

# Folic Acid Decreases Risk of Autism 38%, if used early

Schmidt et al 2013 – CHARGE study of 429 ASD families, 278 typical families

Lower folic acid intake during first month of pregnancy in ASD moms (655 mcg vs 779);

intake above 600 mcg associated with 38% decreased risk of ASD in children, and higher intake decreased risk more.

Most important for mothers with MTHFR 677 C>T variant genotypes.

# Folic Acid decreases risk of ASD if taken near conception (cont.)

Suren et al 2013 – study of 85,176 Norwegian children, including 270 with ASD.

In children whose mothers took folic acid (400 mcg) between 4 weeks prior to conception to 8 weeks after conception, 0.10% (64/61 042) had autistic disorder, compared with 0.21% (50/24 134) in those unexposed to folic acid.

39% lower risk of ASD in those who took prenatal folic acid (400 mcg);

Little benefit if taken after 8 weeks



# Overview of Dietary, Nutritional, and Medical Treatments for Autism

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Our research group is dedicated to finding the causes of autism, how to prevent autism, and how to best help people with autism.

Nutrition: vitamins, minerals, fatty acids, amino acids

Metabolism: glutathione, methylation, sulfation, oxidative stress

Mitochondria – ATP, muscle strength, carnitine

Toxic Metals and Chelation

Gastrointestinal Problems & Treatments

Sleep

Immunology

Seizures

# **Bringing Research to Families**

## **Summary of Dietary, Nutritional, and Medical Treatments**

Based on over 150 research studies

Reviewed by 10 medical and scientific experts

Official publication of Autism Research Institute

50-page summary of 17 major treatments,  
including a summary of the research for each  
treatment and how to implement it

Free copy available at <http://autism.asu.edu>

# Our Philosophy

- Listen to people with autism, parents, physicians, and researchers
- Search for underlying biomedical problems
- Emphasize treatments that will support whole body's natural function – special emphasis on gut function, nutritional support, removal of toxins

# Combining Biomedical and other Therapies

- Biomedical interventions can and should be combined with behavioral therapy, educational program, speech therapy, sensory integration, physical therapy, occupational therapy, and social therapy.
- Biomedical treatment can improve efficacy of other treatments by improving brain and body health.

# **Autism is TREATABLE!**

Many children now greatly improve, and some even recover, due to behavioral and/or biomedical interventions

# Outline of Presentation

- Improve Diet
- Food Sensitivities
- GFCF Diet
- Vitamin/Mineral Supplements
- High-Dose Vitamin B6 & Magnesium
- Essential Fatty Acids
- Gut Treatments
- Amino Acids
- Melatonin
- Thyroid Testing/Supplementation
- Sulfation
- Glutathione
- NADH/Ribose
- Sulphoraphane
- Chelation
- Immune System Regulation
- HBOT

# 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 trans fats
- 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:

	% Worse	% No Change	% Better	Number of Reports
<b>Removed Sugar</b>	2%	51%	48%	3695
<b>Feingold Diet</b>	2%	45%	53%	758

# Benefits of Improving Diet

- Vegetables and fruits contain essential vitamins, minerals, and phytonutrients to improve and maintain mental and physical health.
- Protein is needed to provide amino acids, which are the building blocks for neurotransmitters and many other key amino acids and proteins in the body.
- Reduction in sugar intake can prevent rapid rises and falls in blood sugar, which can cause irritability and difficulty concentrating.
- Pesticides often contain toxic metals, and are suspected as a possible cause of some cases of autism.
- Artificial colors and flavors can irritate some sensitive individuals, causing behavioral and other problems.
  - Large study by McCann et al 2007 found that typical children given artificial colors and/or food preservatives had increased hyperactivity

# Vegetable Juicing

**Rationale:** Fresh vegetable/fruit juice is a rich source of vitamins, minerals, and other nutrients. Commercial juices are “pasteurized” or heated to destroy bacteria, which also causes a loss of some nutrients.

Use a juicer to make fresh vegetable/fruit juice – store in airtight glass container.

Keep all the fiber (do not filter)

The advantage of juicing is that it is often a very easy and tasteful way to get healthy nutrients into children who don't eat fruits/vegetables.

Some of the healthiest vegetables to use include cabbage, spinach, carrots, broccoli, parsley, oregano, mixed with a small amount of fresh fruit for flavor and other nutrients.

Organic vegetables and fruits are preferred, as they have a higher amount of vitamins and minerals and less toxic pesticides. 8-16 ounces/day should be enough for most children and adults, depending on their intake of other vegetables and fruits.

# Food Sensitivities

- Observations: Look for red cheeks, red ears, and dark circles under eyes which may indicate allergies. Also look for changes in behavior.
- Diet Log: Keep a diet log, and look for a pattern between symptoms and foods eaten in the last 1-3 days.
- Blood testing: IgE and IgG testing is offered by many commercial labs. IgE related to an immediate immune response, and IgG relates to a delayed immune response; reliability unclear.
- Elimination diet: remove the most common reactive foods which include gluten (in wheat, rye, barley, possibly oats), dairy, cane sugar, corn, soy, yeast, peanuts, egg, artificial colors and preservatives). If there is improvement, then try challenging with one pure food every 4 days, to see if any can be added back in. Gluten and dairy are the last challenged.

## Benefits:

- Removing allergic foods can result in a wide range of improvements in some children, especially improvements in behavior and attention.

Major US study of 40,000 children found 8% had food allergies, primarily to peanuts (25%), milk (21%), and shellfish (17%) – Gupta et al 2011, Pediatrics

# Food Sensitivities (continued)

## ARI Survey of Parent Ratings of Treatment Efficacy:

	% Worse	% No Change	% Better	Number of Reports
<b>Food Allergy Treatment</b>	3%	37%	61%	560
<b>Rotation Diet</b>	2%	50%	48%	792
<b>Removed Chocolate</b>	2%	49%	49%	1721
<b>Removed Eggs</b>	2%	58%	40%	1096

A study by Vojdani et al. found that many children with autism have food allergies. “Immune response to dietary proteins, gliadin and cerebellar peptides in children with autism.” *Nutr Neurosci.* 2004 Jun;7(3):151-61.

There are also 3 studies by Jyonouchi et al, which found that children with autism had more hypersensitivities to food allergens than typical children, which seemed to contribute to gut problems.

Jyonouchi et al., Dysregulated innate immune responses in young children with autism spectrum disorders: their relationship to gastrointestinal symptoms and dietary intervention. *Neuropsychobiology.* 2005;51(2):77-85.

Jyonouchi et al., Evaluation of an association between gastrointestinal symptoms and cytokine production against common dietary proteins in children with autism spectrum disorders. *J Pediatr.* 2005 May;146(5):605-10.

Jyonouchi et al., Innate immunity associated with inflammatory responses and cytokine production against common dietary proteins in patients with autism spectrum disorder. *Neuropsychobiology.* 2002;46(2):76-84.

# More Research on Food Sensitivities and Gut Function

A study by Lucarelli et al found that an 8-week diet which avoided allergic foods resulted in benefits in an open study of 36 children.

Lucarelli et al, Food allergy and infantile autism. *Panminerva Med.* 1995 Sep;37(3):137-41.

