl)] [In French]. Rev Neurol (Paris). 1978;134:797-801.
116. Martineau J, Garreau B, Barthelemy C, et al. Effects of vitamin B6 on averaged evoked potentials in infantile autism. Biol Psychiatry. 1981;16:627-641.
117. Martineau J, Barthelemy C, Cheliakine C, et al. Brief report: an open middle-term study of combined vitamin B6-magnesium in a subgroup of autistic children selected on their sensitivity to this treatment. J Autism Dev Disord. 1988;18:435-447.
118. Martineau J, Barthelemy C, Roux S, et al. Electrophysiological effects of fenfluramine or combined vitamin B6 and magnesium on children with autistic behaviour. Dev Med Child Neurol. 1989;31:721-727.
119. Menage P, Thibault G, Barthelemy C, et al. CD 4+ CD 45 RA+ T lymphocyte deficiency in autistic children: effect of a pyridoxine-magnesium treatment. Brain Dysfunct. 1992;5:326-333.
120. Barthelemy C, Garreau B, Leddet I, et al. [Biological and clinical effects of oral magnesium and associated magnesium-vitamin B6 administration on certain disorders observed in infantile autism (author's transl)] [In French]. Therapie. 1980;35:627-632.
121. Barthelemy C, Garreau B, Leddet I. Behavioral and biological effects of oral magnesium, vitamin B6 and combined magnesium–vitamin B6 administration in autistic children. Magnes Bull. 1981;2:150-153.
122. Jonas C, Etienne T, Barthelemy C, et al. [Clinical and biochemical value of Magnesium + vitamin B6 combination in the treatment of residual autism in adults] [In French]. Therapie. 1984;39:661-669.
123. Martineau J, Barthelemy C, Garreau B, et al. Vitamin B6, magnesium, and combined B6-Mg: therapeutic effects in childhood autism. Biol Psychiatry. 1985;20:467-478.
124. Lelord G, Muh JP, Barthelemy C, et al. Effects of pyridoxine and magnesium on autistic symptoms—initial observations. J Autism Dev Disord. 1981;11:219-230.
125. Lelord G, Callaway E, Muh JP. Clinical and biological effects of high doses of vitamin B6 and magnesium on autistic children. Acta Vitaminol Enzymol. 1982;4:27-44.
126. Rimland B, Callaway E, Dreyfus P. The effect of high doses of vitamin B6 on autistic children: a double-blind crossover study. Am J Psychiatry. 1978;135:472-475.
127. Tolbert L, Haigler T, Waits MM, et al. Brief report: lack of response in an autistic population to a low dose clinical trial of pyridoxine plus magnesium. J Autism Dev Disord. 1993;23:193-199.
128. Findling RL, Maxwell K, Scotese-Wojtila L, et al. High-dose pyridoxine and magnesium administration in children with autistic disorder: an absence of salutary effects in a double-blind, placebo-controlled study. J Autism Dev Disord. 1997;27:467-478.
129. Kuriyama S, Kamiyama M, Watanabe M, et al. Pyridoxine treatment in a subgroup of children with pervasive developmental disorders. Dev Med Child Neurol. 2002;44:284-286.
130. Nye C, Brice A. Combined vitamin B6-magnesium treatment in autism spectrum disorder. Cochrane Database Syst Rev. 2005;(4):CD003497.
131. Mousain-Bosc M, Roche M, Polge A, et al. Improvement of neurobehavioral disorders in children supplemented with magnesium-vitamin B6. II. Pervasive developmental disorder-autism. Magnes Res. 2006;19:53-62.
132. McGuire JK, Kulkarni MS, Baden HP. Fatal hypermagnesemia in a child treated with megavitamin/megamineral therapy. Pediatrics. 2000;105:E18.
133. Wakefield AJ, Murch SH, Anthony A, et al. Ileal-lymphoid-nodular hyperplasia, non-specific colitis, and pervasive developmental disorder in children. Lancet. 1998;351:637-641.
134. Lowe TL, Cohen DJ, Miller S, et al. Folic acid and B12 in autism and neuropsychiatric disturbances of childhood. J Am Acad Child Psychiatry. 1981;20:104-111.
135. Gillberg C, Wahlstrom J, Johansson R, et al. Folic acid as an adjunct in the treatment of children with the autism fragile-X syndrome (AFRAX). Dev Med Child Neurol. 1986;28:624-627.
136. Nakano K, Noda N, Tachikawa E, et al. A preliminary study of methylcobalamin therapy in autism. Journal of Tokyo Women's Medical University. 2005;75:64-69.
137. James SJ, Melnyk S, Fuchs G, et al. Efficacy of methylcobalamin and folinic acid treatment on glutathione redox status in children with autism. Am J Clin Nutr. 2009;89:1-6.
138. Moretti P, Peters SU, Del Gaudio D, et al. Brief report: autistic symptoms, developmental regression, mental retardation, epilepsy, and dyskinesias in CNS folate deficiency. J Autism Dev Disord. 2008;38:1170-1177.
