

CAM Therapies for ASD with RCTs

An Evidence-Based, Clinician's Guide

Note: This guide is not intended as individual medical advice. These recommendations are intended to help create meaningful conversations between families and their physician and/or nutritionist about evidence-based complementary and alternative medicine (CAM).

Introduction: It has been 76 years since the first description of autism, yet no drug has been FDA approved to treat the core symptoms of autism spectrum disorder (ASD) [1]. Possibly because the root cause of ASD is not yet understood. A milestone article was published in 2005, which showed that autistic patients have active inflammation in the brain and suggested that future therapies might involve modifying inflammatory responses in the brain [2]. In 2007, the American Academy of Pediatrics (AAP) recognized that medications do not correct the core problems in autism and addressing underlying medical conditions, such as active inflammation, can eliminate the need for psychopharmacological agents in autism [3]. A 2010 consensus report from Massachusetts General, the teaching hospital for Harvard University, reviewed evidence connecting the previously seen inflammation with GI issues, disordered sleep and problem behaviors such as aggression, irritability and self-injuring [4]. Multiple investigations have found that autistic children have more locally inflamed tissues and systemic inflammation than non-autistic children, specifically higher inflammatory MDC, TARC and cytokines in their blood, which may reflect a dysfunctional immune activation [5, 6]. Although there have been over 20 years of modern clinical trial efforts and many children with ASDs are currently treated with medical interventions, strikingly little evidence exists to support benefit for most treatments [7].

This guide is to provide the clinician with scientific evidence for the consideration of complementary and alternative medicine (CAM) in patients with ASD. CAM interventions included in this list have undergone the gold standard in medical research, randomized controlled trials (RCTs). They are listed in recommended priority order based on study designs and risk to benefit ratios. Most of these therapies have been shown to address underlying medical conditions, especially inflammation and immune dysfunction, in a significant number of people with ASD or related conditions. It is recommended to use supplements or medicines first demonstrated to be effective for specific symptoms, such as improving verbal communication or social interaction, you want to address in randomized controlled trials (RCTs) using participants that are as close to the patient as possible, such as the same age group or symptom severity. Also, be sure to use the same supplement or medicine type and dose that was tested. If the therapeutic goals are not completely achieved, then consider trying supplements or medicines that were tested in similar participants, but require the least amount of extrapolation, like a study on 3 to 10 year-olds for improving symptoms in a 15 year old. Using these scientific principles should help achieve the best results with your patients in an efficient, cost-effective manner.

1. Special Multivitamins for ASD.

- a. **Effects:** Children and adults showed slightly better improvements on average in expressive language, receptive language, play, cognition, GI symptoms, sociability, eye contact and overall symptoms based on a large, randomized, double-blind, placebo-controlled study. "The improvements were greatest in the group under age 18, but there were some reported benefits in the adult group as well" [8].

In the Autism Treatment Effectiveness Survey, 51 respondents tried Special Multivitamins for ASD and 57% reported a general benefit. 25% noticed improvement in health, 23% saw benefits in attention and cognition and 18% observed improvements in language/communication. Overall benefit score of Special Multivitamins for ASD was 3 and there were extremely low adverse effects.

- b. **Background:** “The primary role of vitamins and minerals is to act as enzymatic co-factors for many important reactions in the body” [8]. “...there are over 26 studies reporting on biomarkers of increased oxidative stress in children with autism” [9].
- c. **Dosing and Recommended Products:** Follow ANRC guidelines for bodyweight and gradually increase dosage over 4 weeks. Note that 2-3 months is usually required to observe benefit.
 - i. Capsules: ANRC Essentials Plus.
 - ii. Powder: ANRC Essentials Plus.

ANRC Essentials Plus is unflavored so that the powder can be easily mixed with your favorite juice or other drink (we suggest orange, mango or cranberry). Give a sip of pure juice, then the vitamin/juice mixture, then pure juice. High-dose vitamins/mineral supplements have a strong taste, but in a published study of a similar vitamin/mineral supplement, over 95% of the children and adults were able to take the supplement successfully.

- iii. “Tastes like a fiesta in my mouth”
– young boy with ASD in ASU research study.

