



Published in final edited form as:

*Child Adolesc Psychiatr Clin N Am.* 2008 October ; 17(4): 803–ix. doi:10.1016/j.chc.2008.06.004.

## “Complementary and Alternative Medicine Treatments for Children with Autism Spectrum Disorders”

Susan E. Levy, M.D.<sup>a,a</sup> and Susan L. Hyman, M.D.<sup>b,b</sup>

<sup>a</sup>*Clinical Professor of Pediatrics, University of Pennsylvania School of Medicine, The Children's Hospital of Philadelphia*

<sup>b</sup>*Associate Professor of Pediatrics, University of Rochester School of Medicine, Golisano Children's Hospital at Strong*

### SYNOPSIS

Complementary and alternative medical treatments are commonly used for children with autism spectrum disorders. This review discusses the evidence supporting the most frequently used treatments, including categories of mind-body medicine, energy medicine, biologically based, manipulative and body-based practices, with the latter two the most commonly selected by families. It is important for clinical providers to understand the evidence for efficacy (or lack thereof) and potential side effects. Some CAM practices have evidence to reject their use, such as secretin, others have emerging evidence to support their use, like melatonin. Most treatments, however, have not been adequately studied and do not have evidence to support their use.

### Keywords

autism; autism spectrum; complementary and alternative treatments; evidence based

---

Autism spectrum disorders (ASD) are common disorders (affecting 1 in 150 children)<sup>2</sup> and are typically first recognized in early childhood. ASDs are characterized by core deficits in socialization, communication and behavior<sup>5</sup> with a wide range of severity of symptoms. Disorders include autism, Asperger's Disorder, Childhood Disintegrative Disorder, Rett syndrome and Pervasive Developmental Disorder - Not Otherwise Specified (PDD-NOS). For the purpose of this paper, we will include autism, Asperger's Disorder and PDD-NOS as the ASDs for discussion, as Childhood Disintegrative Disorder and Rett's Disorder have different characteristics, outcome and treatment. Function and outcome is affected not only by core deficits but by frequently associated comorbid behaviors<sup>34,62</sup>, such as irritability, sensory abnormalities, hyperactivity, affective disorders and others. Outcome is further affected by the presence or absence of language and by overall cognitive ability.

---

Correspondence to: Susan L. Hyman.

<sup>a</sup>Corresponding author for proof and reprints: Susan E. Levy, M.D. University of Pennsylvania School of Medicine The Children's Hospital of Philadelphia 3405 Civic Center Boulevard Philadelphia, PA (215) 590-7528 FAX 215 590-6804 levys@email.chop.edu

<sup>b</sup>coauthor address: Susan L. Hyman, M.D. University of Rochester School of Medicine Golisano Children's Hospital at Strong Box 671, 601 Elmwood Avenue Rochester, NY 14642 (585)275 2986 FAX (585)275 3366 susan\_hyman@urmc.rochester.edu

**Publisher's Disclaimer:** This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

While existing scientific data suggests the etiology is largely genetic with the plausibility of environmental factors, the specific causes are often not known. In addition, the symptoms are behaviorally defined, heterogeneous and change with acquisition of developmental skills. For these reasons families of children with autism and related disorders may turn to therapies that are not based in the realm of conventional medical or psychological practice.

In this review we will discuss the common use of complementary and alternative medicine (CAM) by families of children with autism spectrum disorders (ASD), investigate the reasons families seek CAM, review the commonly used CAM therapies for ASD, and describe the issues faced by conventional practitioners whose patients are interested in CAM use. The combination of conventional practice and complementary techniques which have some supportive evidence is often called "Integrative Medicine." Some interventions originally considered CAM are embraced into conventional practice as evidence supports their use.

## Treatments for Children with ASD

Research has shown that the most effective treatment is a combination of specialized and supportive educational programming, communication training (such as speech/language therapy), social skills support and behavioral intervention<sup>60,72</sup>. Other treatments such as occupational therapy and physical therapy may promote progress as they address possible comorbid difficulties of motor coordination and sensory deficits. Progress may be slow, in part due to the pervasive nature of the core deficits and comorbid features.

## Prevalence of CAM Use for Symptoms of Autism in Children

The use of CAM is increasing for both adults and children. The National Center for Complementary and Alternative Medicine (NCCAM) reports that over ¾ of American adults use CAM for treatment of disease or to maintain health ([http://nccam.nih.gov/news/camsurvey\\_fs1.htm](http://nccam.nih.gov/news/camsurvey_fs1.htm)). The use of CAM in children mirrors the treatment choices of their parents. It is estimated that 2-50% of children in the United States are given CAM therapies<sup>19</sup>. This is likely to be an underestimate.

Children with chronic illness, such as cancer, asthma, rheumatoid arthritis, and neurodevelopmental disorders such as autism, are treated with CAM therapies at even higher rates. Up to 50 to 75% of children with autism may be treated with CAM<sup>39,113</sup>. CAM use may be even more likely in children with comorbid intellectual disability. Levy et al<sup>58</sup> reported that almost 1/3 of young children referred for evaluation of ASD were being treated with dietary therapies by their parents even before confirmation of diagnosis.

A wide range of CAM therapies are used in children. NCCAM groups CAM therapies into four domains, including mind-body medicine, biologically based practices, manipulative and body-based practices and energy medicine. The most commonly used CAM treatments for ASD fall into the categories of biologically based practice and manipulative and body-based practices. Approximately half of families of children with ASD will use a biologically based therapy, 30% a mind body therapy, and 25% a manipulation or body based method<sup>39</sup>. The range of reported response about usage is dependent upon the population queried and how the question is asked. Hanson<sup>39</sup> reported that 41% of respondents endorsed benefit with dietary and nutritional treatments, while Wong and Smith<sup>113</sup> found that 75% of respondents thought their treatments were helpful.

## Who Uses CAM Therapies and Why

Conventional medicine has been directed at the goals of diagnosis, treatment, and when possible, cure, of disease states. CAM practices add promotion of health and involvement of

the patient in a process of healing that must ultimately address the underlying cause of illness as interpreted by the practitioner<sup>18</sup>.

