Integrative & Functional Medicine 101: Basic Concepts Across the Lifespan

Presented by:
Emily Gutierrez, DNP, CPNP, PMHS, IFM-CP

My journey in nursing

- **Allopathic:**
  -Primary Care, Urgent Care
- **Integrative:**
  -Westlake lessons in primary care
  -Doctoral focus- *how do we intelligently integrate holistic medicine into mainstream care?*
- **Functional**: A focus shift from treating the symptoms to treating the SOURCE of the symptoms

Functional Medicine, Founded 2013
Emily Gutierrez, DNP, PNP, PMHS, IFM-CP and Jana Roso, PNP

Allopathic medicine doesn't *always have it right*

- **1992 US Department of Agriculture issued food pyramid recommending 6-8 servings daily of grains**
  - World Health Organization, 2015, "Limit sugars to <10% of total energy intake, <5% has additional benefits (25grams)".

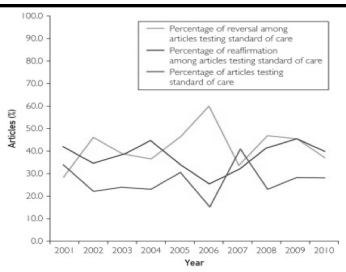
The Villainized EGG- no eggs, only whites, the whole egg

- American Heart Association & American Cardiology Association, 2015, "There are no limits on healthy dietary cholesterol".
- **Low fat diets led to increased obesity**
  - American Medical Association, Ludwig & Mozaffarian, 2015 US Dietary Guidelines, "No health benefits to low fat diets at all."

A Decade of Reversal: An Analysis of 146 Contradicted Medical Practices

Vinay Prasad, MD, Andrae Vandross, MD, Caitlin Toomey, MD, Michael Cheung, MD, Jason Rho, MD, Steven Quinn, MD, Satish Jacob Chacko, MD, Durga Borkar, MD, Victor Gall, MD, Senthil Selvaraj, MD, Nancy Ho, MD, Adam Cifu, MD

Mayo Clinic Proceedings
Volume 88, Issue 8, Pages 790-798
(August 2013)



363 standard of care papers reviewed
38% reaffirmed standard of care
40% reversed the practice

"The reversal of established medical practice is common and occurs across all classes of medical practice."

Mayo Clinic Proceedings 2013 88, 790-798DOI: (10.1016/j.mayocp.2013.05.012)

The Translational Gap

From bench to bedside=

17 YEARS

Morris, Wooding, Grant, 2011

Learning Objectives

- Build foundational knowledge about integrative and functional medicine across the lifespan
- Explore applications for acute conditions in primary care
- Explore applications for chronic health conditions and diseases
- Apply knowledge to interactive case studies

What is Integrative Medicine?

- Whole Person Treatment
- Evidence Based Methodologies
- Choosing the treatment modality that yields the best patient outcomes *(despite assigned title)*

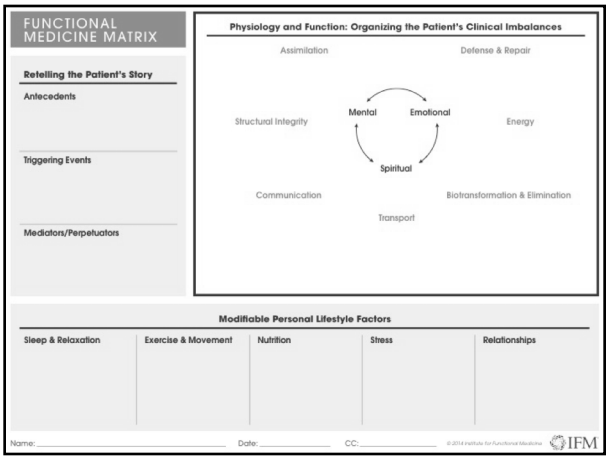
What is Functional Medicine?

A biological systems based approach to treating the root cause of illness by looking at the interactions between the genetic, environmental, and lifestyle factors of an individual. By shifting the traditional disease-centered focus of medical practice to a more patient-centered approach, functional medicine addresses the whole person, not just an isolated set of symptoms.

THE INSTITUTE FOR FUNCTIONAL MEDICINE®

Goose Bumps? Butterflies?

Our biological systems are *connected*



Integrative Medicine	Functional Medicine
• Asks the question what ELSE can I use for this condition outside of allopathic training? • Mind body therapies • Energy work • Nutraceuticals • Herbs • Exercise/Diet	• Asks the question WHY this condition exists? • What was the trigger? • What are the underlying imbalances? • What mediates and perpetuates this condition? • WHY, WHY, WHY, WHY???

IM & FM often used together

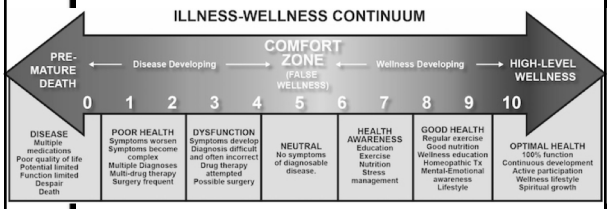
Our Functional Approach: Decreasing the Body Burden

Biological illness is set within an interconnected set of systems that do not work in isolation. When body systems are stressed, this creates an overall increase in the body burden, leading to more disease. When stress is identified and treated, hence lowering the overall body burden, every part of the body may feel benefits from the improvement.

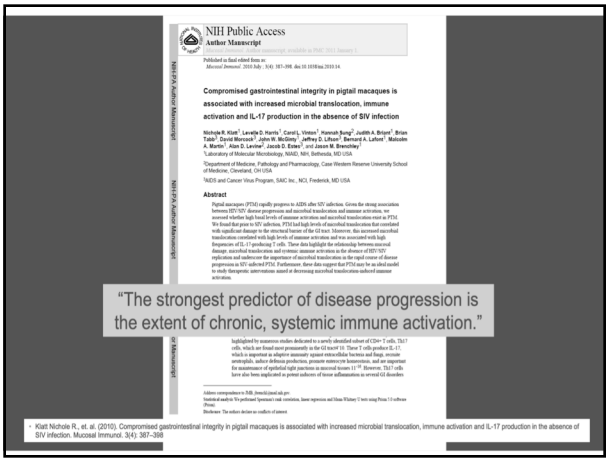
Martha Herbert, MD, PhD, Harvard

Herbert, 2018

Where are you on the continuum?



Where are your patients on the continuum?



What are Supplements?

- Vitamins & Minerals
- Dietary Supplements
- Homeopathic Medicines
- Herbal & Traditional Medicines
- Probiotics
- Natural Health Products
- Amino Acids & Essential Fatty Acids

Beware of Nomenclature

(Health Canada, 2014)

Patients seek information about supplements the **LEAST** from their allopathic providers

(Zhang, Fein, E. & Fein, B., 2011)

SIGNIFICANCE

- **Approximately 31% of children and over *half* of adults use NHPs-** (CDC, NHANES, 2013).
- $14.8 Billion spent on NHPs in 2007, approximately 1/3 of total spending on prescription drugs (NCCAM, 2012).
- There are more than 85,000 NHPs on the market and growing (Fabricant, 2013).

Antiviral/immune support for acute viral illness

Vitamin C

Has the ability to prevent the common cold, and reduce its duration and severity (especially in children) (Cochrane Syst Rev, 2004).

Dosing ranges from **200-3,000 mg daily**.

Half life is @ 30 minutes, so the frequency of dosing should be short such as every 2 hours.

The most common side effect of high dose vitamin C is GI upset, so this may be the rate-limiting factor when using it to treat the illness (Roxas, 2007).

- *1 orange contains an average of 51mg of C; for a URI therapeutic dose, a patient would have to eat 4-60 oranges/day.*

- No co-administration with acetaminophen (decreases liver excretion, increases risk of hepatoxicity)
- Food sources rich in vitamin C include oranges, kiwi, bell peppers, strawberries, papaya, broccoli, brussels sprouts, kale and guava.

Zinc

Essential mineral with clear immune modulating benefit.

Dosages used in adults throughout the literature include 9-24mg of elemental zinc, given every 2 hours, to achieve reduction in illness of a mean of 3 days (333-337).

Meta-analysis in 2017 showed a 3-fold rate of recovery for the common cold when taken within 24 hours on onset of illness symptoms (Hemilä, 2017).

Young children, zinc supplementation should be limited to 45mg/day for up to 3-5 days.

Long-term supplementation with high doses of zinc can lead to toxicity, however this is rare and often children are deficient at the onset of illness and will benefit from high dose repletion.

Cashew tree

- *Picky eaters and zinc deficiency correlation? Possibly- RBC serum zinc*
- Foods high in sources of zinc include lamb, pumpkin, beef, chickpeas, cocoa, cashews, kefir, mushroom, spinach, and chicken.
- ***Intranasal** zinc can cause anosmia*

(Hemila & Chalker, 2013 & Science, et al., 2012)

Umckaloabo (pelargonium sidoides)

- herbal remedy for common viral illnesses
- Conchrane Collaboration found to possibly be effective in relieving URI symptoms in adults and children (Cochrane, 2013).
- Systematic review showed safety and efficacy for children under the age of 6 years (Kamin, 2017).
- Has immunomodulatory effects on natural killer cell activation, stimulation of interferon-*B* and release of nitric oxide and tumor necrosis factor *a*.
- Side effects are rare, but if occur may include GI upset, including diarrhea**.**
- Herbal extractions are typically diluted in water **(140mg/.7mls) and given in 2 ounces of fluid up to 4x daily**.

SUGGESTED USE
Shake Well Before Using. Add 1 full squeeze of the dropper bulb to 2 oz. of water or juice, 2 to 4 times per day. Best taken between meals.