A study by Kushak and Buie found that children with autism may have low levels and/or underactive digestive enzymes for complex sugars, which reduces the ability to fully digest starches and sugars.

Several studies by Horvath, Buie, and others have demonstrated that gut inflammation is common in autism. This may result in a “leaky gut” that may allow partly-digested food to pass into the blood, potentially causing an allergic response.

Horvath K et al, Gastrointestinal abnormalities in children with autistic disorder,” *J. Pediatrics* 135 no. 5 (1999) 559-563.

Horvath K and Perman JA “Autistic disorder and gastrointestinal disease,” *Curr. Opinion in Pediatrics*, 14 (2002) 583.

Kushak R and Buie T “Disaccharidase deficiencies in patients with autistic spectrum disorders,” presented at DAN! New Orleans Jan 2004.

# Gluten, milk antibodies increased in ASD

Major study of 162 children with ASD vs. 44 controls (de Magistris 2013)

Total gliadin IgG increased in 37% ASD vs. 23% controls,  $p=0.004$ . Only 2 ASD with celiac disease.

Milk IgE increased in 18% ASD vs. 5% controls (IgG similar)

Intestinal permeability increased in 26% of ASD vs. 2% of controls,  $p<0.001$  (lactulose/mannitol test)

# **Gluten-Free, Casein-Free Diet (and 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 two problems:

1. They are common food allergens, especially in children and adults with autism.
2. Certain peptides from gluten and casein can bind to opioid-receptors in the brain, and can have a potent effect on behavior (like heroin or morphine), causing problems including sleepiness, giddiness, inattention/"zoning out", and aggressive and self-abusive behavior. Like opioids, they can be highly addictive, and a lack of them can cause severe behaviors.

**These problems appear to be due to:**

- 1) A failure of the digestive tract to fully digest the gluten and casein peptides into single amino acids
- 2) Inflammation of the gut, allowing the gluten and casein peptides to enter the bloodstream and reach opioid receptors in the brain.
- 3) lactose (milk sugar) intolerance due to decreased lactase (digestive enzyme)

# Implementing GF/CF Diet

## Explanation of Treatment:

- Total, 100% avoidance of all gluten products and all dairy products. Even small amounts, like a bite of a cookie, can cause allergic and/or opioid problems. Many foods have trace contamination with gluten, such as dusting French fries and raisins with wheat powder to keep them from sticking, so it can be very difficult to avoid all foods and contaminated foods.
- Digestive enzymes can also be helpful, especially if there is an accidental exposure, but they are probably not as helpful as a total avoidance of casein and gluten.
- Many children with autism also benefit by removing corn and/or soy products.

## Benefits:

Children who most crave dairy and/or wheat, and who eat a lot of it, are most likely to benefit.

Casein-free diets usually produce benefits within a month, and sometimes within a week. Gluten free diets usually take 1-3 months to produce benefits. In some children there is a worsening of symptoms for a few days (similar to a drug withdrawal) followed by improvement

# GFCF Diet (continued)

## ARI Survey of Parent Ratings of Treatment Efficacy:

	<b>% Worse</b>	<b>% No Change</b>	<b>% Better</b>	<b>Number of Reports</b>
<b>Gluten- and Casein-Free Diet</b>	3%	32%	65%	1446
<b>Casein-Free Diet</b>	2%	49%	49%	5574
<b>Wheat-Free Diet</b>	2%	50%	48%	3159

**Safety Note:** It is important that a **calcium supplement** be taken while on a dairy-free diet unless a child has an exceptionally nutritious diet rich in calcium.

## Research on GFCF Diet:

Reichelt has conducted several studies which have found abnormal peptides in the urine of people with autism, and he has conducted long-term treatment studies which found significant improvement from a GF/CF diet. Reichelt et al., Biologically active peptide-containing fractions in schizophrenia and childhood autism. *Adv Biochem Psychopharmacol.* 1981;28:627-43. Review.

Single-blind study of 10 children with autism found that 8 benefitted from a GFCF diet. Knivsberg AM, Reichelt KL, Hoiem T, Nodland M. A randomised, controlled study of dietary intervention in autistic syndromes. *Nutr Neurosci.* 2002 Sep;5(4):251-61.

A 12-week, double-blind, cross-over study of a GFCF diet in 15 children with autism did not find significant benefits, but parents reported benefits that were not identified by the testing. Elder et al, The gluten-free, casein-free diet in autism: results of a preliminary double blind clinical trial. *J Autism Dev Disord.* 2006 413-420.

A 12-month, single-blind study of 55 children with ASD found that the GFCF group had significantly greater improvements than the regular diet group, including improvements in communication (ADOS- blinded observer), and parent observations of improvements in social interaction, inattention, hyperactivity, and daily living skills – Whitely et al 2010, *Nutr. Neurosci.*

# More Research on GFCF diet

Cade found that long-term use of digestive enzymes was beneficial, but that the GFCF diet was even more helpful.

Cade's large study of 150 children with autism found that 87% had IgG antibodies (allergy) to gluten, vs. 1% of the age and gender-matched controls, and 90% had IgG antibodies to casein, vs. 7% of the controls.

Cade also studied 70 autistic children who followed a GFCF diet for 1-8 years, and found that 81% improved significantly by the third month, with improvements continuing over the next 12 months. Large improvements were observed in social isolation, eye contact, mutism, learning skills, hyperactivity, stereotypic activity, and panic attacks. Among the 19% who did not improve, about 1/3 of them were not following the GFCF diet, and had high amount of gluten and casein peptides still in their blood.

•Cade R, Privette M et al. "Autism and Schizophrenia: Intestinal Disorders" Nutr. Neurosci 3 (2000) 57-72. Published by Overseas Publishers Association, (OPA) N.V.

•Knivsberg AM, Reichelt KL, Nodland M. Reports on dietary intervention in autistic disorders. Nutr Neurosci. 2001;4(1):25-37. Review.

# **GFCF Diet - Testing, Other Diets**

**Testing:** There are tests available for allergies to wheat and dairy. However, a negative allergy test does not mean that dairy and wheat are ok, as they can also cause problems due to opioid action. **A trial of avoiding the foods is the best test.**

## **Other Diets:**

Several other diets are being investigated currently. One alternative diet is the Specific Carbohydrate Diet (SCD), which involves avoiding all carbohydrates and most sugars (except monosaccharides in fruit). For more information on this diet, see [www.pecanbread.com](http://www.pecanbread.com)

**For more information, go to:**

**Autism Network for Dietary Intervention: [www.autismndi.com](http://www.autismndi.com)**

# Vitamin/Mineral Supplements

**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.

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

	<b>% Worse</b>	<b>% No Change</b>	<b>% Better</b>	<b>Number of Reports</b>
<b>Vitamin A</b>	2%	58%	41%	618
<b>Calcium<sup>E</sup>:</b>	2%	62%	36%	1378
<b>Folic Acid</b>	3%	54%	42%	1437
<b>Magnesium</b>	6%	65%	29%	301
<b>P5P (Vit. B6)</b>	13%	37%	51%	213
<b>Vitamin B3</b>	4%	55%	41%	659
<b>Vitamin B6 alone</b>	8%	63%	30%	620
<b>Vitamin B6 with Magnesium</b>	4%	49%	47%	5780
<b>Vitamin B12</b>	4%	33%	63%	192
<b>Vitamin C</b>	2%	57%	41%	1706
<b>Zinc</b>	2%	51%	47%	1244