CAM is often perceived as “natural”, without the side effects of conventional medical treatments. The reasons why families use CAM have been studied in other chronic disorders of childhood. Adverse effects from conventional medication was the only significant predictor for CAM use in children with inflammatory bowel disease<sup>41</sup>. Similarly, for children with asthma, CAM use was predicted by older age, worse control of symptoms, more medications, more medical visits and more side effects<sup>94</sup>. A survey in Italy identified fear of side effects as the most common reason for parents to choose a CAM therapy for routine illness. Satisfaction was reported in 81% and successful symptom resolution attributed to the CAM therapy<sup>18</sup>. Adults who use CAM believe that a combined approach of CAM and conventional therapy is more likely to be successful than either one alone, that nutritional support is an important part of health maintenance, and prefer not to take prescription medications<sup>63</sup>. Among families of children with ASD surveyed by Hanson et al<sup>39</sup>, over 75% of families chose therapies based on their perception of safety, absence of side effects or prior experience with side effects. Despite the common use of CAM, 2/3 of families report that they base their therapeutic choices on the recommendation of their health care provider or scientific support. Approximately 50% of families report that they desire more control over the therapies elected, choose CAM because of a hope for a cure, or because of recommendations by friends or families of other children with ASD. Only 39% elect CAM because they prefer “natural” therapies and 25% report choices based on media. CAM therapies are pursued to treat core symptoms of ASD, as well as to increase attention, to enhance relaxation, to decrease gastrointestinal symptoms, regulate sleep, and to promote general health, in that order<sup>113</sup>.

Patients who seek out CAM providers may be seeking the longer visits typically offered in CAM settings and perceive that the CAM provider pays more attention to the symptoms of concern to the family. Parents who use CAM for their children tend to use CAM for their own health and be better educated. It is not dissatisfaction with conventional care that leads families to employ CAM. The most commonly reported reasons are concern regarding side effects, a desire to include multiple approaches to address symptoms, and personal beliefs about health. With changes in society such as self determination in health care, greater accessibility to information on the internet and a decline in the faith in science and technology people seek more control over their own medical decision making<sup>63,96</sup>.

## CAM Therapies

All treatments should be based on principles of evidence-based medicine (EBM), integrating clinical expertise, patient (or family) values, and the best evidence for efficacy<sup>50,59,89</sup>. The selection of some treatments may reflect a bias, affected by the caregiver's clinical experience, education or skills, and the families' unique concerns and expectations. Studies of efficacy of treatment should be judged by standards of scientific research, guiding study design and the hierarchy of types of study. The hierarchy of strength of evidence includes randomized, controlled clinical trials, which are at the peak, followed by cohort studies, case control studies and then case reports. The most robust evidence would include metaanalyses, which thoroughly examine a number of valid studies on a topic. Meta-analysis combines results using accepted statistical methodology as if they were from one large study or a systemic review which focuses on a clinical question and includes an extensive literature search to identify all studies with sound methodology. Unfortunately, even some commonly used medical treatments have not met these standards. For the purposes of this paper, we reviewed the existing literature and report the strength of the evidence as Grade A (randomized controlled trials, reviews and/or meta-analyses), Grade B (other evidence such as isolated well-designed controlled and

uncontrolled studies), or Grade C (case reports or theories). This grading refers to the strength of the evidence; evidence that supports or refutes the use of the intervention.

## Mind-Body Medicine

### Yoga - Grade C

Decreasing anxiety through nonpharmacologic techniques has great attraction to both families and clinicians. Yoga is a mind-body approach that enjoys popular practice for increasing the sense of well being and control with the potential to decrease anxiety. A trial of yoga for symptoms of ADHD was underpowered to demonstrate effect, but suggested some benefit in children on medication<sup>48</sup>. Relaxation therapy decreased symptoms of anxiety in inpatients with anxiety on a child psychiatry service<sup>83</sup> and in children with mental retardation<sup>104</sup>. No studies have yet been published related to symptoms of autism and response to yoga techniques.

### Music Therapy - Grade B

Use of music to reinforce communication is frequently applied in the context of educational interventions. The use of music in a discrete therapeutic format to enhance social skill and communication development in children with autism has been examined in small trials with the potential for positive effects on spoken and gestural communication<sup>36</sup>. No effect on overall behavior was reported. Clinical practice often pairs music with other interventions with subjective benefit<sup>53</sup>. Further study of the neurobiology of music processing in people with autism may provide additional rationale for music therapy as a discrete treatment or a part of other educational interventions.<sup>40,108</sup>

## Biologically Based Practices

### Dietary supplements

**B6/Mg++ - Grade B**—Vitamin supplements to improve symptoms of mental health disorders have been in use for over 50 years with B6 and Magnesium a popular treatment for autism over the past 20 years. This treatment has been the subject of reviews by several authors<sup>76,77,82</sup>. Due to the small number of studies, methodological deficits, small sample sizes meta-analysis could not be done and the evidence was not adequate to support use of this supplement.

The most recent Cochrane Review<sup>76</sup> identified three studies completed between 1993 and 2002 which compared outcomes to either placebo or non-treated group. A total of 28 subjects were treated in these trials. Findling and colleagues<sup>29</sup> studied 12 participants using a randomized, double blind placebo-controlled trial following a 2 week pre-randomization placebo lead in period. No effects of treatment were seen in the 10 subjects who completed the study. More recently Kuriyama<sup>56</sup> and colleagues reported improvement in IQ and social quotient scores in 8 children treated with B6 and Mg++. Despite the fact that these studies met criteria for Cochrane review, they all suffered from significant methodological weaknesses, including inadequate description of diagnosis and selection criteria and outcome measures. One additional study with similar methodological issues has been published since this review, describing an open study of 33 children with ASD who were reported to improve in symptoms after Mg-B6 treatment<sup>71</sup>.

**DMG - Grade B**—Dimethyl glycine (DMG) and a related compound, trimethyl glycine (TMG), are commonly used nutritional supplements. An older case series suggested improvement in language and attention in a group of children with intellectual disability treated with DMG. Two small, double blind studies of DMG have not demonstrated positive effects on symptoms of autism compared to placebo<sup>9,52</sup>.