Supplement Facts
Serving Size: 0.7 ml
Servings: about 84

Amount Per Serving
Umckaloabo root (Pelargonium sidoides) extract 657 mg

Andrographis

- Andrographis Paniculata is an Ayurveda herb that has anti-inflammatory, antibacterial, antineoplastic, and immunomodulatory properties.
- Children- treatment of upper respiratory infections, 3-6g of andrographis, containing 180-360mg of andrographolide constituents, divided TID can be given up to 7 days (Natural Medicines, 2018) .
- Adults: 3-6g (containing 48-500mg of the andrographolide constituents) divided into three or four daily doses, has been taken by mouth for 4-10 days particularly for respiratory infections

Ingredient	Amount	Daily Value
Andrographis (*Andrographis paniculata*) Leaf Extract [standardized to 5% (10 mg) andrographolides]	200 mg	*
Amla (*Embilica officinalis*) Fruit 3:1 Extract (containing tannins)	200 mg	*
A 5:1† Proprietary Herbal Extract Blend of:	200 mg	*
Glehnia (*Glehnia littoralis*) Root,		
Apricot (*Prunus armeniaca*) Seed,		
White Mulberry (*Morus alba*) Leaf,		
Gardenia (*Gardenia jasminoides*) Fruit,		
Soybean (*Glycine max*),		
Zhejiang Fritillary (*Fritillaria thunbergii*) Bulb,		
Pear (*Pyrus pyrifolia*) Fruit)		

Product contains 1 tablet= 200mg of andrographis
Children URI tx 180-360 divided TID= .5-1 tablet TID
Adults URI tx up to 500mg TID= 1-1.5 tablets TID
Do not give to pregnant or breastfeeding women

Elderberry: Natures Antiviral

Mechanism of Action: Inhibits growth of influenza viruses and significantly shortens the duration of influenza symptoms while enhancing antibody levels against influenza virus

- When given to adults within 48 hours of onset of influenza at 1 tablespoon (5.7grams Elderberry, 190.5mg *Sambucus Nigra*) QID, there was a 56% reduction in symptoms 3-4 days earlier than placebo (Zakay-Rones, 2004).
- Children (> 4) were given (same formula above) 2 tablespoons divide BID, and adults were given 4 tablespoons BID. Ninety percent of patients showed complete cure of flu in 2-3 days whereas the placebo group took up to 6 days (Zakay-Rones, 1995).

Supplement Facts
Serving Size 2 teaspoons (10ml)
Serving Per Container 12

Amount Per Serving		% Daily Value
Calories	11	
Total Carbohydrate	3g	1%†
Sugars	0g	**
European elder (Sambucus nigra) berry extract 30:1 (derived from 3.8 g of European elder berry^)	127mg	**

†Percent Daily Values are based on a 2,000 calorie diet.
****Daily Value not established.**

OTHER INGREDIENTS: PURIFIED WATER, GLYCERIN, ELDERBERRY NATURAL FLAVOR^, CITRIC ACID, XANTHAN GUM, REB-A (STEVIA NONNUTRITIVE SWEETENER), NATURAL FLAVOR^, POTASSIUM SORBATE (PRESERVATIVE).
FREE FROM ARTIFICIAL COLORS, FLAVORS AND GLUTEN. ^ ADDS A TRIVIAL AMOUNT OF SUGAR.

Suspension dosing 127mg Sambucus nigra per 2 teaspoons

Adult dosing for influenza (190.5mg QID)= 1 tablespoon QID

Supplement Facts

Serving Size 1 piece (2.8g)
Serving Per Container 30

Amount per Serving

Calories 7		Calories from Fat 0
		% Daily Value*
Sodium	10mg	1%
Total Carbohydrate	2g	1%
Dietary Fiber	0g	0%
Sugars	1.5g	
Vitamin C (Ascorbic Acid)	45mg	75%
Zinc (Zinc Citrate)	3.75mg	25%
Black Elderberry (*Sambucus Nigra*) Extract (equivalent to 1.8 gram Black Elderberry Fruit)	50mg	**

Percent Daily Values are based on a 2,000 calorie diet.
****Daily Value not established.**

OTHER INGREDIENTS: DRIED CANE SYRUP, ORGANIC TAPIOCA SYRUP, WATER, PECTIN, SODIUM CITRATE, CITRIC ACID, NATURAL RASPBERRY FLAVOR WITH OTHER NATURAL FLAVORS, COCONUT OIL, CARNAUBA WAX.

FREE FROM GLUTEN, DAIRY, SOY, WHEAT, NUTS, EGGS ARTIFICIAL COLOR AND FLAVORS OR PRESERVATIVES.

Gummy dosing= 1 piece contains 50mg Sambucus Nigra

Children (>4) dosing for influenza 190.5mg BID = 4 gummies 2X daily

Echinacea- *flowering herb*

Used for prevention and reduction of URIs

500-1,000mg TID X 2-3 weeks for adults, 100mg QD (>12years)

- 2016 the largest trial to date was conducted with over 670 adult subjects using Echinacea purpurea extract. Subjects were given 2400mg of extract daily, divided into TID dosing. This well designed study demonstrated efficacy with Echinacea as a preventive cold treatment, beneficial in long-term prevention, effective for cold episode reduction, and reduction in the number of days with an illness (Ross, 2016)
- Echinacea is contraindicated in with patients with progressive and systemic disease, and *not used in children younger than 12 years* due to the risk of allergic reaction (Medicines and Healthcare Products Regulatory Agency, 2012).

(Cravotto, et al., 2010 & Di, et al., 2012)

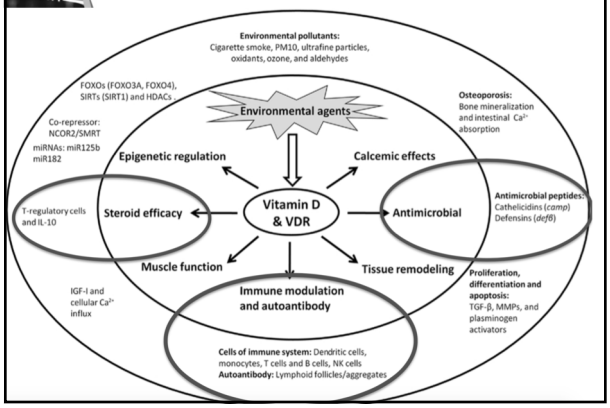
Vitamin D

- **Hormone**: Vitamins help regulate cellular enzyme activity, hormones bind to cells to regulate cellular function
  - D2 plant derivative
  - D3 made by human skin when exposed to sunlight
- At risk populations for deficiency: breast-fed infants, dark skin, Chrohn's dx, celiac, video gamers, and obesity
- Etiology: Deficient intake, limited sun exposure, kidneys cannot convert 25(OH)D to its active form, or limited gut absorption
- Symptoms: **Asymptomatic**, immune dysfunction, endocrine dysfunction, cognitive impairments, and more

(NIHODS, 2014 & Smoldersa, et al., 2008)

- Vitamin D down regulates autoimmune processes and has **panacea antibiotic and adjunctive properties in a diversity of infections and chronic conditions** (Ann N Y acad Sci, 2014).
- Deficiency in 25-hydroxyvitamin D has been associated with increased frequency infections in children (Bozzetto, 2012).
- Shown to significantly reduce the incidence of upper respiratory infections and influenza when given in winter months in children (Urashima, 2010).
- A study in 2018 showed that high dose Vitamin D (1200IU/day) showed rapid relief from influenza A symptoms, a rapid decrease in viral loads, and expedited disease recovery in comparison to the low dose (400IU/day) group (Zhou, 2018).

Vitamin D Functions



Vitamin D Deficiency Treatment

Standardized Dosing: AAP Guidelines 400IU daily exclusive BF infants; 0-12mth 400IU, 1-70yrs 600IU/NIHODS

Does this need to change?

To achieve an optimal vitamin D status of 50-75ng/mL, research suggests an intake for adults of 1,000-10,000 IU QD

Recheck levels Q4-12 weeks; maintenance dose will vary (typically 1,000-5,0000IU daily)

Vitamin D Deficiency Treatment, Cont.

Side Effects: Toxic levels (>100ng/mL) can produce nausea, anorexia, polyuria and heart arrhythmias; increased risk of kidney stones & vascular calcification.

Interactions: Several drug and herb interactions; meds for seizures, cholesterol, and steroids

Clinically side effects and interactions are RARE even at high serum levels.

(Bischoff-Ferrari, et al., 2006 & Vasquez et al., 2004)

Vitamin D Receptor

- This gene encodes the nuclear hormone receptor for Vitamin D3
- Regulates pathways involved in immune response and cancer
- Mutations associated with Type II Diabetes, Vitamin D resistant rickets, poor immunity and more
- Associated SNPs- fok, **taq**, bsm
- Don't assume healthy levels, **check them!**

US National Library of Medicine, 2016

Inflammation External Source *VDR (Vitamin D receptor)*

- **Vitamin D Receptor taq**
  - Hetero / Homo = **Decreased activity**
  - Seco steroid with epigenetic and immune modulating effects
  - Very complicated physiology
  - Poor Vitamin D delivery:
    - Decreases T reg cell function
    - Increases Th1 activity
    - Decreases Th2 activity
    - Osteopenia

Is the Sun Enough?