# Vitamin D

- Several but not all studies found vitamin D lower in children with autism
- One study found lower levels of vitamin D correlated with more severe autism, but one did not
- Most people are low in vitamin D due to low exposure to sun
- Most supplements contain at most 400 IU, but about 5000 IU needed to increase levels
- Strongly recommend testing and supplementing at 5000 IU or more if low

# Iron

- Low iron during pregnancy doubles risk of ASD
- Low iron during infancy is a leading cause of permanent intellectual disability
- Test iron (especially in young children) and supplement if low
- Frequently test iron in girls/women post puberty
- Only supplement in men if low (excess iron is a problem in 5% of males)

# **Results of ASU Vitamin/Mineral Study**

(Adams et al 2011, Nutrition and Metabolism, and another paper)

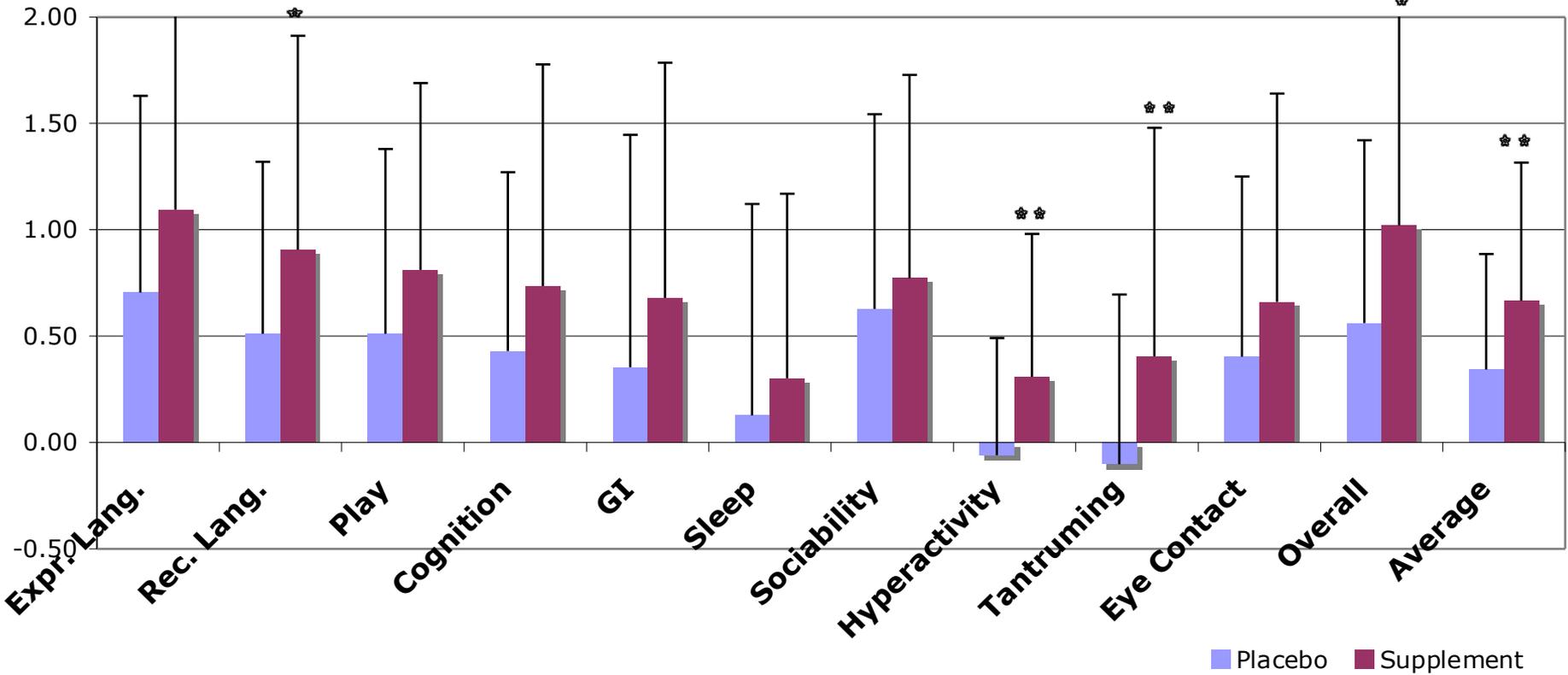
12 week, randomized, double-blind placebo-controlled study with

Many abnormalities in autism in vitamins, minerals, glutathione, methylation, oxidative stress, sulfation, neurotransmitters

These abnormalities are associated with variation in autism severity

Supplement seems to improve or normalize levels of almost all of them.

## Parental Global Impressions - Revised



Treatment group did better than placebo on all scores, with significantly better improvements on Average Score, Receptive Language, Hyperactivity, Tantrumming, and Overall

# High-Dose Vitamin B6 and Magnesium

**Rationale:** Over 20 studies on the treatment efficacy of vitamin B6 with Magnesium, including 12 double-blind, placebo-controlled studies, making it one of most studied treatments for autism. Almost all studies found that 45-50% of children and adults with autism benefited from high-dose supplementation of vitamin B6 with magnesium.

Vitamin B6 is required for over 100 enzymatic reactions, including the production of major neurotransmitters (serotonin, dopamine, and others) and glutathione (needed for detoxification). Magnesium is used to prevent the possibility of hyperactivity, which can occur if vitamin B6 is taken by itself.

## **Possible Mechanism:**

- 1) a decreased ability to convert vitamin B6 to its active form, and
- 2) defective enzymes for making key neurotransmitters that require an unusually high amount of the active form of vitamin B6.

Adams et al, Abnormally high plasma levels of vitamin B6 in children with autism not taking supplements compared to controls not taking supplements. *J Altern Complement Med.* 2006 Jan-Feb;12(1):59-63.

**Recommended Dosage:** about 8 mg/pound of vitamin B6 (maximum of 1000 mg) and half as much magnesium

# 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).

Most importantly four published studies have found that children with autism have lower levels of omega –3 fatty acids than the general population.

- S. Vancassel et al., Plasma fatty acid levels in autistic children, Prostaglandins Leukot Essent Fatty Acids 2001 65:1-7.
- Bell et al Essential fatty acids and phospholipase A2 in autistic spectrum disorders. Prostaglandins Leukot Essent Fatty Acids. 2004 Oct;71(4):201-4.
- Wiest et al Plasma fatty acid profiles in autism: a case-control study Prostaglandins Leukot Essent Fatty Acids. 2009 Apr;80(4):221-7.
- Bell et al 2010, Br. J. Nutri. 103 1160-7.

# Essential Fatty Acids – Research on treating autism

One small open study by Foster et al. found that fish oil provided some general improvements in symptoms.

One small double-blind, placebo-controlled treatment study by Amminger et al. found that fish oil might have some benefit in reducing hyperactivity. “Omega-3 Fatty Acids Supplementation in Children with Autism: A Double-blind Randomized, Placebo-controlled Pilot Study.” Biol Psychiatry. 2006 Aug 22.

One double-blind, placebo-controlled study by Adams et al. found that 2 months supplementation of fish oil (rich in DHA) led to small improvements in sociability and other areas, especially those who consumed 0-1 servings of fish/month.