139. Moretti P, Sahoo T, Hyland K, et al. Cerebral folate deficiency with developmental delay, autism, and response to folinic acid. Neurology. 2005;64:1088-1090.
140. Ramaekers VT, Blau N, Sequeira JM, et al. Folate receptor autoimmunity and cerebral folate deficiency in low-functioning autism with neurological deficits. Neuropediatrics. 2007;38:276-281.
141. Ramaekers VT, Sequeira JM, Blau N, et al. A milk-free diet downregulates folate receptor autoimmunity in cerebral folate deficiency syndrome. Dev Med Child Neurol. 2008;50:346-352.
142. Niederhofer H. First preliminary results of an observation of Ginkgo Biloba treating patients with autistic disorder. Phytother Res. 2009 Mar 9. [E-pub ahead of print.]
143. Levine J, Aviram A, Holan A, et al. Inositol treatment of autism. J Neural Transm. 1997;104:307-310.
144. Lozoff B, Beard J, Connor J, et al. Long-lasting neural and behavioral effects of iron deficiency in infancy. Nutr Rev. 2006;64:S34-43; discussion S72-91.
145. Halterman JS, Kaczorowski JM, Aligne CA, et al. Iron deficiency and cognitive achievement among school-aged children and adolescents in the United States. Pediatrics. 2001;107:1381-1386.
146. Bruner AB, Joffe A, Duggan AK, et al. Randomised study of cognitive effects of iron supplementation in non-anaemic iron-deficient adolescent girls. Lancet. 1996;348:992-996.
147. Latif A, Heinz P, Cook R. Iron deficiency in autism and Asperger syndrome. Autism. 2002;6:103-114.
148. Dosman CF, Drmic IE, Brian JA, et al. Ferritin as an indicator of suspected iron deficiency in children with autism spectrum disorder: prevalence of low serum ferritin concentration. Dev Med Child Neurol. 2006;48:1008-1009.

149. Cornish E. A balanced approach towards healthy eating in autism. Journal of Human Nutrition and Dietetics. 1998;11:501-509.
150. Dosman CF, Brian JA, Drmic IE, et al. Children with autism: effect of iron supplementation on sleep and ferritin. Pediatr Neurol. 2007;36:152-158.
151. Sandler RH, Finegold SM, Bolte ER, et al. Short-term benefit from oral vancomycin treatment of regressive-onset autism. J Child Neurol. 2000;15:429-435.
152. Brudnak MA, Rimland B, Kerry RE, et al. Enzyme-based therapy for autism spectrum disorders—is it worth another look? Med Hypotheses. 2002;58:422-428.
153. Brudnak MA. Probiotics as an adjuvant to detoxification protocols. Med Hypotheses. 2002;58:382-385.
154. Blades M. Autism: an interesting dietary case history. Nutrition and Food Science. 2000;30:137-140.
155. Niederhofer H. St John's Wort treating patients with autistic disorder. Phytother Res. 2009;Mar 9[Epub ahead of print].
156. Bolman WM, Richmond JA. A double-blind, placebo-controlled, crossover pilot trial of low dose dimethylglycine in patients with autistic disorder. J Autism Dev Disord. 1999;29:191-194.
157. Kern JK, Miller VS, Cauller PL, et al. Effectiveness of N,N-dimethylglycine in autism and pervasive developmental disorder. J Child Neurol. 2001;16:169-173.
158. McDougle CJ, Naylor ST, Cohen DJ, et al. Effects of tryptophan depletion in drug-free adults with autistic disorder. Arch Gen Psychiatry. 1996;53:993-1000.
159. Sverd J, Kupietz SS, Winsberg BG, et al. Effects of L-5-hydroxytryptophan in autistic children. J Autism Child Schizophr. 1978;8:171-180.
160. Cannell JJ. Autism and vitamin D. Med Hypotheses. 2008;70:750-759.
161. Stewart C, Latif A. Symptomatic nutritional rickets in a teenager with autistic spectrum disorder. Child Care Health Dev. 2008;34:276-278.
162. Clark JH, Rhoden DK, Turner DS. Symptomatic vitamin A and D deficiencies in an eight-year-old with autism. JPEN J Parenter Enteral Nutr. 1993;17:284-286.
163. Steinemann TL, Christiansen SP. Vitamin A deficiency and xerophthalmia in an autistic child. Arch Ophthalmol. 1998;116:392-393.
164. Uyanik O, Dogangun B, Kayaalp L, et al. Food faddism causing vision loss in an autistic child. Child Care Health Dev. 2006;32:601-602.
165. Megson MN. Is autism a G-alpha protein defect reversible with natural vitamin A? Med Hypotheses. 2000;54:979-983.
166. Shaywitz BA, Siegel NJ, Pearson HA. Megavitamins for minimal brain dysfunction. A potentially dangerous therapy. JAMA. 1977;238:1749-1750.