You need the right genes:
VDR SNPs need more Vitamin D

You need the right kind of light: Ultraviolet (UV) B radiation with a wavelength of 290–320 nanometers

You need the right kind of time: approximately 5–30 minutes of sun exposure between 10 AM and 3 PM at least twice a week to the face, arms, legs, or back *without sunscreen*

You need the right conditions: Season, time of day, length of day, cloud cover, smog, skin melanin content, and sunscreen are among the factors that affect UV radiation exposure and vitamin D synthesis

(NIHODS, 2014)

Functional Considerations for Acute Illness

Are they more susceptible due to an underlying immune burden? Allergies, immunoglobulin deficiencies, autoimmune up regulation from inflammatory sources, genetic influences

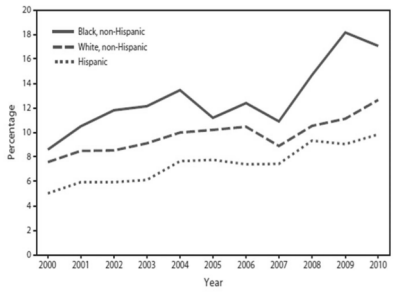
How is their home, school, work environment? Water damaged buildings, contaminated drinking water, exposure to toxic metals (toys from Mexico), no exposure to sunlight

Are they nutritionally deficient? They only eat 3 foods, they are overfed yet under nourished, high exposure to glycophosphates, high sugar/carbohydrate diet?

Is there a psycho social component? Recent trauma, poor access to healthy food, disbelief in preventative lifestyle

Applications for chronic conditions

Childhood Eczema or Any Skin Allergy (2000-2010)



- National Health Interview Survey, 2000–2010. Available at http://www.cdc.gov/nchs/nhis.htm.
- https://www.cdc.gov/mmwr/preview/mmwrhtml/mm6044a9.htm?s_cid=mm6044a9_w

Eczema

Remove potential triggers- **think food first!**
Eczema often starts in the gut- what can you take out that is not needed and put in what is?

IgG/IgE food allergies
Dysbiosis (dysbiotic bacteria, fungal overgrowth, parasites, insufficiency dysbiosis)
MOM AND CHILD ARE ONE

Supplements:
Immunoglobulins (IgG, bovine)
Probiotics (S. boulardii, complex)
Essential fatty acids (high dose)
Optimize Vitamin D

Natural Medicines, 2017

Bacteriology Profile, stool

BACTERIOLOGY CULTURE

Expected/Beneficial flora	Commensal (Imbalanced) flora	Dysbiotic flora
4+ Bacteroides fragilis group	3+ Hemolytic Escherichia coli	3+ Klebsiella oxytoca
4+ Bifidobacterium spp.	1+ Klebsiella pneumoniae ssp pneumoniae	
4+ Escherichia coli		
1+ Lactobacillus spp.		
4+ Enterococcus spp.		
1+ Clostridium spp.		
NG = No Growth		

Urea	1	*
DAIRY & EGG		
Cheddar Cheese	0	
Cottage Cheese	0	
Egg, White	0	
Egg, Yolk	0	
Milk, Cow's	0	
Mozzarella Cheese	0	
Yogurt	0	
BEVERAGES & MISC		
Black Tea	0	
Cocoa	0	
Coffee	0	
Honey	0	
Yeast, Baker's	0	
Yeast, Brewer's	0	

Onion	1	*
Potato	0	
Potato, Sweet	0	
Spinach	0	
Squash	0	
Tomato	0	
LEGUMES & PULSES		
Green Pea	1	*
Lima Bean	1	*
Peanut	1	*
Soybean	0	
NUTS, SEEDS & OILS		
Almond	3	***
Cashew	2	**
Chia Seed	1	*
Cola	0	
Safflower	2	**
Sesame	3	***
Sunflower Seed	2	**
Walnut	3	***

GRAINS & STARCHES		
Barley	1	*
Bran	0	
Corn	0	
Gluten	0	
Malt	0	
Oats	1	*
Rice	0	
Rye	0	
Wheat	0	
HERBS, SPICES, FLAVORINGS		
Basil	0	
Bay Leaf	0	
Black Pepper	0	
Cinnamon	0	
Dill	0	
Ginger	0	
Mustard	1	*
Oregano	0	

Allergic Rhinitis

- N-Acetyl-Cysteine- Natural mucolytic (also
- increases glutathione)
- Bromelain- Reduces inflammation and swelling (found in pineapple stems)
- Quercetin- Stabilizes Mast Cells
- Stinging Nettles- Helps mitigate histamine reaction

Functional considerations:
Poor methylation?
Environmental triggers?
Higher histamine containing foods?
DAO SNPs?

Natural Medicines, 2017

Quercetin

- Quercetin, a dietary bioflavonoid found in foods such as onions, green tea, and berries, has properties of mast cell stabilization for allergic disease
- Quercetin also can offer anti-inflammatory effects due to inhibition of histamines, leukotrienes and prostaglandins.
- Standard dosing includes **100-500mg given QD-TID**. Quercetin has shown clear associations in reducing allergic disease symptoms with little side effects (Ariano, 2015 & Mlcek, 2016).

Chronic Ear Infections (Clinical Practice Guidelines)

- Look for underlying environmental factors and control these
  - Breastfeeding – if BF for > 4 months, reduced risk of developing ear infections for the next 12 months after breast feeding ends
  - Smoking – increases risk 30-40%
  - Allergies or sensitivities
    - **Especially milk**
    - Also consider wheat/gluten, eggs, citrus, soy, corn, peanuts
    - 78% chronic ear infections associated with food allergies
    - 86% children better when they eliminated these foods

- Rosenfeld et al, Otolaryngol Head Neck Surg, 2016

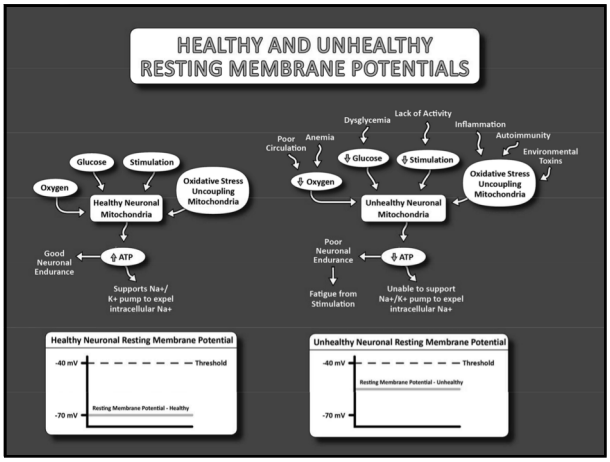
Xylitol

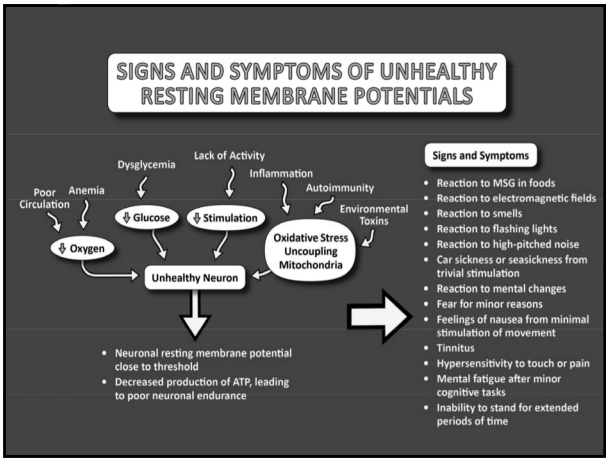
- Natural sugar found in fruits such as strawberries and plums, strongest evidence for integrative treatment of otitis media.
- Mechanism of action is its ability to prevent ***S pneumonia*** from growing or attaching to nasopharyngeal cells (Bukutu, 2008).
- Four RCT's have been conducted in children as young as 7 months of age.
- Studies show that giving up to 9.6 grams/day of Xylitol (via lozenge or chewing gum) can reduce the duration and recurrence of otitis media **up to 41%** (Bukutu, 2008).
- Side effects are rare but include gas and diarrhea when given in large doses.

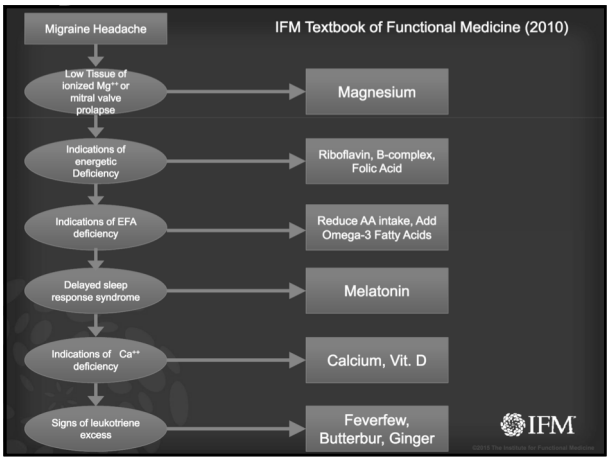
Headaches/Migraines

- Resting membrane potential of the neuron determines HA triggers
- Complex and multifactorial
- Environmental triggers can often be mitigated and decrease the incidence of reoccurrence

Common triggers:
Nutritional deficiencies (riboflavin, B6, B12, folate, EFAs)
Food intolerances and allergies







Hypertension

Risk Factors: Hs CRP (inflammation), genetics, metals (lead, cadmium, arsenic), certain medications (stimulants), SNPs

May worsen:
High fat/salt meals, sleep apnea, PCOS, Type 1, pre eclampsia and malaria

MAGNESIUM-
"Wasters"
Hypermagnesaemia is rare, hypomagnesaemia is more common (loss from gut or kidneys, poor understood)
Glycinate, citrate, threonate

Other considerations:
Garlic, Omega's, Calcium, Coenzyme Q10, Yoga/Meditation
Natural Medicines, 2017 & Swaminathan, 2003