One open study by Audhya et al. was a 9-month treatment study. They found little improvement by 6 months, but substantial improvements by 9 months. The largest improvement was in gut function (verified by pre and post endoscopies in many cases), but also improvements in other areas.

One study by Bell et al. 2010 found that fish oil supplementation improved omega 3 levels in children with autism.

## ARI Survey of Parent Ratings of Treatment Efficacy:

	<b>% Worse</b>	<b>% No Change</b>	<b>% Better</b>	<b>Number of Reports</b>
Fatty Acids	2%	42%	55%	622

# Testing and Recommendations

**Testing:** Measure essential fatty acids in red blood cell membranes. Since most people in US have low levels of omega 3's, desirable to reach levels at top of the "normal" range.

However, since fish is the major source of omega 3's, can simply assume low if consuming less than 4 servings/month of fish. Fish oil is very safe, and many studies show it also improves cardiovascular health.

## **Recommendation (if no testing done):**

Omega 3: 20-60 mg of omega 3/kg-bodyweight, from fish oil

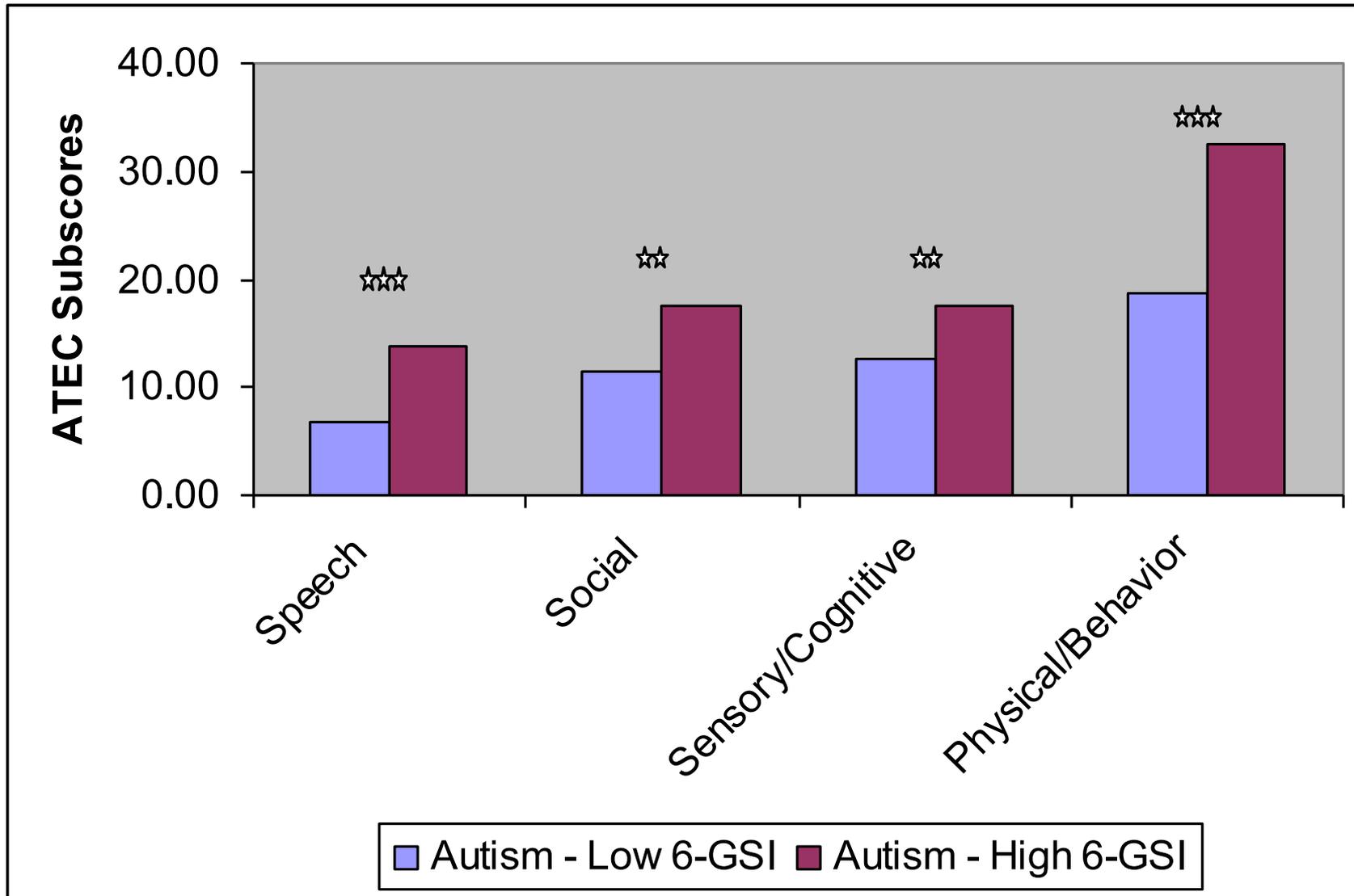
Omega 6:  $\frac{1}{4}$  as much omega 6 as omega 3; evening primrose oil or borage oil

**Note:** quality of fish oil can be judged by smell – rancid smell is bad.

## **Safety:**

1-2% of children with autism have a severe behavioral reaction to fish oil, due to a carnitine deficiency. Small amounts of carnitine (200 mg) allow them to tolerate fish oil without any problem. The reason is that carnitine is needed to transport long chain fatty acids into the mitochondria, and carry short and medium chain fatty acids out of the mitochondria.

# Gut Problems associated with worse symptoms (all four areas) – Adams et al 2011



# Digestive Enzymes

## Testing:

- 1) Loose stools or gaseousness, especially after eating milk products
- 2) Measure digestive enzymes during endoscopy

**Research:** Studies by Horvath et al. and Buie et al have found that many children with autism have defective carbohydrate digestion:

- Horvath K et al, "Gastrointestinal abnormalities in children with autistic disorder," J. Pediatrics 135 no. 5 (1999) 559-563.
- Horvath K and Perman JA "Autistic disorder and gastrointestinal disease," Curr. Opinion in Pediatrics, 14 (2002) 583.

Open-label treatment study by Brudnak et al 2002; 46 started study, 29 finished; improvements in many areas, especially socialization and hyperactivity

## ARI Survey of Parent Ratings of Treatment Efficacy:

	% Worse	% No Change	% Better	Number of Reports
<b>Digestive Enzymes</b>	3%	42%	56%	737

# Gut Bacteria

**Rationale:** The human gut contains a large number of bacteria (10x more gut bacteria than cells in the entire body). Most of these gut bacteria are beneficial, and help with food digestion, water balance, and limiting the growth of harmful bacteria and yeast.

Some children with autism may have low levels of beneficial bacterial, and/or high levels of harmful bacteria and yeast. The harmful bacteria and yeast produce toxins that can severely affect mental functioning and behavior; alcohol is just one of many toxins that yeast can produce, and is a good example of a yeast toxin that can severely affect behavior.

# Gut Bacteria Research

About 1000 different types of bacteria live in human gut, and most are beneficial, helping with digestion water balance, producing certain vitamins (biotin, vitamin K), and protecting vs. pathogenic bacteria.