**Melatonin - Grade B**—Some nutritional supplements have known pharmacologic properties. Melatonin is a hormone produced by the pineal gland that regulates sleep. Clinical studies have demonstrated abnormalities in melatonin production or release in individuals with ASD<sup>69</sup>. Clinical benefit in sleep onset and maintenance has been demonstrated in at least one large case series at doses from 0.75 mg to 6 mg prior to bedtime<sup>7</sup>. This would be predicted by the large effect size in small randomized trials<sup>33</sup>. Few side effects were reported. Of 107 children with autism, many of whom were also being treated with psychotropic medications, treated with melatonin by Andersen et al<sup>7</sup> side effects of early morning sleepiness or enuresis were reported in three cases. No effect on seizures was noted.

**Vitamin C - Grade B**—Vitamin C is not commonly used as an isolated treatment but is frequently added to vitamin mixtures used by children with ASD. Dolske and colleagues<sup>23</sup> reported positive results of decreased stereotyped behavior in a 30 week double-blind/ placebo controlled trial in 18 children with ASD. To date this study has not been replicated. Other reports have implicated vitamin C in its role with oxidative stress.

**Amino Acids - Grade C; Carnosine - Grade B**—Amino acids are both precursors to neurotransmitters and act as neurotransmitters themselves<sup>67</sup>. As such, it is not surprising that some complementary approaches attempt to manipulate neurochemical actions by nutritional supplementation. The abnormalities in peripheral serotonin levels in people with autism and their family members was one of the first biologic findings in autism<sup>84</sup>. Supplemental tryptophan might increase brain production of serotonin because the uptake across the blood brain barrier is sensitive to concentration in the bloodstream. However no trials have examined clinical effect of tryptophan supplementation on symptoms of autism. In adults with autism, tryptophan depletion exacerbated symptoms<sup>68</sup>. There are no peer reviewed studies to date examining the effects of supplementation with other amino acids such as taurine, lysine, or GABA in children with autism although they are often part of a CAM nutritional supplementation strategy. Taurine is a semi-essential sulphur containing amino acid derived from methionine and cystine. It has antioxidant properties and has been associated with improved visual learning in rodents. L-Carnosine is a dipeptide that was demonstrated in one double blind placebo controlled trial in 31 children with autism to improve expressive and receptive vocabulary and subjective improvement on the Gilliam Autism Rating Scale over an 8 week trial at 800 mg/day<sup>14</sup>. Lysine is an amino acid exogenously obtained from meat and milk products. With methionine it can be endogenously made into carnitine<sup>16</sup>. Carnitine is involved in intracellular transport of long chain fatty acids and therefore is important in energy generation. Although carnitine has documented usefulness in specific deficiency states and in the presence of certain medications such as valproic acid, it has never been evaluated as a treatment for motor or behavioral symptoms of autism. There is one case series of children with autism with elevated alanine and low carnitine suggesting that some children with autism may have mitochondrial disease<sup>28</sup>.

**Omega 3 fatty acids - Grade B**—Polyunsaturated fatty acids, in particular Omega 3 fatty acids, are crucial for brain development and cannot be manufactured in the body. Dietary consumption occurs through ingestion of fish or fish oils. Oral supplementation with essential fatty acids has become popular for children with developmental differences including autism and ADHD<sup>57</sup>. Studies have examined differences in plasma levels of children with autism which are decreased compared to typical volunteers<sup>99,105</sup> without clinical correlations. Recently, Amminger and colleagues<sup>6</sup> reported improvement in behavior following a randomized double-blind placebo-controlled 6 week pilot trial of oral supplementation in 13 children with ASD with severe behavior difficulties. No side effects were noted beyond gastrointestinal symptoms.

**Folate and Oxidative stress - Grade C**—It has been hypothesized that exposure to toxic agents or endogenous abnormalities that lead to oxidative stress may cause neuronal insult and lead to the regression seen in up to 1/3 of children with autism<sup>51</sup>. Neuroanatomic differences in white and gray matter, cerebellar pathology (e.g., Purkinje cell loss), and other evidence of cellular disruption<sup>4</sup> as well as functional abnormalities<sup>35</sup> led to the search for potential environmental causes of atypical brain development. Abnormal levels of antioxidants, transferrin, lipid peroxidases, methionine and other biochemical intermediates have been reported in children with autism<sup>80</sup>, without clinical correlation. James and colleagues<sup>46</sup> have described abnormal metabolic profiles in 20 children with autism compared to 33 controls, consistent with a presumed impaired methylation capacity. Laboratory findings normalized following a trial of folinic acid, betaine and methylcobalamin. However, no clinical outcome data was reported. James and colleagues<sup>47</sup> also reported decreased measured indicators of methylation capacity in a larger population (80 with autism and 73 controls) also without clinical correlation.. At present there are no randomized, controlled treatment trials reported in the scientific literature. These hypotheses require further study.

**Diet - Gluten-free/ Casein-free diet (GF/CF) - Grade B**—In addition to supplementation with vitamins or other nutritional supplements to address hypothetical deficiencies or to provide pharmacologic effect, modification of dietary intake has been a popular intervention for behavioral modification in children with ASD. It has been suggested that the elimination of the proteins gluten (found in barley, wheat, and rye) and casein (found in milk products) which either cause or aggravate symptoms of ASD after absorption across a damaged (“leaky”) intestinal lining by acting as false opiate neuropeptides will improve behavior of children with ASD. The significance of reports of increased levels of metabolites of casein and gluten in the urine of people with autism remains unclear<sup>92</sup>. Urinary peptides are not used in conventional practice to prescribe or monitor dietary restriction. Anecdotal reports and case series of dietary restriction leading to subjective improvement in the symptoms of autism have resulted in a report of a small single blind trial that suggested some improvement<sup>54</sup> and a double blind trial that did not identify objective improvement in language or behavior although some parents reported subjective differences<sup>25</sup>. It is not yet clear whether some of the perceived improvements are due to elimination of lactose in children who are lactose intolerant or other changes related to the alteration in protein source and food composition. Families who desire to try the gluten/casein free diet must be counseled that adequate calcium and vitamin D intake must be maintained with supplements or supplemented foods. Attention to protein intake is also important since many young children obtain much of their protein through dairy products. Vegetable based beverages including rice, potato, and almond “milk” do not contribute to protein sufficiency as soy based products do. Consultation with a registered dietitian should be recommended.