2. Essential Fatty Acids (EFAs).

- a. **Effects:** 3 to 18 year-olds demonstrated improvements in social withdrawal, restricted interests and problem behaviors based on a meta-analysis of 4 small randomized controlled trials (RCTs) with a total of 107 individuals [10].

In the Autism Treatment Effectiveness Survey, Cod Liver Oil was the highest rated essential fatty acid. Out of 49 respondents who tried Cod Liver about 34% observed cognition improvements and 30% reported a general benefit. 20% noticed improvements in attention and language/communication. Overall benefit score of Cod Liver Oil was 2.9 and there were extremely low adverse effects.

- b. **Background:** A meta-analysis, “compared blood levels of omega-3 long chain polyunsaturated fatty acid supplementation (LCPUFA), and their ratios arachidonic acid (ARA) to docosahexaenoic acid (DHA), ARA to eicosapentaenoic acid (EPA), or total n-6 to total n-3 LCPUFA in ASD to those of typically developing individuals (with no neurodevelopmental disorders)... Compared with typically developed, ASD populations had lower DHA, EPA, and ARA and higher total n-6 LCPUFA to n-3 LCPUFA ratio” [10]. The conclusion of two meta-analyses was, “Populations with ASD have lower n-3

LCPUFA status and n-3 LCPUFA supplementation can potentially improve some ASD symptoms” [11].

In addition, studies suggest low gut microbiota diversity is associated with impaired immune system development [9, 12-14]. In a RCT, omega-3 PUFA supplementation reversibly increased the abundance of several genera, including *Bifidobacterium*, *Roseburia* and *Lactobacillus*. [15] Lastly, ASDs commonly have strong proinflammatory cytokine production [16, 17] and omega-3 fatty acids can reduce cytokine and other types of inflammation [18-25].

- c. **Dosing and Recommended Products:** 800 mg to 3200 mg based on weight. Start with a minimum dose and then double after 1 week. If patient weight is above 51 lbs. triple starting dose after 10 days. If patient weight is above 100 lbs. quadruple starting dose after 13 days.
 - i. Liquid: ProOmega by Nordic Naturals.
 - ii. Capsules: ProEPA Xtra by Nordic Naturals.
 - iii. Liquid: DHA Junior Liquid Strawberry by Nordic Naturals.
 - iv. Chewable soft gels: DHA Junior by Nordic Naturals.
 - v. Gummies: Omega-3 Fishies by Nordic Naturals.

3. Stem Cells

- a. **Effects:** 3 to 18 year-olds administered allogenic stem cells showed, “both objective functional and subjective improvements were observed in visual, emotional and intellectual responses, body use, adaption to change, fear or nervousness, nonverbal communication and activity level assessed by CARS, as well as in lethargy/social withdrawal, stereotypic behavior, hyperactivity and inappropriate speech evaluated by ABC in both the CBMNC and Combination groups” in a partially RCT of 37 participants [26]. “...the combination of CBMNCs and UCMSCs showed larger therapeutic effects than the CBMNC transplantation alone” [26].
- b. **Background:** ASDs are, “neurodevelopmental pathologies with well-defined inflammatory conditions and immune system dysfunction” [27]. Stem cell therapy may help the inflammation balance through immune regulation [27, 28]. However, studies using autologous stem cell treatments have shown mixed results for ASD [29-34]. Many reasons have been proposed such as study design (open-label vs. RCT), stem cell dose and the sub-population of ASD individuals studied [34]. However, stem cells from cesarean section deliveries and diseased individuals, including individuals with ASD, may have altered epigenetic states and reduced cell function and power [35-37]. In addition, if some genetic modifications are present in the ASD subject, these changes will be kept by autologous stem cells [38]. Allogenic stem cells are a possible solution [26, 28, 38]. Intrathecal administration increases adverse risks and does not pass the blood brain barrier as many physicians believe [39]. The partially RCT listed in the effects section above, administered four transplantations of allogenic cord blood stem cells or allogenic cord blood and Wharton’s jelly stem cells at an interval of 5 to 7 days. Approximately 2 ×

10^6 /kg CBMNCs and 1×10^6 /kg UCMSCs were infused with normal saline intravenously (20 ml) and/or intrathecally (2 ml), respectively, per treatment.

