Allergies

• Magnesium
  – Benefit seen in a one month RCT of 28 patients administered either placebo or 365 mg/day of magnesium as magnesium pidolate (*Magnes Res.* 1990. 3. 109-112).
  – Benefit seen in a 4 month RCT of 55 patients administered either placebo or magnesium 365 mg/day as magnesium aspartate hydrochloride (*Magnes Res.* 1996. 9. 81).
  – Theoretical mechanism of action – supplementation reduces allergic reactivity.

• Natural D-Hist
  – Brand name product which contains quercitin, stinging nettle leaf, NAC, vitamin C, and bromelain.
  – Many anecdotes of benefit.
Allergies (cont.)

• Quercitin (a bioflavonoid), 250-500 mg twice a day between meals as a preventative, starting 2 months before allergy season.
  – Inhibits histamine and cytokine release from mast cells and basophils.
  – Bromelain (250-500 mg twice a day) administered with quercitin may enhance absorption of quercitin
  – Enzymatically modified isoquercitin (EMIQ) – 100 mg daily, starting 4 weeks prior to pollen release shown beneficial in two small RCTs (Int Arch Allergy Immunol. 2009. 149. 359-368; Allergol Int. 2009. 58. 373-382).
  – WARNING – increases plasma levels of fexofenadine and may increase bioavailability of many additional drugs
Allergies (cont.)

- **Vitamin C** 200-2000 mg/day
  - No RCTs published as of 2008.
  - Theoretical mechanism of action – prevents the release or blocks the action of histamine.
Allergies (cont.)


• Allergy elimination diet – Dr Alan Gaby cites 14 published studies, dating back to 1930, which showed that anywhere from 25-91% of individuals with allergic rhinitis improve on an allergy elimination diet (Gaby, Alan. *Natural Treatments for Allergic Rhinitis*. *IMCJ*. 2008. 7[4]. 36-41).
Anxiety

- 5-HTP 200 mg/day for panic attacks
  - BEWARE if evening cortisol level is high, 5-HTP at bedtime can cause/worsen insomnia.


- Chamomile – reduced total HAM-A scores at 8 weeks in a RCT of 57 patients. Active treatment group dosed at one capsule daily of a standardized extract (1.2% apigenin) for 2 weeks, then two capsules daily, with dose increased if necessary up to 5 capsules daily. The difference in HAM-A scores in active treatment versus placebo was both clinically and statistically (p=0.047) significant (*J Clin Psychopharmacol.* 2009. 29. 378-382).
Anxiety (cont.)

• GABA 500-1000 mg bid on an empty stomach, or GABA tea.
  - GABA supposedly does not cross the BBB, but practitioners such as Aileen Burford-Mason, Phyllis Bronson PhD, and Hyla Cass, MD have observed significant benefit with oral supplementation.
  - Benefit in humans observed (Biofactors. 2006. 26. 201-208).

• Inositol
  - Sugar alcohol located primarily in cell membranes, hypothesized to act via the intracellular phosphatidyl inositol second messenger cycle, serving as a second messenger for 5-HT-2 receptors (Natural Medications for Psychiatric Disorders. 2002. Pgs 110 and 115).
  - James Greenblatt, MD recommends starting with ½ teaspoon (1.4 grams) tid and slowly titrating dose up, as rapid dose titration sometimes associated with GI discomfort.
  - **BEWARE** those with low histamine levels may get worse.
Anxiety (cont.)

• Iron if iron deficient – in a 3 month open label study of 207 women, significant improvements were seen in the Beck Anxiety Inventory and the Female Sexual Function Index (*J Sex Med.* 2014. 11. 1042-1046).

• Kava kava – 60-75 mg kavalactones tid (products are usually standardized to 30% kavalactones).
  - Concerns regarding liver toxicity – use of aqueous extract (as opposed to ethanol extract) and use of root (rather than stem) minimizes the risk.
Anxiety (cont.)