Foods to Avoid in Hypertension

- Sodium (limit to 2,000 mgs-about 1 teaspoon-per day)
- Processed foods (packaged, canned) and frozen meals
- Fast foods
- Soft drinks
- Added sweeteners
- Caffeinated beverages
- Alcohol
- Use of oils in high-heat cooking

Foods to Include in Hypertension

Dietary Patterns
Individual Foods
Bio-Actives

Proteins:
- Soy, (fermented) 30 grams daily: natto, tofu, tempeh, miso
- Hydrolyzed whey (30 grams daily)
- Legumes (vegetable protein)
- Cold water fish: sardines, herring, haddock, salmon or trout
- Foods high in L-arginine: lentils, hazelnuts, walnuts, peanuts
- Mixed nuts (unsalted)
- Cocoa (30 grams dark chocolate per day, or about 1 square of baker's chocolate)

Vegetables and Fruit:
- Blueberries
- Leafy greens high in nitrates
- Seaweed (hijiki and wakame), 3 to 4 grams per day
- Garlic, 1-4 fresh cloves/day
- Mushrooms – ½ cup shitake, maitake
- Celery, 4 stalks/day
- Foods high in lycopene: tomatoes, guava, watermelon, apricots, pink grapefruit, papaya
- Pomegranate juice

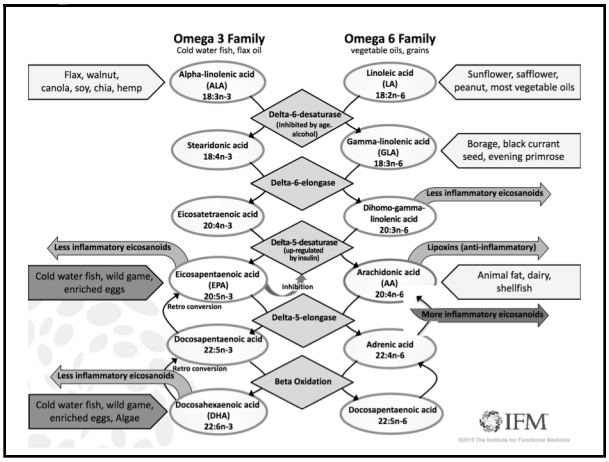
Fats and Oils:
- Olive, flaxseed, and sesame oils

Carbohydrates:
- Increase complex carbohydrates
- Increase high fiber whole grains: oatmeal, oatbran, barley, wheat
- Fiber: psyllium 7gm

IFM

Dyslipidemia

- There are healthy and unhealthy types of cholesterol
- What we eat and and how much sugar and alcohol we ingest plays a critical role
- Cholesterol particle size matters (fractionated lipid panels/Boston Heart)
- Children will often have low total cholesterol and high VLDL
- We want high Omega's (1:1 ratio with Omega3/Omega 6)
- Avoid arachidonic acid by limiting shellfish, dairy, animal fat, and sugar
- Limit sugar (increases Delta-5-desaturase which shifts the omega pathway to inflammatory eicosanoids)
- Fiber is critical for healthy cholesterol balance



Foods to Avoid in Dyslipidemia

Dietary Patterns
Individual Foods
Bio-Actives

- **Sucrose**
- Processed foods
- Fast foods
- Refined carbohydrates
- Trans fats (found in processed foods)
- High saturated fats (e.g., creams, full-fat cheeses, fatty meat)
- Margarine

Foods to Include in Dyslipidemia

- Fish
- Green leafy vegetables
- Low-glycemic index fruits
- Tomatoes
- Extra-virgin olive oil (about 5 TBSP per day)
- Green tea
- Soybeans (e.g., soymilk, tofu, tempeh)
- Dark chocolate
- Pomegranate
- Seeds and nuts (e.g., especially sesame)
- Red wine (check with your healthcare practitioner)
- Garlic (1 to 2 cloves per day)
- Rice bran oil

Summary IFM Dyslipidemia Treatment Recommendations Based on Reported Action

Agent	Dose	Reported Action	↓ HDL	↑ TG	Pattern B	Mod LDL
Trans Resveratrol	250 mg QD	Reduces TC, TG, and LDL; blocks uptake of modified LDL by CD36SR (1)		♥		
N-Acetyl-Cysteine	1000 mg BID	Blocks uptake of modified LDL by CD36SR (1)				♥
Aged Garlic Extract	600-900 mg BID	Reduces CAC and plaque progression and lowers HS-CRP (2,3)				
Niacin (B3) Nicotinic Ac.	500 to 4000 mg QD as tolerated	Reduces TC, LDL, APO-B, TG, and shifts LDL from small type B to large type A (4)	♥	♥	♥	
Red Yeast Rice	2400-4800 mg QD	Statin like effects (5)		♥		
Curcumin	500 mg BID	Inhibits atherosclerosis, increases HDL, anti-inflammatory (6, 7)	♥	♥		
Green Tea/EGCG	500-1000 mf QD or 60oz tea	Inhibits HMG-CoA, reduces oxLDL and APO-B, increases PON-1 and LDL receptor; decreases inflammation decreases body fat. (8, 9)		♥	♥	♥
Plant Sterols	2-3 g QD	Reduces TC and LDL, anti-inflammatory (10, 11)		♥		♥
Pomegranate	8 oz. juice or 1-2 cups of seeds QD	Anti-inflammatory, improves function of HDL, inhibits platelets, reduces IMT (12, 13, 14)	♥	♥		♥
Pantethine	300 mg TID or 450 mg BID	Reduces TC, LDL, APO-B, and TG; increases HDL and APO-A1 (15, 16)	♥	♥	♥	
Probiotics	60-100b organisms QD	Reduce TC, LDL, and TG (17)		♥	♥	
Berberine HCL	500 mg QD	Reduces TC, LDL, and TG (19)		♥	♥	
Omega-3 Fatty Acids	1-5g QD mixed EPA DHA	Reduces TG (18), COX-2 inhibition by DHA, (21), IL-1b inhibition by EPA (22), Increases HDL/HDL2 (23), EPA reduces pattern-B, sdLDL & CRP (24)	♥	♥		♥

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The Omega RX

Vegetarians= 1-2 tbs of ground flax daily (or chia, hemp, walnuts)

EPA/DHA= 3-6 grams daily (<1.5 is not effective, >7 no added benefit)

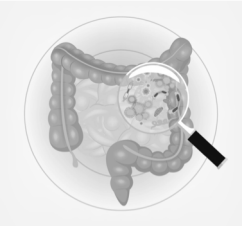
EPA comes from cold water fish, enriched eggs, and wild game

EPA/DHA ratio should be 2:1

Keratosis pilaris
Increase omega 3 essential fatty acids

The Microbiome

- The microflora in our gut weighs 3-5 pounds
- Microbial cells outnumber human cells 10:1 (100 trillion)
- Microbial DNA outweighs our own DNA 100:1



NIH, 2016

Role of the Microbiome

- break down foods
- produce nutrients
- protect against pathogens
- foster healthy immunity (2/3 lymphocytes found in the lining of your gut) **GALT**
- support detoxification (unfriendly bacteria produce neurotoxins)
- modulate the NERVOUS SYSTEM (95% of serotonin is made in your gut)

American Psychological Association, 2016

Psychoemotional Impact on the Microbiome

- **Stress** suppresses Lactobacillus, Bifido-bacteria, & sIgA
- **Catecholamines** stimulate growth of gram-negative organisms *(Yersinia, Pseudomonas)*
  - 45-50% of total body production of norepinephrine occurs in mesenteric organs
- **Anger or fear** increases *Bacteroides fragilis*

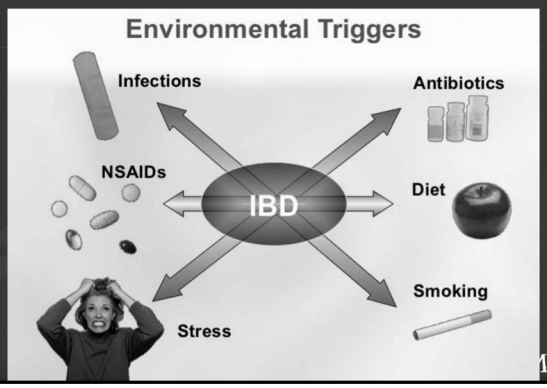
IFM

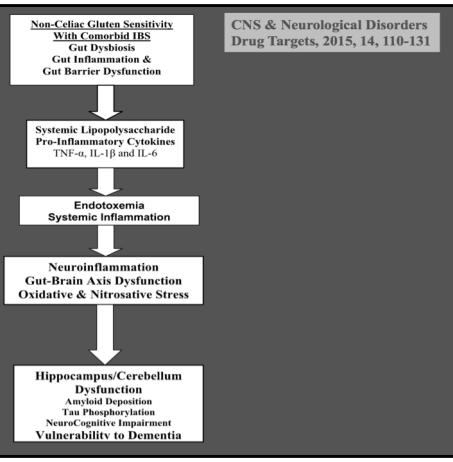
Bailey, M. T., & Coe, C. L. (1999). Maternal separation disrupts the integrity of the intestinal microflora in infant rhesus monkeys. *Developmental Psychobiology*. doi:10.1002/(SICI)1098-2302(199909)35:2<146::AID-DEV7>3.0.CO;2-G

Irritable Bowel Syndrome

- Multifactorial etiology stemming from malabsorption to maldigestion
- Environmental triggers can be identified and removed
- Dysbiotic flora or pathogen (such as harmful bacteria, yeast, or parasite)
- Insufficiency in bile acids, enzymes, HCL
- Anitgenic foods (IgE, IgG allergens)
- Stress; Cortisol increases bacteriodities, decreases lactobacillus and bifido strains

