Complementary and Alternative Medicine in Autism: An Evidence-Based Approach to Negotiating Safe and Efficacious Interventions with Families

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Summary: This review focuses on helping clinicians identify resources and develop strategies they may use to effectively negotiate safe and effective use of complementary and alternative medicine (CAM) treatments with families of children with autism spectrum disorders (ASD), as well as other neurodevelopmental disorders. Since new types of CAM continue to be introduced into the autism community, emphasis is placed on providing clinicians with tools to help families negotiate the myriad of available treatments and make decisions based on current safety and efficacy data, while remaining mindful of the reasons families may be considering these treatments. We familiarize readers with high-quality, evidence-based resources that providers and families may use to ascertain current information about specific types of CAM, verify the content of biologically-based treatments, identify ongoing CAM research and obtain toolkits designed to help healthcare providers raise the topic of CAM usage and facilitate disclosure and discussion of CAM use with patients and their families. **Key Words:** Complementary and alternative medicine, autism, integrative medicine, gluten-free casein-free diet, melatonin, chelation, hyperbaric oxygen treatment, evidence-based medicine.

INTRODUCTION AND DEFINITIONS

Complementary and alternative medicine (CAM) is widely used by families of children with autism spectrum disorders (ASD),[1] and the American Academy of Pediatrics recommends discussion of CAM with the family of every patient.[2] The National Center for Complementary and Alternative Medicine (NCCAM) defines CAM as "a group of diverse medical and health care systems, practices, and products that are not generally considered part of conventional medicine" (http://ww.nccam.nih.gov). Complementary medicine is typically defined as nontraditional treatments that are used together with conventional medicine, such as using hypnosis in addition to pain medication to treat acute pain. Alternative medicine is described as being used in place of conventional medicine, such as using melatonin instead of sedatives to treat insomnia. A newer term is *integrative medicine*, which is preferred by experts in the field because it more comprehensively describes the goals of optimal CAM usage. An American Academy of Pediatrics[3] report defines integrative medicine as "relationship-based care that combines mainstream and complementary therapies for which there is some high-quality scientific evidence of safety and effectiveness to promote health for the whole person in the context of his or her family and community."

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AUTISM SPECTRUM DISORDER: DESCRIPTION AND REVIEW OF CURRENT UNDERSTANDING

Autism spectrum disorders (ASD) affect approximately 1 in 110 children in the United States.[4] The core features of ASD include impairments in socialization, communication, and behavior.[5] These core symptoms are frequent targets of medical, behavioral, and educational interventions.[6] Associated symptoms such as hyperactivity, anxiety, aggression, insomnia, and gastrointestinal symptoms are also common in ASD and are frequent targets of both conventional treatments and CAM therapies.[6–9] Autism spectrum disorders are highly heritable, but phenotypic heterogeneity and environmental influences on gene expression complicate identification of

causal factors.[10] Although many genetic conditions (e.g., 22q11.2 deletion syndrome, fragile X syndrome) and a few in utero environmental exposures (e.g., divalproex sodium, thalidomide)[11] have been implicated as underlying etiologies for ASD in some individuals, single gene and chromosomal disorders do not account for the majority of ASD cases.[10] In addition, the incidence of ASD continues to rise; this increase is not fully explained by factors such as earlier identification or diagnostic substitution,[12] leading families to pursue alternative hypotheses for their child's autism.

Over the last two decades, there has been significant progress in the development of treatment strategies for both core and associated symptoms of ASD. Multisite research networks have been established,[13,14] and clinical practice guidelines for the identification and treatment of children with ASD have recently clarified the role of the primary care provider.[6,15] Additionally, a stronger evidence base is emerging for educational and behavioral treatments.[16,17] Recently, several very well-designed medication trials have begun to clarify the evidence base for medications that physicians use for some of the most problematic associated symptoms of ASD.[13,14,18,19]

For many families, however, geographic and economic barriers continue to limit access to high-quality behavioral and educational interventions,[20,21] and many concerns endorsed by families of children with ASD remain difficult to treat.[6,9,13] Additionally, despite increasing use of conventional psychiatric medications in children with ASD,[14,19] the evidence base supporting such use remains limited, and well-designed studies have found increased adverse effects and no clinical benefit from some medications that have been widely prescribed to children with ASD.[14] These inconsistencies can be challenging for families and contribute to the increased levels of treatment uncertainty reported by parents of children with ASD.[22.]

Prevalence of CAM usage in ASD

Use of treatments categorized as CAM has increased considerably in children over the last two decades. In 2007, the Centers for Disease Control and Prevention (CDC) estimated that 11.8% of U.S. children had used some type of CAM therapy in the preceding 12 months,[23] with considerably higher use in children with special health care needs or chronic health conditions.[3,24] Prevalence of CAM use in children with ASD is among the highest of any population, with reported use between 52% and 95%.[1,9,25,26] CAM use for children with ASD has been reported to be elevated in families with higher socioeconomic status, especially when at least one parent has completed a 4-year college degree.[9,21] Families of children with ASD choose many types of CAM treatments, with studies reporting that 50%–70% of children receive biologically based CAM.[1,9]

Why do families choose CAM?

