Title
Considering biomedical/CAM treatments.

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Authors
Cheng, Jenna X
Widjaja, Felicia
Choi, Jae Eun
et al.

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Autism

Biomedical Complementary Treatment Approaches

Robert L. Hendren, DO

KEYWORDS

• Autism • Complementary and alternative treatment • Integrative treatment
• Biomedical treatment

KEY POINTS

- Families commonly seek alternative and complementary biomedical treatments with children with autistic spectrum disorders (ASD).
- Although there are many biomedical CAM treatments in use, there is little evidence from well-conducted randomized controlled trials (RCT) to support claims of efficacy or safety.
- A potential rationale for biomedical CAM treatments in autism is their potential beneficial effect on epigenetic processes, which are increasingly shown to play a role in the gene-environment interactions underlying the development of ASD.
- Three agents with a rationale for use with ASD, at least one RCT showing efficacy, and safety data include melatonin, omega-3, and micronutrients.
- Additional agents with promise include N-acetylcysteine and methylcobalamin (methyl B12), digestive enzymes, and memantine.
- Care providers should be prepared to thoughtfully discuss biomedical CAM treatments with families to help them make informed decisions regarding the best options for their child and for their family's values.

INTRODUCTION

This article provides an overview of the biomedical subgroup of complementary and alternative medicine (CAM) treatments for autism spectrum disorders (ASD). These biomedical treatments include a variety of natural products, such as vitamins and minerals, melatonin, and digestive enzymes; procedures, such as neurofeedback and

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Child and Adolescent Psychiatry, Department of Psychiatry, University of California, San Francisco, 401 Parnassus Avenue, LP-360, San Francisco, CA 94143-0984, USA
E-mail address: Robert.Hendren@ucsf.edu

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chelation; some conventional medications that are being examined for new applications in treating autism, such as antifungals and memantine; diets; and nutraceuticals. Nutraceutical agents are foods or food products that purportedly provide health and medical benefits, including the prevention and treatment of disease. Biomedical CAM treatments are integrative in nature, and most of them can be used in combination with conventional treatments for autism.

The authors do not review the large number of CAM treatments that are less biomedical in nature, such as mind/body approaches; body-based practices, such as physical manipulation; or alternative medical systems, such as Ayurvedic or traditional Chinese medicine, despite the promising suggestive findings for some of these treatments.

This article begins with a description of the evolving understanding of the cause of ASD and how the recent shift in the etiologic paradigm is leading to increasing assessment of treatment targets and the use of biomedical and CAM treatments. Many of the potential biomedical CAM treatments are listed, and the ones with the most evidence or most focus of public interest are reviewed briefly, along with a discussion of the research models necessary to identify which children will be most likely to respond to which treatments. Finally, a model is discussed for working with families who have a member with an ASD when considering biomedical/CAM treatments. When the term *autism* is used alone, it refers to *autistic disorder* as defined in the *Diagnostic and Statistical Manual of Mental Disorders* (Fourth Edition). When *ASD* is used, it refers to the spectrum of autism disorders from mild to severe.

Complementary and alternative treatments are commonly used. Although 12% of children and adolescents in the United States use CAM treatments,[1] up to 70% of children with ASD are reported to use some form of biologic treatment (either CAM or conventional),[2] and an even higher percentage (up to 74%) of children with recently diagnosed autism use only CAM and not conventional psychopharmacologic agents.[3] The main reasons for families' choice of CAM were related to concerns with the safety and side effects of prescribed medications.[3] Families are reported to expect their primary care physicians to have knowledge about CAM treatments,[4] yet many physicians do not feel knowledgeable about them.

Cause of Autism and the Biomedical Concept

The cause of autism is widely accepted to be strongly genetic in origin, but the increasing prevalence and recent studies of the genetics of autism[5,6] suggest that the cause of autism is also related to gene-by-environment interactions expressed through or manifest in epigenetic processes. Epigenetics refers to the reversible regulation of various genomic functions, independent of DNA sequence, mediated principally through DNA methylation, chromatin sequence, and RNA-mediated gene expression.[7] The related endophenotypes (measurable components along the epigenetic pathway between the genotype and the distal symptom, personal characteristic, or phenotype) are simple biologic aspects of a disease that can be observed in unaffected relatives with a similar endophenotype at a higher rate than in the general population[8] and that are potentially reversible through nutrition, social factors, behavioral interventions, and drugs.[9] Executive and frontal lobe functions shared by family members may be examples.