Environmental Triggers and IBD

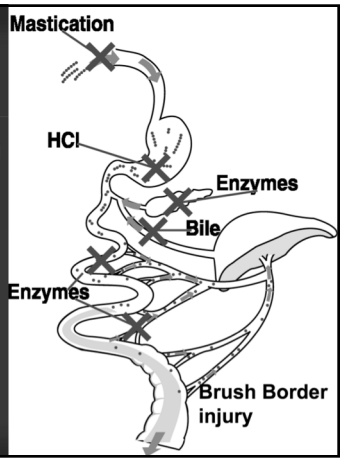




CNS & Neurological Disorders Drug Targets, 2015, 14, 110-131

Impairments in Digestion and Absorption

- Inadequate mastication
- Hypochlorhydria
- Pancreatic insufficiency
- Bile insufficiency
- Brush Boarder Injury



Dysbiosis: Assessment

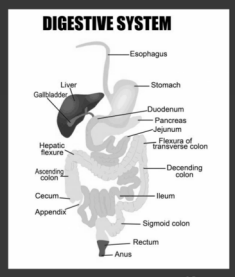
- **Stool Testing** – Culture / PCR / Metabolites
- **Stool EIA Antigen Testing** –
  - *H. pylori, C. difficile*
  - *Entabmoeba histolytica, Giardia, Cryptosporidia*
- **Breath Testing** – SIBO, *H. pylori*
- **EGD with Jejunal aspirates** – fungus, SIBO
- **Urinary Organic Acids** – Arabinitol, Hippuric Acid
- Response to treatment:
  - Objective markers (e.g. ESR, CRP)
  - Subjective tools (e.g. MSQ)

There are Various Types of Elimination Diets

- **Comprehensive** elimination diet
- **Six Food** Elimination Diet (SFED) - *wheat, eggs, dairy products, legumes/peanuts, soy, seafood/fish*
- **Four Food** Elimination Diet (FFED) - *wheat, eggs, dairy products, legumes/peanuts*
- **Simplified** elimination diet (Caveman Diet) – lamb, rice, pear, sweet potato
- **Single Food** group elimination
  - Gluten / Egg / Dairy
- **Sugar**
- **FODMAP**
- **PALEO**

Top Gut Repair Nutrients

- DGL (upper digestive lining)
- Butyrate (colon)
- Probiotics
- Aloe Vera
- Gamma Oryzanol
- Zinc L-Carnosine
- L-Glutamine



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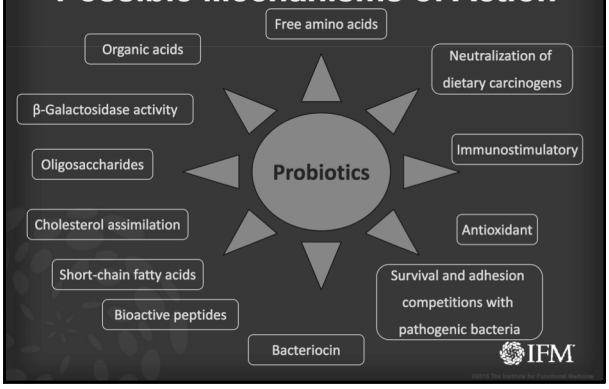
Probiotics: Possible Mechanisms of Action



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Lactobacillus (Probiotic Species)

There are several strains of lactobacillus in our microbiome. While evidence is emerging on what particular strain has what disease implication, there are a few strains that have been documented for specific disease implementation in IBS.

Lactobacillus rhamnosus has been shown to reduce diarrhea by 1-2 days in young children and infants affected with the rotovirus (4369,4377).

Lactobacillus reuteri has also shown similar efficacy with rotovirus (7751).

Lactobacillus casei has shown ability to decrease the duration of diarrhea illness in children (1253).

Bifidobacterium (Probiotic Species)

- Ykult and associates reported bifidobacterium was effective for **constipation**.
- Their study showed 1-100 billion CFUs given daily to children ages 3-16 years increased defecation frequency, improved stool consistency, and decreased abdominal pain.

Saccharomyces Boulardii
(Probiotic Yeast Species)

- The research on Saccharomyces Boulardii is abundant. This probiotic yeast species has shown many beneficial implications for diarrhea.
- It has been shown effective in treating acute diarrhea in children and infants.
- It has shown beneficial in prevention of diarrhea associated with tube feedings and with the use of antibiotics.
- Shown benefit to eradication/reduction of clostridia species

Bovine Immunoglobulins

In study by Maciej, 2017, demonstrated immunoglobulin therapeutic benefit. They studied a sample of 16 of athletes, and after administration of bovine colostrum for three weeks, intestinal permeability was significantly restored (by measuring zonulin concentrations in the stool and lactulose/mannitol ratio in the urine) (Maciej, et al).

Enteragam is a serum derived bovine immunoglobulin/protein isolate packaged as a prescription medical food.

Enteragam has been shown to improve IBS symptoms in children down to 6 months. The mechanism of action is binding microbial components (such as yeast, dysbiotic bacteria, and food antigens), helping the GI tract achieve homeostatic balance, improving tight junction protein expression, and nutrient and water absorption.

Integrative Insomnia Therapies

Melatonin

- Melatonin, produced primarily in the pineal gland, regulates of sleep/wake cycles and annual biological rhythms (van Geijlswijk, 2010 & Kunz, 2004).
- Melatonin (3mg) has been shown to increase sleep latency (sleep onset) in children down to age 7 (Van Maanan, 2017).
- Typical dose is between .5-10mg in children given 30-60 minutes prior to the desired onset of sleep.
- Fast acting, verses extended relief- anecdotal data thus far, clinically useful when fast acting not effective

Melatonin, Cont.

- Children with neurodevelopmental disorders and genetic single nucleotide polymorphisms in their CYP1A2 activity are more likely to have slower metabolism of melatonin and could see additional efficacy for those receiving exogenous supplementation (Bruni, 2017).
- Long term effects and safety of melatonin in children have not been fully established, however it appears to be safe and effective, especially in those with comorbid ADHD (Hoebert, 2009).
- Parents perceive melatonin to be effective in alleviating sleep disturbances and assisting in the restoration of family functioning (Waldron, 2016).

(Barrett, Tracy & Giaroli, 2014 & Natural Standard, 2014)

Applications and Approaches To Chronic Pain Management

Inflammation is at the ROOT of chronic disease

- All foods are either "causing the fire" or "helping to put out the fire"
- S.A.D= Standard American Diet- packaged, processed, convenience NON-foods
- Typical inflammatory foods
  -Gluten, soy, dairy, artificial dyes, SUGAR
- Typical anti-inflammatory foods- fresh fruits, veggies, meat, fish, nuts, & limited non-gluten grains
- Nutrient deficiencies make a patient more susceptible to prolonger recovery and pain

High Glucose Enhances Neurotoxicity and Inflammatory Cytokines

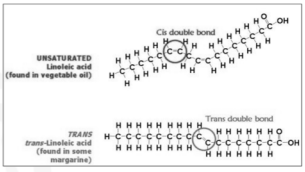
"…hyperglycemia in T2DM may be one of the factors contributing to the observed increased risk of AD by exacerbating astrocyte-mediated neuroinflammation and neuronal injury caused by disease-associated agents."

Bahniwal M, Little JP, Klegeris A. High Glucose Enhances Neurotoxicity and Inflammatory Cytokine Secretion by Stimulated Human Astrocytes. Curr Alzheimer Res. 2017 Jan 16

IFM

Dietary Effects of Trans Fatty Acids

- Average consumption in industrialized countries is 4 –7% of total dietary fat.
- **TFA have been shown to raise markers of systemic inflammation.**



- Mozaffarian D, Pischon T, Hankinson SE, et al: Dietary intake of trans fatty acids and systemic inflammation in women. *Am J Clin Nutr* 2004; 79:606-612.
- Mozafarrian D, Rimm EB, King IB, et al: Trans fatty acids and systemic inflammation in heart failure. *Am J Clin Nutr* 2004; 80:1521-1525.

IFM

Long Term Intake of Dietary Antioxidants Lowers Inflammation

A dietary pattern with high vegetables and vegetable oils, leading to high intakes of antioxidant micronutrients and essential fatty acids, **was significantly and negatively associated with risk of elevated CRP**.

Julia C, Meunier N, Touvier M, et al. Dietary patterns and risk of elevated C-reactive protein concentrations 12 years later. *British Journal of Nutrition*. 2013;110(04):747-754.

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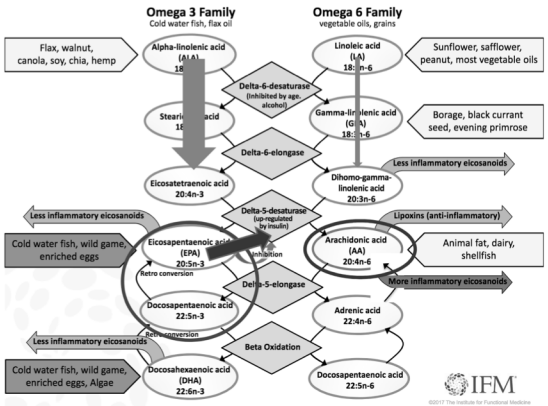
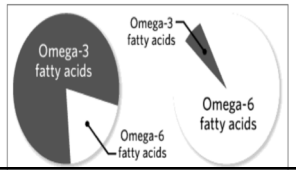


- A ratio of 4/1 was associated with a 70% decrease in total mortality in a CVD secondary prevention trial.
- A ratio of 2.5/1 reduced rectal cell proliferation in patients with colorectal cancer, but not 4/1.
- A ratio of 2-3/1 suppressed inflammation in patients with rheumatoid arthritis.
- A ratio of 5/1 had a beneficial effect on patients with asthma.
- **Optimal ratio may vary with the disease, but overall ratio of 4-5/1 seems reasonable goal.**



Summary: The Omega 3 Rx for Inflammatory Disease - Vegetarians

DHA:
- **Algae: main vegetarian source** DHA
  - A few brands contain low EPA.