Families of children with ASD choose CAM for a wide variety of reasons. Qualitative studies investigating the rationale for CAM use by the parents of children with a variety of disabilities have found that receiving out of date information from the conventional systems of care, limited provider knowledge of their child's condition, parental frustration with discouraging prognoses, and attempts to construct an alternative identity for their children and themselves all contribute to increased CAM use.[27–29] These findings are consistent with a shift toward understanding CAM as a potentially adaptive method that parents use to gain more control over medical decision-making while exercising more self-determination in healthcare.[29–31]

Although most families with children with ASD report using CAM therapies for general health maintenance,[9] parents also report using CAM therapies to treat a wide variety of specific symptoms, including moodiness, aggression, irritability, hyperactivity, inattention, GI symptoms, and sleep difficulties.[9] Many CAM products are marketed to fill voids in treatment not addressed with conventional treatments, and CAM use may be higher when access to quality traditional care is limited.[21] Families using CAM also cite concerns about the safety of medications, personal beliefs about healthcare, and the desire to use multiple approaches to address symptoms.[21,30,31]

A friend or family member is the most likely source of information about a CAM treatment. The Internet is the second most likely way to learn about a CAM treatment.[9] The development of parent-driven, online autism communities has provided families with unprecedented access to parent-to-parent support groups and ASD-specific information. The positive contribution of these forums cannot be understated: many families have developed a better understanding of their child's condition and found support networks that facilitate the identification of helpful resources and high-quality teachers, therapists, and doctors. Nonetheless, the Internet has also increased families' exposure to sophisticated marketing, testimonials, and unproven claims.[2,30,31] Providers may perceive pressure from parents to perform tests or treatments based on their desire to participate in CAM treatment. This tension may increase when parents feel urgency due to limited progress or an increase in symptoms that are disruptive to the entire family, such as insomnia, aggression, or self-injurious behavior.

NEGOTIATING SAFE AND EFFICACIOUS INTERVENTIONS WITH FAMILIES

Most children who receive CAM also receive conventional care.[32] In an American Academy of Pediatrics survey conducted in 2001, 87% of the pediatricians that patients routinely asked about CAM, but only 20% reported asking their patients about CAM, with most in-

quiries restricted to herbal therapies, special diets, and dietary supplements.[33] Problematically, the majority of parents of children receiving CAM do not inform their doctor that their child is using CAM.[34] It is critical that providers ask about CAM use at every visit,[2] so that once disclosure is accomplished, healthcare providers can use the information gained to better understand the challenges the family is facing by understanding the goals they hope to accomplish by CAM usage.[2]

Physicians can also help families become better consumers of healthcare by emphasizing the importance of using informed consumer practices, a context that will be quite familiar to most patients. Hierarchy of evidence and the need for controlled studies to truly establish safety and efficacy can be discussed with families.[6] This is critical, given that several studies have demonstrated that patients continue to desire and value the advice of their healthcare providers to inform their decision-making in regard to choosing specific types of CAM.[1,9,22] Maintaining the quality of the relationship between the health care professional, the patient, and family significantly affects patient outcomes and family function,[35] but this can be difficult when providers are asked to endorse or provide a therapy that they themselves consider risky or potentially harmful.[36–40]

CLASSIFICATION OF TYPES OF CAM

In the NCCAM classification system, types of CAM fall into five domains:

1. Mind–body therapies. These include meditation, prayer, mental healing.
2. Biologically based practices. These treatments include herbs, vitamins, and dietary supplements.
3. Manipulative and body-based practices. These include chiropractic and massage therapy.
4. Energy medicine (e.g., qigong, reiki, therapeutic touch). These are not widely used in children with ASD, and there is no evidence to support their use in the treatment of ASD. The present review, therefore, offers no further discussion of this domain.
5. Whole medical systems. This final type incorporates all four of the domains just listed. An example is naturopathic medicine.

EVIDENCE BASE FOR COMMON TYPES OF CAM

The principles of evidence-based medicine involve "integrating individual clinical expertise with the best available external clinical evidence from systematic research."[41] Consideration of the hierarchy of evidence is essential when determining what is the best available evidence. Evidence must be stratified, based on the likelihood of excluding bias, and producing accurate results, with strongest support for systematic reviews and meta-analyses of randomized controlled trials (RCT) and individual RCTs, followed by well-designed (nonrandomized) controlled and uncontrolled (case-control and cohort) studies, and finally descriptive case reports.[42] When evaluating CAM studies, it is important to note in terms of publishing bias that CAM studies with negative results are more likely to be published in mainstream journals in English, whereas CAM studies with positive results are often published in other languages or in less prestigious journals,[3,43] despite the fact that the quality of randomized controlled trials and meta-analyses of CAM have been equal or superior to the quality of trials for conventional medicine.[44,45]

	Effective	Efficacy Inconclusive
Safe	Recommend	Tolerate. Encourage objective monitoring
Unsafe or Safety Unknown	Monitor closely or discourage	Discourage

FIG 1. Ethical, practical framework for evaluating individual CAM therapies with families of children with autism spectrum disorders. Adapted with permission from: Kemper K, Cohen M. Ethics meet complementary and alternative medicine: new light on old principles. Contemporary Pediatrics 2004;21:61.

Responsible, ethical, and legally defensible decisions about CAM use can be made through evaluating the evidence that supports the treatment's efficacy and potential for harm or injury and then discussing this evidence with patients in a format that they can understand.[46] Treatments with well-supported efficacy and safety can be recommended. Treatments with little or no efficacy and high likelihood for harm should be discouraged. Both CAM therapies with good evidence of efficacy and inconclusive evidence of safety and CAM therapies with unknown efficacy but a proven safety profile can be tolerated or monitored closely by the physician. FIG. 1 demonstrates an approach to discussing information about CAM with families that can be used to inform treatment decisions and establish monitoring for all types of CAM. Here, we apply this efficacy–safety model in reviewing many of the most common CAM treatments used for ASD.