In autism, this process of gene-environment interaction and the resulting endophenotypes might be viewed schematically as a model in which the layers of the earth represent the expression of the genotype into various types of the phenotype (**Fig. 1**). The surface of the earth represents the personal expression and symptoms we see (phenotype), and the core of the earth represents the genes of that person

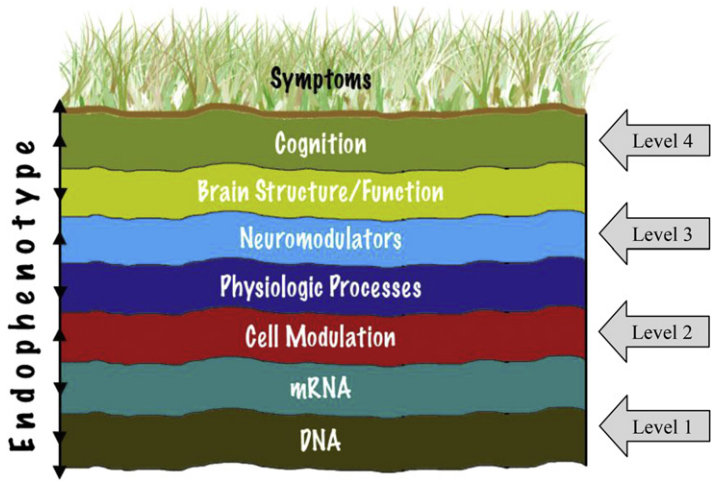

Fig. 1. Surface (phenotype) to core (genotype) model of endophenotype.

(genotype). In between is the complex and interactive layering of developmental processes that represent the endophenotype. Interventions targeting the surface level 4 might include behavioral interventions, such as applied behavior analysis and the external provision of structure. Levels 3 to 4 can be targeted with occupational therapy, physical therapy, speech and language therapy, and cognitive behavioral therapy; levels 3 to 2 with pharmacotherapy; deeper into levels 3 and 2 with biomedical and CAM therapies; and level 1 with treatments that result in gene modification.

This middle earth of levels 2 and 3 is the target of biomedical therapy in autism and other neurodevelopmental disorders and entails various active biochemical or physiologic processes such as the following:

- Immune abnormalities/inflammation[10]
- Oxidative stress[11]
- Disturbed methylation[11]
- Mitochondrial dysfunction[12]
- Free fatty acid metabolism[13]
- Excitatory/inhibitory imbalance[14]
- Hormonal effects[15]

Such abnormal epigenetic processes are not found in all people with ASD or may be active only during particular periods of time (**Fig. 2**). Therefore, treatment research should recruit subjects for trials based on the state of their previously validated endophenotypic biomarkers[16] to know if an intervention is targeting an active biomedical process in the subject at that time. For instance, identifying an inflammatory process through a biomarker such as a cytokine abnormality could be entry criteria to a study of an antiinflammatory agent for the treatment of autism. Other biomarkers of the active epigenetic process might be such measures as glutathione (GSH) metabolites, glutamate and γ-aminobutyric acid, magnetic resonance imaging, genomic arrays, and others based on the current gene-by-environment interaction altering the epigenetic process[17] and are discussed further in studies presented later in this article.

Various biochemical and physiologic processes operate at levels 2 and 3; various biomedical CAM therapies can target these processes, including CAM therapies described by Levy and Hyman[18–20]:

- Neurotransmitter production or release (dimethylglycine, vitamin B6 with magnesium, vitamin C, omega-3 fatty acids, St. John's wort)
- Food sensitivities and gastrointestinal function (gluten-free casein-free [GFCF] diets, secretin, digestive enzymes, famotidine [Pepcid], antibiotics)
- Putative immune mechanism or modulators (antifungals, intravenous immunoglobulin [IVIG], vitamin A/cod liver oil)
- Potential heavy metal toxin removal (chelation)
- Methylation (methylcobalamin, folinic acid)
- Nonbiologic (craniosacral manipulation, transcranial magnetic stimulation, acupuncture)

Biomedical Treatments

Biomedical treatments include both conventional treatments, such as psychopharmacological agents, and less studied and less medically accepted treatments, such as nutraceuticals, as well as other types of treatments, including devices like transcranial magnetic stimulation.

