Nutritional and Dietary Treatment Study for Children and Adults with Autism

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Director, ASU Autism/Asperger’s Research Program

Study Reference: Adams, Nutrients 2018, PMID: 29562612
Personal Background

• Director of Autism/Asperger’s Research Program at ASU
• President, Autism Nutrition Research Center
• President of Greater Phoenix Chapter of ASA
• Chair, Scientific Advisory Board of Neurological Health Foundation
• Co-leader of Science Advisory Committee of Autism Research Institute
• Father of adult daughter with autism
• Autism research includes:
  – Nutrition: vitamins, minerals, fatty acids, amino acids, ribose
  – Metabolism: glutathione, methylation, sulfation, oxidative stress
  – Mitochondria – ATP, muscle strength, carnitine
  – Toxic Metals and Chelation
  – Gastrointestinal Problems & Treatments
  – Immunology
  – Seizures
Research Team

James Adams, Ph.D. – Principal Investigator
Robert Hellmers, MD – pediatrician & immunologist
Jessica Mitchell, ND – 2nd study physician
Tapan Audhya, Ph.D. – nutritional biochemist
Dana Laake, Julie Matthews - nutritionists
Liz Geis – lead study nurse
Eva Gehn – study coordinator
Elena Pollard – clinical evaluator (ADOS, CARS, IQ)
Becky Adams – Vineland evaluator
Several other nurses, medical technicians, and phlebotomists for blood draws
Background

- Autism now affects 1 in 59 children in US
- Autism risk can be decreased about 40% if supplemented with folic acid at preconception or first two months – little benefit afterward.
- Vitamin B12 and iron also associated with decreased risk
Overview

Study Purpose
Background on Nutritional/Dietary Treatments
Study Design
Results
Implications
Questions
Study Purpose

Evaluate the possible effectiveness of a combination of nutritional and dietary interventions in reducing the symptoms of autism.

The study will also determine the nutritional and metabolic status of individuals with autism compared to individuals without autism.

Study approved by ASU’s Human Subject Institutional Review Board

Funded by Zoowalk for Autism Research and the Autism Research Institute
Study Treatments

Customized Vitamin/Mineral Supplement
Essential Fatty Acids (fish oil)
Epsom Salt Baths (magnesium sulfate)
Carnitine (support mitochondria)
Digestive Enzymes
Healthy, gluten-free, casein-free, soy-free diet
Vitamins and Minerals

**Rationale:** The definition of an essential vitamin or mineral is that lack of it results in disease or even death. Most people in the US consume less than the Required Daily Allowance (RDA) of one or more vitamins and minerals. For example, many women lack enough calcium and iron, leading to osteoporosis and anemia, respectively.

**Explanation of Treatment:**
Vitamins and minerals are available in vegetables, fruits, meat, and other sources. However, the typical U.S. diet is lacking in key vitamins and minerals, so many people need to take a supplement.
Vitamin/Mineral Supplements

Two previous studies by Prof. Adams (randomized, double-blind, placebo-controlled)

First study found significant improvements in sleep and gut problems – *Adams, JACM, 2004*

Second study found many problems in nutritional and metabolic status, and found that supplement improved them and improved some symptoms

Summary of 2nd Vitamin/Mineral Treatment Study

Major abnormalities in autism include:
• Low vitamins (biotin, B5, vit E, carotenoids) and abnormal vit B6
• Low ATP/NADH/NADPH
• Low glutathione
• High oxidative stress
• Impaired methylation (low SAM, high uridine)
• Very low sulfate
• Low neurotransmitters (norepinephrine, epinephrine, serotonin, acetylcholine) and abnormal dopamine
• Low plasma amino acids (tryptophan, phenylalanine, tyrosine, isoleucine)
• Subset with low iodine – should test thyroid function and iodine
• Low lithium (in whole blood)
• High toxic metals: thallium, lead, tin, tungsten

Supplement improved almost all of these, and often normalized them.
Treatment group did better than placebo on all scores, with significantly better improvements on Average Score, Receptive Language, Hyperactivity, Tantrumming, and Overall.
Essential Fatty Acids

**Rationale:** Essential fatty acids are critical nutrients for humans. They exist in the cell membrane of every cell, and roughly 20% of an infant’s brain is composed of essential fatty acids. Mother’s milk is very rich in essential fatty acids, but some infant formulas lack this key ingredient needed for brain development.