Common dietary approaches to symptoms of inattention in children with ADHD are also often considered for children with ASD with hyperkinesis. Double blind, placebo controlled methods have consistently demonstrated no relationship of sugar to attention or related behaviors<sup>112</sup>. Although not specific for symptoms of ASD, there may be subgroups of children who do have a behavioral response to elimination of chemicals used as food colors<sup>91</sup>.

**GI medications - Grade C**—Dietary treatments are not the only gastrointestinal treatments that are pursued. Gastrointestinal symptoms of gastroesophageal reflux, constipation, diarrhea, feeding refusal and others are frequently reported in clinical settings<sup>57</sup> although there is not yet documentation of increased population based prevalence of gastrointestinal abnormalities<sup>26,55</sup>. Given the frequent report of symptoms, digestive enzymes are used by some families<sup>12</sup>. No evidence based studies are available to evaluate efficacy. Probiotics are also used to improve the microbial environment in the intestine<sup>11</sup>.

**Secretin - Grade A**—Secretin, a gastrointestinal hormone, has the distinction of being one of the most extensively studied pharmacotherapeutic agent for autism. It came to light as a potential treatment after a lay television show highlighted a report of a case series by Horvath<sup>43</sup> describing improvement in symptoms of autism after administration during endoscopy to examine pancreatic secretions. More than a dozen well designed, well-executed studies have been published, failing to demonstrate efficacy of secretin for symptoms of autism<sup>57</sup>. A recent Cochrane review reported 14 randomized controlled trials, with a total of 618 children. Nine studies used a crossover treatment design. The authors concluded that there is no evidence that single or multiple dose intravenous secretin is effective for treatment of ASD<sup>109</sup>.

**Hyperbaric Oxygen Therapy (HBOT) - Grade C**—Hyperbaric Oxygen Therapy (HBOT) is used in conventional practice to treat carbon monoxide poisoning, to enhance wound healing and for pressure equalization after diving injuries<sup>3,13</sup>. HBOT provides pressurized oxygen at pressures greater than or equal to 2 atm. HBOT is generally considered to have few side effects other than a potential for exacerbation of ear pain or seizures, but little data is available. Because of attributed properties of increasing blood flow and/or oxygen to the brain and decreasing inflammation, it has been evaluated therapeutically in disorders of the central nervous system, including cerebral palsy, dementia, and traumatic brain injury. Randomized controlled trials of HBOT in children with cerebral palsy at 100% O<sub>2</sub> at 1.75 atm compared to a control condition of room air at 1.3 atm reported no difference in motor and behavioral symptoms<sup>65,66</sup>.

There is increasing popular interest in using HBOT for symptoms of autism because of hypotheses regarding inflammation of the gut or brain, brain hypoperfusion, and aberrant oxidative stress response which proponents of HBOT suggest might be improved by upregulation of the metabolic pathways by HBOT<sup>86</sup>. In an open clinical trial, 18 children with autism were given 40 sessions of HBOT at 1.3atm and 24% O<sub>2</sub> (n=6) or 1.5 atm and 100% O<sub>2</sub> (n=12) in a non random fashion.<sup>87</sup> Metabolic markers for oxidative stress, C reactive protein to evaluate inflammation and parental report of behavior on the Aberrant Behavior Checklist, Social Responsiveness Scale, and ATEC were recorded before treatment then after each 10 sessions. Each child received 40 sessions. Many children were already on antioxidant therapy, which is noted by the authors when they report no difference in markers of oxidative stress. CRP decreased in the subgroup with the highest values. Parents reported subjective improvements in several areas. The subjective data and potential confounds make this study difficult to interpret. There are no randomized controlled trials of HBOT for symptoms of ASD to support the clinical use of this modality.

**Chelation - Grade C**—Reports of increased prevalence rates of autism, likely due to multiple factors, has resulted in a search for potential environmental causes. Questions of the relationship to vaccine administration came about in part because symptoms of autism are identified during late infancy and toddlerhood, and a temporal relationship with immunizations is noted in some cases,<sup>22,81</sup>. A paper published in 2001<sup>8</sup> developed a hypothesis relating symptoms of mercury intoxication to symptoms of autism. Meta-analysis completed by Ng and colleagues<sup>74</sup> of 2 studies concluded that there was not enough evidence to show that hair mercury level was lower in autistic children than typical. A number of epidemiologic studies have failed to confirm a link between use of thimerosal as a vaccine preservative and elevated autism prevalence<sup>21,44,45,61,64,73,79,81,88,100,102,103,106</sup>. Despite the lack of scientific evidence of a link between the exposure to ethyl mercury in thimerosal (the mercury containing preservative used in vaccines that has been largely eliminated in the US since 2001), chemical chelation treatments are a popular intervention. Chelation is the process of administering either DMPS (2,3-dimercaptopropane-1-sulfonate) or DMSA (2,3-dimercaptosuccinic acid) to bind heavy metals such as mercury and facilitate elimination from the body. There are no controlled studies that examine the safety or efficacy of prescription or nonprescription chelation regimens

for children with autism. More importantly, there have been deaths reported from inappropriate use of a chelator, EDTA, from hypocalcemia<sup>10</sup>. Proponents of this therapy suggest that mercury is poorly eliminated by children with autism and that it interferes with immune function and other biochemical systems.

**Immune Therapies - Grade C**—There is increasing evidence that prenatal immune response may affect fetal brain development. The data regarding immune function in children with autism, however, varies among reported populations<sup>101,111</sup>. Jyonouci et al<sup>49</sup> found that dietary restriction did not alter immune findings in children with or without gastrointestinal symptoms. Three case series report trials of children who were infused with intravenous immunoglobulin-G to treat purported immune deficits and symptoms of autism. One open trial reported improvement in subjective data<sup>38</sup> but subsequent trials with specific outcome measures and better subject characterization did not corroborate this finding<sup>20</sup>. Other treatments for immune function have been proposed, but remain without support in the peer reviewed literature<sup>37</sup>. In the absence of conventional symptoms of immune disorders, work up and treatment of immune status is not currently recommended in children with autism<sup>72</sup>.