167. Kimmoun A, Leheup B, Feillet F, et al. [Hypercalcemia revealing iatrogenic hypervitaminosis A in a child with autistic troubles] [In French]. Arch Pediatr. 2008;15:29-32.
168. Jory J, McGinnis WR. Red-cell trace minerals in children with autism. Am J Biochem Biotech. 2008;4:101-104.
169. Pfeiffer CC, Braverman ER. Zinc, the brain and behavior. Biol Psychiatry. 1982;17:513-532.
170. Yorbik O, Olgun A, Kirmizigul P, et al. [Plasma zinc and copper levels in boys with oppositional defiant disorder] [In Turkish]. Turk Psikiyatri Derg. 2004;15:276-281.
171. Jackson MJ, Garrod PJ. Plasma zinc, copper, and amino acid levels in the blood of autistic children. J Autism Child Schizophr. 1978;8:203-208.
172. Yorbik O, Akay C, Sayal A, et al. Zinc status in autistic children. J Trace Elem Exp Med. 2004;17:101-107.
173. Panksepp J. A neurochemical theory of autism. Trends Neurosci. 1979;2:174-177.
174. Vojdani A, Campbell AW, Anyanwu E, et al. Antibodies to neuron-specific antigens in children with autism: possible cross-reaction with encephalitogenic proteins from milk, Chlamydia pneumoniae and Streptococcus group A. J Neuroimmunol. 2002;129:168-177.
175. Vojdani A, Pangborn JB, Vojdani E, et al. Infections, toxic chemicals and dietary peptides binding to lymphocyte receptors and tissue enzymes are major instigators of autoimmunity in autism. Int J Immunopathol Pharmacol. 2003;16:189-199.
176. Vojdani A, O'Bryan T, Green JA, et al. Immune response to dietary proteins, gliadin and cerebellar peptides in children with autism. Nutr Neurosci. 2004;7:151-161.
177. Vojdani A, Bazargan M, Vojdani E, et al. Heat shock protein and gliadin peptide promote development of peptidase antibodies in children with autism and patients with autoimmune disease. Clin Diagn Lab Immunol. 2004;11:515-524.
178. Jyonouchi H, Sun S, Itokazu N. Innate immunity associated with inflammatory responses and cytokine production against common dietary proteins in patients with autism spectrum disorder. Neuropsychobiology. 2002;46:76-84.
179. Ashwood P, Anthony A, Torrente F, et al. Spontaneous mucosal lymphocyte cytokine profiles in children with autism and gastrointestinal symptoms: mucosal immune activation and reduced counter regulatory interleukin-10. J Clin Immunol. 2004;24:664-673.
180. Afzal N, Murch S, Thirrupathy K, et al. Constipation with acquired megarectum in children with autism. Pediatrics. 2003;112:939-942.
181. Barcia G, Posar A, Santucci M, et al. Autism and coeliac disease. J Autism Dev Disord. 2008;38:407-408.
182. Lucarelli S, Frediani T, Zingoni AM, et al. Food allergy and infantile autism. Panminerva Med. 1995;37:137-141.
183. Evangeliou A, Vlachonikolis I, Mihailidou H, et al. Application of a ketogenic diet in children with autistic behavior: pilot study. J Child Neurol. 2003;18:113-118.
184. O'Banion D, Armstrong B, Cummings RA, et al. Disruptive behavior: a dietary approach. J Autism Child Schizophr. 1978;8:325-337.
185. Sponheim E. [Gluten-free diet in infantile autism. A therapeutic trial] [In Norwegian]. Tidsskr Nor Laegeforen. 1991;111:704-707.
186. Reichelt KL, Ekrem J, Scott H. Gluten, milk proteins and autism: dietary intervention effects on behavior and peptide secretion. J Appl Nutr. 1990;42:1-11.
187. Knivsberg AM, Wiig K, Lind G, et al. Dietary intervention in autistic syndromes. Brain Dysfunction. 1990;3:315-327.
188. Knivsberg AM, Reichelt KL, Nodland M, et al. Autistic symptoms and diet: a follow-up study. Scand J Ed Research. 1995;39:223-236.
189. Whiteley P, Rodgers J, Savery D, et al. A gluten-free diet as an intervention for autism and associated spectrum disorders: preliminary findings. Autism. 1999;3:45.
190. Cade R, Privette M, Fregly M, et al. Autism and schizophrenia: intestinal disorders. Nutritional Neuroscience. 2000;3:57-72.
191. Christison GW, Ivany K. Elimination diets in autism spectrum disorders: any wheat amidst the chaff? J Dev Behav Pediatr. 2006;27:S162-S171.
192. Goin-Kochel RP, Mackintosh VH, Myers BJ. Parental reports on the efficacy of treatments and therapies for their children with autism spectrum disorders. Research in Autism Spectrum Disorders. 2009;3:528-537.