Risperidone and aripiprazole are the only medications that the Food and Drug Administration (FDA) has given approval for marketing for the indication of *irritability associated with autism*. Irritability is not a core symptom of autism, and no drug has

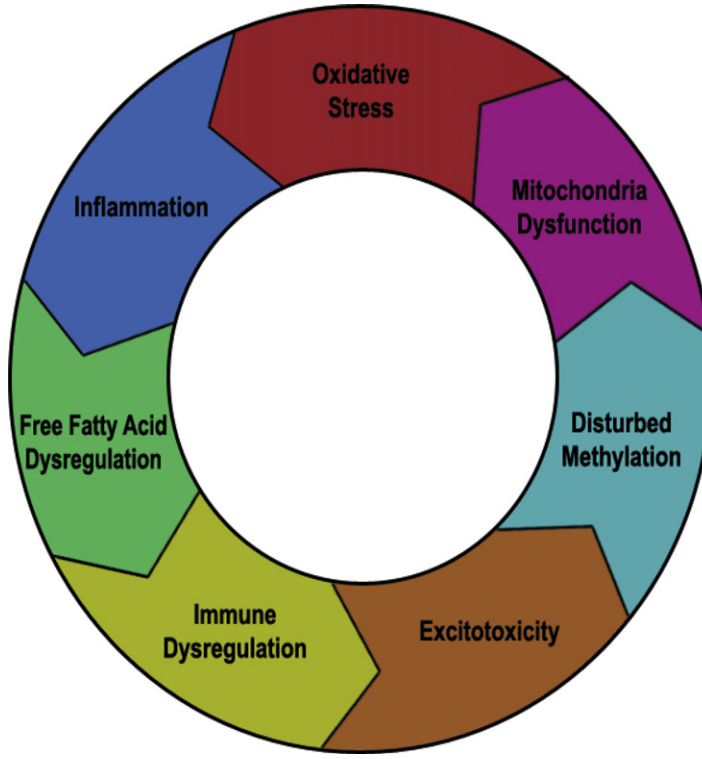

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Fig. 2. Endophenotype stress cycle.

the FDA's marketing approval for the indication of autism itself or for any core symptom of autism.

Conventional pharmacologic treatments for symptoms associated with ASD include stimulants, antidepressants, antipsychotics, anticonvulsants, and anxiolytics. Each of these agents has been examined for autism-related symptoms in published studies, and comprehensive critical reviews of this literature are available in 2 excellent recent articles.[21,22]

Pharmacologic agents that are not traditionally considered as treatments of ASD or associated symptoms but that have one or more published studies for the treatment of symptoms associated with autism include propranolol,[23] amantadine,[24] D-cycloserine,[25] cholinesterase inhibitors,[26] nicotinic agonist,[27] memantine,[28] naltrexone,[29] and buspirone.[30]

The list of potential biomedical CAM treatments is long and most have inadequate evidence to judge potential efficacy. See **Box 1** for a list of most of the biomedical CAM treatments of ASD. Two comprehensive reviews of those treatments with reasonable efficacy data have been recently published.[31,32]

For this short article, the biomedical CAM treatments that have the most published evidence, that have generated the greatest interest or controversy, and/or that nonetheless have significant promise for treating autism or autism-associated symptoms are briefly discussed. These treatments include melatonin, omega-3, injectable methylcobalamin (methyl B12), N-acetylcysteine (NAC), memantine, pancreatic digestive enzymes, micronutrients, immune therapies, and chelation.

Melatonin

Melatonin is an endogenous neurohormone released by the pineal gland in response to decreasing levels of light. It causes drowsiness and sets the body's sleep clock. ASD is associated with a high frequency of sleep problems, and melatonin is increasingly used to help children with ASD fall asleep.[33,34] Rossignol and Frye[35] published a review and meta-analysis of 35 studies. They described reports of abnormalities in melatonin levels in patients with ASD (9 studies: 7 low, 2 high, 4 circadian); significant correlations between melatonin levels and ASD symptoms (4 studies); and gene abnormalities associated with decreased melatonin production (5 studies). Of 18 treatment studies of melatonin, there were 5 randomized controlled trials (RCTs) involving a total of 61 patients treated with nightly doses of 2 to 10 mg. These RCTs showed positive effects on sleep in that sleep duration was increased (44 minutes, Effect Size [ES] = 0.93) and sleep onset latency was decreased (39 minutes, ES = 1.28), but nighttime awakenings were unchanged. The duration of the studies varied between 4 weeks and 4 years. One study suggested a loss of benefit at 4 weeks, whereas the study of 4 years reported continued benefits. The side effects were minimal to none.