Mind–body medicine

Music therapy—Safe, unknown efficacy: Tolerate, encourage objective monitoring. Music therapy is frequently used to promote communication and expression, most often in educational settings. A 2006 Cochrane review of music therapy in ASD concluded that music therapy was "superior to 'placebo' therapy with respect to verbal and gestural communicative skills," but effects on behavior were not significant; the authors

noted also that the studies were of "limited applicability to clinical practice" and that more research is needed to establish whether the effects of music therapy are lasting.[47] Two recent randomized controlled studies, by the same researchers,[48,49] used a single-subject comparison design to compare improvisational music therapy to play sessions with toys. They found the intervention superior to play at facilitating joint attention behaviors, nonverbal social communication skills, more and longer events of "joy," "emotional synchronicity," and "initiation of engagement" behaviors in children, and a phenomenon that the authors described as "more yes, less no." Although these studies were small (n = 13 and n = 10), with incomplete blinding of coders, subjects were well characterized, with appropriate measures. Additionally, the intervention, materials, and coding were all methodically standardized, with a logical theoretical basis.[49] Nonetheless, larger studies are needed to establish efficacy.

Yoga—Safe, unknown efficacy: Tolerate, encourage objective monitoring. No studies of yoga in children with ASD were found through searches at PubMed and at http://www.clinicaltrials.gov. Yoga has, however, been demonstrated to be safe in studies of children with other neurodevelopmental conditions, including attention deficit–hyperactivity disorder and intellectual disability.[50,51] An underpowered study suggested yoga may have some benefit as a complementary treatment for boys with attention deficit–hyperactivity disorder who are "already stabilized on medication, particularly for its evening effect when medication effects are absent."[50]

Biologically based practices

Melatonin—Safe, effective: Encourage where indicated by symptoms, continue behavioral interventions, emphasize sleep hygiene. Melatonin, which is a hormone secreted by the pineal gland,[52] is well established as a regulator of circadian rhythms, with possible effects as an antioxidant and modulator of neuronal plasticity.[53] Children with ASD experience sleep disorders and atypical sleep architecture.[54] Low melatonin levels and abnormal melatonin synthesis in ASD have been reported, although the significance of this is currently unknown.[55] Melatonin has been found to be safe and effective in reducing sleep onset latency (SOL) in children with some primary and secondary sleep disorders.[56] Several small RCTs demonstrated benefits in reducing SOL and in various quality of sleep measures in children with ASD.[57,58] Meta-analysis of three crossover studies indicated a significant improvement in SOL for melatonin over placebo in children with developmental disabilities.[59] Another small RCT (n = 12) used a 4-week crossover design to evaluate the benefits of melatonin in children with ASD and children with fragile X syndrome. The authors reported significant improvements in SOL in children with ASD and fragile X syndrome.[58] Improvement in treatment-resistant chronic delayed sleep and in impaired sleep maintenance has been documented in children with neurodevelopmental disabilities receiving melatonin therapy. Importantly, treatment was also effective in reducing family stress.[60] A cohort study demonstrated encouraging results for both safety and improvement of parentally reported sleep difficulties; adverse effects were uncommon, with either enuresis or morning somnolence reported in 3 of 107 children.[61]

There have been conflicting results regarding seizures and melatonin. In 1998, Sheldon[62] reported improved sleep, but increased seizure activity in four of six children with severe neurological impairment who were receiving melatonin via gastrostomy tube; each child returned to baseline level of seizure activity after cessation of melatonin. However, a subsequent study of six children reported improvement in seizure activity in five of the six subjects treated with melatonin.[63] A wide variety of melatonin preparations are available, and, although dosing is not standardized, melatonin appears to be safe in children at doses of up to 7.5 mg. Short-term release products are usually recommended for children with difficulty initiating sleep, and long-term release products are likely to be most helpful for children with difficulty maintaining sleep (i.e., children who experience frequent night-time awakening).[56]

Vitamin C—Generally safe at recommended doses and from dietary intake, unknown efficacy: Tolerate, encourage objective monitoring. Vitamin C is not typically used as a sole treatment in ASD, but it can be added to dietary supplement regimens, primarily for its role related to oxidative stress. However, there are no well-designed studies investigating vitamin C as a dietary supplement in ASD. In 1993, Dolske et al.[64] postulated that vitamin C may have some ability to block dopamine receptors, and therefore offer pharmacological effects similar to those of traditional neuroleptics. These investigators completed a double-blind, 30-week, placebo-controlled trial of 18 children with ASD and reported decreased stereotyped behavior in children receiving vitamin C. This result has not been replicated. Of note, there have been two recent case reports of scurvy in children with autism.[65] Therefore, if the dietary history indicates concerns of vitamin C deficiency, supplementation should be considered and can be provided in the form of a multivitamin.

Multivitamins—Safe, unknown efficacy: Tolerate, encourage objective monitoring. Children with ASD and either self-restricted or caretaker-imposed dietary restrictions can be at risk for clinically significant nutritional deficiencies,[66] and there have been case reports of specific vitamin deficiencies in children with ASD.[65,67] Nutritional assessment of children with ASD with restricted diets should include careful monitoring of vitamin intake.

However, vitamin toxicity has also been reported in children taking excessive doses of vitamins in dietary supplements.[68,69] Because many dietary supplements are vitamin fortified and because a number of families provide multiple supplements to their children with ASD, caution must be exercised to avoid inadvertent excessive intake of individual vitamins. Parents should be cautioned to read labels, with particular attention placed on avoiding excessive doses of fat-soluble vitamins, such as vitamins A, D, and E.