193. Knivsberg AM, Reichelt KL, Hoien T, et al. A randomised, controlled study of dietary intervention in autistic syndromes. Nutr Neurosci. 2002;5:251-261.
194. Elder JH, Shankar M, Shuster J, et al. The gluten-free, casein-free diet in autism: results of a preliminary double blind clinical trial. J Autism Dev Disord. 2006;36:413-420.
195. Millward C, Ferriter M, Calver S, et al. Gluten- and casein-free diets for autistic spectrum disorder. Cochrane Database Syst Rev. 2008;(2):CD003498.
196. Adams SJ, Burton N, Cutress A, et al. Development of double blind gluten and casein free test foods for use in an autism dietary trial. J Hum Nutr Diet. 2008;21:374.
197. Arnold GL, Hyman SL, Mooney RA, et al. Plasma amino acids profiles in children with autism: potential risk of nutritional deficiencies. J Autism Dev Disord. 2003;33:449-454.
198. Hediger ML, England LJ, Molloy CA, et al. Reduced bone cortical thickness in boys with autism or autism spectrum disorder. J Autism Dev Disord. 2008;38:848-856.
199. Perry EK, Lee ML, Martin-Ruiz CM, et al. Cholinergic activity in autism: abnormalities in the cerebral cortex and basal forebrain. Am J Psychiatry. 2001;158:1058-1066.
200. Chez MG, Aimonovitch M, Buchanan T, et al. Treating autistic spectrum disorders in children: utility of the cholinesterase inhibitor rivastigmine tartrate. J Child Neurol. 2004;19:165-169.
201. Hardan AY, Handen BL. A retrospective open trial of adjunctive donepezil in children and adolescents with autistic disorder. J Child Adolesc Psychopharmacol. 2002;12:237-241.
202. Chez MG, Nowinski CV, Buchanan CP. Donepezil use in children with autistic spectrum disorders. Ann Neurol. 2000;48:541.
203. Chez MG, Buchanan TM, Becker M, et al. Donepezil hydrochloride: a double-blind study in autistic children. J Pediatr Neurol. 2003;1:83-88.
204. Hertzman M. Galantamine in the treatment of adult autism: a report of three clinical cases. Int J Psychiatry Med. 2003;33:395-398.
205. Nicolson R, Craven-Thuss B, Smith J. A prospective, open-label trial of galantamine in autistic disorder. J Child Adolesc Psychopharmacol. 2006;16:621-629.
206. Niederhofer H, Staffen W, Mair A. Galantamine may be effective in treating autistic disorder. BMJ. 2002;325:1422.
207. Campbell M, Anderson LT, Small AM, et al. Naltrexone in autistic children: a double-blind and placebo-controlled study. Psychopharmacol Bull. 1990;26:130-135.
208. Leboyer M, Bouvard MP, Launay JM, et al. Brief report: a double-blind study of naltrexone in infantile autism. J Autism Dev Disord. 1992;22:309-319.
209. Willemsen-Swinkels SH, Buitelaar JK, Weijnen FG, et al. Placebo-controlled acute dosage naltrexone study in young autistic children. Psychiatry Res. 1995;58:203-215.
210. Bouvard MP, Leboyer M, Launay JM, et al. Low-dose naltrexone effects on plasma chemistries and clinical symptoms in autism: a double-blind, placebo-controlled study. Psychiatry Res. 1995;58:191-201.
211. Kolmen BK, Feldman HM, Handen BL, et al. Naltrexone in young autistic children: a double-blind, placebo-controlled crossover study. J Am Acad Child Adolesc Psychiatry. 1995;34:223-231.
212. Willemsen-Swinkels SH, Buitelaar JK, van Engeland H. The effects of chronic naltrexone treatment in young autistic children: a double-blind placebo-controlled crossover study. Biol Psychiatry. 1996;39:1023-1031.
213. Elchaar GM, Maisch NM, Augusto LM, et al. Efficacy and safety of naltrexone use in pediatric patients with autistic disorder. Ann Pharmacother. 2006;40:1086-1095.
214. Koshes RJ, Rock NL. Use of clonidine for behavioral control in an adult patient with autism. Am J Psychiatry. 1994;151:1714.
215. Ming X, Gordon E, Kang N, et al. Use of clonidine in children with autism spectrum disorders. Brain Dev. 2008;30:454-460.
216. Fankhauser MP, Karumanchi VC, German ML, et al. A double-blind, placebo-controlled study of the efficacy of transdermal clonidine in autism. J Clin Psychiatry. 1992;53:77-82.
217. Jaselskis CA, Cook EH Jr, Fletcher KE, et al. Clonidine treatment of hyperactive and impulsive children with autistic disorder. J Clin Psychopharmacol. 1992;12:322-327.