**Antibiotics - Grade C**—Reports of frequent respiratory or gastrointestinal infections during the early years of development of children with autism have suggested these exposures may be etiologic agents by promoting gut dysbiosis or as confirmation of immune dysfunction. Niehus and Lord<sup>75,85</sup> reported a cohort of young children with ASD who had a history of more frequent episodes of otitis media, but no more illness related fevers or use of antibiotics compared to typically developing peers. Reports of frequency of gastrointestinal infection or colonization are inconsistent, and suffer from methodologic difficulties such as small sample size, lack of clinical correlation to laboratory findings<sup>30</sup> and lack of a control group<sup>27</sup>. Sandler and colleagues<sup>90</sup> reported short term behavioral improvement in 11 children treated with oral vancomycin. No further data or studies are available, and even the investigators suggested vancomycin should not be a routine clinical treatment.

**Antifungal Agents - Grade C**—Treatment with anti-fungal agents is based upon an earlier report of presumed candidal overgrowth in 2 boys with autistic behavior who demonstrated what was interpreted as yeast metabolites in urine organic acids<sup>93</sup> and reports suggesting yeast overgrowth due to antibiotic use or sugar ingestion<sup>17</sup>. Yeast overgrowth is conjectured to be secondary to intestinal dysbiosis or to some other immune factors unique to autism. No controlled trials have tested this intervention to date despite the popularity of probiotic use and medications such as nystatin (Mycostatin) and fluconazole (Diflucan) for treatment of yeast overgrowth.

## Manipulative and Body-Based Practices

### Chiropractic - Grade C

The peer reviewed literature does not include reports that specifically address either chiropractic manipulation or craniosacral massage for symptoms of autism. Chiropractic care is a common approach used by many families for general health issues. The potential for harm is low, however it has been associated with injury from spinal manipulation and missed medical diagnoses<sup>107</sup>

### Craniosacral Massage - Grade C

Physical manipulation of the skull and cervical spine has been used by chiropractors, osteopathic physicians, occupational therapists and others for specific therapeutic purposes. Despite claims that practitioners can alter and sense cerebrospinal fluid (CSF) flow or the Cranial Rhythm Impulse, no movement of bony sutures or alteration of pressure could be

demonstrated in a laboratory model<sup>24</sup>, or in humans<sup>70</sup> It is possible that perceived therapeutic response might be secondary to another aspect of the therapy such as touch. No studies are reported that examine this modality for use in autism.

### **Massage/therapeutic touch therapies - Grade C**

Sensory differences are frequently described by parents, but do not figure prominently in the DSM IV criteria for diagnosis of autism. Therapeutic approaches in this category include massage<sup>95</sup> and Aroma Therapy<sup>110</sup>.

### **Auditory integration - Grade B**

The goal of Auditory integration training (AIT) is to ameliorate auditory processing deficits and improve concentration<sup>98</sup>. Many parents also report improved behaviors. Different methods of AIT include listening through headphones to electronically modified music, voice or sounds in an effort to improve function. Recent systematic reviews<sup>97,98</sup> included 6 randomized controlled trials, which all showed significant methodological weaknesses, prohibiting meta-analysis. The authors of the Cochrane review agreed with the recommendations of the American Academy of Pediatrics, that AIT should be considered an experimental treatment until evidence based trials support its use<sup>1,97</sup>

## **Energy Medicine**

### **Transcranial Magnetic Stimulation - no grade**

Transcranial magnetic stimulation (TMS) involves placement of an electromagnetic coil on the scalp with the production of low level electrical currents in cortex secondary to rapid magnetic pulses<sup>31</sup>. This research tool is currently being used to examine the potential overconnectivity of cortical neurons in autism<sup>78</sup> and to examine neurologic function in other disorders such as ADHD<sup>42</sup>. Treatment trials are underway for depression, pain syndromes, and motor function in other disease states. This technology is unrelated to the use of commercially obtained magnets applied topically as a type of community based energy medicine. There are no reports of therapeutic use of transcranial magnetic stimulation or other magnet therapy for symptoms of autism to date.

## **When Your Patient Elects CAM**

Traditionally trained clinicians know that many families they treat also elect to use CAM for their children with ASD. Although there is a beginning literature about the reasons people choose CAM, the attitudes and response of traditional practitioners to the requests for information or prescription of CAM is less well studied<sup>18</sup>. While over half of families indicate that they would like to ask their doctors about CAM, many reasons are given for not disclosing CAM use. These include a perceived lack of knowledge about CAM therapies on the part of the physician, the physician not asking, not seeing the necessity of reporting use of other therapies, and concern regarding disapproval by the physician<sup>113</sup>.

Although families often report that they use CAM because of fear of side effects, there is limited data regarding side effects of CAM practices themselves. Side effects may range from direct systemic or topical toxicity, to allergic reaction, to presence of contaminants, to interactions with prescribed medications<sup>15</sup>. Given the popularity of CAM, the interaction of CAM with prescription medication requires further study. CAM use may be underreported and the dosage and type of exposure is often unknown<sup>32</sup>. Only if there is an open dialogue about CAM, will the CAM practices used be reported to the health care provider and potential side effects and interactions can be adequately studied and monitored. The health care provider needs to discuss

the importance of continuing pharmacologic or other therapeutic interventions while CAM therapy is being used.

Nutritional supplements are not regulated as drugs but as foods, so there is little oversight regarding quality control. Variability in response may be due to family or social factors or due to variable delivery of active compound.

## Summary

As health care providers are increasingly looking toward the evidence for conventional medical practices, we should also be examining the evidence for CAM practices that patients may be using. We should encourage families to share all interventions that they are pursuing, whether or not prescribed or endorsed, by conventional practice. This is important for health monitoring of side effects and for the potential for drug interactions. Some CAM practices have evidence to reject their use, such as secretin. Some CAM practices have emerging evidence to support their use in traditional medical practice, like melatonin. Most treatments, however, have not been adequately studied and do not have evidence to support their use. Although not direct effects of CAM practices, undesired side-effects may relate to the delay or discontinuation of otherwise effective treatments.