- c. **Dosing and Recommended Products:** 1 to 4 infusions have shown improvements and low adverse effects, although data on intervals and number of cells and infusions is limited.
 - i. IV: Cord blood stem cells 2×10^6 /kg CBMNCs infused with normal saline.
 - ii. IV: Cord blood and Wharton's jelly stem cells 2×10^6 /kg CBMNCs and 1×10^6 /kg UCMSCs were infused with normal saline.

4. L-Carnitine

- a. **Note:** 1 scoop ANRC provides 120 mg L-Carnitine.
- b. **Effects:** 2 to 10 year-olds displayed improvements in hand muscle strength, concentration, eye contact, language development and motor skills, repetitive movements, cognitive scores and CARS scores in two RCTs with a total of 60 individuals [40, 41].

In the Autism Treatment Effectiveness Survey 28 respondents tried carnitine and 32% reported a general benefit. 25% noticed improvement in lethargy and 11% observed improvements in health. Overall benefit score of carnitine was about 2.3% and there were extremely low adverse effects.

- c. **Background:** Levocarnitine (L-carnitine) is an essential co-factor for utilizing fat and plays a key role in mitochondria function [42]. In a random retrospective chart review of 100 children with ASD, 83% had total and free carnitine levels below the reference mean [43]. Clinical and biochemical assessment of 25 patients with ASD indicated an enzyme- or mutation-defined mitochondrial electron transport chain (ETC) dysfunction [44]. Supplying precursors or co-enzyme and alternative substrates was hypothesized to stimulate and enhance mitochondrial function [45]. Two RCTs of L-carnitine supplementation in children with ASD demonstrated serum carnitine level and clinical improvements [40, 41].
- d. **Dosing and Recommended Products:** First week start at 25 mg/kg bodyweight (so about 750 mg for a 30 kg, or 65 lb, child) and second week increase to 50 mg/kg bodyweight (so about 1500 mg for a 30 kg, or 65 lb, child). Maximum of 2 grams. This dosage was used in 2 previous studies [40, 46] and found to be beneficial. Note that one study [41] used 2x this dosage and found even better results after 6 months.

ANRC recommends L-carnitine instead of acetyl-L-carnitine since they found L-carnitine was better absorbed. Now Foods is one reputable supplier (www.nowfoods.com), and they used their carnitine in their 2018 study.

- i. Liquid: L-Carnitine Liquid 3000mg Citrus Flavor by NOW Sports. 3,000 mg L-carnitine per 15 ml (1 tbsp.).

- ii. Liquid: L-Carnitine Liquid 1000mg Citrus Flavor by NOW Sports. 1,000 mg L-carnitine per 15 ml (1 tbsp.).
- iii. Liquid: L-Carnitine Liquid 1000mg Tropical Punch by NOW Sports. 1,000 mg L-carnitine per 15 ml (1 tbsp.).
- iv. Liquid: CarniClear Liquid Carnitine by Designs for Health. 2500 mg L-carnitine per 5 ml (1 tsp.)

5. Vitamin D

- a. **Note:** 1 scoop ANRC provides 24.8 mcg of vitamin D3 (as Cholecalciferol).
- b. **Effects:** 3 to 10 year-olds significantly improved irritability, hyperactivity, social withdrawal, stereotypic behavior, inappropriate speech and cognitive awareness while decreasing repetitive hand movements, creation of noises, jumping, and restricted interests in a small RCT with 109 individuals [47].

In the Autism Treatment Effectiveness Survey, vitamin D showed an overall benefit score about 3.1 and there were extremely low adverse effects.

- c. **Background:** “New researches indicated that vitamin D insufficiency may be a significant risk factor in ASD. Vitamin D has a potential role in brain homeostasis and development, such as neuronal differentiation, neuronal migration and growth, neurotransmission, and synaptic function” [47].
- d. **Dosing and Recommended Products:** Consider testing and supplement if necessary, to achieve normal levels. In the RCT listed in the effects section above, participants received vitamin D3 drops, 300 IU/kg/day not to exceed 5,000 IU/day (cholecalciferol drops) for 4 months and their mean vitamin D increased from 26.3 ± 12.7 to 45.9 ± 17.2 [47]. This parameter could serve as an initial therapeutic target.
 - i. Capsules: Pro Vitamin D3 5000IU by Nordic Naturals.
 - ii. Gummies: Vitamin D3 Gummies 1,000IU by Nordic Naturals.
 - iii. Gummies: Vitamin D3 Gummies Kids by Nordic Naturals.
 - iv. Liquid: Baby’s vitamin D3 by Nordic Naturals.