Two general categories of essential fatty acids are omega-3 and omega-6. Omega-3 fatty acids have relatively short shelf-lives, so commercial food processing often hydrogenates or partially hydrogenates them, which provides long shelf life but eliminates their nutritional value. Thus, over 80% of the US population has low levels of omega 3 fatty acids – this is one of the most widespread nutritional problems in the US.
EFA’s - continued

Low levels of essential fatty acids are associated with a wide range of psychological disorders, including depression, post-partum depression, bipolar (manic/depression) and Rett’s syndrome (similar to autism).

Meta-analysis of fifteen case-control studies (n = 1193) found that, compared with typically developed individuals, the ASD group had lower EPA, DHA, and arachidonic acid (AA), and a lower ratio of total omega-3 to total omega-6 fatty acids.

Mazahery, Nutrients 2017
A meta-analysis of four small randomized controlled trials (n = 107) found that compared with placebo, omega-3 fatty acid supplementation improved social withdrawal (p < 0.02) and restricted interests and behaviors (p = 0.05), but did not have a significant effect on communication, irritability, or hyperactivity (per ABC).

These studies only lasted 6–16 weeks (too short to observe full effect, since omega-3 supplementation requires about six months to reach steady-state levels in erythrocytes, and about 1–1.5 months for half of that change).

Low doses of 0.5–1.5 g/day of omega-3 fatty acids.

Mazahery, Nutrients 2017

Two other small randomized studies did not find significant effects on symptoms despite longer duration (6 months), possibly due to small sizes (under 35 participants) or low dose (200 mg DHA) in one study

Mankad, Mol. Autism, 2015; Voight, JPGN 2017

### ARI Survey of Parent Ratings of Treatment Efficacy:

<table>
<thead>
<tr>
<th></th>
<th>% Worse</th>
<th>% No Change</th>
<th>% Better</th>
<th>Number of Reports</th>
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</thead>
<tbody>
<tr>
<td>Fatty Acids</td>
<td>2%</td>
<td>42%</td>
<td>55%</td>
<td>622</td>
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Sulfation

Rationale: Many children with autism have excess loss of sulfate in their urine, resulting in a low level of sulfate in their body. Sulfate 4th most common mineral in the body; important for detoxification (including Tylenol/acetaminophen), inactivation of neurotransmitters, synthesis of brain tissue, sulfation of mucins in GI tract, and more

Treatment:
Tapan Audhya evaluated many different ways to increase plasma sulfate levels in children with autism who had low levels. The two most effective methods were oral MSM and Epsom Salt (magnesium sulfate) baths

Vitamin/mineral supplement with MSM significantly improved sulfate, but more needed
Sulfate

Research:
High sulfate in the urine of children with autism (Waring 2000); ATP required to resorb sulfate, and ATP is low in autism and correlated with low levels of free and total plasma sulfate (Adams et al 2011)

Waring 2000 reported high levels of urinary sulfite in children with autism, suggesting that there was a problem of converting sulfite to sulfate in the mitochondria. In 38% of cases (14/38) urinary sulfite and sulfate levels improved by giving 50 mcg of molybdenum, presumably since the enzyme for converting sulfite to sulfate (sulfite oxidase) contains molybdenum.
Carnitine Treatment Study

Rationale – carnitine is needed to transport long-chain fatty acids (fuel) across membrane into mitochondria;
One study found decreased carnitine in children with autism (Filipek et al)

Two small randomized, double-blind, placebo-controlled studies for children with ASD found significant improvements in CARS
- 3 month, 50 mg/kg: Geier et al 2011, Med. Sci. Monitor
- 6 month, 100 mg/kg: Fahmy et al 2013, Research ASD
Mitochondria occupy about 25% of cell volume; essentially a “cell within a cell”, with its own DNA
Digestive Enzymes

Studies by Horvath et al. and Kusha et al have found that many children with autism have defective carbohydrate digestion, especially lactase (needed to digest lactose, or milk sugar)