The U.S. National Academies–Institute of Medicine has established tolerable upper intake levels (UL) for vitamin consumption in healthy children. For vitamins, these levels are age dependent and are provided here as maximum daily doses for children (see Office of Dietary Supplements links at http://nccam.nih.gov/health/vitamins/). Vitamin A: 0–3 years, UL = 600 μg; 4–8 years, UL = 900 μg; 9–13 years, UL = 1700 μg; >14 years, UL = 2800 μg. Vitamin D: 0–1 year, UL = 25 μg; >1 year, UL = 50 μg. Vitamin E: 1–3 years, UL = 200 mg; 4–8 years, UL = 300 mg; 9–13 years, UL = 600 mg; >14 years, UL = 800 mg.

Gluten-free, casein-free diet—Generally safe: Tolerate, encourage objective monitoring. The gluten- and casein-free (GFCF) diet has been among the most commonly used CAM treatments in children with ASD.[1,9] It has been promoted as a treatment for both the core neurobehavioral symptoms of ASD and the gastrointestinal symptoms that may be present in some individuals with autism. The unproven rationale for this treatment is based on the "opioid excess" hypothesis, which holds that individuals with ASD have an impaired ability to completely break down dietary proteins present in gluten and casein, and that this results in the formation of opioid-like peptides, which then cross the intestinal membranes, enter the bloodstream, and finally act centrally as endogenous opioids in the brain, contributing to the neurobehavioral symptoms of autism.[70–72]

Anecdotal reports and case series have reported improvement in ASD symptoms and GI symptoms with the GFCF diet, but controlled studies have been limited. A Cochrane review in 2008 identified only two small RCTs (n = 35) that met review criteria. The review cited lack of evidence to support the use of GFCF diets as an effective intervention in ASD and also noted the absence of research on potential harm of GFCF diets.[73] The reviewed trials included a 12-month, single-blind trial (n = 10) of Norwegian children; this study showed some reduction in autistic traits and modest improvement on standardized measures of communication and interaction and social isolation.[72] The second study reviewed was a small, 12-week, randomized, double-blind study (n = 15) that revealed no statistically significant benefits of the diet, although several parents had reported improvement in their children[74]; the authors stressed an urgent need for well-conducted and adequately powered, randomized, controlled trials in this area.

Some families who use the GFCF diet hope to address both neurobehavioral symptoms and persistent GI symptoms. In fact, treatment of GI symptoms is one of the most common reasons for families of children with ASD seek CAM.[9] At present, however, the relationship between gastrointestinal symptoms and the GFCF diet is unclear. In 1979, McCarthy and Coleman[75] reported that children with autism do not have increased rates of celiac disease, but other studies have revealed mucosal pathologies in children with ASD and GI symptoms and apparent improvement on the GFCF diet.[76] This is another area in which further study is urgently needed.

Investigators attempting to identify biomarkers to support the "opioid excess" hypothesis have reported increased peptide excretion in urine.[70,71] However, significant problems with the analytical methods initially used to test for peptiduria have recently come to light. Recently, rigorously designed studies have used more accurate methods (mass spectrometry) to investigate the validity of peptiduria and have refuted the initial findings.[77,78] From a study reported in 2008, Cass et al.[77] concluded that, in the absence of evidence for opioid peptiduria in children with ASD, urinary peptides cannot serve as a biomedical marker for ASD, nor can they be used to monitor response to the GFCF diet. These authors also stressed that children with ASD should not be subjected to urinary testing for peptiduria, and their parents should not be subjected to the expense of testing that has been clearly established to have no role in the diagnosis or management of ASD.[77]

The GFCF diet can be difficult for families to implement, with common challenges including increased preparation time, increased food-related expenses, and children refusing to eat the dietary selections. Families must consider the implications of further dietary restriction in a child who may already have a limited food repertoire. Because bone loss has been reported in children on the GFCF diet,[79] clinicians should counsel families about the need to ensure adequate calcium, vitamin D, and protein intake from dietary supplements or supplemented foods. Many vegetable-based milks made from potato, rice, or almond do not provide an adequate source of protein.[42] Consultation with a registered dietician is recommended.[80] Lastly, three controlled trials are currently underway (NCT00090428, NCT01116388, and NCT00614198; http://www.clinicaltrials.gov).

Chelation—Definitely unsafe: Discourage (deaths of children have been reported in children and human studies have not demonstrated efficacy). Chelating agents, which bind and remove heavy metals from the body, were originally developed as treatments of lead toxicity. They have recently been marketed as treatments for ASD, based on the unproven theory that some children with ASD have impairments in the elimination of

mercury and other heavy metals that can interfere with immune function and other biochemical systems.[81,82] Proponents assert that chelation of these heavy metals can result in neurocognitive recovery in children with ASD. This theory has not been substantiated by scientific research and has a number of basic theoretical flaws, in that the neurocognitive effects of chelation of individuals with known toxicities appear to range from minimally beneficial to detrimental.