6. CoQ10

- a. **Note:** 1 scoop ANRC provides 40 mg CoQ10.
- b. **Effect:** 3 to 10 year-olds taking CoQ10 significantly improved communication with parents (in 12%), verbal communication (in 21%), playing games of children (in 42%), sleeping (in 34%), and food rejection in a small clinical trial with 24 children [48]. Systematic reviews and meta-analyses of randomized controlled trials conclude CoQ10 can significantly lower the inflammatory markers CRP, IL-6 and TNF- α [49, 50].

In the Autism Treatment Effectiveness Survey, CoQ10 showed an overall benefit score about 2.9 and there were extremely low adverse effects.

- c. **Background:** Oxidative stress and lower levels of antioxidants have been demonstrated in individuals with ASD [51, 52]. Coenzyme Q10 (CoQ10) is an essential factor for cellular energy production and reduces oxidative stress [38]. Liposomal ubiquinol has been shown to be bioavailable and increase baseline levels of CoQ10-OX, CoQ9 in brain tissues [53]. This data suggests CoQ10 administration may modulate neuronal activities in specific brain regions [53]. A clinical trial of children aged 3 to 6 with ASD were given 50 mg of CoQ10 a day during the first week and then 50 mg twice a day (morning and at lunch with meal) for 11 weeks [48]. Liquid liposomal CoQ10 was diluted in milk, tea, or juice prior to administration. Ubiquinol supportive therapy significantly improved symptoms in children with autism and CoQ10 plasma levels [48].

Daily dose range for reducing inflammation in a systemic review and meta-analysis was 60 mg to 500 mg for participants ranging from 19.9 to 69.1 years old. Duration of treatment ranged from 1 week to 4 months to reduce CRP, IL-6 and TNF- α levels [54]. “As it is already known that pharmaceutical forms (powder, suspension, oil solution, or solubilized form) affect CoQ10 bioavailability [33]. Solubilized CoQ10 is preferred because of better absorption and higher plasma concentrations, resulting in improved bioavailability (3–6 times higher compared to powder) which translates into its high cardioprotective effect” [50].

- d. **Dosing and Recommended Products:** Liquid Q[®] is the same one used in the ASD study above for 3 to 6 year-olds. 60 mg to 500 mg can be used and adjusted for symptoms or inflammatory marker levels.
- i. Liquid: Liquid Q[®] LiQsorb[®] Liposomal CoQ10 Drops (Non Flavored, Sugar Free, Non GMO) 30ml by Tishcon Corp.
 - ii. Softgels: Qunol Ultra CoQ10 (fat-soluble) 100mg by Qunol.

7. Sulforaphane

- a. **Effects:** 13 to 27 years-olds taking sulforaphane significantly improved social interaction, abnormal behavior (i.e., irritability, lethargy, stereotypy and hyperactivity) and verbal communication in a RCT of 29 young men for 18 weeks [55].
- b. **Background:** In 25 patients with ASD, “levels of blood lactate, plasma alanine, and serum ALT and/or AST were increased at least once in 76%, 36%, and 52% of patients, respectively” [44]. These elevated levels suggest abnormal liver burden. Sulforaphane (derived from broccoli sprouts), “is the most potent natural phase 2 enzyme-inducer known” and boosts our own detoxifying enzymes [56, 57]. “The decision to test sulforaphane to treat ASD was based on four premises. First, extensive evidence shows that sulforaphane counteracts many of the same biochemical and molecular abnormalities associated with ASD, including oxidative stress and reduced antioxidant capacity, defects in glutathione synthesis, mitochondrial dysfunction and low oxidative phosphorylation, increased lipid peroxidation, and neuroinflammation. Although it is unclear whether these anomalies are etiological or secondary manifestations, their correction often improves ASD behavior” [55]. A placebo-controlled, randomized,

double-blind clinical trial was performed on 29 males, 13 to 27 years-old. They were given sulforaphane capsules daily for 18 weeks and then discontinued taking them for 4 weeks. Significant improvements were observed in social interaction, abnormal behavior and verbal communication.