Five studies found that children with autism had increased use of oral antibiotics as infants vs. controls, primarily for ear infections.

Oral antibiotics destroy most beneficial bacteria, and can result in overgrowth of pathogenic bacteria/yeast.

A small open-label treatment study with a potent non-absorbable antibiotic (Vancomycin) found temporary improvement in gut function and behavior, but the gains were lost when the treatment was stopped. This study demonstrated the importance of abnormal gut bacteria, and the difficulty in treating them long-term.

- *Sander et al, J Child Neurol. 2000 Jul;15(7):429-35.*

# Gut Bacteria Research (continued)

Three small studies using culture-based methods found some limited evidence of abnormal anaerobic bacteria, primarily increases in clostridia.

- Song Y, Liu C, Finegold SM. *Appl Environ Microbiol.* 2004.
- Finegold et al, *Clin Infect Dis.* 2002
- Parracho HM et al., *J Med Microbiol.* 2005.

Three small studies using DNA-based methods found some abnormalities in gut flora. One study found 20% decrease in diversity, which is associated with an unhealthy gut, and low amounts of three genera of beneficial bacteria.

# Yeast in autism?

Many anecdotal reports of yeast overgrowth in children with autism, and many anecdotal reports of benefits of antifungals. However, Adams et al 2011 did not find elevated yeast (by culture or microscopically) in study of 58 children with autism vs 39 controls.

Similarly, Dr. Tim Buie (Harvard Medical School) has scoped over 1000 children with autism, and rarely observed yeast overgrowth.

# Gut Treatments: Anti-fungals and Probiotics

## Testing:

- 1) Stool analysis of gut bacteria and yeast
- 2) Visual: want formed, medium/dark brown stool, 1-3x/day (note that half of stool is bacteria)
- 3) Check EFA levels – low omega-3 can cause gut problems

## Treatments: (more research needed)

**Probiotics:** 30-500 billion CFU's

**Antifungals:** Nystatin, Diflucan – high dose, 2-week trials

**Non-prescription antifungals:** caprylic acid, oregano concentrate, citrus seed extract, undecylenic acid, pau d'arco, saccharomyces boulardii (yeast that fights other yeast).

**Low-sugar diet:** avoiding sugars and simple carbohydrates

**Fecal Transplant:** natural way to restore beneficial bacteria

## ARI Survey of Parent Ratings of Treatment Efficacy:

	% Worse	% No Change	% Better	Number of Reports
<b>Antifungals<sup>C</sup>: Diflucan</b>	5%	41%	55%	330
<b>Antifungals<sup>C</sup>: Nystatin</b>	5%	46%	49%	986
<b>Antibiotics (not recommended)</b>	31%	57%	12%	1799

# Amino Acids

**Rationale:** Some children with autism have self-limited diets that are low in protein, and some have digestive problems that limit their ability to digest protein into individual amino acids. Either of these problems can lead to insufficient amino acids, which are needed to make neurotransmitters, hormones, enzymes, antibodies, immunoglobulins, glutathione, and many other substances.

**Testing:** Fasting plasma amino acids, or 24 hr urine (but unusually high levels in urine may indicate wasting)

## **Treatments:**

Increase protein intake

Digestive enzymes

Customized amino acid

Vitamin/mineral supplementation?

## **Research:**

Children with autism had lower plasma levels of several important amino acids, including tryptophan (needed to make serotonin), and phenylalanine and tyrosine (to make dopamine) – Adams et al 2011

They also had lower levels of serotonin, and many had low levels of dopamine.

# Thyroid Supplementation

**Rationale:** Perhaps 10% of general population has low thyroid levels, and at least that many children with autism also may have that problem.

Also, 1 study found that children with autism have unusually low iodine levels, and low iodine is the major cause of mental retardation worldwide (over 80 million cases), and is becoming more common in US due to decreased use of iodinated salt. Adams et al., Biol Trace Elem Res. 2006 Jun;110(3):193-209.

Recent study found 25% of children with autism have low levels of urinary iodine.  
Adams et al 2011

Old, 1980 study found no difference in thyroid hormones in autism, but iodine levels have fallen 50% in last 20 years. Cohen et al, 1980

## Testing:

Measure body temperature before waking;

Measure iodine levels

Thyroid test (caution re. reference ranges being too broad in some cases)

## Treatment:

Iodine supplementation if low

Thyroid supplements, preferably natural animal extracts.

**Caution:** too much thyroid supplement can cause weight loss and other problems, so monitor levels regularly.

# Melatonin

**Rationale:** Many children with autism have sleep problems. Melatonin is the substance the body makes to regulate sleep. It is made from serotonin, and some children with autism have low serotonin, so they may have low melatonin.

**Testing:** Based on observation of sleep problems by parents.

**Treatment:** Start with low dose, and increase if necessary. Also, turn off all lights in room, as even a nightlight can greatly reduce melatonin production. 1 mg of melatonin (0.5 mg for children), and increase up to 2-5 mg if necessary (1-3 mg for children).

Alternatively, give tryptophan or 5-HTP, as they are the precursor to serotonin, which is then converted to melatonin

**ARI Survey Data:** 61% benefit, 30% no benefit, 8% worse.

**Research:** Nine studies found abnormalities in melatonin levels/cycle in ASD  
Five double-blind, placebo-controlled trials found melatonin improved falling asleep and sleep duration, but not night-time awakening

Review by Rossignol & Frye, 2011 Dev Med Child Neurol

# 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 4<sup>th</sup> 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

**Testing:** Blood testing best to check for levels of free and total plasma sulfate. Urine testing of free and total sulfate is useful to check for excessive loss of sulfate.

## **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 (500-2000 mg depending on size and sulfate level) and Epsom Salt (magnesium sulfate) baths – 2 cups of Epsom salts in warm/hot water, soak for 20 minutes, 2-3x/week, with half-cup baking soda (to improve absorption).

Vitamin/mineral supplement with MSM significantly improved sulfate

# Sulfate

## Research:

Low free and total plasma sulfate in children with autism – (Waring 1997, Geier 2009, Adams 2011)

Decreased ability to detoxify acetaminophen (Tylenol) – (Waring 1997, O'Reilly 1993, Alberti 1999, Horvath 2002)

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.

# Glutathione

## Research:

- A study by James et al. found low glutathione, and higher fraction of oxidized (inactive) glutathione in children with autism vs. controls. Treatment with 800 mcg of folinic acid and 1000 mg of TMG somewhat improved plasma glutathione levels. Adding subcutaneous injections of methyl-Vitamin B12 (methyl-cobalamin) resulted in normalization of plasma glutathione levels.
  - “Metabolic endophenotype and related genotypes are associated with oxidative stress in children with autism.” *Am J Med Genet B Neuropsychiatr Genet.* 2006 Dec 5;141(8):947-56.
- A large study by James et al confirmed her original finding of low glutathione in children with autism due to abnormalities in their methionine pathway. She also found that children with autism were more likely to have genetic polytypes associated with abnormalities in the methionine pathway.
  - “Metabolic endophenotype and related genotypes are associated with oxidative stress in children with autism.” *Am J Med Genet B Neuropsychiatr Genet.* 2006 Dec 5;141(8):947-56.