Rogan et al.[83] found that, although treatment with chelating agents can lead to decreased serum lead levels after an immediate ingestion, recovery of neurocognitive function after chelation is extremely limited and occurs only in children with very high serum lead levels (>45 μg/dL). This may be because chelating agents can actually cause lead levels to rise after periods of treatment, because of redistribution of lead from bone stores to soft tissues and blood.[84] Chelation therapy has nonetheless gained popularity, based on concerns about elevated mercury levels from ethyl mercury in thimerosol, a vaccine preservative that was largely eliminated in 2001, and from other environmental sources, such as fish consumption. No studies have found evidence of either a causal relationship or an association between thimerosol exposure and risk of developing ASD.[85–87] Additionally, a 2007 meta-analysis concluded that there was no evidence to support an association between mercury poisoning and autism.[88]

Chelation is also associated with major risks including, but not limited to, Stevens–Johnson syndrome, alterations in liver function, kidney dysfunction, neutropenia, headache, neuralgia, and paresthesias. Chelation can remove essential minerals, including calcium and iron, which can lead to fatal hypocalcemia and significant iron deficiency. Between 2003 and 2005, three deaths were attributed to chelation therapy that resulted in a hypocalcemia related cardiac arrest, including one death of a child with autism.[89] Federal government investigators halted a clinical trial testing chelation therapy as a treatment for autism[90] after a rodent study from 2006 found that chelation produced indications of lasting cognitive impairment.[91] Additionally, the FDA has recently warned consumers to be wary of chelation therapy, because industrial products designed to separate metals in mining operations are currently being marketed as heavy metal chelators to families of children with ASD. Many of these products have never been tested in humans, nor in animals, and families should be directly cautioned against their use and warned of potential risk of serious harm, including death.[92]

Secretin—Likely safe, definitely not efficacious: Discourage (complete lack of efficacy is clearly established in multiple, rigorously designed studies). Secretin is one of the most thoroughly studied biological treatments in autism. More than 700 children with confirmed ASD have been studied in well-designed double-blind, placebo-controlled studies with excellent outcome measures, and none of these studies has demonstrated efficacy of secretin for treatment of symptoms of autism.[93] A Cochrane review[94] completed in 2005 concluded that "there is no evidence that single or multiple dose intravenous secretin is effective and as such it should not currently be recommended or administered as a treatment for autism." Although no serious adverse effects due to secretin administration in ASD have been reported, the risk to a child of serious adverse events is likely to increase with repeated doses, and more adverse events are likely to be reported as secretin is made more widely available.[94]

Antifungal agents—Unsafe, efficacy unknown: Discourage. Reports in the lay press of a child whose autism symptoms supposedly improved after treatment with nystatin and dietary modifications to reduce *Candida* yeast infection sparked interest in the hypothesis that yeast overgrowth may contribute to autism symptoms.[95,96] Shaw et al.[97] postulated that the unusual urinary metabolites found in two boys with autistic behavior could be due to a new genetic disorder, or to bacterial or yeast overgrowth with no causal relation to autism, or to infection with one or more microorganisms with metabolites "causally related to the disease through inhibition of mitochondrial Krebs cycle activity." The authors acknowledged the limitations of this single case report and the need for further study.[97] To date, however, there have been no controlled studies to assess the validity of these treatments. Currently, there is no scientific evidence to support use of antifungal treatments or stool or urinary testing for candidal overgrowth in autism. Additionally, the alternative laboratories that promote these tests can charge hundreds of dollars per test. Antifungal treatments (including nystatin, fluconazole, ketoconazole, and probiotics) are associated with significant safety concerns, and therefore should be used only to treat proven illness. Important toxicities include cardiac sudden death (in individuals with prolonged QT syndrome), Stevens–Johnson syndrome, seizures, liver and bone marrow toxicity, and gastrointestinal symptoms.

Hyperbaric oxygen therapy—Possible safety concerns, no evidence of efficacy: Discourage. Hyperbaric oxygen therapy (HBO_2T) is widely available, with treatment centers in more than 50 countries, and with more than 500 treatment centers in the United States alone.[98] This therapy can be a life-saving intervention for individuals affected by decompression sickness, carbon monoxide poisoning, or severe wound infections, particularly infections involving compromised tissue.[99] Unfortunately, there is a long history of HBO_2T being promoted as a treatment for various conditions for which there is no scientific evidence to support its use.[99–101] In response to this phenomenon, the Undersea & Hyperbaric Medical Society (UHMS) has undertaken to rigor-

ously monitor the scientific validity of claims made regarding the safety and efficacy of HBO_2T in specific conditions.[98] In the past, treatment of various CNS conditions has been explored, but Cochrane reviews and reports from the UHMS have found no proven benefit of HBO_2T in patients with multiple sclerosis, traumatic brain injury, or ischemic stroke.[100–102] Early uncontrolled studies of HBO_2T demonstrated benefit in children with cerebral palsy, but later controlled studies clearly established no benefit of treatment with HBO_2T, compared with placebo.[102,103]

Hyperbaric oxygen therapy is generally regarded as safe, but there are some common adverse effects, with reversible myopia due to direct oxygen toxicity of the lens and otic barotrauma occurring in up to 20% of individuals.[104] More serious adverse effects can occur, including seizures, hypoglycemia, tympanic membrane rupture, and pulmonary complications.[104] Several conditions can increase the risk of complications, including existing pulmonary disease, underlying seizure disorder, recent otitis media, and recent surgery to tympanic membranes or sinuses.[104] Additionally, complications appear to be significantly more likely to occur in children with neurodevelopmental disorders, with 35% to 52% of subjects with cerebral palsy requiring placement of pressure equalization tubes to continue study participation, and as many as 12% of children with cerebral palsy experiencing seizures that resulted in their withdrawal from the study.[103]