"When we broke the code that revealed who was receiving sulforaphane and who got the placebo, the results weren't surprising to us, since the improvements were so noticeable," coinvestigator Andrew Zimmerman, MD, observed.

There is an ongoing trial with 46 ASD individuals registered at John's Hopkins University [58].

- c. **Dosing and Recommended Products:** The participants in the study mentioned in the effect section were dosed according to body weight: 50 μmol (one capsule) of sulforaphane for <100 lb, 100 μmol (two capsules) for 101–199 lb, and 150 μmol (three capsules) for >200 lb [55]. Supporting information (Singh et al. 10.1073/pnas.1416940111) indicated ALFA Specialty Pharmacy encapsulated the sulforaphane product used in the study above. The pharmacist said the product is no longer available and one of the researchers from Johns Hopkins University had commercially available products tested. The data was not published, but they found the following three products equivalently acceptable:
- i. Capsules: Oncoplex by Xymogen.
 - ii. Capsules: Crucera-SGS by Thorne.
 - iii. Capsules: Avmacol by Nutramax. Product website claims the product is used in clinical trials and is the only one with myrosinase.
 1. Note: There are two versions available. Uncoated Avmacol tablets may be swallowed or crushed and mixed with foods such as yogurt, applesauce or smoothies for easier consumption.

8. Melatonin

- a. **Effect:** In 2 to 28 years-olds with autism and sleeping problems, melatonin significantly improved total sleep duration, number of night-time awakenings and sleep onset latency in a systematic review and meta-analysis of 18 studies [59].

In the Autism Treatment Effectiveness Survey, melatonin was the highest rated sleep medication. Out of 152 respondents who tried melatonin about 73% observed benefits in falling asleep and 33% noticed improvements in staying asleep. Overall benefit score of melatonin was 3 and there were very low adverse effects.

- b. **Background:** Melatonin is a hormone that is a major regulator of the sleep cycle [60]. Normally, melatonin levels in the blood are low during the day, high at night and peak typically 3 to 4 hours after falling asleep [59]. It also has anti-inflammatory, immunomodulatory, neuronal network modulatory (via direct effect of synaptic receptors) [60], antioxidant, and anti-coagulopathic properties [61, 62].

According to several studies, many children and adults with ASD experience sleeping problems and have low blood or urine levels of melatonin [63-65]. A systematic review and meta-analysis of 18 studies of people with autism found that 0.75 mg to 25 mg of night-time melatonin supplementation significantly shortened time to fall asleep, but did not result in earlier wake time [59]. One study even provided evidence-based average effect on time frames. “In children with autism and sleeping problems, melatonin improves sleep onset by up to 27 minutes and sleep duration by up to 29 minutes with minimal to no adverse effects” [66]. Melatonin is often effective in 1 week of treatment and some of the participants experienced improvements in daytime behavior as well [59].

- c. **Dosing and Recommended Products:** 0.75 mg to 25 mg melatonin supplemented at night-time.
 - i. Capsules: Melatonin 3mg by DaVinci Labs.
 - ii. Capsules: Melatonin 10mg by Vital Nutrients.
 - iii. Capsules: Melatonin 20mg by Vital Nutrients.
 - iv. Chewables: Melatonin 3 mg by Kirkman.
 - v. Gummies: Melatonin 1.5 mg by Nordic Naturals.
 - vi. Liquid: Fast-Acting Liquid Melatonin Citrus-Vanilla Flavor by Life Extension.
 - vii. Spray: Melatonin Liposomal by DaVinci Labs.
 - viii. Spray: Sleep Tight by Little DaVinci (Labs).

9. Digestive Enzymes

- a. **Effects:** 3 to 9 year-olds taking digestive enzymes significantly improved emotional response, general impression score, general behavior and gastrointestinal symptoms (quality of stools, abdominal pain, vomiting and food variety) in a RCT of 47 individuals for 3 months [67].

2 to 21 year-olds taking digestive enzymes demonstrated significant improvements in socialization, hyperactivity, attention, eye contact and comprehension in an open-label treatment of 22 individuals for 12 weeks [68].