**Testing:** Measure level of glutathione (fasting plasma or RBC).

**Treatment:** Oral glutathione is poorly absorbed (perhaps 10%). Alternatives include IV glutathione, N-acetyl cysteine, 500 mg vitamin C, DMSA therapy, Ribose, NADH.

# **New Study on NADH Therapy and Ribose Therapy**

**(Freeddenfeld et al, Autism Insight, 2011)**

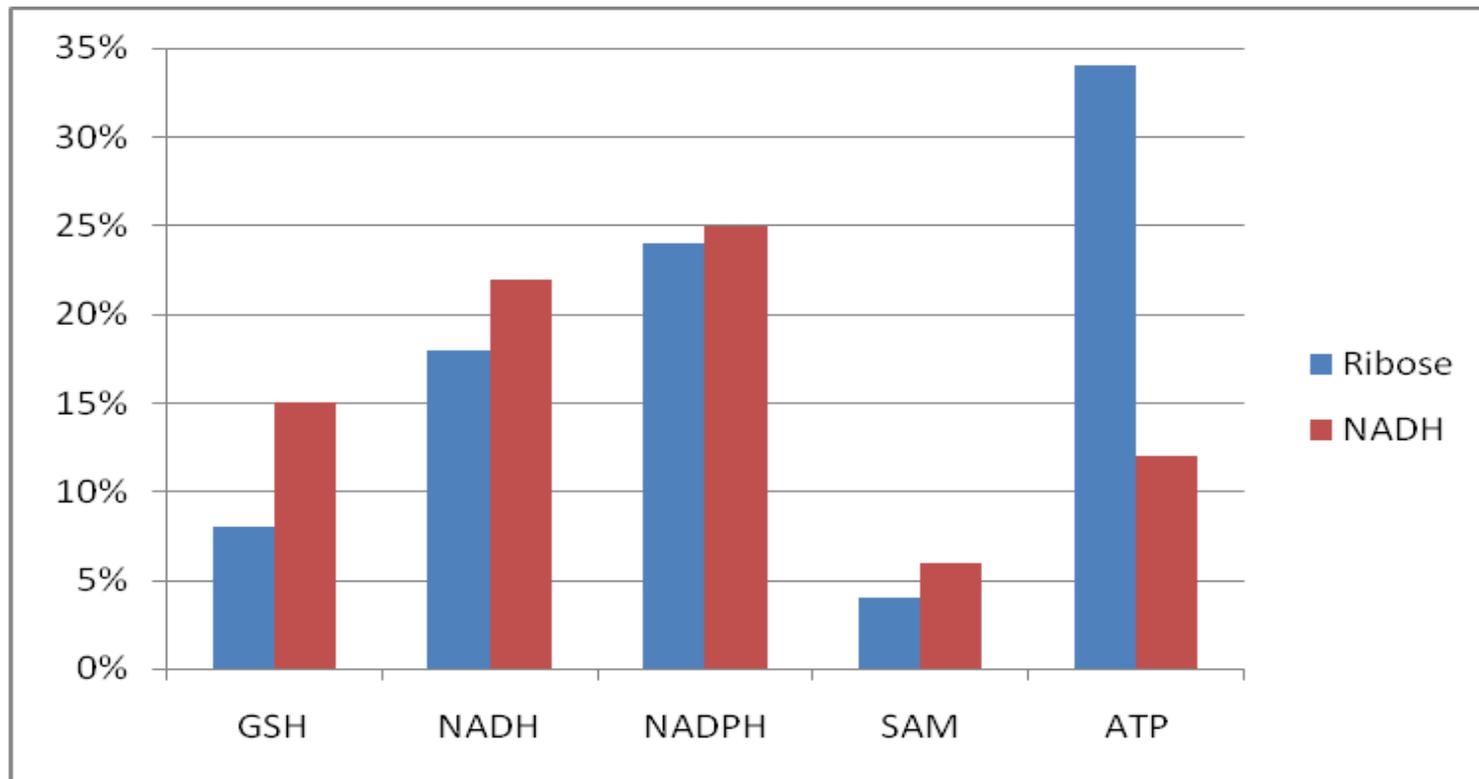
Two weeks of therapy with NADH (5-10 mg) or Ribose (5 g)

Many improvements in glutathione, methylation, NADH, NADPH, ribose, and ATP.

Ribose is a special sugar available in tiny amounts in food; mostly made in the body from glucose (requires NADP to make it, which is low in autism).

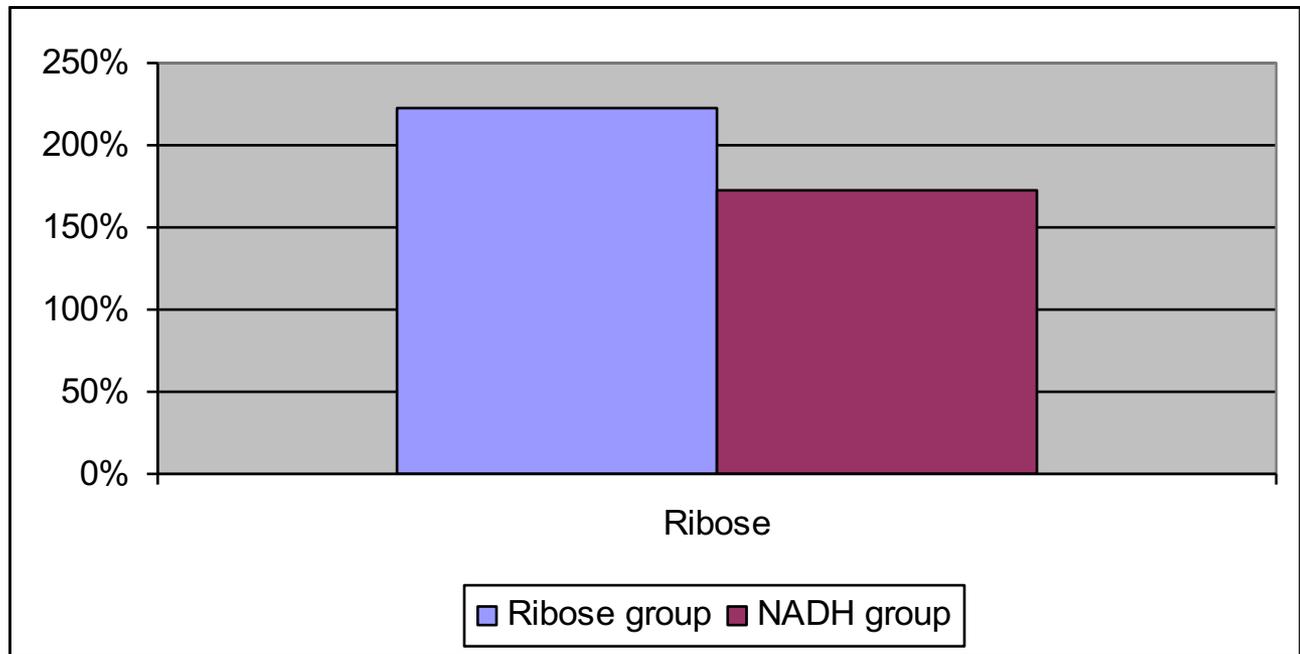
Ribose is a building block for DNA, RNA, ATP, GTP, NADH, NADPH, FADH, riboflavin, co-enzyme A and other nucleotides.