## Acknowledgements

Dr. Hyman was supported in part by NIMH PO1HD35466 and National Center for Research Resources (NCRR) NIH UL1RR024160

## References

1. American Academy of Pediatrics; Committee on Children with Disabilities. Auditory integration training and facilitated communication for autism. *Pediatrics* 1998;102:431. [PubMed: 9685446]
2. Prevalence of autism spectrum disorders--autism and developmental disabilities monitoring network, six sites, United States, 2000. *MMWR Surveill Summ* 2007;56:1.
3. Al-Waili NS, Butler GJ. Effects of hyperbaric oxygen on inflammatory response to wound and trauma: possible mechanism of action. *ScientificWorldJournal* 2006;6:425. [PubMed: 16604253]
4. Amaral DG, Schumann CM, Nordahl CW. Neuroanatomy of autism. *Trends Neurosci.* 2008
5. American-Psychiatric-Association. Text Revised. Fourth Edition. American Psychiatric Association; Arlington, VA: 2000. Diagnostic and Statistical Manual of Mental Disorders.
6. 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. [PubMed: 16920077]
7. Andersen IM, Kaczmarek J, McGrew SG, et al. Melatonin for Insomnia in Children With Autism Spectrum Disorders. *J Child Neurol.* 2008
8. Bernard S, Enayati A, Redwood L, et al. Autism: a novel form of mercury poisoning. *Med Hypotheses* 2001;56:462. [PubMed: 11339848]
9. Bolman WM, Richmond JA. A double-blind, placebo-controlled, crossover pilot trial of low dose dimethylglycine in patients with autistic disorder. *Journal of Autism and Developmental Disorders* 1999;29:191. [PubMed: 10425581]
10. Brown MJ, Willis T, Omalu B, et al. Deaths resulting from hypocalcemia after administration of edetate disodium: 2003-2005. *Pediatrics* 2006;118:e534. [PubMed: 16882789]
11. Brudnak MA. Probiotics as an adjuvant to detoxification protocols. *Med Hypotheses* 2002;58:382. [PubMed: 12056873]
12. 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. [PubMed: 12056881]
13. Calvert JW, Cahill J, Zhang JH. Hyperbaric oxygen and cerebral physiology. *Neurol Res* 2007;29:132. [PubMed: 17439697]

14. 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. [PubMed: 12585724]
15. Cohen MH, Kemper KJ. Complementary therapies in pediatrics: a legal perspective. *Pediatrics* 2005;115:774. [PubMed: 15741385]
16. Crill CM, Helms RA. The use of carnitine in pediatric nutrition. *Nutr Clin Pract* 2007;22:204. [PubMed: 17374794]
17. Crook WG. Nutrition, food allergies, and environmental toxins. *J Learn Disabil* 1987;20:260. [PubMed: 3598369]
18. Cuzzolin L, Zaffani S, Murgia V, et al. Patterns and perceptions of complementary/alternative medicine among paediatricians and patients' mothers: a review of the literature. *Eur J Pediatr* 2003;162:820. [PubMed: 14513372]
19. Davis MP, Darden PM. Use of complementary and alternative medicine by children in the United States. *Arch Pediatr Adolesc Med* 2003;157:393. [PubMed: 12695237]
20. 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. [PubMed: 10382136]
21. DeStefano F. Vaccines and autism: evidence does not support a causal association. *Clin Pharmacol Ther* 2007;82:756. [PubMed: 17928818]
22. Doja A, Roberts W. Immunizations and autism: a review of the literature. *Can J Neurol Sci* 2006;33:341. [PubMed: 17168158]
23. 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. [PubMed: 8255984]
24. Downey PA, Barbano T, Kapur-Wadhwa R, et al. Craniosacral therapy: the effects of cranial manipulation on intracranial pressure and cranial bone movement. *J Orthop Sports Phys Ther* 2006;36:845. [PubMed: 17154138]
25. 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. [PubMed: 16555138]
26. Erickson CA, Stigler KA, Corkins MR, et al. Gastrointestinal Factors in Autistic Disorder: A Critical Review. *J Autism Dev Disord* 2005:1.
27. Fernell E, Fagerberg UL, Hellstrom PM. No evidence for a clear link between active intestinal inflammation and autism based on analyses of faecal calprotectin and rectal nitric oxide. *Acta Paediatr* 2007;96:1076. [PubMed: 17465982]
28. Filipek PA, Juranek J, Nguyen MT, et al. Relative carnitine deficiency in autism. *J Autism Dev Disord* 2004;34:615. [PubMed: 15679182]
29. Findling RL, Maxwell K, Scotese-Wojtala 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. *Journal of Autism and Developmental Disorders* 1997;27:467. [PubMed: 9261669]
30. Finegold SM, Molitoris D, Song Y, et al. Gastrointestinal microflora studies in late-onset autism. *Clin Infect Dis* 2002;35:S6. [PubMed: 12173102]
31. Frye RE, Rotenberg A, Ousley M, et al. Transcranial magnetic stimulation in child neurology: current and future directions. *J Child Neurol* 2008;23:79. [PubMed: 18056688]
32. Fugh-Berman A. Herb-drug interactions. *Lancet* 2000;355:134. [PubMed: 10675182]
33. 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. [PubMed: 16919138]
34. Gillberg C, Billstedt E. Autism and Asperger syndrome: coexistence with other clinical disorders. *Acta Psychiatr Scand* 2000;102:321. [PubMed: 11098802]
35. Glahn DC, Thompson PM, Blangero J. Neuroimaging endophenotypes: strategies for finding genes influencing brain structure and function. *Hum Brain Mapp* 2007;28:488. [PubMed: 17440953]
36. Gold C, Wigram T, Elefant C. Music therapy for autistic spectrum disorder. *Cochrane Database Syst Rev* 2006:CD004381. [PubMed: 16625601]
37. Gupta S. Immunological treatments for autism. *J Autism Dev Disord* 2000;30:475. [PubMed: 11098887]