In the Autism Treatment Effectiveness Survey, digestive enzymes were ranked at about a 1.4 on the 0 to 4 effectiveness score for constipation and a 0.5 for diarrhea.

- b. **Background:** Gastrointestinal problems are common in children with ASD. Children and adults with ASD have been shown in multiple studies to commonly exhibit enzyme deficiencies [46]. Low enzyme activity correlated with loose stool and/or gaseousness [46]. “The problems seemed to be equally common in children and adults, suggesting that these problems are lifelong” [46]. Results of benefits using digestive enzymes in ASD are mixed, but each study used different types and proportions of enzymes [46, 67-69].

Two trials showed benefits with enzyme supplement use [67, 68]. The first beneficial trial used Kirkman EnZymAid containing caso-glutenase, bromelain, acid fast protease, lactase, phytase and galactose [68]. The second beneficial trial used Neo-Digestin oral solution containing papain, pepsin and sanzyme. Interestingly, none of the enzymes in each formula overlap and the formulas of digestive enzymes that were ineffective overlap 1 or 2 ingredients, but the remaining enzymes are very different. However, studies measuring enzyme levels in hundreds of ASD children reported that many had deficiencies in disaccharidases (enzymes for digesting simple sugars) [70-72]. Lactase and maltase deficiencies were the most common, followed by lower activity of sucrase, palatinase and glucoamylase [70-72]. None of the enzymes tested in the mentioned studies used products containing maltase, surcease or palatinase. Thus, products containing these disaccharidases may be superior to the ones tested even with some benefits. Furthermore, undigested disaccharides was associated with gut dysbiosis with decreases in Bacteroidetes, increases in the ratio of Firmicutes to Bacteroidetes and increases in Betaproteobacteria [73].

- c. **Dosing and Recommended Products:** Enzymes that have been shown to be deficient in individuals with ASD are recommended. These are lactase, maltase, sucrase, palatinase and glucoamylase [70-72]. Or the enzymes used in the beneficial studies that are available in the U.S.
 - i. Chewables: Vital-Zymes Chewable by Klaire Labs.
 - ii. Capsules: Vital-Zymes Complete by Klaire Labs.
 - iii. Capsules: EnZymAid Multi-Enzyme Complex by Kirkman.

10. Exercise

- a. **Effects:** 8 to 11 year-olds performing physical activity intervention (basketball skill learning) exhibited greater SE, shorter SOL, longer SD, and reduced WASO than those in the control group during both weekdays and weekend in a RCT with 19 ASD participants for 12 weeks [74]. In 3 to 6 year-olds performing aerobic exercise (15 minutes of running/jogging) followed by a classroom task improved academic responding in a within-subjects crossover design with 9 ASD participants for 3 weeks [75].

In the Autism Treatment Effectiveness Survey, exercise was one of the most beneficial interventions. Out of 59 respondents who tried exercise experienced improvements in about 68% body awareness and gross motor coordination/muscle tone, 64% balance, 49% fine motor coordination and 35% attention. Overall benefit score of exercise was about 4.2 and there were no adverse effects.

- b. **Background:** “Petrus et al conducted a current, systematic review of studies measuring the effects of exercise on stereotypic behaviors of children with ASD. The 7 studies included a total of 25 subjects. Twenty-two were older children (6–15 years old) with ASD, and 3 were younger children (3–5 years old). In the 3 studies including younger children, the exercise programs involved walking versus jogging, jogging, and jogging versus ball playing. Only jogging resulted in a decrease in stereotypic behaviors. Three of

the 7 studies also measured academic performance following exercise. Watters and Watters reported no effect on academic responding following exercise, but 2 studies did report improved academic responding following jogging. In addition, Rosenthal-Malek and Mitchell¹⁶ documented an increase in on-task behavior after aerobic exercise” [75]. “Recent evidence suggests that aerobic exercise improves the diversity and abundance of genera from the Firmicutes phylum, which may be the link between the positive effects of exercise on the gut and brain” [76].

- c. **Dosing and Recommendation:** Perform a physical fitness assessment and determine the aerobic power and strength of the patient. Compare with age and gender normative data. Start with proven programs to address the areas of most insufficiency.

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