Melatonin is one of the best-studied biomedical CAM treatments of ASD. Although small sample sizes, variability in sleep assessments, and lack of follow-up limit the value of these studies in supporting its use, treatment with melatonin has a clear physiologic rationale; and it is sensible, easy, cheap, and safe.

Omega-3 Fatty Acids

Omega-3 long-chain fatty acid supplementation is reasonable to consider because omega-3 fatty acids are essential to brain function and development.[36] They are a critical component of neuronal membranes, they are essential for their optimal functioning, and they serve as substrates for the production of the eicosanoids, such as prostaglandins, which are necessary for cell communication and immune regulation. The two omega-3 fatty acids of primary interest are eicosapentaenoic acid (EPA) and

Box 1
Potential biomedical CAM treatments of ASD

Pioglitazone hydrochloride (Actos)
Acupuncture
Animal-assisted therapy
Antibiotics
Antifungals (fluconazole [Diflucan], nystatin)
Antiviral (valacyclovir hydrochloride [Valtrex])
Amino acids
Auditory integration therapy (music therapy)
Chelation
Chiropractic
Cholestyramine
Coenzyme Q10
Craniosacral therapy
Curcumin
Cyproheptadine
Dehydroepiandrosterone
Digestive enzymes
Dimethylglycine, trimethylglycine
Fatty acids (omega-3)
5-hydroxytryptophan
Folic/folinic acid
GSH
GFCF diet
Food-allergy treatment
Hyperbaric oxygen treatment
Iron
Infliximab (Remicade)
Immune therapies
IVIG
L-carnosine
Magnesium
Melatonin
Methylcobalamin (methyl B12)
N-acetylcysteine
Naltrexone
Neurofeedback
Oxalate (low) diet
Oxytocin

Pyridoxal phosphate
Probiotics
Ribose and dehydroepiandrosterone
S-adenosyl-methionine
Secretin
Sensory integration therapy
Specific carbohydrate diet
St. John's wort
Steroids
Transfer factor
Vitamin A
Vitamin B3
Vitamin B6 with magnesium
Vitamin C
Zinc

docosahexaenoic acid (DHA). Based on data from other disorders, they might be expected to improve mood, attention, and activity level as well as, conceivably, actual symptoms of autism. Low levels of omega-3 fatty acids have been reported in children with ASD.[37–39]

There have been 4 open trials[35,38,40] and 2 double-blind, placebo-controlled, randomized pilot trials in children with ASD.[41,42] Amminger and colleagues[42] randomized 13 children (aged 5–17 years) to EPA 840 mg and DHA 700 mg daily (n = 7) or placebo (n = 6) for 6 weeks. There were no significant differences between groups on the Aberrant Behavior Checklist, possibly because of the small sample and insufficient power; but omega-3 seemed nominally superior to placebo for stereotypy (Cohen's d = 0.72), hyperactivity (d = 0.71), and inappropriate speech (d = 0.39). In a study by Bent and colleagues,[43] 27 children (aged 3–8 years) with ASD were randomly assigned to 12 weeks of omega-3 fatty acids (1.3 g/d) or an identical placebo. Hyperactivity seemed to improve more in the omega-3 group than in the placebo group, although not with statistical significance (2.7 $\pm$ 4.8 vs 0.3 $\pm$ 7.2, P = .40). Correlations were found between decreases in the levels of 5 different fatty acids and decreases in hyperactivity, with milder changes in other behaviors. There were no differences in side effects. A larger Internet-based study of omega-3 fatty acid supplementation is currently underway.

With only 2 small placebo-controlled RCTs totaling 38 children, and all 4 open studies without statistically significant effects (possibly a power issue), the evidence is small for omega-3 supplementation in ASD. This effect of omega-3 supplementation on hyperactive behavior might mirror recent suggestions of a modest,[44] though debatable,[45] effect of omega-3 fatty acids in treating attention-deficit hyperactivity disorder (ADHD). Despite the weak evidence and the modest effect, it has a rationale for its use; and it is sensible, easy, inexpensive, and safe.