EPA:
- **Use ALA as oil if being used to produce EPA**
  - 5-10% ALA converts to EPA
- **If using seeds, Chia may be more efficiently converted** to EPA than flax
- **DHA supplementation** will retroconvert to EPA (~12%)

Lab monitoring recommended – blood spot fatty acids

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Summary: The Omega 3 Rx for Inflammatory Disease

- **ALA as ground flax: 1-2 TBS/day** (~5g ALA/d)
- **EPA/DHA: 3-6 grams per day**
- Generally speaking-
  - Greater than ~7 grams, no improved efficacy
  - Less than ~1.5 grams, not effective
- **Ratio EPA/DHA: ~1.5:1** (EPA usually higher)

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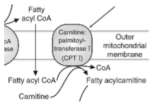
Acetyl L-Carnitine



- Amino acid that shuttles fatty acids into the mitochondria before oxidation
- Acetyl-L-carnitine is thought to slow neuronal degeneration and decrease excessive neural excitability and firing.
- Used in children for a variety of reasons; ADHD, ASD, Fatigue. Typical dosing rages from 750-1,500mg/day
- Taking acetyl-L-carnitine 1000 mg two or three times daily significantly reduces pain related to diabetic neuropathy.
- RX version is Carnitor (comes in liquid and tablets).

Pop-Busui et al. & Quatraro et al.

Curcumin/Turmeric

- Curcumin is the active ingredient in turmeric.
- The powerful antioxidant effects of turmeric have been found sufficient to reduce the action of oxidative stress on the BDNF system, synaptic plasticity, and cognitive function.
- Synergistic effects with essential fatty acids

Turmeric

- Turmeric contains active polyphenols called **curcuminoids** that have over 100 different molecular targets; they have been shown to **modify genomic, epigenetic, and cell-signaling pathways**
- Anti-inflammatory Mechanisms
  - Downregulation of **NFkB**
  - Downregulation of **COX**
  - Downregulation of **LOX**
  - Inhibition of **iNOS**
  - Inhibition of **matrix metalloproteinases**
  - Inhibited production of pro-inflammatory **cytokines**: *TNFalpha Interleukins 1, 2, 6, 8, 12, and Chemokines*
  - **Upregulation of Nrf2 (anti-inflammatory signaling pathway)**

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Turmeric

- Typical oral dose **750 to 1500 mg/day**
- Product should be standardized to curcuminoids (90-95%)
- Curcuminoids are **exceedingly safe and nontoxic**, even at very high concentrations. Doses exceeding 2.5 g/kg fed to rats, guinea pigs, and monkeys confer no evidence of harm or genetic damage.

Supplement Facts
Serving Size: 1 Capsule
Servings Per Container: 60

	Amount Per Serving	% DV
Turmeric *(Curcuma longa)* (root)	450 mg	†
Turmeric Extract *(Curcuma longa)* (root) (Standardized to contain 95% Curcuminoids)	50 mg	†

† % Daily Value (DV) not established.

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Magnesium

- Plays an essential role in more 300 cellular reactions.
- Extracellular magnesium is critical to both maintaining nerve and muscle electrical potentials and transmitting impulses across neuromuscular junctions.
- Magnesium has been shown to have neuroprotective effects, preventing post-hypoxic brain injury by blocking the excess release of glutamate in the calcium channel.

Symptoms of Magnesium Deficiency

- **Skeletal muscle**: twitches, cramps, muscle tension, muscle soreness, headaches and jaw joint (or TMJ) dysfunction.
- **Respiratory**: chest tightness, a peculiar sensation that one can't take a deep breath; sighing a lot.
- **Smooth muscles:** constipation; urinary spasms; menstrual cramps; difficulty swallowing, a lump in the throat, photophobia, loud noise sensitivity from stapedius muscle tension in the ear.
- **Central nervous system:** insomnia, anxiety, hyperactivity, restlessness with constant movement, panic attacks, agoraphobia, and premenstrual irritability. **Peripheral nervous system:** numbness, tingling, other abnormal sensations - zips, zaps and vibratory sensations.

Baker, S.M. Magnesium Deficiency in Primary Care and Preventive Medicine, *Magnesium and Trace Elements*, 1991-1992; 10:251-262

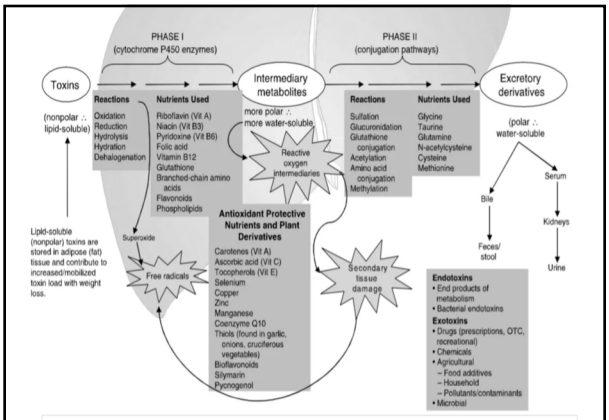
- Dietary sources of magnesium include legumes, whole grains, vegetables (especially broccoli, squash, and green leafy vegetables), seeds, and nuts (especially almonds).

- Picky eaters are at risk for deficiency.
- Multiple different salt forms: ***magnesium threonate*** found enhance memory and learning.
- Dosing studied with headaches 300-3625 mg divided twice daily (>8 years).
- Epsom salts (mg sulfate) baths alternative to oral administration.

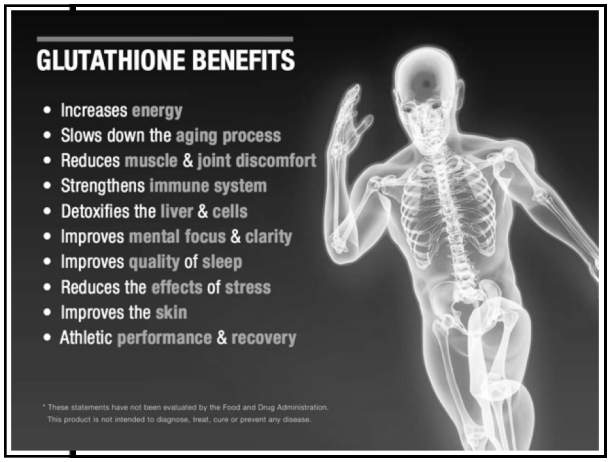
Neuron 65, 165–177, January 28, 2010

Glutathione

- Most powerful anti-oxidant in our body
- Helps to prevent damage to cells caused by reactive oxygen species
- 65x more potent than Vitamin C
- Helps detoxify drugs (phase 2 detox)
- Liver protective



Liver detoxification pathways and supportive nutrients



Glucosamine Sulfate and Chondroitin Sulfate

- Glucosamine is believed to work by retaining fluid in the joint. Chondroitin is thought to increase the viscosity of the synovial fluid.
- Over 20 clinical studies, lasting up to 3 years and enrolling over 2500 patients, have been conducted evaluating glucosamine for osteoarthritis. The vast majority of these studies evaluated glucosamine SULFATE for osteoarthritis of the knee. Overall, when the findings of these studies are pooled, glucosamine appears to reduce pain scores by 28% to 41%, and to improve functionality scores by 21% to 46%.
- **Typical dose 300-500mg/day**

Poolsup, et al.

S- Adenosylmethionine (*SAMe*)

- Major amino acid methyl donor in the body in variety of reactions in the body.
- It contributes to the synthesis, activation, and/or metabolism of hormones, neurotransmitters, nucleic acids, proteins, phospholipids, and some drugs.
- The strongest evidence supports is use in depression, osteoarthritis, and fibromyalgia.
- Typical doses range from 200-400mg QD-BID

Vetter & Maccagno, et al.

Surgical Contraindications

- Essential fatty acids- >3 grams/day has antiplatelet effects
- CBD inhibits CYP2D6 pathway- caution for increased serum concentrations of pain and seizure meds

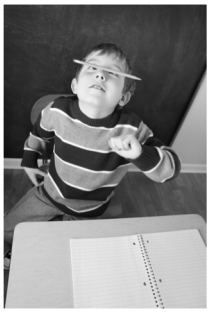
AAP does not endorse CBD at this time; future promise for pain?

Chronic neurological & neurodevelopmental disorders through a functional and integrative lens

ADHD

Allopathic Treatment

- Stimulant psychotropics
- Non stimulant psychotropics



ADHD

Integrative Therapies

- Omega 3 Fatty Acids

Essential omega 3 fatty acids; fish oil contains both docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA) No published RDA; Studies in children for ADHD support higher ratio of EPA to DHA (558/174).

- Zinc- 34-40mg max QD
- Vitamin B6- careful with toxicity, P5P (>200mg day)
- Magnesium (glycinate preferable salt form unless constipation a concern) (Richardson & Montgomery, 2005 & Mousain-Bosc, et. al, 2007)

Phosphatidylserine (PS)

- Natural phospholipid in the brain that appears to increase levels of acetylcholine, norepinephrine, serotonin, and dopamine.
- Children ages 4-14 were given 200mg of PS for 2 months and had significant improvement in their symptoms of ADHD (Hirayama, 2014).
- Another study by Manor and associates in 2012 showed another significant improvement when giving 150mg of PS with 60 of omegas daily for 15 weeks (Manor, 2012).
- The product studied was the medical food, Vayarin, which is available by prescription only. PS can also be accessed without a prescription from natural product dispensaries and could be a more affordable option for the family if insurance will not cover Vayarin.