218. Posey DJ, Puntney JI, Sasher TM, et al. Guanfacine treatment of hyperactivity and inattention in pervasive developmental disorders: a retrospective analysis of 80 cases. J Child Adolesc Psychopharmacol. 2004;14:233-241.
219. Scahill L, Aman MG, McDougle CJ, et al. A prospective open trial of guanfacine in children with pervasive developmental disorders. J Child Adolesc Psychopharmacol. 2006;16:589-598.
220. Handen BL, Sahl R, Hardan AY. Guanfacine in chil-

dren with autism and/or intellectual disabilities. J Dev Behav Pediatr. 2008;29:303-308.
221. Boellner SW, Pennick M, Fiske K, et al. Pharmacokinetics of a guanfacine extended-release formulation in children and adolescents with attention-deficit-hyperactivity disorder. Pharmacotherapy. 2007;27:1253-1262.
222. Rossignol DA. Hyperbaric oxygen therapy might improve certain pathophysiological findings in autism. Med Hypotheses. 2007;68:1208-1227.
223. Rossignol DA, Rossignol LW. Hyperbaric oxygen therapy may improve symptoms in autistic children. Med Hypotheses. 2006;67:216-228.
224. Rossignol DA, Rossignol LW, James SJ, et al. The effects of hyperbaric oxygen therapy on oxidative stress, inflammation, and symptoms in children with autism: an open-label pilot study. BMC Pediatr. 2007;7:36.
225. Chungpaibulpatana J, Sumpatanarax T, Thadakul N, et al. Hyperbaric oxygen therapy in Thai autistic children. J Med Assoc Thai. 2008;91:1232-1238.
226. Rossignol DA, Rossignol LW, Smith S, et al. Hyperbaric treatment for children with autism: a multicenter, randomized, double-blind, controlled trial. BMC Pediatr. 2009;9:21.
227. Shenoy S, Arnold S, Chatila T. Response to steroid therapy in autism secondary to autoimmune lymphoproliferative syndrome. J Pediatr. 2000;136:682-687.
228. Stefanatos GA, Grover W, Geller E. Case study: corticosteroid treatment of language regression in pervasive developmental disorder. J Am Acad Child Adolesc Psychiatry. 1995;34:1107-1111.
229. Chez MG, Loeffel M, Buchanan C, et al. Pulse high dose steroids as combination therapy with valproic acid in epileptic aphasia patients with pervasive developmental delay or autism. Ann Neurol. 1998;44:539.
230. Buitelaar JK, van Engeland H, de Kogel K, et al. The adrenocorticotrophic hormone (4-9) analog ORG 2766 benefits autistic children: report on a second controlled clinical trial. J Am Acad Child Adolesc Psychiatry. 1992;31:1149-1156.
231. Buitelaar JK, van Engeland H, de Kogel KH, et al. The use of adrenocorticotrophic hormone (4-9) analog ORG 2766 in autistic children: effects on the organization of behavior. Biol Psychiatry. 1992;31:1119-1129.
232. Buitelaar JK, van Engeland H, van Ree JM, et al. Behavioral effects of Org 2766, a synthetic analog of the adrenocorticotrophic hormone (4-9), in 14 outpatient autistic children. J Autism Dev Disord. 1990;20:467-478.
233. Boris M, Kaiser CC, Goldblatt A, et al. Effect of pioglitazone treatment on behavioral symptoms in autistic children. J Neuroinflammation. 2007;4:3.
234. Bradstreet JJ, Smith S, Granpeesheh D, et al. Spironolactone might be a desirable immunologic and hormonal intervention in autism spectrum disorders. Med Hypotheses. 2007;68:979-987.
235. Gupta S, Rimland B, Shilling PD. Pentoxifylline: brief review and rationale for its possible use in the treatment of autism. J Child Neurol. 1996;11:501-504.
236. Heuer L, Ashwood P, Schauer J, et al. Reduced levels of immunoglobulin in children with autism correlates with behavioral symptoms. Autism Res. 2008;1:275-283.
237. Gupta S, Aggarwal S, Heads C. Dysregulated immune system in children with autism: beneficial effects of intravenous immune globulin on autistic characteristics. J Autism Dev Disord. 1996;26:439-452.
238. Plioplys AV. Intravenous immunoglobulin treatment of children with autism. J Child Neurol. 1998;13:79-82.
239. Gupta S. Immunological treatments for autism. J Autism Dev Disord. 2000;30:475-479.
240. DelGiudice-Asch G, Simon L, Schmeidler J, et al. Brief report: a pilot open clinical trial of intravenous immunoglobulin in childhood autism. J Autism Dev Disord. 1999;29:157-160.
241. Plioplys AV. Intravenous immunoglobulin treatment in autism. J Autism Dev Disord. 2000;30:73-74.
242. Boris M, Goldblatt A, Edelson SM. Improvement in children with autism treated with intravenous gamma globulin. J Nutritional Environmental Medicine. 2005;15:169-176.