- Lavender essential oil
  - Potentiates expression of GABA-A receptors
  - Beneficial in a 10 week placebo-controlled RCT of 221 adults at 27 general and psychiatric practices, at a dose of an 80 mg softgel daily. HAM-A decreased a mean of 16 points in the treatment group, compared with 9.5 points in placebo group. 76.9% of treatment group were responders, compared with 49.1% in placebo group (p<0.001), and 60.6% of treatment group entered remission, compared with 42.6% remitters in placebo group (p=0.009) [Int Clin Psychopharmacol. 2010. 25. 277-287].
  - Beneficial in a phase III RCT of 77 subjects randomized to lorazepam versus a standardized extract (Silexin, WS® 1265, 80 mg daily. Response rate 52.5% and remission rate 40% in lavender group versus 40.5% and 27% in lorazepam group (Phytomedicine Int J Phytotherapy Phytopharmacol. 2010. 17. 94-99).
  - Beneficial in a multi-center trial, 10 week, four arm trial of 539 patients, comparing Lavela WS 1265™ 160 mg and 80 mg with conventional treatment and with placebo. The product was standardized to contain approximately 70% of linalool and linalyl acetate. The HAM-A total score decreased by 14.1±9.3 in the 160 mg group, 12.8±8.6 in the 80 mg group, 11.3±8.0 and 9.5±9.0 for the conventional and placebo group respectively (Kasper S, Gastpar M, Müller WE, et al. Int J Neuropsychopharmacol. 2014 Jun;17(6):859-69).
Anxiety (cont.)

• Omega 3 fatty acids
  - A 12 week RCT of 68 medical students showed that those who received 2085 mg EPA + 348 mg DHA daily had a 20% reduction in anxiety symptoms (and a 14% decrease in IL-6, a marker of inflammation) [Kiecolt-Glaser et al. *Brain Behav Immun.* Epub 7/19/11].

• Passion flower – 100-200 mg bid or tid, or 3-8 grams of leaf as a tea.
  - Exhibited an anxiolytic effect similar to oxazepam in a double-blind trial in 36 patients with GAD. There was no placebo group in this trial (*J Clin Pharm Ther.* 2001. 26. 363-367).
Anxiety (cont.)

• Rhodiola (roseroot)
  – Beneficial for stress related fatigue at 576 mg/day (4 tabs/day), based on a 28 day RCT in 60 individuals (Nordic J Psychiatry. 2007. 61. 343-348).
  – Swedish extract, SHR-5, is most commonly recommended. Most extracts have 3% rosavin and 1% salidroside.

• Taurine 500-1000 mg bid empty stomach – anecdotes (Optimum Nutrition for the Mind).
Anxiety (cont.)

- Theanine 100-200 mg as needed, up to 400 mg bid or 200 mg qid
  - Data is based on two small studies in healthy individuals in which alpha brain wave activity was increased 30-40 minutes after taking L-theanine (Altern Med Review. 2005. 10. 136-138).
  - Mechanism of action – glutamate receptor antagonist.

- Valerian 1-3 grams of dried root, 400 mg of aqueous extract of dried root by capsule, or one teaspoonful of tincture.
  - Many anecdotes; very limited published data.
Anxiety (cont.)


- Meditation - Cochrane review concluded evidence insufficient (Cochrane Database Syst Rev. 2006. CD004998).

Asthma

- Antioxidants - 120 mg per day of Q gel® along with 400 mg of alpha tocopherol (vitamin E) and 250 mg of vitamin C reduced the amount of steroid medications required to keep asthma under control in a study in 41 patients (Biofactors. 2005. 25. 235-240).

- ASHMI (Phytocort®)
  - 3 herbs in combination, derived from a traditional 14-herb Chinese remedy.
  - Symptom improvement benefit comparable to that with steroids, based on results of a 4 week RCT in 91 subjects comparing 12 ASHMI capsules per day, each containing 0.3 mg of dried aqueous extract with 20 mg of prednisone daily. The total daily dosage of the 3 herbs in this study was 20 g of raw Ling-Zhi, 9 g of Ku-Shen, and 3 g of Gan-Cao. Based on measurements of serum cortisol at the end of the trial, adrenal function appeared improved in the herbal group (J Allergy Clin Immunol. 2005. 116. 517-524).
Asthma (cont.)

- Boswellia with 30-65% boswellic acids, 100-400 mg daily. In a 6 week RCT in 80 patients with chronic stable asthma, significant benefit seen in symptoms and FEV1 (Eur J Med Res. 1998. 3. 511-514).

- Carnitine – in a 6 month RCT of 50 Egyptian children with moderate, persistent asthma, those administered 1050 mg of L-carnitine daily showed significant improvements in pulmonary function (FEV1) and overall asthma control (score on Childhood Asthma Control Test). Mechanism of action is unknown (Al-Biltagi M et al. J Allergy [Cairo]. 2012. 2012. 509730).