Methylcobalamin (Methyl B12)

Methyl B12 is a vital cofactor for the regeneration of methionine from homocysteine, by providing methyl groups for metabolic pathways involving transmethylation and

transsulfuration. Reduced activity in the transsulfuration pathway can lead to reduced levels of cysteine and GSH, which are crucial antioxidants responsible for minimizing macromolecular damage produced by oxidative stress.

James and colleagues[11] showed that many children with ASD exhibit low levels of GSH and a decreased GSH/GSSG redox ratio. In an open-label trial in 40 children with autism, administration of methyl B12 for 1 month resulted in a significant increase in plasma GSH concentrations, although behavioral assessments were not done in this study.[11] Improvements were noted in social relatedness, language, and behavior problems.

In a recent study, 30 patients completed a 12-week, double-blind RCT of subcutaneously injected methyl B12 at a dosage of 64.5 mcg/kg every 3 days; 22 patients completed the 6-month extension study.[46] The supplement was well tolerated. No statistically significant differences in behavior tests or in GSH status were identified between active and placebo groups. However, 9 (30%) patients demonstrated clinically significant improvement on the Clinical Global Impression–Improvement Scale and at least 2 behavioral and language measures. Improvements in social interaction and language were most consistently reported. Notably, this subgroup of responders exhibited significantly increased concentrations of GSH and GSH/GSSG compared with the nonresponders. This study is the only published RCT, but a new RCT from the same group will be completed in early 2013. Additional research is needed to delineate a subgroup of responders and ascertain a biomarker of response to methyl B12.

Methyl B12 is typically administered at dosages of 64.5 to 75.0 mcg/kg with subcutaneous injections every 2 to 3 days. There are no studies in ASD of oral or nasal methyl B12, which do not maintain consistently high levels and are thought to be less effective. Subcutaneous injectable methyl B12 does seem to be safe. Although initial studies are promising for a subgroup of children with ASD, and subcutaneous injectable methyl B12 supplementation seems to be safe and well tolerated, additional study is needed to determine whether this will become a recommended treatment of ASD. However, despite reasonable cost, with repeated frequent injections, this treatment is not easy to use.

NAC

NAC is a glutamatergic modulator and an antioxidant. There is one published report of a 12-week, double-blind, randomized, placebo-controlled study of NAC in children with autism.[47] Patients (31 boys, 2 girls; aged 3–10 years) were randomized, and NAC was initiated at 900 mg daily for 4 weeks, then 900 mg twice daily for 4 weeks, and 900 mg 3 times daily for 4 weeks. Compared with placebo, oral NAC resulted in significant improvements on the Aberrant Behavior Checklist (ABC) irritability subscale ($P<.001$; $d = 0.96$) and induced limited side effects. The results are promising, especially because the supplement is well tolerated; but this study will need to be replicated before recommendations can be offered.

Memantine

There are biochemical studies suggesting that aberrant functioning of the N-methyl D-aspartic acid (NMDA) receptor and/or altered glutamate metabolism may play a role in autism. Memantine is a moderate-affinity antagonist of the NMDA glutamate receptor and is hypothesized to potentially modulate learning by blocking excessive glutamate effects that can include neuroinflammatory activity. Its capacity to block glutamate neurotoxicity and neuroinflammatory activity and to stimulate synapse formation makes it an interesting candidate for treating autism. An open-label case series reported significant improvement in language and socialization in children with

autism.[28] Memantine is well tolerated in children, and a multisite RCT is currently underway. This treatment could be considered off-label use of a conventional medication approved for the treatment of Alzheimer disorder rather than as a CAM treatment.

Pancreatic Digestive Enzymes

Enzyme deficiencies in children with autism result in a reduced ability to digest protein, which affects the availability of amino acids essential for brain function. There is increasing evidence for a gut-brain connection associated with ASD, at least in some cases.[48] This finding suggests a possible benefit from a comprehensive digestive enzyme supplement with meals to aid digestion of all proteins and peptides, especially for those children with ASD who have gastrointestinal disturbance.

Probiotics (consisting of microorganisms thought to improve digestive health by repopulating the gastrointestinal tract with favorable flora) have also been proposed to improve digestion and gut-brain activity in children with ASD. Some proponents suggest these agents may also help remove toxins and improve immune function.