In 2006, Rossignol and Rossignol[105] hypothesized that treating children with ASD using HBO_2T would improve cerebral hypoperfusion and neuroinflammation. They then published two case series suggesting improvement in ASD symptoms with HBO_2T.[105,106] The only controlled trial of HBO_2T in ASD was reported by the same team in 2009.[107] This was a multisite, randomized, double-blind trial of 62 well-characterized young children with ASD. Children were randomized to receive 40 one-hour sessions over a 4-week period of either active treatment (24% oxygen at 1.3 atmospheres absolute [ATA]) or control treatment (21% oxygen at 1.03 ATA). Outcome measures included the Clinical Global Impression scale (CGI), the Aberrant Behavior Checklist (ABC), and the Autism Treatment Evaluation Checklist (ATEC). The authors reported that children in the treatment group had significant improvements in overall functioning, receptive language, social interaction, eye contact, and sensory and cognitive awareness, compared with children who received slightly pressurized room air.[107]

In response to this controversial report, the UHMS[108] published a position paper in 2009 outlining concerns of ascertainment bias, loss of data, author conflict of interest, and most fundamentally a concern that the very low oxygen and pressures used in the so-called treatment (24% O_2 and 1.3 ATA) do not actually constitute HBO_2T. This position paper refutes the findings of the Rossignol team's 2009 RCT report,[107] stating that the purported positive findings were invalid interpretations of the data and that in fact, no significant differences were demonstrated between the control and treatment arms. The UHMS position paper goes on to point out that "one does not require a [hyperbaric] chamber to deliver this dose."[108] In fact, pressures in this range have been used in studies as a sham therapy in control groups.[109] The same studies also demonstrated very high rates of improvement in the control groups at 1.3 ATA, which was attributed to the participation effect or Hawthorn effect.[108,109] The UHMS position statement concludes with the statement, "At this time, the UHMS cannot recommend the routine treatment of ASD with HBO_2T outside appropriate comparative research protocols."[108]

The temerity of the authors of the HBO_2T study[107] presents a new dilemma for clinicians and families, in the form of disguising a group of physicians' preferred treatments as legitimate science. These authors took great pains to design and execute a multisite, randomized, double-blinded trial of HBO_2T in a group of well-characterized children with ASD, essentially ensuring that every possible measure of legitimacy was used to give the impression of a research design with a low propensity for bias. They then introduced bias by essentially comparing two placebo therapies to each other, while fundamentally misinterpreting data to support the efficacy of their preferred intervention.

Understandably, many families of children with ASD have become interested in HBO_2T, and it appears that the UHMS position paper[108] has not been disseminated as widely as the Rossignol article[107] it analyzes. Because families seeking care may receive HBO_2T at therapeutic pressures, counseling families about the potential risks of barotrauma and exacerbation of pulmonary disease and seizures is critical. Additionally, families should understand that this treatment is very expensive and also time consuming, with 40 weeks the average duration of treatment and estimated costs between $1600.00 and $2400.00.[108] To ensure that families who are considering this treatment are well informed, clinicians should direct families to the UHMS website (http://www.uhms.org), because this is the professional organization that ensures quality patient care and scientific rigor in hyperbaric medicine.

Vitamin B_6, Magnesium—Safe, inconclusive efficacy: Tolerate, encourage objective monitoring. Vitamin B_6 is important in neurotransmitter production and is a cofactor for many enzymes related to protein metabolism. It also has effects on the immune system (NCCAM, http://ods.od.nih.gov/factsheets/vitaminb6.asp). A Cochrane review[110] identified three randomized controlled trials of combined B_6 and magnesium treatment in autism. Results from two of those studies did not demonstrate treatment effects in standardized behavior rating scales of autism symptoms,

hyperactivity, or obsessive compulsive behaviors.[111,112] Kuriyama et al.[113] reported no differences on cognitive scores or social maturity scales between treated and control groups, except for higher gains in verbal IQ in the treated group (11.2 vs 6 points, $p = 0.01$), which consisted of only four subjects.

Adverse effects associated with vitamin B_6 include sensory neuropathy, skin reactions, allergic reactions, gastrointestinal symptoms, headache, and hypotonia. Seizures after large doses have also been reported (http://www.nlm.nih.gov/medlineplus/druginfo/natural/patient-b6.html). The Institute of Medicine has established an upper tolerable intake level for vitamin B_6 of 100 mg per day in adults. Some authors have recommended higher doses of vitamin B_6 for treatment of children with autism. For example, Rimland[114] recommended concomitant administration of magnesium at doses of 200–400 mg per day, with the goal of ameliorating these symptoms; the dosing recommendations seem to be the result of observations made by the author and his colleagues. Even if magnesium is used, caution should be exercised, given that neuropathy appears to be dose dependent. Tolbert et al.[111] stated that "doses of 500 mg/day pyridoxine for up to two years have not been associated with neuropathy, while doses above 1000 mg/day for variable periods of time have been almost consistently associated with neuropathy."

Carnosine (amino acids)—Safe, inconclusive efficacy: Tolerate, encourage objective monitoring. Carnosine, an amino acid dipeptide, has antioxidant properties. It may also affect GABAergic receptors[115] and is hypothesized to have neuroprotective effects. In a double-blind, placebo-controlled trial, 800 mg per day of oral L-carnosine was given daily over an 8-week treatment period; improvements were noted in receptive language scores and the Gilliam Autism Rating Scale.[116] No replication studies exist, so efficacy and optimal dosing of L-carnosine remain unclear. Adverse effects include hyperactivity and irritability.