- Magnesium 250-500 mg daily. Published data is mixed.
  - Low serum magnesium is associated with exacerbations of chronic asthma (Eur Resp J. 2000. 16. 427-431).
  - Higher oral magnesium intake is correlated with fewer asthma symptoms (Lancet. 1994; 344:357-362; Eur Respir J. 1997; 10:2225-2229).
  - May inhibit NMDA glutamate receptors in the bronchus.
Asthma (cont.)

- Omega 3 fatty acids - most likely mediate the late-phase reaction of asthma (in contrast to the acute inflammatory response).
  - A Cochrane review concludes there is not conclusive evidence to support supplementation (Cochrane Database Syst Rev. 2002. CD001283).
  - A crossover RCT of EFA supplementation in 16 patients with exercise-induced asthma found that PFTs improved in the treatment group, bronchodilator use decreased, and there was a reduced concentration of inflammatory mediators in the sputum (Chest. 2006. 129. 39-49).
  - An intriguing RCT in 553 pregnant women administered either omega 3 fatty acids 2.7 grams per day or olive oil (placebo) from week 30 of pregnancy until delivery showed a statistically significant 63% reduction (p=0.03) in asthma in their offspring at 16 years of age (Am J Clin Nutr. 2008; 88: 167-175).
  - In a RCT in 60 children with moderate persistent asthma, 1 gm/day omega 3 fatty acids for 6 weeks associated with significant improvement in childhood asthma control test, PFTs, and sputum inflammatory markers. Additional benefit in this trial when combined with zinc 15 mg/day and vitamin C 200 mg/day (Acta Paediatr. 2009. 98. 737-742).
• Vitamin C 1 gm bid
  - The hypothesized mechanism of benefit of vitamin C in asthma is as an antihistamine.
  - Negative trial - 16 week parallel group RCT of 201 asthmatics (Clin Exp Allergy. 2003; 33:1355-1359).
  - In a RCT of 16 subjects with exercise induced asthma, those receiving 1500 mg daily showed significant improvement in FEV-1 post exercise, a significant decrease in asthma symptoms, and a decrease in urinary markers of airway inflammation (Respir Med. 2007. 101. 1770-1778).
  - In a RCT of 60 children with moderate persistent asthma, vitamin C 200 mg/day for 6 weeks associated with significant improvement in childhood asthma control test, PFTs, and sputum inflammatory markers. Additional benefit in this trial when combined with zinc 15 mg/day and 1 gm/day omega 3 fatty acids (Acta Paediatr. 2009. 98. 737-742).
Asthma (cont.)

- **Vitamin D – conflicting data**
  - Higher serum levels are associated with a higher FEV1, based on NHANES III data (*Chest*. 2005. 128. 3792-3798).
  - Additional data shows that low vitamin D levels are a risk factor for exacerbations of asthma in children, and that vitamin D supplementation (1200 IU daily) reduces the risk of exacerbation, based on prespecified subgroup analysis in a RCT of vitamin D for influenza A prevention (*Am J Clin Nutr*. 2010. 91. 1255-60).
  - However, in a 28 week RCT of 408 patients with persistent asthma and vitamin D insufficiency, vitamin D3 100,000 IU once, followed by 4000 IU daily did not reduce the rate of first treatment failure or exacerbation (*JAMA*. 2014. 311. 2083-2091).
Asthma (cont.)

• Zinc
  - In a RCT of 60 children with moderate persistent asthma, zinc 15 mg/day for 6 weeks associated with significant improvement in childhood asthma control test, PFTs, and sputum inflammatory markers. Additional benefit in this trial when combined with vitamin C 200 mg/day and 1 gm/day omega 3 fatty acids (Acta Paediatr. 2009. 98. 737-742).
  - In an 8 week RCT of 284 children with asthma, on inhaled steroids and with a low initial zinc level, 50 mg daily of zinc was associated with improved zinc levels, improved symptoms, and improved spirometry values (Ghaffari J et al. East Mediterr Health J. 2014. 18. 391-396).
Asthma (cont.)