Methyl Folate (L-5MTHF)

- Children with genetic mutations (MTHFR 677T, 1298C) in their folate genes have been shown in preliminary studies to have association with ADHD behaviors (Saha, 2014).
- Folate is a key precursor in serotonin and dopamine synthesis.
- Lower folate status in pregnant women may also be associated with a greater likelihood of hyperactivity in childhood (Scholtz, 2010).
- Dosages to consider are between **1-5mg QD-BID** for repletion and support of ADHD symptoms.
- Methyl folate and folic acid are NOT the same thing

5-Methyltetrahydrofolate

Active Folic Acid

Function-

- DNA repair and synthesis
- Production of neurotransmitters
- Role in conversion of homocysteine into methionine in the synthesis of S-adenosylmethionine (SAMe)

Deficiency-

- Megaloblastic anemia, neural tube defects, mood disorders, impaired growth, cerebral folate deficiency

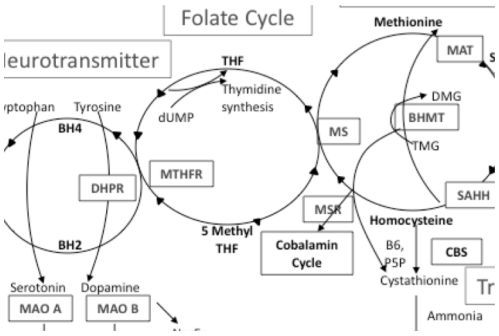
Endres, M. et. al, (2004) Ramaekers, V., Sequeira, J., & Quadros, E. (2013)

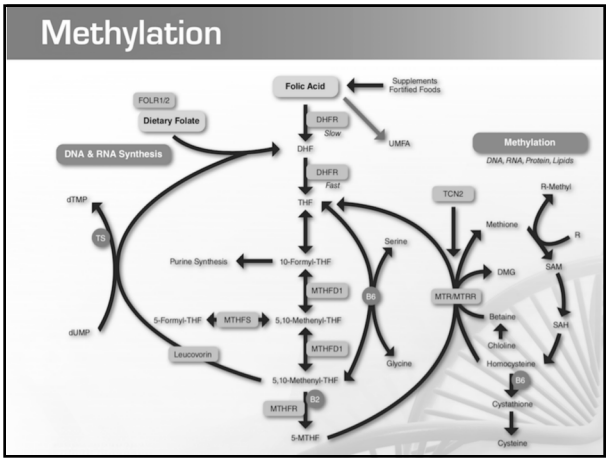
Your genes load the gun but the environment pulls the trigger.

Methylenetetrahydrofolate Reductase (MTHFR)

- Decreased production of MTHFR leading to decreased conversion of folate to methyl folate
- Risks include depression, autism, decrease in dopamine (ADHD), norepinephrine, serotonin synthesis

Stahl, S. (2008)
Yi-Le Wu, et. al, (2013) &





MTHFR C677T

- Helps convert homocysteine into methionine
- Global effects for immune function, muscle metabolism, neurochemical production, regulation, & detoxification
- Has been linked to increase risk for cardiovascular disease, stroke, & blood clots due to rise in homocysteine levels
- Necessary to supplement with L-methyl folate: 2-15mg QD-BID depending on age

MTHFR A1298C

- Helps to pull homocysteine into the cycle and keep levels within a healthy range
- No link to increased coronary artery disease, stroke, and blood clots
- If heterozygous- 10% reduction in folic acid break down, if homozygous- 30% reduction

Gilbody, S., Lewis, S., & Lightfoot, T. (2006)

Methylation SNP
GIF

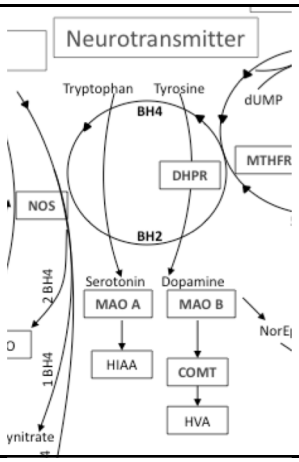
- ***Gastric Intrinsic Factor (GIF)***
  - Hetero / Homo = **decreased activity (1% / 10%)**
  - Produced in stomach
  - Required for B12 absorption in the small intestines
  - Typically causes low B12 and high homocysteine in plasma
  - **Treatment: Methyl-B12, Hydroxo-B12**

Anesthesia, Mitochondrial Function, Neurodevelopmental Delays

- Baum VC. (2007).When Nitrous oxide is no laughing matter: Nitrous oxide and pediatric anesthesia. *Pediatric Anesthesia*, 17;9:82
- Kalikiri PC, Sachan R. (2004). Nitrous Oxide Induced Elevations of Plasma Homocysteine and Methylmalonic Acid Levels and Their Implications. *The Internet Journal of Anesthesiology*, 8;2
- Selzer RR , Rosenblatt DS, Laxova R, Hogan K. (2003) Adverse Effects of Nitrous Oxide in a Child with 5, 10-Methylenetetrahydrofolate Reductase Deficiency. *New England Journal of Medicine* 349;1:45-50

"Today's bipolar and depressed patient, is tomorrow's single nucleotide polymorphism"

Robert Rountree, MD, IFM
2015 Linus Pauling Award Winner



rsID	Gene	Genetic Result	Therapeutics Associated With Positive Result
rs4680	COMT V158M	+/-	Taurine, Choline, Trimethylglycine (TMG), Dimethylglycine (DMG), Methionine, SAMe, Inositol
rs4633	COMT H62H	+/-	
rs769407	GAD1	-/-	Prescription Amantadine, Ketamine, Glycine, N-Acetyl-Cysteine (NAC), Beta Phenyl GABA, Zinc, Magnesium, Oxaloacetate, Elderberry, L-Theanine, Melatonin
s3828275	GAD1	+/+	
rs6323	MAO-A	+/-	B2 (Riboflavin), Methyl Donors (Taurine, Choline, Trimethylglycine (TMG), Dimethylglycine (DMG), Inositol, Methionine
s1799836	MAO-B	-/-	B2 (Riboflavin), Methyl Donors (Taurine, Choline, Trimethylglycine (TMG), Dimethylglycine (DMG), Inositol, L-Methionine
rs6313	HTR2	+/-	5-HTP (Hydroxytryptophan)
s1042173	SLC6A4	-/-	

COMT V158M +/+

- The met/met version of the enzyme is *slower* than normal leading to higher dopamine levels due to reduced breakdown.
- Signs include wakefulness, alertness, cognitive performance, and restlessness.
- Necessary cofactors to support COMT Met/Met include methyl folate & magnesium

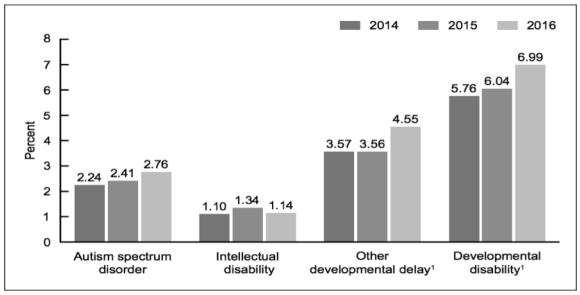
Frank, M. J., & Fossella, J. A. (2011) & Cools, R., & D'Esposito, M. (2011)

Neurotransmitter SNP
GAD 1

- ***Glutamic Acid Decarboxylase (GAD1)***
  - Hetero / Homo = **Decreased function**
  - Converts Glutamic Acid to GABA
    - Pyridoxal-5-phosphate (B6) cofactor
  - Decrease levels of GABA create:
    - Dysphoria
    - Anxiety
    - "Half Glass Empty" syndrome
    - Sleep Disorders
    - Spasticity
    - Low Libido
  - **Treatment: Glycine, Zinc, Magnesium, GABA, B6**

The prevalence of children diagnosed with any developmental disability increased from 2014 to 2016.

Figure 1. Prevalence of children aged 3–17 years ever diagnosed with selected developmental disabilites, by year: United States, 2014–2016



[1]Linear increase from 2014 to 2016 is statistically significant ($p < 0.05$).
NOTES: Developmental disability includes autism spectrum disorder, intellectual disability, and any other developmental delay.
Access data table for Figure 1 at: https://www.cdc.gov/nchs/data/databriefs/db291_table.pdf#1.
SOURCE: NCHS, National Health Interview Survey, 2014–2016.

Psych meds for toddlers?

Several common ADHD medications are now FDA approved for ages ***3 and above***.

Dirty Drugs

- Pharmaceuticals can save lives, but they often come with a ***high price***
- **Organ Damage**
- **Secondary chronic diseases**
- **Microbiome disruption**
- **Nutrient depletions**
- **Death**

Its more than you think…

Food is information-
Build and repairs DNA, detoxification, hormones, metabolism, controls or creates inflammation, and so on…

When our bodies don't receive *the right information* (nutritional deficiencies) this leads to chronic disease. Our environment and **our genes** play a role.

Depression/Anxiety

Be curious about SNPs, in particular, MTHFR and COMT.
Medical food RXs:
Deplin, Enlyte, XaQuil

Supplements for depression:
Methyl folate, B12, B6, omegas, 5HTP
Supplements for anxiety:
Methyl folate, phenibut (activated GABA), inositol, glycine, magnesium (l-threonate)

Look for nutrient cofactor deficiencies:
EFAs, zinc, B6, B12, homocysteine, folate (>20 does not mean cellular utility or repletion is not needed).