Carnitine (amino acids)—Safe, unknown efficacy: Tolerate, encourage objective monitoring. Carnitine transports long-chain fatty acids into mitochondria and is important in energy production. Carnitine deficiency has been noted in mitochondrial disease, fatty acid oxidation defects, and valproic acid treatment.[117] A retrospective chart review of carnitine levels in children with ASD identified lower carnitine levels and higher alanine and ammonia levels, compared with the laboratory reference range mean,[117] although these children did not have clinical signs of mitochondrial disease. No studies have evaluated treatment effects of carnitine.

Immune therapies (including intravenous and oral Ig)—Unknown safety, unknown efficacy: Discourage. Immunoglobulin treatment has been studied in autism due to reports linking abnormalities in various immune system markers (antibodies, cytokines, cellular immunity) and gastrointestinal symptoms in children with ASD.[118–120] In Canada, the IVIG Hematology and Neurology Expert Panel[121] reviewed three case series and recommended against use of intravenous immunoglobulin (IVIG) as a treatment for autism. Two double-blind placebo-controlled crossover trials have been published studying Ig treatment. Niederhofer et al.[122] reported improvements in parent and teacher ratings on the Aberrant Behavior Checklist after one dose of IVIG, including eye contact and speech; however, clinician ratings (Children's Psychiatric Rating Scale) did not differ by treatment group. A large, double-blind placebo-controlled trial of oral Ig did not yield significant differences in GI dysfunction or autism symptoms.[123] IVIG can have serious adverse effects, and 3–15% of recipients experience a systemic reaction to infusion.[121] This expensive therapy should be limited to treating conditions with sufficient evidence of efficacy to support its use.

Essential fatty acids—Safe, inconclusive efficacy: Tolerate, encourage objective monitoring. Long-chain highly unsaturated fatty acids are essential fatty acids that cannot be synthesized in the body and so must be obtained from dietary sources. Omega-3 fatty acids, including docosahexaenoic acid and eicosapentaenoic acid, are important in brain development. Omega-3 fatty acids are found in fish and fish oil, which are less plentiful in Western diets than elsewhere. One randomized, double-blind placebo-controlled study examining the use of omega-3 supplementation in children with autism who were not taking psychotropic medications found a nonsignificant trend for decreases in hyperactivity and stereotypy domains on the Aberrant Behavior Checklist.[124] A review, which also included four uncontrolled, open-label studies, concluded that there was insufficient evidence regarding efficacy, but that future studies should target hyperactivity as the primary outcome measure.[125]

Methyl B_{12} (methylcobalamin), folic acid, dimethylglycine, glutathione—Safe, inconclusive efficacy: Tolerate, encourage objective monitoring. Detoxification, immune function, and DNA repair all rely on antioxidant function and removal of reactive oxygen species. The transfer of methyl groups is an important reaction in this metabolic pathway, and some hypothesize that oxidative stress and toxicity are responsible for the neuronal insult involved in ASD.[126] Abnormal metabolic profiles and impaired methylation have been reported in some children with ASD,[127,128] although no behavioral correlations were investigated. There are no randomized controlled trials published regarding the efficacy of molecules in this pathway on symptoms of ASD.

The cofactors methylcobalamin (methyl B_{12}) and folinic acid are required for proper functioning of metabolites in the methionine pathway, such as glutathione, an antioxidant, and *S*-adenosylhomocysteine, a methyl group donor. James et al.[129] reported improvement in glutathione

and *S*-adenosylhomocysteine levels following open-label administration of methylcobalamin (methyl B_{12}) and folinic acid; again, however, there was no clinical correlation. Two double-blind, placebo-controlled studies on dimethylglycine (a methyl donor with potential activity at NMDA receptors) showed no treatment effects on Vineland Adaptive Scores, Aberrant Behavior Checklist, or Children's Psychiatric Rating Scale scores.[130,131]

Manipulative and body-based practices

Chiropractic—inconclusive safety, inconclusive efficacy: Discourage. Manipulation of the spine has been used to treat a variety of medical conditions, including pain, musculoskeletal disorders, asthma, and colic. The rationale for its use in the treatment of core symptoms of autism is unknown. There are no published randomized studies comparing the effects of chiropractic manipulation in children with autism. Khorshid et al.[132] noted improvements in autism symptoms in children receiving full-spine and cervical adjustment. Methodological weaknesses include lack of a control group, unclear criteria for ASD diagnosis, and use of an unvalidated tool for measurement of autism improvement.

Adverse events have been associated with pediatric spinal manipulation, including subarachnoid hemorrhage, quadriplegia, vertebral dislocation, and missed medical diagnoses.[133] It is important to identify pre-existing conditions, such as spinal cord tumors before receiving chiropractic therapy. The cervical spine in children may be particularly vulnerable to injury.[134]

Craniosacral manipulation—Safe, inconclusive efficacy: Tolerate, encourage objective monitoring. Craniosacral therapy involves manipulation of the craniosacral system, which involves all organs in contact with cerebrospinal fluid (brain, spinal cord, protective membranes). Palpation and gentle pressure are used to correct imbalances in the system due to restriction of movement due to cranial sutures or disruptions in craniosacral rhythm impulses. There are no published randomized studies comparing the effects of craniosacral therapy in children with autism, and evidence is inadequate to support the efficacy of craniosacral treatment or association between craniosacral misalignment and health outcomes.[135]

Massage and therapeutic touch—Safe, inconclusive efficacy: Tolerate, encourage objective monitoring. Touch therapy and massage are best known for their use in stress reduction, although there is some evidence to support the use of massage to improve sensory impairment (but not core symptoms) in children with ASD. Silva et al.[136] reported no differences in language or Autism Behavior Checklist scores. Escalona et al.[137] observed decreases in stereotypic behaviors in the classroom in children receiving daily massage, compared with children whose parents read to them for the same amount of time daily. Improvement in Sensory Profile and Vineland adaptive scores[136] and in attention[137] have also been reported, although all of these studies involved small samples and require replication. Subjective decreases in sleep[136,137] and gastrointestinal problems[136] were also reported, but these symptoms were not systematically studied.