• Acupuncture (*Alt Med Alert.* 2007. 10. 91-94)
  - A systematic review of 13 trials concluded that no recommendations could be made due to the poor quality of the studies (*Thorax.* 1991. 46. 799-802).
  - A systematic review of 11 trials concluded that no recommendations could be made due to the poor quality of the studies (*Eur Respir J.* 2002. 20. 846-852).
  - A 2004 Cochrane review of 11 studies (n=324) of variable quality found that acupuncture had no significant effect on pulmonary function or global assessment of well-being (*Cochrane Database Syst Rev.* 2004. 1:CD000008).
  - A RCT of 90 asthmatics found equal improvements in pulmonary function in the acupuncture and sham acupuncture groups (*Zhongguo Zhen Jiu.* 2005. 25. 158-160).
  - A systematic review of RCTs identified 35 trials but only 3 met the inclusion criteria. There was no evidence that true manipulation was any more effective than sham manipulation in improving either subjective symptoms or objective measures of lung function (*Respir Med.* 2009. 103. 1791-1795).
Asthma (cont.)

- Buteyko method of breathing (www.buteyko-usa.com)
  - Method developed in 1950’s by Ukranian physician, and involves shallow breathing, with 5-7 training sessions of 1-2 hours each.
  - Theory is that hyperventilation in asthma results in excess alkalinity in tissues and blood, as well as smooth muscle spasm in bronchioles.
  - Data from small RCTs suggests that this does not alter underlying disease process but changes patient perception such that symptoms are perceived as less severe, thus leading to less beta agonist use (Med J Aust. 1998. 169. 575-578; Thorax. 2003. 58. 674-679).
  - Hypothesized by pulmonologist at U of Arizona, John Mack, to decrease airway inflammation, but no clinical trials to date.
Asthma (cont.)

- Exercise – a 3 month RCT in 101 asthmatics receiving pharmacological therapy and who were clinically stable for at least 30 days showed that those randomized to twice weekly 30 minutes sessions of aerobic training had significantly more symptom-free days (24 versus 16 per month, p<0.001) and significant improvements in anxiety and depression scores from baseline (p<0.001) whereas the control group did not show improvement in these symptom scores. Finally, those in the aerobic training group showed significant improvement in total asthma-related quality of life scores (p<0.001). The improvements in the treatment group correlated with improvement in aerobic capacity – pulmonary function testing showed no significant change in pulmonary function in the exercise group (Mendes FA et al. *Chest*. 2010. 138. 331).
Asthma (cont.)

• Journaling
  - In a published trial in which the experimental group wrote about past or present stressful life experiences for at least 20 minutes over 3 consecutive days, and the control group wrote about mundane topics for 20 minutes over 3 consecutive days, and in which those in the experimental group were specifically instructed that the content of the writing should describe how they feel/felt about the event, and how it is/was affecting them mentally and physically, 4 months after the ‘journaling’ intervention, patients in the experimental group showed improvements in lung function (the mean percentage of predicted forced expiratory volume in 1 second [FEV1] improved from 63.9% at baseline to 76.3% at the 4-month follow-up; P<.001), whereas control group patients showed no change (JAMA. 1999; 281:1304-1309).
  - Negative trial – a RCT of 137 patients found no significant impact of structured writing on PFT results (Psychosom Med. 2005. 67. 130-136).
  - A RCT of 50 adolescents which did not examine PFTs did report a decrease in asthma symptoms and functional disability in the journaling group (J Pediatr Psychol. 2006. 31. 557-568).
  - [www.journaltherapy.com](http://www.journaltherapy.com) for journal therapists
Asthma (cont.)

- Papworth Method
  - This is a multi-component integrated breathing and relaxation technique.
  - A RCT in 85 adults with mild-to-moderate asthma in which the treatment group received 5 Papworth treatment sessions from a respiratory therapist showed that this technique improves dysfunctional breathing, respiratory symptoms, anxiety, and quality of life at 6 and 12 months of follow up (Holloway EA, West R. *Thorax*. 2007. Epub).
Arrhythmias

• Magnesium – 260 mg per day of elemental magnesium beneficial in a 30 day RCT of 60 symptomatic patients (Arq Bras Cardiol. 2012. 98. 480-487).

• Acupuncture – methodologic limitations to published data; may be an effective treatment for atrial fibrillation, paroxysmal SVT, symptomatic PVCs (multiple citations in review article. Am J Cardiol. 2014. 113. 897-903).
Attention Deficit Hyperactivity Disorder (ADHD) – vitamins and minerals

• Vitamin B6 with magnesium
  – Beneficial in an 8 week study (open label) at a daily dose of magnesium 200 mg daily with vitamin B6 20 mg (Magnes Res. 2006. 19. 46-52).
  – Anecdotally, beneficial in as many as 1 in 7 children.