# Effects of Ribose therapy and NADH therapy on primary biomarkers (% change).



Very similar results, although NADH better for improving GSH, ribose better for improving ATP

# Effect of Ribose therapy and NADH therapy on level of Ribose (% change).



Both therapies very effective in increasing level of Ribose.

# Summary

Ribose and NADH have similar benefits, and can quickly improve methylation, glutathione, and ATP problems in autism.

Larger, longer-term trials needed to determine effect on symptoms, but likely to be beneficial with minimal risk of side-effects.

# Carnitine Treatment Study

Rationale – carnitine is needed to transport long-chain fatty acids (fuel) across membrane into mitochondria;

Carnitine can be made to a limited extent by the body, but primary source is beef and pork – people who eat no beef/pork and have low energy/muscle strength likely need carnitine

One study found decreased carnitine in children with autism (Filipek et al)

So, carnitine supplementation may be helpful.

# Carnitine (cont.)

Carnitine Treatment Study: (Geier et al 2011, Med. Sci. Monitor)

Randomized, double-blind, placebo-controlled; 90 days treatment

Dosage: 50 mg L-carnitine/kg bodyweight/day (similar to that for prescription carnitine)

Generally well-tolerated with minimal side effects (a few cases of irritability and/or stomach discomfort);

30 starting participants (19 treatment, 11 placebo); 7 withdrawals (4 in treatment group, 3 in placebo)

# Results

	Treatment	Placebo	t-test
CGI	50% improved	0%	p=0.03
CARS	-6%	0%	p=0.02
ATEC			
-speech	-21%	+4%	p=0.09
-social	-31%	-9%	n.s.
-cognitive	-28%	-4%	p=0.01
-physical/behavioral			
	-28%	-25%	n.s.
Muscle	+5%	0%	n.s.
Strength			

Overall, modest but significant improvements in 50% of participants in only 90 days.

L-carnitine therapy significantly increased serum carnitine concentrations, and significant correlations between changes in serum free-carnitine levels and positive clinical changes were observed.

# 2<sup>nd</sup> Carnitine Study

30 participants, 2x dose (100 mg/kg bodyweight), 2x duration (6 months)

Overall, well-tolerated

At 3 months,

Treatment group improved 11% on CARS vs. vs. 6% for placebo group,  $p < 0.001$

At 6 months:

Treatment group improved 25% on CARS vs. vs. 9% for placebo group,  $p < 0.001$

So, longer duration beneficial

Combination with other mitochondrial supplements (co-Q10, NADH, ribose, vitamins/minerals) may increase effectiveness

# Sulphoraphane

- Sulphoraphane is a phytochemical whose precursors (glucoraphanin and myrosinase enzyme) come from broccoli and other cruciferous vegetables) .
- It acts by up-regulating genes that allow aerobic cells to protect themselves against oxidative stress, inflammation, DNA-damaging electrophiles, and radiation.

# Sulphoraphane Study (Singh et al 2015)

- Randomized, double-blind, placebo-controlled study for 18 weeks + 4 weeks follow-up
- 44 males ages 13-27 yr with moderate to severe ASD
- Placebo group: < 3% change in symptoms
- Treatment group:
  - 34% reduction in ABC ( $p < 0.001$ ),
  - 17% reduction in SRS ( $p < 0.02$ )
  - Significant gains in some parts of CGI (social interaction, abnormal behavior, and verbal communication) but not overall ASD

Most gains lost after 1 month of no treatment

# Sources

- Difficult to extract precursors of sulphoraphane
- I think some reputable sources are:
  - Zymogen – Oncoplex SGS- glucoraphanin
  - Thorne – Crucera SGS – glucoraphanin
  - Nutramax – Avmacol – glucoraphanin and the active myrosinase enzyme

# Detoxification Therapy

**Rationale:** Low/inactive glutathione results in less excretion of mercury and toxic metals/chemicals, resulting in a higher body burden.

Also, many children with autism had increased use of oral antibiotics in infancy, which alter gut flora and thereby almost completely stop the body's ability to excrete mercury.

**Testing:** Urinary porphyrins reveal presence of mercury and other toxic metals by evaluating steps in porphyrin pathway.

Nataf et al, Porphyrinuria in childhood autistic disorder: implications for environmental toxicity. *Toxicol Appl Pharmacol.* 2006 Jul 15;214(2):99-108.

**Treatment:** DMSA (FDA-approved for lead poisoning in infants) or DMPS. See DAN! consensus report at [www.autismresearchinstitute.com](http://www.autismresearchinstitute.com)

## ARI Survey of Parent Ratings of Treatment Efficacy:

	% Worse	% No Change	% Better	Number of Reports
Chelation	2%	22%	76%	324

# DMSA Therapy (Adams et al 2009)

Toxic metals (especially lead, antimony, and mercury) associated with 22-45% of autism severity.

DMSA is a safe way to remove several toxic metals (especially lead), normalize glutathione, normalize platelets/inflammation

DMSA therapy should involve some supplementation with chromium, and increased consumption of fruits/vegetables

20% of children had low initial excretion (no need to treat)

20% only needed treatment for 1-2 months

60% needed treatment for at least 3 months, probably longer

Conclusion: all children with autism should be tested

# Immune System Regulation

Several studies found altered immune system in autism, generally with shift to Th-2, and some evidence for auto-immunity.

Molloy et al., Elevated cytokine levels in children with autism spectrum disorder, J. Neuroimmunol 172 (2006) 198-205.

**Treatments include IVIG, ACTOS, low-dose Naltrexone:**

**IVIG:** Gupta et al., found IVIG benefited 4 of 10 children, with 1 case of marked improvement.

Treatment of children with autism with intravenous immunoglobulin. J Child Neurol. 1999 Mar;14(3):203-5.

Twenty six autistic children received intravenous gamma globulin (IVIG) every 4 weeks for 6 months at a dose of 400mg/Kg. Aberrant behaviors, speech, hyperactivity, inappropriate stims and social interactions significantly improved. However 22 of the 26 children regressed within 4 months after discontinuing IVIG.

Boris m, Goldblatt A, Edelson SM; Improvement in children with autism treated with intravenous gamma globulin. Journal of Nutritional & Environmental Medicine, Dec 2005; 15(4): 169-176.

# Immune System Regulation (continued)

**ACTOS:** An open study of ACTOS in 25 children with autism for 3-4 months found substantial improvements in irritability, lethargy, stereotypy, and hyperactivity, with greater benefits in the younger children. Doses were 30 mg (younger children) and 60 mg (older children). ACTOS (pioglitazone) has multiple effects, including the ability to decrease inflammation.

Boris et al., Effect of pioglitazone treatment on behavioral symptoms in autistic children, accepted in J. Neuroinflammation 2007.

However, the ARI survey data (below) suggests that it is only rarely beneficial (19% worse, 60% no change, 21% better).

**Safety Concern: The FDA has issued a “black box” warning that ACTOS may increase the risk of congestive heart failure, fluid retention, and edema (swelling due to fluid build-up under the skin).**

**Low-Dose Naltrexone:** It has been suggested that low-dose naltrexone, at about 3-5 mg/day (much lower than normally used) may be beneficial to children with autism and may improve the regulation of their immune system. More research is needed.