243. Schneider CK, Melmed RD, Barstow LE, et al. Oral human immunoglobulin for children with autism and gastrointestinal dysfunction: a prospective, open-label study. J Autism Dev Disord. 2006;36:1053-1064.
244. Handen BL, Melmed RD, Hansen RL, et al. A double-blind, placebo-controlled trial of oral human immunoglobulin for gastrointestinal dysfunction in children with autistic disorder. J Autism Dev Disord. 2009;39:796-805.
245. Stubbs EG, Budden SS, Burger DR, et al. Transfer factor immunotherapy of an autistic child with congenital cytomegalovirus. J Autism Dev Disord. 1980;10:451-458.
246. Fudenberg HH. Dialysable lymphocyte extract (DLyE) in infantile onset autism: a pilot study. Biotherapy. 1996;9:143-147.
247. Bartz JA, Hollander E. Oxytocin and experimental therapeutics in autism spectrum disorders. Prog Brain Res. 2008;170:451-462.
248. Lerer E, Levi S, Salomon S, et al. Association between the oxytocin receptor (OXTR) gene and autism: relationship to Vineland Adaptive Behavior Scales and cognition. Mol Psychiatry. 2008;13:980-988.
249. Wu S, Jia M, Ruan Y, et al. Positive association of the oxytocin receptor gene (OXTR) with autism in the Chinese Han population. Biol Psychiatry. 2005;58:74-77.
250. Jacob S, Brune CW, Carter CS, et al. Association of the oxytocin receptor gene (OXTR) in Caucasian children and adolescents with autism. Neurosci Lett. 2007;417:6-9.
251. Modahl C, Green L, Fein D, et al. Plasma oxytocin levels in autistic children. Biol Psychiatry. 1998;43:270-277.
252. Domes G, Heinrichs M, Michel A, et al. Oxytocin improves "mind-reading" in humans. Biol Psychiatry. 2007;61:731-733.
253. Hollander E, Novotny S, Hanratty M, et al. Oxytocin infusion reduces repetitive behaviors in adults with autistic and Asperger's disorders. Neuropsychopharmacology. 2003;28:193-198.
254. Hollander E, Bartz J, Chaplin W, et al. Oxytocin increases retention of social cognition in autism. Biol Psychiatry. 2007;61:498-503.
255. Cohen DJ, Johnson WT, Caparulo BK. Pica and elevated blood lead level in autistic and atypical children. Am J Dis Child. 1976;130:47-48.
256. Accardo P, Whitman B, Caul J, et al. Autism and plumbism. A possible association. Clin Pediatr (Phila). 1988;27:41-44.
257. Eppright TD, Sanfacon JA, Horwitz EA. Attention deficit hyperactivity disorder, infantile autism, and elevated blood-lead: a possible relationship. Mo Med. 1996;93:136-138.
258. Lidsky TI, Schneider JS. Autism and autistic symptoms associated with childhood lead poisoning. Journal of Applied Research. 2005;5:80-87.
259. Kidd PM. Autism, an extreme challenge to integrative medicine. Part II: medical management. Alternative Medicine Review. 2002;7:472-499.
260. Lonsdale D, Shamberger RJ, Audhya T. Treatment of autism spectrum children with thiamine tetrahydrofurfuryl disulfide: a pilot study. Neuro Endocrinol Lett. 2002;23:303-308.
261. Geier DA, Geier MR. A clinical trial of combined anti-androgen and anti-heavy metal therapy in autistic disorders. Neuro Endocrinol Lett. 2006;27:833-838.
262. Patel K, Curtis LT. A comprehensive approach to treating autism and attention-deficit hyperactivity disorder: a prepilot study. J Altern Complement Med. 2007;13:1091-1097.
263. Nataf R, Skorupka C, Amet L, et al. Porphyrinuria in childhood autistic disorder: implications for environmental toxicity. Toxicol Appl Pharmacol. 2006;214:99-108.
264. Bradstreet JJ, Geier DA, Kartzinel JJ, et al. A case-control study of mercury burden in children with autistic spectrum disorders. Journal of American Physicians and Surgeons. 2003;8:76-79.
265. Soden SE, Lowry JA, Garrison CB, et al. 24-hour provoked urine excretion test for heavy metals in children with autism and typically developing controls, a pilot study. Clin Toxicol (Phila). 2007;45:476-481.
266. Shannon M, Graef JW. Lead intoxication in children with pervasive developmental disorders. J Toxicol Clin Toxicol. 1996;34:177-181.
267. Geier DA, Geier MR. A prospective assessment of porphyrins in autistic disorders: a potential marker for heavy metal exposure. Neurotox Res. 2006;10:57-64.
268. Geier DA, Geier MR. A prospective study of mercury toxicity biomarkers in autistic spectrum disorders. J Toxicol Environ Health A. 2007;70:1723-1730.