38. 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. [PubMed: 8863094]
39. 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. [PubMed: 16977497]
40. Heaton P. Interval and contour processing in autism. *J Autism Dev Disord* 2005;35:787. [PubMed: 16283085]
41. Heuschkel R, Afzal N, Wuerth A, et al. Complementary medicine use in children and young adults with inflammatory bowel disease. *Am J Gastroenterol* 2002;97:382. [PubMed: 11866277]
42. Hoepfner J, Wandschneider R, Neumeier M, et al. Impaired transcallosally mediated motor inhibition in adults with attention-deficit/hyperactivity disorder is modulated by methylphenidate. *J Neural Transm.* 2008
43. Horvath K, Stefanatos G, Sokolski K, et al. Improved social and language skills after secretin administration in patients with autistic spectrum disorders. *Journal of the association for academic minority physicians* 1998;9:9. [PubMed: 9585670]
44. Hviid A. Postlicensure epidemiology of childhood vaccination: the Danish experience. *Expert Rev Vaccines* 2006;5:641. [PubMed: 17181438]
45. Hviid A, Stellfeld M, Wohlfahrt J, et al. Association between thimerosal-containing vaccine and autism. *Jama* 2003;290:1763. [PubMed: 14519711]
46. 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. [PubMed: 15585776]
47. 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. [PubMed: 16917939]
48. Jensen PS, Kenny DT. The effects of yoga on the attention and behavior of boys with Attention-Deficit/ hyperactivity Disorder (ADHD). *J Atten Disord* 2004;7:205. [PubMed: 15487477]
49. Jyonouchi H, Geng L, Ruby A, et al. Dysregulated innate immune responses in young children with autism spectrum disorders: their relationship to gastrointestinal symptoms and dietary intervention. *Neuropsychobiology* 2005;51:77. [PubMed: 15741748]
50. Kazdin AE. Evidence-based assessment for children and adolescents: issues in measurement development and clinical application. *J Clin Child Adolesc Psychol* 2005;34:548. [PubMed: 16026218]
51. Kern JK, Jones AM. Evidence of toxicity, oxidative stress, and neuronal insult in autism. *J Toxicol Environ Health B Crit Rev* 2006;9:485. [PubMed: 17090484]
52. 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. [PubMed: 11305684]
53. Kern P, Wolery M, Aldridge D. Use of songs to promote independence in morning greeting routines for young children with autism. *J Autism Dev Disord* 2007;37:1264. [PubMed: 17120150]
54. Knivsberg AM, Reichelt KL, Høien T, et al. A randomised, controlled study of dietary intervention in autistic syndromes. *Nutr Neurosci* 2002;5:251. [PubMed: 12168688]
55. Kuddo T, Nelson KB. How common are gastrointestinal disorders in children with autism? *Curr Opin Pediatr* 2003;15:339. [PubMed: 12806268]
56. 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. [PubMed: 11995900]
57. Levy SE, Hyman SL. Novel treatments for autistic spectrum disorders. *Ment Retard Dev Disabil Res Rev* 2005;11:131. [PubMed: 15977319]
58. 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. [PubMed: 14671475]
59. Lilienfeld SO. Scientifically unsupported and supported interventions for childhood psychopathology: a summary. *Pediatrics* 2005;115:761. [PubMed: 15741383]
60. Lord, C.; McGee, J., editors. National Research Council. National Academy Press; Washington, D.C.: 2001. *Educating Children with Autism.*

61. Madsen KM, Lauritsen MB, Pedersen CB, et al. Thimerosal and the occurrence of autism: negative ecological evidence from Danish population-based data. *Pediatrics* 2003;112:604. [PubMed: 12949291]
62. Matson JL, Nebel-Schwalm MS. Comorbid psychopathology with autism spectrum disorder in children: an overview. *Res Dev Disabil* 2007;28:341. [PubMed: 16765022]
63. McCaffrey AM, Pugh GF, O'Connor BB. Understanding patient preference for integrative medical care: results from patient focus groups. *J Gen Intern Med* 2007;22:1500. [PubMed: 17846846]
64. McCormick MC. The autism "epidemic": impressions from the perspective of immunization safety review. *Ambul Pediatr* 2003;3:119. [PubMed: 12708887]
65. McDonagh M, Carson S, Ash J, et al. Hyperbaric oxygen therapy for brain injury, cerebral palsy, and stroke. *Evid Rep Technol Assess (Summ)* 2003:1.
66. McDonagh MS, Morgan D, Carson S, et al. Systematic review of hyperbaric oxygen therapy for cerebral palsy: the state of the evidence. *Dev Med Child Neurol* 2007;49:942. [PubMed: 18039243]
67. McDougle CJ, Erickson CA, Stigler KA, et al. Neurochemistry in the pathophysiology of autism. *J Clin Psychiatry* 2005;66(Suppl 10):9. [PubMed: 16401145]
68. 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. [PubMed: 8911222]
69. Melke J, Goubran Botros H, Chaste P, et al. Abnormal melatonin synthesis in autism spectrum disorders. *Mol Psychiatry* 2008;13:90. [PubMed: 17505466]
70. Moran RW, Gibbons P. Intraexaminer and interexaminer reliability for palpation of the cranial rhythmic impulse at the head and sacrum. *J Manipulative Physiol Ther* 2001;24:183. [PubMed: 11313614]
71. 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. [PubMed: 16846101]
72. Myers SM, Johnson CP. Management of children with autism spectrum disorders. *Pediatrics* 2007;120:1162. [PubMed: 17967921]
73. Nelson KB, Bauman ML. Thimerosal and autism? *Pediatrics* 2003;111:674. [PubMed: 12612255]
74. Ng DK, Chan CH, Soo MT, et al. Low-level chronic mercury exposure in children and adolescents: meta-analysis. *Pediatr Int* 2007;49:80. [PubMed: 17250511]
75. Niehus R, Lord C. Early medical history of children with autism spectrum disorders. *J Dev Behav Pediatr* 2006;27:S120. [PubMed: 16685178]
76. Nye C, Brice A. Combined vitamin B6-magnesium treatment in autism spectrum disorder. *Cochrane Database Syst Rev* 2005:CD003497. [PubMed: 16235322]
77. Nye C, Brice A. Combined vitamin B6-magnesium treatment in autism spectrum disorder. *Cochrane Database Syst Rev* 2002:CD003497. [PubMed: 12519599]
78. Oberman LM, Ramachandran VS. The simulating social mind: the role of the mirror neuron system and simulation in the social and communicative deficits of autism spectrum disorders. *Psychol Bull* 2007;133:310. [PubMed: 17338602]
79. Offit P, Golden J. Thimerosal and autism. *Mol Psychiatry* 2004;9:644. [PubMed: 15111982]author reply 645
80. Pardo CA, Eberhart CG. The neurobiology of autism. *Brain Pathol* 2007;17:434. [PubMed: 17919129]
81. Parker SK, Schwartz B, Todd J, et al. Thimerosal-containing vaccines and autistic spectrum disorder: a critical review of published original data. *Pediatrics* 2004;114:793. [PubMed: 15342856]
82. Pfeiffer SI, Norton J, Nelson L, et al. Efficacy of vitamin B6 and Magnesium in the treatment of autism: A methodology review and summary of outcomes. *Journal of Autism and Developmental Disorders* 1995;25:481. [PubMed: 8567594]
83. Platania-Solazzo A, Field TM, Blank J, et al. Relaxation therapy reduces anxiety in child and adolescent psychiatric patients. *Acta Paedopsychiatr* 1992;55:115. [PubMed: 1585802]
84. Ritvo ER, Yuwiler A, Geller E, et al. Increased blood serotonin and platelets in early infantile autism. *Arch Gen Psychiatry* 1970;23:566. [PubMed: 5482649]
85. Rosen NJ, Yoshida CK, Croen LA. Infection in the first 2 years of life and autism spectrum disorders. *Pediatrics* 2007;119:e61. [PubMed: 17200260]