# ARI Survey of Parent Ratings of Treatment Efficacy

	% Worse	% No Change	% Better	Number of Reports
<b>IVIG</b>	7%	39%	54%	142
<b>Actos</b>	19%	60%	21%	140
<b>Low-dose naltrexone</b>	11%	52%	38%	190

# Hyperbaric Oxygen Therapy (HBOT)

## **Rationale:**

Over 10 studies show evidence of decreased blood flow in brains of children and adults with autism, suggesting need for more oxygen. Two studies found decreased blood flow in brain correlated with more severe autism/symptoms. Cause is unknown.

HBOT increases oxygen in blood temporarily, and two studies for other brain injuries suggest it can temporarily increase blood flow to brain.

Also, HBOT is effective for improving general wound healing, and might help with gut problems.

**Treatment:** Typically 40 1-hour sessions, 1-2x/day, in a chamber with 40% increased oxygen pressure, which temporarily increases level of oxygen in blood.

# HBOT – Research on Autism

Several open-label studies of HBOT therapy for children with autism, and most suggest that HBOT therapy might be helpful, but one open-label study with rigorous pre/post assessment showed no benefit.

Two randomized, double-blind, placebo-controlled studies, with one study showing statistically significant benefit in one of the measures but not the others, and the other study showing no benefit.

Two recent reviews of HBOT for autism are Rossignol, et al 2012 and Ghanizadeh 2012.

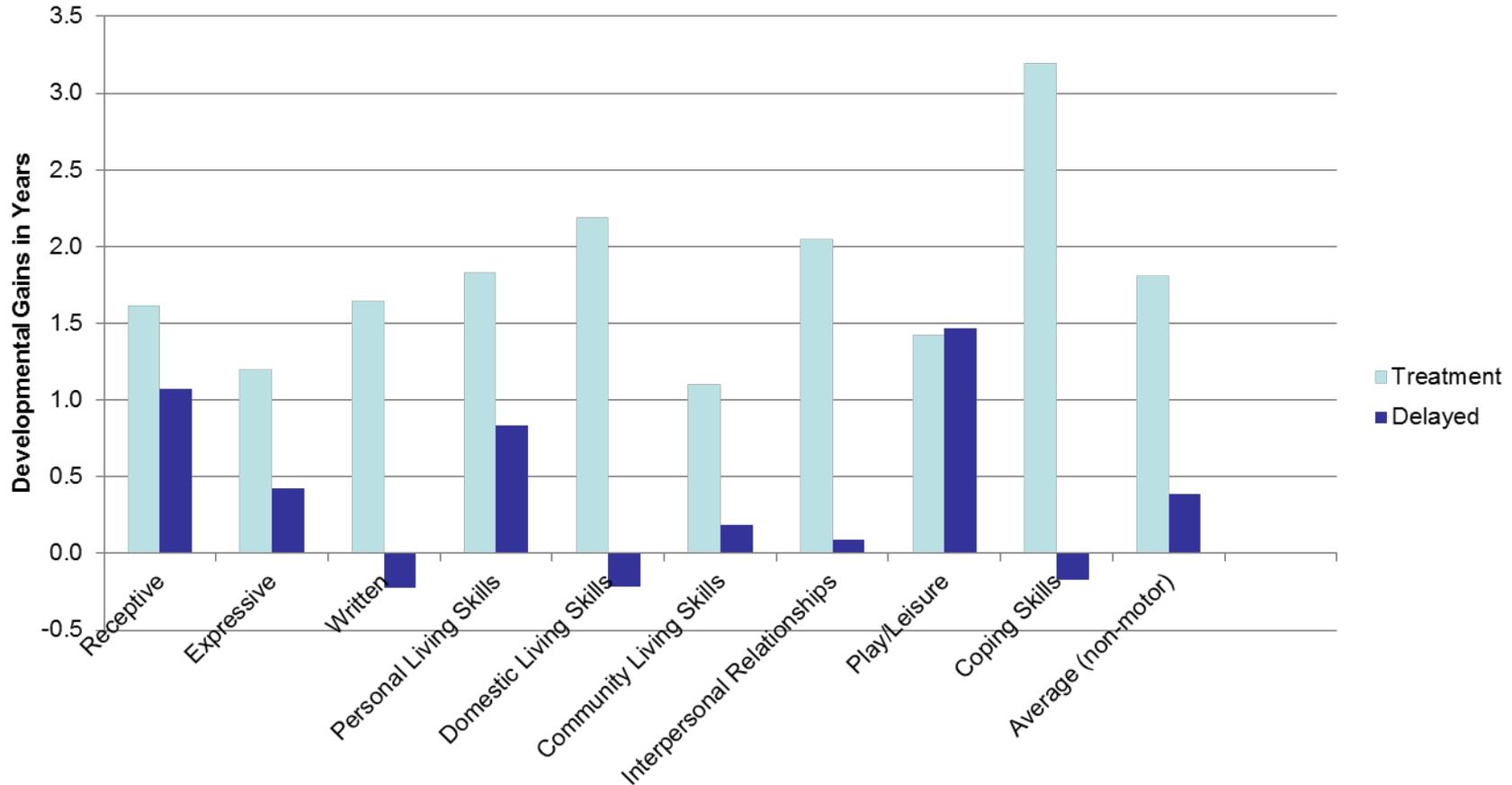
# HBOT – safety concerns

- Decreased glutathione (already low in children with ASD) in a small treatment study – Rossignol *BMC Pediatr* 2007
- **Contraindicated for primary mitochondrial disease** (which a few % of children with ASD have) – can cause serious injury or death in those cases - Scientific Advisory Board of the United Mitochondrial Disease Foundation (UMDF) *Mitochondrial News* 12: 1 and 20, 2007.
- Seizures – anecdotal reports it might increase seizures; however, national survey found it actually helpful in decreasing seizures and improving symptoms, especially communication – Frye et al *BMC Pediatrics* 2011

# 12-month Treatment Study

Randomized, single-blind, controlled study of 6 nutritional and dietary treatments.

Treatment group gained 22 months of development, vs. 5 months for non-treatment group



# 3 Top Treatments

- Vitamin/Mineral – ANRC Essentials
- Essential Fatty Acids (fish oil) – Nordic Naturals
- Healthy, GFCF diet



**AUTISM NUTRITION  
RESEARCH CENTER**

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[www.AutismNRC.org](http://www.AutismNRC.org)

# Summary

Many research studies have documented a wide range of biomedical abnormalities in children with autism. All of those abnormalities can be treated to some degree, and some treatments have been successfully documented by research studies.

By following the testing and treatments suggested here, many children will improve to some degree, and sometimes dramatically over time. Use the checklist and physician advice as to order of testing/treatments. Some treatments require physician assistance, but some can be done by parents.

For more information, see “Summary of Dietary, Nutritional, and Medical Treatments for Autism” at <http://autism.asu.edu>

**Start today - Autism is TREATABLE!**

# Making a Personal Plan

List 1-3 treatments to consider

Possibly consult with physician

Test if appropriate

Try only 1 treatment at a time, and observe results

# Healthy Child Guide

- Recommendations for preconception and pregnancy to greatly decrease risk of autism and many other neurological and physical problems
- Available for free from [www.neurologicalhealth.org](http://www.neurologicalhealth.org)