269. Van der Linde AA, Pillen S, Gerrits GP, et al. Stevens-Johnson syndrome in a child with chronic mercury exposure and 2,3-dimercaptopropane-1-sulfonate (DMPS) therapy. Clin Toxicol (Phila). 2008;46:479-481.
270. Brown MJ, Willis T, Omalu B, et al. Deaths resulting from hypocalcemia after administration of edetate disodium: 2003-2005. Pediatrics. 2006;118:e534-536.
271. Chen ZK, Lu ZQ. Sodium dimercaptopropane sulfonate as antidote against non-metallic pesticides. Acta Pharmacol Sin. 2004;25:534-544.
272. Flora SJ, Pande M, Mehta A. Beneficial effect of combined administration of some naturally occurring antioxidants (vitamins) and thiol chelators in the treatment of chronic lead intoxication. Chem Biol Interact. 2003;145:267-280.
273. Flora SJ, Flora G, Saxena G, et al. Arsenic and lead induced free radical generation and their reversibility following chelation. Cell Mol Biol (Noisy-le-grand). 2007;53:26-47.
274. Rogan WJ, Dietrich KN, Ware JH, et al. The effect of chelation therapy with succimer on neuropsychological development in children exposed to lead. N Engl J Med. 2001;344:1421-1426.
275. Dietrich KN, Ware JH, Salganik M, et al. Effect of chelation therapy on the neuropsychological and behavioral development of lead-exposed children after school entry. Pediatrics. 2004;114:19-26.
276. Bhattacharya A, Shukla R, Auyang ED, et al. Effect of succimer chelation therapy on postural balance and gait outcomes in children with early exposure to environmental lead. Neurotoxicology. 2007;28:686-695.
277. Mitka M. Chelation therapy trials halted. JAMA. 2008;300:2236.
278. Gudarzi SS, Yasamy M, Akhondzadeh S. Cyproheptadine in treatment of autism. Eur Psychiatry. 2002;17:230-231.
279. Akhondzadeh S, Erfani S, Mohammadi MR, et al. Cyproheptadine in the treatment of autistic disorder: a double-blind placebo-controlled trial. J Clin Pharm Ther. 2004;29:145-150.
280. Linday LA. Oral famotidine: a potential treatment for children with autism. Med Hypotheses. 1997;48:381-386.
281. Linday LA, Tsiouris JA, Cohen IL, et al. Famotidine treatment of children with autistic spectrum disorders: pilot research using single subject research design. J Neural Transm. 2001;108:593-611.
282. Purcell AE, Jeon OH, Zimmerman AW, et al. Postmortem brain abnormalities of the glutamate neurotransmitter system in autism. Neurology. 2001;57:1618-1628.
283. Moreno-Fuenmayor H, Borjas L, Arrieta A, et al. Plasma excitatory amino acids in autism. Invest Clin. 1996;37:113-128.
284. Erickson CA, Chambers JE. Memantine for disruptive behavior in autistic disorder. J Clin Psychiatry. 2006;67:1000.
285. Erickson CA, Posey DJ, Stigler KA, et al. A retrospective study of memantine in children and adolescents with pervasive developmental disorders. Psychopharmacology (Berl). 2007;191:141-147.
286. Owley T, Salt J, Guter S, et al. A prospective, open-label trial of memantine in the treatment of cognitive, behavioral, and memory dysfunction in pervasive developmental disorders. J Child Adolesc Psychopharmacol. 2006;16:517-524.
287. Chez MG, Burton Q, Dowling T, et al. Memantine as adjunctive therapy in children diagnosed with autistic spectrum disorders: an observation of initial clinical response and maintenance tolerability. J Child Neurol. 2007;22:574-579.
288. Uldall P, Hansen FJ, Tonnby B. Lamotrigine in Rett syndrome. Neuropediatrics. 1993;24:339-340.
289. Mendhekar DN, Duggal HS. Acquired variant of Rett's disorder and response to lamotrigine. J Neuropsychiatry Clin Neurosci. 2007;19:474-475.
290. Kumandas S, Caksen H, Ciftci A, et al. Lamotrigine in

two cases of Rett syndrome. Brain Dev. 2001;23:240-242.
291. Stenbom Y, Tonnby B, Hagberg B. Lamotrigine in Rett syndrome: treatment experience from a pilot study. Eur Child Adolesc Psychiatry. 1998;7:49-52.
292. Uvebrant P, Bauziene R. Intractable epilepsy in children. The efficacy of lamotrigine treatment, including non-seizure-related benefits. Neuropediatrics. 1994;25:284-289.
293. Belsito KM, Law PA, Kirk KS, et al. Lamotrigine therapy for autistic disorder: a randomized, double-blind, placebo-controlled trial. J Autism Dev Disord. 2001;31:175-181.
294. Posey DJ, Kem DL, Swiezy NB, et al. A pilot study of D-cycloserine in subjects with autistic disorder. Am J Psychiatry. 2004;161:2115-2117.