One open-label study found that digestive enzymes improved many symptoms of autism


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<tr>
<th>ARI Survey of Parent Ratings of Treatment Efficacy:</th>
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<tr>
<td>% Worse</td>
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<tr>
<td>Digestive Enzymes</td>
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Improve Diet

- Consume 3-4 servings of nutritious vegetables and 1-2 servings of fruit each day.
- Consume at least 1-2 servings/day of protein
- Greatly reduce or avoid added sugar (soda, candy, etc.)
- Avoid “junk food” – cookies, fried chips, etc.
- Greatly reduce or avoid fried foods or foods containing transfats
- Avoid artificial colors, artificial flavors, and preservatives
- If possible, eat organic foods as they do not contain pesticides, and have more nutrients (vitamins and minerals). If eating non-organic food, wash fruit and vegetables well if eating the outside.

ARI Survey of Parent Ratings of Treatment Efficacy:

<table>
<thead>
<tr>
<th>Treatment</th>
<th>% Worse</th>
<th>% No Change</th>
<th>% Better</th>
<th>Number of Reports</th>
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<tr>
<td>Removed Sugar</td>
<td>2%</td>
<td>51%</td>
<td>48%</td>
<td>3695</td>
</tr>
<tr>
<td>Feingold Diet</td>
<td>2%</td>
<td>45%</td>
<td>53%</td>
<td>758</td>
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</table>
Gluten-Free, Casein-Free Diet (often corn-free and soy-free)

**Rationale:** Human digestive systems have not evolved on a diet containing high amounts of wheat and dairy products. Humans are the only animal who drink milk as adults, and the only animal to drink the milk of another animal. Cows milk is a perfect food for baby cows, but not for humans, especially past age of nursing.

Over the last several hundred years, wheat has been bred to greatly increase its gluten content, and a typical US diet contains far higher amounts of wheat than humans were eating 1000-10,000 years ago. Gluten (in wheat, rye, barley, and possibly oats) and casein (in all dairy products, including milk, yogurt, cheese, ice cream, caseinate) can cause several problems:

1. They are common food allergens, especially in children and adults with autism.
2. Certain peptides from gluten and casein may bind to opioid-receptors in the brain, causing behavior problems
3. Lactose (milk sugar) may not be digested, causing GI upset
4. Milk consumption seems to increase risk of cerebral folate deficiency (immune system attacks cerebral folate transport molecule)
Treatment Schedule

Day 0: Vitamin/Mineral supplementation begins.
Day 30: Essential Fatty Acid supplementation begins.
Day 60: Epsom Salt baths begin (2x/week)
Day 90: Carnitine supplementation begins
Day 180: Digestive Enzyme supplementation begins;
Day 210: Healthy, casein-free, gluten-free diet is begun.
    Group meeting with nutritionist, and then individual
    meeting to review diet planning with family

Day 365: Final assessment of autism severity and overall
functioning status.

Blood and urine collections at beginning and end of study.
Study Design

Randomized, single-blind; treatment and delayed treatment group

Blinded expert evaluator conducted ADOS and IQ testing at beginning and end of study

Blinded expert evaluator interviewed families for pre/post CARS and Vineland (semi-blinded)

Parents also did pre/post evaluations of symptoms (but not blinded)
Participants

Treatment group:  37 started, 28 finished
• 3 dropped (lack of interest)
• 4 disqualified (inconsistent with supplements)
• 2 had possible adverse effect of vitamin/mineral supplement on behavior, stopped all supplements, but had good improvement on special diet

Delay group:  30 started, 27 finished
1 disqualified due to major improvement in diet
2 disqualified due to major change in school
Few Adverse Effects

Most supplements/treatments were very well tolerated with few adverse effects

Vitamins/Minerals: 2 children had possible behavior worsening (stopped all supplements), but they did well on GFCF diet

Carnitine – 1 participant could not tolerate it (sick)

Digestive Enzyme: 2 participant did not tolerate digestive enzyme (1- GI upset; 1- rash after extended use although it improved constipation and behavior)

Healthy GFCFSF diet: implementation of the diet in a strict manner resulted in increased aggression towards peers, inability to problem solve, and increased spinning behavior, probably due to frustration re. removal of favorite foods.