A double-blind placebo-controlled trial of digestive enzyme supplementation using a 6-month crossover design in 43 children with ASD (aged 3–8 years) did not show any clinically significant improvement of ASD symptoms.[49] A possible effect on improvement in the variety of foods eaten was suggested in the results. A commercially developed product (CM-AT by Curemark) has been specifically developed to target enzyme deficiencies that affect the availability of amino acids in children with autism; fecal chymotrypsin is used as a biomarker. Curemark (www.curemark.com) notes that it has reached its targeted enrollment for a phase III study of a total 170 children with autism at 18 sites. The unpublished Curemark study is interesting, and the FDA is reviewing its findings; but further conclusions await the published results. There are no reported trials of probiotics for ASD.

Micronutrients (Vitamins and Minerals)

Although multivitamin and mineral levels generally are not found to be abnormal in children with autism, biomarkers of general nutritional status have been reported to be associated with autism severity.[50] One open-label study of 44 individuals with autism, aged 2 to 28 years, who were selected because they (or their parents) preferred a natural treatment, reported a benefit[51]. There are only 2 RCT clinical trials of multivitamin/multimineral supplements for children with autism, both from the same group. The first randomized 20 children (aged 3–8 years) and reported the micronutrient supplement yielded significantly better sleep and gastrointestinal symptoms than placebo.[52] Another RCT of an oral vitamin/mineral supplement for 3 months with 141 children and adults with ASD showed an improved nutritional and metabolic status of children with autism, including improvements in methylation, GSH, oxidative stress, sulfation, ATP, NADH, and NADPH.[53] The micronutrient-treated group also had significantly greater improvements on measures of global change ($P = .008$), hyperactivity ($P = .003$), and tantrums ($P = .009$).[53]

Despite limited evidence for the efficacy of vitamin and mineral supplements for autism, there is widespread usage. The promising results from 2 RCTs suggest benefit from a safe, easy to use, and relatively inexpensive agent.

Immune Therapies

Evidence is accumulating that there are subgroups of patients with ASD that have immune deficiencies and signs of autoimmunity, such as atopy.[10] Various approaches have been tried to boost immune function or block autoimmunity. One of the most

obvious candidates has been IVIG treatment, and there are now 6 published open-label trials of IVIG treatment with ASD.

In one open-label study, IVIG treatment improved eye contact, speech, behavior, echolalia, and other autistic features.[53] Others have claimed that IVIG treatment led to improvements in gastrointestinal signs and symptoms as well as behavior. Subsequent studies have shown questionable benefits and mixed results for language and behavior.

IVIG is a biomedical treatment whose overall results have been weak, and it carries some significant risks. Other immune-boosting therapies may be of benefit but have not been adequately studied. For future studies, it is unclear if an underlying immunologic dysfunction is present in all individuals with ASD or if treatment trials should target the patients with demonstrable inflammatory changes.

Chelation

Chelation, a process for removing heavy metals from the blood, has been used in treating ASD based on the unproven theory that ASD is caused by heavy metal toxicity; there is no convincing evidence of heavy metal toxicity from biochemical studies in ASD. The hypothesized accumulation of heavy metals, particularly mercury, would presumably be caused by the body's inability to clear the heavy metals, by increased exposure, or both.

Detoxification involves several intermittent courses of oral 2, 3-dimercaptosuccinic acid (DMSA) or the intravenous chelator ethylenediaminetetraacetic acid, with periodic elemental analysis of urine. According to proponents, successful detoxification treatment requires clearing the gastrointestinal tract of harmful dysbiotic flora and bolstering metabolism with essential nutrients, so that the individual can tolerate detoxification.

Two related studies have been published[54,55] involving 65 children with ASD who received one course of DMSA for 3 days. Selected for high urinary excretion of toxic metals following the DMSA administration, 49 were randomly assigned in a double-blind design to receive either 6 additional rounds of DMSA or placebo. DMSA was reportedly well tolerated and resulted in high excretion of heavy metals, normalization of red blood cell GSH, and possibly improved ASD symptoms. Further studies are needed to confirm these results.

Chelation is controversial because of its risks and because of its questionable clinical findings, and the Institute of Medicine recently issued warnings. The most common side effects are diarrhea and fatigue. Less common side effects include abnormal complete blood count, liver function tests, and mineral levels. Renal and hepatic toxicity is possible with oral agents, and seizures have been reported. Some patients may experience a sulfur smell, regression, gastrointestinal symptoms, or rash.