295. Sturmey P. Secretin is an ineffective treatment for pervasive developmental disabilities: a review of 15 double-blind randomized controlled trials. Res Dev Disabil. 2005;26:87-97.
296. Esch BE, Carr JE. Secretin as a treatment for autism: a review of the evidence. J Autism Dev Disord. 2004;34:543-556.
297. Williams KW, Wray JJ, Wheeler DM. Intravenous secretin for autism spectrum disorder. Cochrane Database Syst Rev. 2005;(3):CD003495.
298. Ratliff-Schaub K, Carey T, Reeves GD, et al. Randomized controlled trial of transdermal secretin on behavior of children with autism. Autism. 2005;9:256-265.
299. Boso M, Emanuele E, Minazzi V, et al. Effect of long-term interactive music therapy on behavior profile and musical skills in young adults with severe autism. J Altern Complement Med. 2007;13:709-712.
300. Kern P, Aldridge D. Using embedded music therapy interventions to support outdoor play of young children with autism in an inclusive community-based child care program. J Music Ther. 2006;43:270-294.
301. Kim J, Wigram T, Gold C. The effects of improvisational music therapy on joint attention behaviors in autistic children: a randomized controlled study. J Autism Dev Disord. 2008;38:1758-1766.
302. Corbett BA, Shickman K, Ferrer E. Brief report: the effects of Tomatis sound therapy on language in children with autism. J Autism Dev Disord. 2008;38:562-566.
303. Whipple J. Music in intervention for children and adolescents with autism: a meta-analysis. J Music Ther. 2004;41:90-106.
304. Gold C, Wigram T, Elefant C. Music therapy for autistic spectrum disorder. Cochrane Database Syst Rev. 2006;(2):CD004381.
305. Kaplan M, Carmody DP, Gaydos A. Postural orientation modifications in autism in response to ambient lenses. Child Psychiatry Hum Dev. 1996;27:81-91.
306. Kaplan M, Edelson SM, Seip JA. Behavioral changes in autistic individuals as a result of wearing ambient transitional prism lenses. Child Psychiatry Hum Dev. 1998;29:65-76.
307. Chen WX, Wu-Li L, Wong VC. Electroacupuncture for children with autism spectrum disorder: pilot study of 2 cases. J Altern Complement Med. 2008;14:1057-1065.
308. Allam H, ElDine NG, Helmy G. Scalp acupuncture effect on language development in children with autism: a pilot study. J Altern Complement Med. 2008;14:109-114.
309. Rimland B, Edelson SM. Brief report: a pilot study of auditory integration training in autism. J Autism Dev Disord. 1995;25:61-70.
310. Sinha Y, Silove N, Wheeler D, et al. Auditory integration training and other sound therapies for autism spectrum disorders: a systematic review. Arch Dis Child. 2006;91:1018-1022.
311. Cullen-Powell LA, Barlow JH, Cushway D. Exploring a massage intervention for parents and their children with autism: the implications for bonding and attachment. J Child Health Care. 2005;9:245-255.
312. Williams TI. Evaluating effects of aromatherapy massage on sleep in children with autism: a pilot study. Evid Based Complement Alternat Med. 2006;3:373-377.
313. Escalona A, Field T, Singer-Strunck R, et al. Brief report: improvements in the behavior of children with autism following massage therapy. J Autism Dev Disord. 2001;31:513-516.
314. Silva LM, Cignolini A. A medical qigong methodology for early intervention in autism spectrum disorder: a case series. Am J Chin Med. 2005;33:315-327.
315. Silva LM, Ayres R, Schalock M. Outcomes of a pilot training program in a qigong massage intervention for young children with autism. Am J Occup Ther. 2008;62:538-546.
316. Silva LM, Cignolini A, Warren R, et al. Improvement in sensory impairment and social interaction in young children with autism following treatment with an original Qigong massage methodology. Am J Chin Med. 2007;35:393-406.
317. Jarusiewicz B. Efficacy of neurofeedback for children in the autism spectrum: a pilot study. J Neurotherapy. 2002;6:39-49.
318. Robinson TW. Homeopathic secretin in autism: a clinical pilot study. British Homeopathic Journal. 2001;90:86-91.
319. Warwick TC, Griffith J, Reyes B, et al. Effects of vagus nerve stimulation in a patient with temporal lobe epilepsy and Asperger syndrome: case report and review of the literature. Epilepsy Behav. 2007;10:344-347.
320. Park YD. The effects of vagus nerve stimulation therapy on patients with intractable seizures and either Landau-Kleffner syndrome or autism. Epilepsy Behav. 2003;4:286-290.
321. Danielsson S, Viggedal G, Gillberg C, et al. Lack of effects of vagus nerve stimulation on drug-resistant epilepsy in eight pediatric patients with autism spectrum disorders: a prospective 2-year follow-up study. Epilepsy Behav. 2008;12:298-304.