Essential fatty acids and Epsom salt baths were well-tolerated
Clinician Assessments (blinded)

- Reynolds Intellectual Assessment Scales (RIAS)
- Childhood Autism Rating Scale (CARS)
- Severity of Autism Scale (SAS)
- Vineland
RIAS (IQ/Memory)

- Verbal IQ – little change
- Memory – little change
- Non-verbal IQ – treatment group improved more
  Treatment +6.7; Delay: -0.6; p=0.01
Vineland Adaptive Behavior Scale

Over 12 months, treatment group gained 18 months of development, vs. 4 months in delay group, p<0.01
Childhood Autism Rating Scale (CARS)

Treatment Group: 22% improvement
Delay Group: 14% improvement, p=0.03
Severity of Autism Scale (0-10)  
(professional evaluation)

Treatment Group: 13% improvement  
Delay Group: 6% improvement, p=0.04
Parent Evaluations

- Aberrant Behavior Checklist (ABC)
- Short Sensory Profile (SSP)
- Parent Global Impressions
Social Responsiveness Scale (SRS)

Treatment group improved more than delay group on total SRS, -14% vs. -3%, p=0.004
Aberrant Behavior Checklist (ABC)

Treatment group improved more than delay group on total ABC score, 26% vs. 7%, p=0.001
Short Sensory Profile

Treatment: +12%, Delay: +2%, p=0.0003

So, sensory problems improved but still below normal range (155-190)
Parent Global Impressions

Treatment group had much greater improvement than Delay group on Average PGI-R score, 1.2 vs. 0.1, p<0.0001

Scale: -3 (much worse), 0 – no change, 1-slightly better, 2-better, 3-much better
Parent Global Impressions (cont.)

On Overall Autism Symptoms, parents reported much more improvement in treatment group than delay group.

<table>
<thead>
<tr>
<th></th>
<th>Treatment</th>
<th>Delay</th>
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<tbody>
<tr>
<td>Much Better</td>
<td>14%</td>
<td>4%</td>
</tr>
<tr>
<td>Better</td>
<td>43%</td>
<td>4%</td>
</tr>
<tr>
<td>Slightly Better</td>
<td>39%</td>
<td>23%</td>
</tr>
<tr>
<td>No Change</td>
<td>4%</td>
<td>54%</td>
</tr>
<tr>
<td>Worse</td>
<td>0%</td>
<td>15%</td>
</tr>
</tbody>
</table>
PGI-R vs. time

Rapid improvements during first 3 months, then plateau until 9 months, then slightly more improvements 9-12 months.
GI Symptoms

- Treatment group had much greater improvement than Delay group on 6-item GSI, -30% vs -10% p=0.05
Significantly greater improvement on every measure

[Bar chart showing improvement on various measures]
Parent Ratings of Treatment Effectiveness

Scale:
0–no change; 1–slightly better; 2–better; 3–much better
Treatment Continuation

Vitamin/Mineral – 85% will continue
EFA – 89%
Epsom Salt – 70%
Carnitine – 44%
Digestive Enzyme – 44%
Healthy GFCFSF Diet – 63%
Special Improvements- Case 1

Young man unable to urinate for years; required several catheterizations each day;
Complete cure within 4 days of starting dairy-free diet; temporary loss of ability when challenged with ice cream lasting 4 days, then fully recovered; 1 slice of cheese pizza caused same temporary effect.

“His quality of life has improved dramatically and all behavior issues, including the constant touching of his genitals, have ceased. His social interactions with his peers and family members have improved dramatically and he is overall a much happier person.”
“At about six when “Sue’s” puberty started and her weight increased her muscle tone decreased. Sue became very inactive, stopped carrying her own weight, and stopped walking on her tip toes. Sue was leaning on people and furniture to help support her weight; she could not get in and out of the van, climb stairs or get off of the floor without help. Sue could only walk a quarter of a mile before she would refuse to get up. Sue had a wheelchair that we were using for outings. Sue could support small outbursts of energy but had no endurance.