Summary of Biomedical Treatments for Autism and Future Directions

Research on CAM biomedical treatments for autism remains in its early stages, but emerging data suggest several possible directions for current treatments (**Tables 1** and **2**) and future development. Melatonin for sleep induction is supported by 3 of 5 RCTs in children with ASD. Omega-3 fatty acids have 2 positive trending RCTs suggesting the possibility of clinical value for treating hyperactivity associated with ASD, but this might mirror recent findings of the putative efficacy of omega-3 fatty acids in treating ADHD. Methylcobalamin may induce behavioral improvements, according to a single RCT, but the treatment involves repeated injections several times weekly. NAC has one RCT suggesting improvement in irritability. Memantine, which is an established prescription drug treatment for Alzheimer disease, showed encouraging results on language and socialization in one open-label series. Digestive enzyme

Table 1
Evaluations of biomedical CAM treatments for ASD: the evidence base

Treatment	Quality of Evidence	Strength of Recommendations Based on Data	Evidence Base in Youth
Melatonin	Good	Recommend strongly	18 trials, 5 RCT
Omega-3 fatty acids	Good	Recommend	4 open trials, 2 RCT
Multivitamin/ micronutrients	Fair	Recommend	2 RCTs
NAC	Fair	Neutral/recommend	1 RCT with group significance
Memantine	Fair	Neutral/recommend	3 open trials, ongoing multisite
Digestive enzymes	Poor	Neutral	Anecdotal evidence
Methylcobalamin (methyl B12)	Fair	Neutral	1 RCT w/o significance
Immune therapies intravenous	Poor	Insufficient data	None
Immunoglobulins	Poor	Insufficient data	None
Chelation	Poor	Insufficient data	None

Abbreviation: w/o, without.

supplementation is weakly supported by weak data, but a recent unpublished study suggests possible benefit. Micronutrients (multivitamin and multimineral mixtures), based on 2 RCTs, may improve tantrums, hyperactivity, sleep, and gastrointestinal symptoms. IVIGs have mixed findings in open-label trials (no controlled trials), entail medical risks, and require repeated injections. Chelation showed trends toward improvements in sociability, language, and cognition in a single RCT; but again medical risks are significant.

Taken together, none of these treatments are ready for general usage; but some families might elect to try such treatments. It is desirable for practitioners and families

Table 2
Evaluation of biomedical CAM treatments for ASD: authors' personal clinical opinion

Treatment	Strength of Recommendations Based on Published Data	Author's Clinical Recommendations
Melatonin	Reasonably good studies	Very useful
Omega-3 fatty acids	Improvement trends	Suggest always
Multivitamin/micronutrients	Possible benefit	Routinely recommend
NAC	Promising	Suggest
Memantine	Good open label	Frequently consider
Methylcobalamin (methyl B12)	Promising for subgroup	Suggest cautiously
Digestive enzymes	Not good evidence, yet	Suggest for GI symptoms
Immune therapies	No good data	Discourage
IVIG	No good evidence	Discourage
Chelation	Not good evidence	Discourage

Abbreviation: GI, gastrointestinal.

to work together to review, evaluate, and perhaps select the treatments that offer the most promise, have a rationale for use, fit with the families' values, and have evidence for safety and possible efficacy.

Multiple levels for intervention in the treatment of ASD are possible. Reviewing and monitoring the levels for intervention assures an integrated approach to autism treatment. A thorough medical assessment includes a review of symptoms, including a possible genetic, neurologic, and gastrointestinal workup and consideration of other medical symptoms when indicated. Applied behavioral analysis approaches, speech and language assessment followed by therapies indicated by these evaluations, and possible occupational therapy should be considered. Education, help in identifying appropriate resources, and overall support is an essential part of the collaborative relationship between the practitioner and the family.

Conventional psychopharmacology should be considered for severe symptoms associated with autism, such as aggression, irritability, and anxiety. Integrated into these interventions should be a thoughtful review and possible use of biomedical CAM treatments, including melatonin for sleep, micronutrients, and omega-3 fatty acids. Other interventions with promise and some safety data include NAC, digestive enzymes, and methylcobalamin.

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