• Iron 20-100 mg daily if deficient (Neuropsychobiology. 1997. 35. 178-180). In one study, 84% of ADHD children had abnormally low levels of iron (Arch Pediatr Adolesc Med. 2004. 158. 1113-1115).

• Zinc – beneficial in a RCT (Prog Neuropsychopharmacol Biol Psychiatry. 2004. 28. 181-190), with a suggested dose of 15 mg daily in children and 30 mg daily in adolescents.
ADHD – dietary supplements

- Acetyl-L-carnitine for inattentive ADHD – in a pilot trial in 112 children with ADHD, a subgroup analysis showed significant benefit in those treated with 500 – 1500 mg bid, based on the weight of the child (J Child Adolesc Psychopharmacol. 2007; 17(6): 791-802).

- EMPowerplus™ – 36 ingredients. Loading dose is 15 capsules per day and maintenance dose is 8 capsules per day.
  - Benefit seen in an 8 week open label trial with 14 medication-free adults, aged 18-55 with ADHD and severe mood dysregulation (J Attn Disord. 2011. 15. 79-91).

ADHD - herbs

• Ginkgo biloba 60-120 mg twice daily.
  – In a 6 week RCT of 50 students, ginkgo was more effective than placebo, but less effective than methylphenidate (*Prog Neuropsychopharmacol Biol Psychiatry*. 2010. 34. 76-80).
  – One of the most popular herbs for ADHD, based on survey data (*Pharmacotherapy*. 2003. 23. 222-230).

• Ginseng 100-200 mg twice daily. In an 8 week observational study of 18 students, examining Korean red ginseng 1000 mg twice a day, significant improvements were noted on all rating scales (*J Ginseng Res*. 2011. 35. 226-234).
ADHD (cont.)

• EEG biofeedback (also called neurofeedback or neural therapy).
  – Published research citations can be found in *Alt Med Alert*. 2007. 10. 124-127.
  – Data would suggest that 75% of ADHD patients improve as per Dr. Andrew Weil (in a newsletter article), but 30-50 sessions may be required.
  – As per *Mental Health for the Whole Child* (Scott Shannon, MD. 2013), 14 RCTs of neurofeedback, with an average effect size of 0.69.

• Feingold diet – anecdotes
  – Remove all artificial additives and foods with salicylates (almonds, apples, apricots, black currants, canned cherries, cucumbers, grapes, oranges, plums, prunes, raisins, raspberries, strawberries).
  – Supplementing with DHA, EPA, and GLA may be just as effective as eliminating foods with salicylates (*Optimum Nutrition for the Mind*. Pgs 233-234).
Autism Spectrum Disorder

• In a comprehensive review by DA Rossignal (Ann Clin Psychiatr. 2009. 21. 213-236), each novel treatment for autism was graded on a scale from A to C, based on level of evidence
  - **A**: acetylcholinesterase inhibitors, melatonin, naltrexone, and music therapy
  - **B**: alpha w adrenergic agonists, carnitine, oxytocin, tetrahydrobiopterin, vitamin C, hyperbaric oxygen, immunomodulation, and vision therapy
  - **C**: carnosine, cyproheptadine, famotidine, glutamate antagonists, multivitamin, piracetam, polyunsaturated fatty acids, vitamin B6/magnesium, acupuncture, auditory integration, chelation therapy, elimination diets, massage, and neurofeedback

• Autism Research Institute (ARI) reports Benefit: Worse ratios for many interventions, based on surveys of caregivers.
Autism (cont.)

• Carnitine – benefit seen in a 3 month RCT in 30 children, aged 3-10, using 50 mg/kg body weight per day, in liquid form and delivered in 2 divided doses. In the treatment group, mean score on Childhood Autism Rating Scale improved by 5.3% (p=0.02) [Med Sci Monitor. 2011. 17. P115-P123].

• EMPowerplus™ – 36 ingredients. Loading dose is 15 capsules per day and maintenance dose is 8 capsules per day.
  – Benefit seen in a 3 month naturalistic case-control study comparing EMPowerplus (n=44) with medication treatment (n=44) in those with autism-spectrum disorder (J Child Adolesc Psychopharmacol. 2010. 20. 95-103).
Autism (cont.)