Autism Spectrum Disorder Targeted Approach

- Immunity
- Nutrition
- Toxicity
- Microbiome/GI
- Mitochondria
- Brain Training

ALL SYSTEMS HAVE GENETIC INFLUENCES!

Functional medicine treats ASD as a physiological disorder, not a behavioral one.

ASD Continued…

What to rule **OUT**:

- Do they have something else that looks like ASD, but is not?
- Seizures
- Genetic pathology
- Toxic overload
- IBS/Gut pathology (yeast, dysbiosis, etc)

What to rule **IN:**

- Do they have the right nutrient/methylation support?
- Do they have the right inflammatory support?
- Right mito support?
- Right gut support?
- Right detox support?
- Do they have the right therapy/social support?

Common deficiencies in ASD:

Methylation Support (b12, methyl folate, B6, riboflavin)
Mitochondrial support- carnitine, CoQ10
Essential Fatty Acids
Micro and macro nutrients

Common imbalances in ASD:

Dysbiosis
Allergies
Mitochondrial myopathies
Higher toxic burdens
Poor detoxification
SNPs
Seizures

Herbert & Anderson, 2008

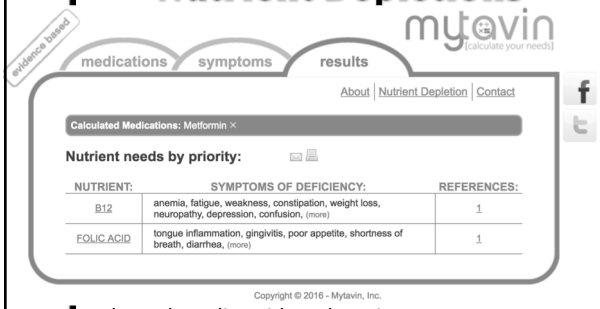
NHP Management Principles

1. **Ask about NHPs**
2. **Have knowledge about NHPs**
3. **Be able to direct patients to reliable NHP sources**
4. **Have reliable sources to assess for potential drug-herb interactions**
5. **Monitor responses to NHPs**
6. **Recognize limitations**

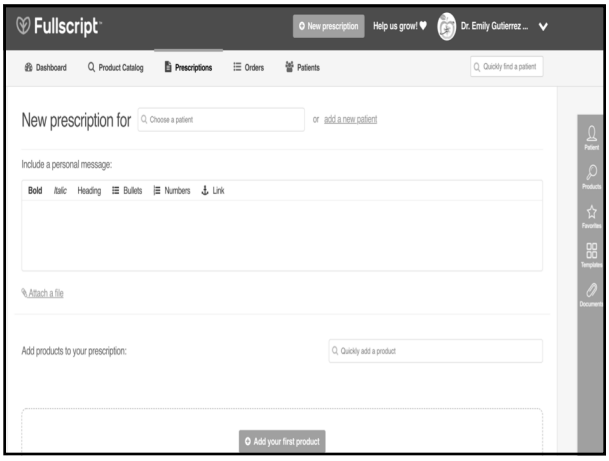
Clinician Management Databases

- Natural Medicines Database-**Gold Standard**
  - **Includes drug/herb interaction checker**
  - **Includes nutrient depletion checker**
- Institute of Functional Medicine
- Medical Academy of Pediatric Special Needs
- National Center for Complementary and Alternative Medicine (NCCAM)
- National Institute of Health's Office of Dietary Supplements (NIHODS)

Nutrient Depletions



- Psych Meds- Folic Acid, Melatonin
- Metformin- B12, Folic Acid
- Statin Drugs- CoEnzyme Q10, Essential Fatty Acids, Zinc, Selenium



All NHPs are *not* created equal

- **Contamination**
  Unidentified herbs, pesticides, metals, and prescription medicines
- **Serving Sizes**
  Absent, ambiguous, or exceed RDA's
- **Numerous Ingredients**
  Synergistic effects with herbs or Rx's

(American Society of Health Pharmacists, 2004)

Dietary Supplements = Food products

"intended to supplement the usual food and drink of man"

(FDA, 2013)

Good Manufacturing Practice Law

- *Poor Compliance*
- *Poor Clinician Confidence*
- *Look for Certification*

(Fabricant, 2013)

Third Party Product Evaluators

- NIH Dietary Supplement Label Database
- National Sanitation Foundation
- Consumerlab.com
- US Pharmacopeia

EXPAND YOUR TOOLBOX!

Provider Dispensary
Pharmaceutical Grade Supplement Companies
Functional Lab Companies
Compounding Pharmacies
Educational Resources
(in Q& A I can provide a list)

Created by NIH/FDA with the purpose of developing greater homogenization in adverse event reporting with medications, foods, and products.

https://www.safetyreporting.hhs.gov/

(FDA, 2014)

Case Study #1

Patient W.G. with ADHD (plus anxiety and depression)
Parents want to manage without RX meds
Genetics, Labs
Findings: anemic, low D, low B12, high homocysteine, low zinc
MTHFR 677T +/+, VDR +/-, COMT +/+
Compounded liquid nutritional supplement (BID dosing): Total daily dose=
10mg methyl folate, 2mg methyl B12, 25mg zinc, 5,000IU D
6 weeks F/U: mood improved dramatically
12 week F/U: sustained attention in the classroom

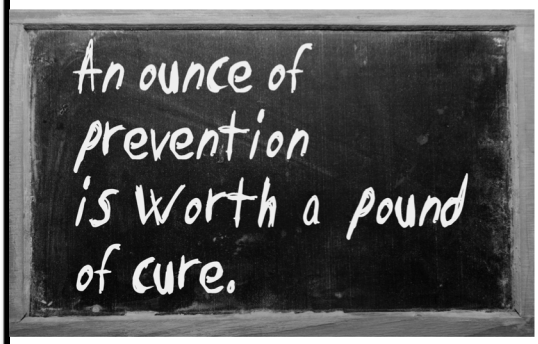
Case Study #2

Patient with IBS and eczema
Ruled out with GI- considered "functional"
S.A.D diet
Stooling accidents, frequent SA
Elimination diet- 4 food (gluten, dairy, soy, nuts)
Labs: Comprehensive Stool Study with Parisitology
Findings: no lactobacillus, moderate candida, high lysozyme, many fats
Treatment: Digestive enzymes (lipase), slowed eating, Nystatin, high dose lactobacillus supplement,
RTC: 6 weeks later no accidents, sleeping better than he ever has, eczema cleared, SA gone

Time for personal/patient clinical questions?

Summary

- Compelling evidence-based science supports integrative/functional medical care for multiple conditions
- Pharmacovigilence of NHPs in the US creates management barriers
- Providers should infuse NHP management principles into decision making when providing patient guidance
- Follow up should be timely, risks/benefits of modalities should be weighed, and informed consent obtained



-Benjamin Franklin-

Questions?

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Authors	Year Published	Nutrient Studied (with dosages)	Study Type and/or Duration of Therapy	Findings	Strength	Quality
Mousain-Bose, et al.	2006	Mg (6mg/kg/day) B6 (.6/mg/kg/day)	8 weeks for therapeutic effect	Mg-B6 regimen in ADHD children decreased symptoms	Level 2	B
Mousain-Bose, et al.	2004	Magnesium/B6 (6mg/kg/day)	8 weeks for therapeutic effect	Improvement in ADHD symptoms	Level 2	B
Mahmoud, et al.	2011	Nutrient levels of zinc, ferritin, magnesium, & copper were evaluated	N/A	Mg, zinc, and ferritin are lower in children with ADHD	Level 3	A

Arnold & DiSilvestro	2005	Zinc	Systematic Review	Zinc levels are typically lower in ADHD children. Zinc may be an effective adjunct treatment to stimulants for ADHD or as a mono therapy. More research is needed.	Level 1	A
Ghanizadeh & Berk	2013	Zinc	Systematic Review	There is a lack of clear evidence to support zinc as a mono or adjunct therapy for ADHD	Level 1	A

Belanger, et al.	2009	1 tab contained; EPA= 250mg DHA=100mg PL= 25mg Vit E=3.75U 16-25kg=2 tabs 26-35kg=3tabs	Double blind, one-way crossover RCT; 16 weeks with 8 week cross-over	Statistical significance was found with improvement in ADHD sx	Level 1	A
Bloch & Qawasmi	2011	Omega 3 Fatty Acids	Systematic Review and Meta-Analysis	Omega 3 fatty acids have statistically significant improvement in control of ADHD sx	Level 1	A
Milte, et al.	2013	Group 1= 1109mg EPA, 108mg DHA Group 2= 264mg EPA, 1032mg DHA	RCT with 3-way cross over; 4 months for each supplementation period, 12 months total	Both DHA and EPA may be beneficial for those with ADHD and comorbid learning disabilities	Level 1	A

Richardson & Montgomery	2005	558 EPA 174 DHA Omega 6= 60mg Vitamin E 9.6mg	RCT with supplement duration of 3 months with a 3 month crossover; total 6 months	Fatty acid supplementation may be beneficial for improvement in learning and attention	Level 1	A
Vaisman, et al.	2008	Group 1; EPA= 153mg DHA= 96mg PS= 300mg Group 2; EPA= 153mg DHA= 96mg Group 3; placebo group	Randomized double blind placebo controlled trial; 3 month duration	Improvement seen with attention in Groups 1 & 2 (greater in group 1)	Level 1	B
Fresham, et al.	2010	Micronutrients& omega 3 supplementation	Literature Review	Micronutrients and omega-3's positively influence cognition	Level 4?	A

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