(Began study at age 9): The most significant change that I saw was her energy level. Sue started to skip around the house, walk without trouble during outings and carry her weight better. Sue was no longer just sitting around she was getting up and getting into things. Sue was able to walk a mile around the lake, and ride a tandem bike with me. She worked better with the physical therapist and I put the wheelchair in storage. Sue did also start to try some new foods including bacon, her first meat. By six to 12 months of the study Sue is riding the bike and pedaling some two and a half miles, walking two miles around the lake, attending outings without tiring, getting in and out of the van, and walking up and down steps one foot at a time.

At six months of the study not only were we impressed by her stamina we started to notice cognitive and social improvements. “

Note: benefits began when carnitine started. Sue did not consume beef/pork, the main dietary sources of carnitine.
Special Improvements – Case 3

Severe pica (eating non-food items) stopped within 1 week of implementing healthy GFCFSF diet.
Oral antibiotics

Oral antibiotic usage age 0-36 months:
Autism – 4.3 rounds
Typical – 0.9 rounds
P=0.003
Consistent with 5 other published studies

Oral antibiotics alter gut flora and decrease ability to excrete mercury by 90%
Autism group had lower hand grip strength, especially at younger ages (50% normal at age 3); lower strength possibly due to limited understanding/motivation despite modelling
Higher toxic metals in autism group

Red Blood Cells:
Lead: 56% higher in autism, p=0.01

Urine
- Lead: 72% higher, p=0.001
- Antimony: 46% higher, p=0.05
- Tin: 176% higher, p=0.007
- Thallium: 50% higher, p=0.0003

- Similar to previous study (Adams et al 2013)
Plasma Amino Acids

Glutamate 24% higher in autism, p=0.01
GABA normal

Glutamate is primary excitatory neurotransmitter; converted to GABA (primary inhibitory neurotransmitter) by vitamin B6

Excess glutamate suspected as major factor in seizures and sub-clinical seizures, repetitive behavior, learning difficulties, and OCD
Summary

Treatments well-tolerated with few adverse effects

Clinician Ratings:
- RIAS: no difference in verbal IQ or memory, but non-verbal IQ improved: +7 IQ pt vs -1 IQ pt, p=0.01
- Vineland: +20 months vs +4 months, p=0.01
- CARS: Treatment: 22% vs Delay: 14%, p=0.07
- SAS: 13% vs 6%, p=0.08

Parent Ratings:
- ABC: 26% vs. 7%, p=0.001
- Sensory Profile: 12% vs 2%, 0=0.0006
- PGI-R: 1.2 vs 0.1, p<0.00001

3 special cases of improvement (urination, energy, pica)
Acknowledgements

• Thanks to the many families for participating in the study
• Thanks to ARI and Zoowalk for Autism for funding
• We thank Aniyka Agrawal, Sara Dessoy, Chiao-May Lee, Rebecca Smith for help with data entry/analysis.
• Thanks to Yasoo, Nordic Naturals, Walgreens, Now, and Houston Enzymes for supplying supplements for the study.
Recommendations on treatments:

Top 3:
Vitamin/mineral supplement – everyone
Essential Fatty acids – if eating fish < 1x/week
Healthy GFCFSF diet – try for 3 months

Others:
Carnitine – if consume beef/pork < 2x/week
Epsom salts – try for 3 months
Digestive enzymes – if loose stools/gaseousness, try for 2 months

More info at: Summary of Dietary, Nutritional, and Medical Treatments for Autism - [http://autism.asu.edu](http://autism.asu.edu)
Do you want to try some of the treatments used in this study?

Low risk, likely to benefit about 80% of children/adults
Time – minutes/day for supplements, inexpensive
Vitamin/Mineral Supplement –
   www.autismnrc.org - ANRC Essentials
   Disclaimer – Prof. Adams is President of ANRC, a non-profit he founded, but he receives no salary or royalties from them
Essential Fatty Acids -   www.nordicnaturals.com – ProEFA
   (similar to Complete Omega, a consumer version)
Epsom Salts – any pharmacy
Carnitine – www.nowfoods.com  (or other brand) – L-carnitine
Digestive Enzymes – www.houstonenzymes.com Trienza -
Healthy GFCFSF diet – 3 month trial

Disclaimer – no financial connection with any company
Questions?