- Gluten free and casein free diet for a minimum 4 weeks, ideally for 3 months.
  - Casein metabolites clear in the urine more quickly than gluten metabolites, so (1) withdrawal symptoms from casein elimination may be more severe and (2) benefits of casein elimination are detectable more quickly, sometimes within 2-3 days.
  - With gluten elimination, there are case reports of benefit delayed for 7-9 months, with maximal improvement at 2 years.
  - Benefit also reported in the randomized, single-blind ScanBrit trial group (*Nutr Neurosci*. 2010. 13. 87-100).
Cancer


  - Education and information
  - Connection with Others
  - The Body as Garden
  - Emotional Healing
  - The Nature of Mind
  - Life Assessment - purpose of life, top 20 goals, how to be remembered
  - The Nature of Spirit
Cancer (cont.)

- Nutrition – anti-inflammatory, low glycemic load, alkaline diet
- Exercise as tolerated
- Social connections, positive outlook
Cancer (cont.)

- Antioxidant supplementation is controversial because antioxidants might negate effects of chemo.
- Glutamine supplementation is controversial because tumors use glutamine as their main fuel source.
- Fish oil supplementation based on theoretical rationale – anti-inflammatory.
- Melatonin for solid tumors (lung, brain, skin, kidney, breast)
  - There are approximately 50 small clinical trials of melatonin in humans with cancer (Alt Med Alert. 2005. 8. 109-113), and a meta-analysis of 10 European trials in 643 patients, using doses of melatonin of 10-40 mg, found a 34% reduction in risk of death at one year (J Pineal Research. 2005. 39. 360-366).
Cancer (cont.)

- Kombucha tea – this is a fermented mixture of yeast, bacteria, black tea, and sugar. Contra-indicated, due to risk of contamination. There are several published case reports of serious, sometimes fatal illness associated with Kombucha tea. Only two articles in PubMed on Kombucha and cancer, and both are negative.

- Laetrile (amygdalin, vitamin B17)
  - Derived from apricot seeds.
  - Anecdotes of benefit
  - 1980 NCI trial of 178 cancer patients negative, and there reported a risk of cyanide toxicity.

- Shark cartilage - the oral use of powdered shark cartilage to treat cancer is not supported by clinical studies (*Alt Med Alert*. 2005. 8. 61-64).
Cancer - boost immune system function

- AHCC® (Active Hexose Correlated Compound) - this is a hybridized mushroom extract.
  - Mildly sweet tasting monosaccharide which is a mycelial extract of a hybridized Shiitake mushroom grown on rice bran extract.
  - Developed in 1987 at University of Tokyo; subject of several books, used in over 700 cancer clinics in Japan.
  - Published clinical trial shows benefit in those with liver cancer;
  - Clinical experience shows this is beneficial in cancers of the breast, colon, kidney, liver, lung, ovary, pancreas, prostate, stomach, testicle, thyroid, and tongue.
  - May be used in conjunction with Avemar®, as mechanisms of action are complementary, but take at least 2 hours before or after taking Avemar.

- Avemar® (AveULTRA™) [Alt Ther Health Med. 2007. 13[2]. 56-63]
  - This is a fermented aqueous extract of wheat germ standardized to contain methoxy-substituted benzoquinones at a concentration of 0.04%.
  - Shown to prolong progression free and overall survival in colorectal cancer patients (Br J Cancer. 2003. 89. 465-469), to delay progression in melanoma patients (Int J Cancer. 2002. 100. 408) and to reduce chemotherapy-induced febrile neutropenia in pediatric cancer patients (J Pediatr Hematol Oncol. 2004. 26. 531-635).
  - May be used in conjunction with AHCC® as long as consumed at least 2 hours apart.
Cancer - boost immune system function

- Mushrooms with immune stimulating activity
  - Coriolus versicolor
  - Maitake
  - Reishi
  - Shiitake
  - Zhu ling mushrooms - show promise in lung cancer.
- My Community® - manufactured by Host Defense, contains 17 different mushrooms.
- Stamets 7® – manufactured by Host Defense, anecdotally beneficial for those with “chemo-brain,” possibly due to the Lion’s mane in the blend.
- Vitamin D
- Low dose naltrexone (3 - 4.5 mg at bedtime, compounded, contra-indicated with narcotics)
Chronic Fatigue Syndrome (CFS)

• Treat the mitochondrial dysfunction
• Detoxification
• Toxic metal provocation testing, and treatment with a medical food if testing shows body burden
• SHINE approach (sleep disturbance, hormonal imbalance, infections/immune system dysfunction, nutritional insufficiencies, exercise to tolerance)