86. Rossignol DA, Rossignol LW. Hyperbaric oxygen therapy may improve symptoms in autistic children. *Med Hypotheses* 2006;67:216. [PubMed: 16554123]
87. 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. [PubMed: 18005455]
88. Rutter M. Incidence of autism spectrum disorders: changes over time and their meaning. *Acta Paediatr* 2005;94:2. [PubMed: 15858952]
89. Sackett DL, Rosenberg WM, Gray JA, et al. Evidence based medicine: what it is and what it isn't. 1996. *Clin Orthop Relat Res* 2007;455:3. [PubMed: 17340682]
90. 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. [PubMed: 10921511]
91. Schab DW, Trinh NH. Do artificial food colors promote hyperactivity in children with hyperactive syndromes? A meta-analysis of double-blind placebo-controlled trials. *J Dev Behav Pediatr* 2004;25:423. [PubMed: 15613992]
92. Shattock P, Lowdon G. Proteins, peptides and autism: II. Implications for the education and care of people with autism. *Brain Dysfunction* 1991;4:323.
93. Shaw W, Kassen E, Chaves E. Increased urinary excretion of analogs of Krebs cycle metabolites and arabinose in two brothers with autistic features. *Clin Chem* 1995;41:1094. [PubMed: 7628083]
94. Shenfield G, Lim E, Allen H. Survey of the use of complementary medicines and therapies in children with asthma. *J Paediatr Child Health* 2002;38:252. [PubMed: 12047692]
95. 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. [PubMed: 17597498]
96. Simpson N, Roman K. Complementary medicine use in children: extent and reasons. A population-based study. *Br J Gen Pract* 2001;51:914. [PubMed: 11761206]
97. Sinha Y, Silove N, Wheeler D, et al. Auditory integration training and other sound therapies for autism spectrum disorders. *Cochrane Database Syst Rev* 2004;CD003681. [PubMed: 14974028]
98. 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. [PubMed: 16887860]
99. 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. [PubMed: 16891996]
100. Stehr-Green P, Tull P, Stellfeld M, et al. Autism and thimerosal-containing vaccines: lack of consistent evidence for an association. *Am J Prev Med* 2003;25:101. [PubMed: 12880876]
101. Stern L, Francoeur MJ, Primeau MN, et al. Immune function in autistic children. *Ann Allergy Asthma Immunol* 2005;95:558. [PubMed: 16400896]
102. Stokstad E. Epidemiology. Vaccine-autism link dealt blow. *Science* 2003;301:1454. [PubMed: 12970526]
103. Thompson WW, Price C, Goodson B, et al. Early thimerosal exposure and neuropsychological outcomes at 7 to 10 years. *N Engl J Med* 2007;357:1281. [PubMed: 17898097]
104. Uma K, Nagendra HR, Nagarathna R, et al. The integrated approach of yoga: a therapeutic tool for mentally retarded children: a one-year controlled study. *J Ment Defic Res* 1989;33(Pt 5):415. [PubMed: 2795647]
105. Vancassel S, Durand G, Barthelemy C, et al. Plasma fatty acid levels in autistic children. *Prostaglandins Leukot Essent Fatty Acids* 2001;65:1. [PubMed: 11487301]
106. Verstraeten T, Davis RL, DeStefano F, et al. Safety of thimerosal-containing vaccines: a two-phased study of computerized health maintenance organization databases. *Pediatrics* 2003;112:1039. [PubMed: 14595043]
107. Vohra S, Johnston BC, Cramer K, et al. Adverse events associated with pediatric spinal manipulation: a systematic review. *Pediatrics* 2007;119:e275. [PubMed: 17178922]
108. Whippell J. Music in intervention for children and adolescents with autism: a meta-analysis. *J Music Ther* 2004;41:90. [PubMed: 15307805]
109. Williams KW, Wray JJ, Wheeler DM. Intravenous secretin for autism spectrum disorder. *Cochrane Database Syst Rev* 2005;CD003495. [PubMed: 16034901]

110. Williams TI. Evaluating effects of aromatherapy massage on sleep in children with autism: a pilot study. *Evid Based Complement Alternat Med* 2006;3:373. [PubMed: 16951722]
111. Wills S, Cabanlit M, Bennett J, et al. Autoantibodies in autism spectrum disorders (ASD). *Ann N Y Acad Sci* 2007;1107:79. [PubMed: 17804535]
112. Wolraich ML, Wilson DB, White JW. The effect of sugar on behavior or cognition in children. A meta-analysis. *Jama* 1995;274:1617. [PubMed: 7474248]
113. 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. [PubMed: 16897395]