Acupuncture—Safe, inconclusive efficacy: Tolerate, encourage objective monitoring. Acupuncture may be helpful for treating pain,[138] whether used alone or in conjunction with other treatments. It typically involves the insertion of needles through the skin to activate nerve fibers and correct energy imbalance.[139] There are no published randomized studies of the effects of acupuncture in children with autism. Acupuncture is considered generally safe, although adverse effects may include infection, pain, and organ damage with improper needle placement (NCCAM, http://nccam.nih.gov/health/acupuncture/introduction.htm).

CONCLUSIONS

As the prevalence of both autism spectrum disorders and CAM use continues to rise, the need for reliable sources of information about specific CAM therapies for children with ASD becomes more essential. One way for healthcare providers to ensure safe use of CAM by their patients is to engage the family in discussions about CAM use and to cooperatively develop a strategy that they can jointly use to evaluate the evidence that supports or refutes the value of specific CAM treatments. A summary of reliable resources that may be used to facilitate discussions about CAM is given in Table 1.

Familiarizing parents with concepts such as the hierarchy of evidence and basic research practices is important. Families will also benefit from understanding that not all positive findings are actually related to the CAM treatment studied. In fact, the history of many CAM treatments used in ASD is strikingly similar, with early case reports of improvement after a treatment, followed by a search for a plausible biological mechanism, some positive results from small uncontrolled studies, and then refutation of those results in larger, more rigorously designed trials that use adequate controls.

Some confounders are particularly relevant to the study of CAM in children with neurodevelopmental disabilities. When motivated parents participate in CAM studies, placebo or participation effects have repeatedly proven to be powerful confounders.[103,140] Additionally, child development is dynamic, and improvement over time is expected, which makes distinguishing the effects of individual treatments, whether they be conventional treatments or CAM treatments, especially problematic in uncontrolled studies.[6] Understanding the power of these confounders will help clinicians and parents avoid therapies that are either potentially harmful or that simply have no benefits over placebo in producing the desired

Table 1. *Recommended Resources on Complementary and Alternative Medicine (CAM)*

Resource	Available At
National Institutes of Health–National Center for Complementary and Alternative Medicine (NCCAM)	http://nccam.nih.gov/
Research, training, and grant funding related to CAM	http://nccam.nih.gov/research/
NCCAM Clearinghouse. Answers questions about specific CAM therapies, in English or Spanish. Open Monday–Friday, 8:30 a.m.–5:00 p.m. ET (except Federal holidays).	Toll-free in the U.S.: 1-888-644-6226 TTY (for deaf and hard-of-hearing callers): 1-866-464-3615 E-mail: info@nccam.nih.gov
Time To Talk campaign. The NCCAM provides materials to help facilitate disclosure through the Time To Talk campaign, including a downloadable toolkit for healthcare providers, as well as packets for patients and for community organizations.	http://nccam.nih.gov/timetotalk/
Dietary Supplements Labels Database. This U.S. National Library of Medicine site provides information about the ingredients in dietary supplements.	http://dietarysupplements.nlm.nih.gov/dietary/
U.S. FDA, Center for Food Safety and Applied Nutrition (CFSAN), Office of Nutrition, Labeling and Dietary Supplements	http://www.fda.gov/AboutFDA/Basics/ucm193949.htm

See also Otten JJ, Hellwig JP, Meyers LD. Dietary reference intakes: the essential guide to nutrient requirements. Washington, DC: National Academies Press, 2006. This 2006 consensus report from the U.S. Institute of Medicine of the National Academies summarizes and updates the eight previous volumes (http://www.iom.edu/Reports/2006/Dietary-Reference-Intakes-Essential-Guide-Nutrient-Requirements.aspx). Provides recommended intake guidelines and also upper tolerable intake limits.

outcome. Although using therapies that are safe but not efficacious may not cause immediate physical harm, the redirection of limited time and financial resources may result in missed opportunities and can be a significant family stressor, especially when there is disagreement between caretakers about the use of limited resources. It is nonetheless important to realize that some CAM therapies will eventually be proven to be effective and some conventional therapies will eventually be proven to be ineffective.[3]

Families typically want physician input about CAM to be given in a nonjudgmental manner. When families experience negative responses from their pediatricians regarding CAM, they are more likely to seek alternative care without consulting their pediatrician,[141,142] thus increasing the risk that complementary care will become alternative care. Although the seemingly endless varieties of CAM change frequently,[143] healthcare providers must maintain their position as a trusted resource for families by carefully eliciting the reasons for possible CAM usage, responding to issues raised by facilitating the discussion of safety and efficacy data, suggesting evidence-based traditional treatments, and encouraging families who choose CAM to use objective monitoring whenever possible. Using the safety–efficacy model proposed in this review as a framework will promote what Cohen et al.[46] rightly proposed: responsible, ethical, and legally defensible decisions about CAM use.

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