References:
• Teitelbaum, Jacob. *From Fatigued to Fantastic!* 2001.
CFS- treat the mitochondrial dysfunction

- Acetyl-L-carnitine (ALC), propionyl-L-carnitine, or carnitine 500-1000 mg tid for 8 weeks, then trial of a lower dose or discontinuation
  - L-carnitine 3 grams per day beneficial in an 8 week RCT (*Neuropsychobiology*. 1997. 35. 16-23).
  - In a small open-label 24 week study, the clinical global impression of change scale improved significantly in 59% of patients taking acetyl-L-carnitine and 63% of patients taking propionyl-L-carnitine (*Psychosom Med*. 2004. 66. 276-282).
  - Beneficial in a RCT with 102 patients, in which the treatment group received two capsules per day of 500 mg ALC/capsule + one intramuscular injection of 500 mg ALC, for 2 weeks, followed by 3 capsules per day of 500 mg ALC/capsule for another 8 weeks (*Clin Exp Rheumatol*. 2007; 25(2): 182-188).
CFS- treat the mitochondrial dysfunction

• Coenzyme Q 10 100-300 mg daily.
  – Regarding dosage, extent of absorption is a function of the formulation.

• NADH (also known as Coenzyme I) 10 mg/day for at least 2 months, first thing in the morning, on an empty stomach, ½ hour before any food. If no benefit, consider trial of 20 mg/day.
  – Benefit of 10 mg daily reported in a 1 month RCT (*Ann Allergy Asthma Immunol*. 1999. 82. 185-191).
CFS- treat the mitochondrial dysfunction

• NT Factor Energy Lipids® – proprietary lipid blend (soy lecithin extract) which contains Phosphatidic acid, Phosphatidyl-choline (PC), Phosphatidyl-ethanolamine (PE), Phosphatidyl-glycerol(PG), Phosphatidyl-inositol (PI), Phosphatidyl-serine (PS), Digalactosyldiacylglyceride (DGDG), and Monogalactosyldiacylglyceride (MGDG).
  - Benefit seen in a 12 week clinical trial of elderly with severe fatigue (J Chronic Fatigue Syndr. 2003. 11. 23-26).
  - 31% improvement in fatigue in a 60 day trial in 58 patients with CFS/fibromyalgia/Gulf War Illness and 17 patients with Chronic Lyme disease (Int J Clin Med. 2012. 3. 163-170).
CFS- treat the mitochondrial dysfunction

- Ribose (D-ribose) 1 scoop (5 grams) tid for 3 weeks, than bid
  - Significant improvement seen in an uncontrolled study in 41 patients with CSF or fibromyalgia (*J Altern Compl Med.* 2006. 12. 857-862). If hyper/anxious, reduce the dose.
  - Significant (statistical and clinical) improvement seen in a 3 week open-label, multicenter trial in 203 patients, examining endpoints of energy, well-being, sleep, mental clarity, and pain (*The Open Pain Journal.* 2012. 5. 32-37).
CFS – SHINE approach


• This study showed that at a median follow up of 101 days, 16 active treatment group patients were ‘much better,’ 14 ‘better,’ 2 ‘same,’ 0 ‘worse,’ and 1 ‘much worse.’ At a median follow up of 98 days, 3 placebo group patients were ‘much better,’ 9 ‘better,’ 11 ‘same,’ 6 ‘worse,’ and 4 ‘much worse’ (p<0.0001 Cochran-Mantel-Haenszel trend test).
Coronary artery disease (CAD)

• Treat the mitochondrial dysfunction
• Treat the endothelial dysfunction
• Inhibit platelet function – data is mixed regarding benefits of fish oil supplementation
• Treat atherosclerosis
• EECP
CAD - treat the mitochondrial dysfunction

- Coenzyme Q 10 50-100 mg tid
  - Anecdotally it may take one month to see symptomatic benefit.
  - In 4 week, double-blind, placebo-controlled, randomized, cross over protocol using 12 patients and 50 mg Co Q 10 three times a day, exercise time increased (p < 0.05) and time until 1 mm depression increased (p < 0.01) [Am J Cardiol. 1985. 56. 247-251].
  - A RCT of 144 participants enrolled within 72 hours of experiencing an acute MI showed that those taking 60 mg Co Q 10 twice a day had fewer total cardiac events, 24.6% in the treatment group versus 45.0% in the placebo group. Limitations of this study include small size, questionable true blinding since placebo capsules were not identical to Co Q 10 capsules, average age of participants in both groups less than 48 years, more smokers in the 10 group despite randomization, and only 20% of participants received beta blockers (Mol Cell Biochem. 2003. 246. 75-82).
CAD - treat the mitochondrial dysfunction

• L-carnitine 500 mg -1 g bid
  – There are a number of published papers reporting effects of carnitine supplementation in healthy humans, including a RCT of 30 men and women showing improvement in flow-mediated vasodilation after a high fat meal in the treatment group, administered 2 g/day L-carnitine (Am J Cardiol. 2008. 102. 1413-1417).
  – In a RCT of 160 MI survivors, 12 month all-cause mortality in the carnitine group was 1.2%, compared with 12.5% in the placebo + conventional medical therapy group (Drugs Exp Clin Res. 1992. 18. 355-365).

• Ribose 5 gm daily for mild disease, 5 gm tid for severe disease, with a carbohydrate meal. Reduces exercise induced angina (J Cardiovasc Pharmacol Ther. 2000. 5. 249-258).
CAD - treat the endothelial dysfunction

- L-arginine 2-3 grams tid, especially if ADMA (asymmetrical dimethylarginine) level is elevated.
  - Significant improvement in angina class, systolic blood pressure at rest, and quality of life in a 4 week study using a dose of 2 gm tid in a study in 13 hypertensive patients with microvascular angina [i.e. normal coronary arteries by angiogram] (Am J Cardiol. 2004;93. 933-935).
  - A 30 day RCT in 792 patients with STEMI found that L-arginine 3 grams tid was associated with a nonsignificant trend towards reduction of major clinical events (Kardiol Pol. 2005. 62. 421-7).
  - A 6 month RCT (VINTAGE-MI) in 153 patients with STEMI found that the addition of L-arginine 3 grams tid to standard therapy was associated with a higher death rate. (JAMA. 2006. 295. 58-64). A critique of this study notes that there were surprisingly no deaths in the control group, that the mechanism postulated to explain the increased death rate in the arginine group is flawed, and the statement that arginine supplementation increases homocysteine is incorrect (JAMA. 2006. 9[2]. 1-3).

CAD - treat atherosclerosis

- Vitamin K2 - minimum of 150 mcg daily, maximum of 15 mg tid
  - In the Rotterdam Heart Study, an observational study of 4807 subjects who were tracked for 7 years, inverse associations were found between vitamin K2 intake and severe aortic calcification, as well as all-cause mortality (J Nutr. 2004. 134. 3100-3105).
  - Data in 16,057 postmenopausal women showed high consumption of natural vitamin K2 was correlated with reduced risk of CHD at 8 years of follow up. Consumption of vitamin K1 had no effect (Gast GC et al. Nutr Metab Cardiovasc Dis. 2009. epub).
  - In a 3 year RCT in 380 healthy men and women aged 60-80, those receiving a multivitamin with 500 mcg per day of vitamin K1 and with compliance with taking > 85% of the doses showed a slower rate of progression of coronary artery calcification than those in the control group taking a multivitamin without the high dose of vitamin K1 [p=0.03] (Am J Clin Nutr. 2009. 89. 1799-1807).
CAD - treat atherosclerosis

• Chelation treatment
  - Intravenous disodium EDTA – in the TACT trial of 1708 stable patients (at 134 clinical sites) with a history of MI (median of 4.6 years prior to enrollment), intravenous chelation modestly reduced the risk of adverse cardiovascular outcomes, during a mean follow up of 55 months. The primary endpoint, a composite of total mortality, recurrent MI, stroke, coronary revascularization, or angina occurred in 18% fewer patients in the chelation therapy group than the placebo group (p=0.035). This was a 2 x 2 trial design, with an oral and intravenous vitamin regimen, along with intravenous chelation and placebo. The infusions were administered weekly for 30 weeks, and then 2-8 weeks apart for the final 10 infusions. Median age of patients at the time of enrollment was 65, and median BMI was 30. Creatinine > 2 mg/dl was an exclusion criteria. No safety issues identified, and > 55,000 infusions administered in conjunction with this trial (JAMA. 2013. 309. 1241-1250).
CAD – References

· Houston, Mark. *What Your Doctor May Not Tell You About Heart Disease.* 2012
· Levy, Thomas E. *Stop America’s #1 Killer!* 2006
· Sinatra ST and Roberts JC. *Reverse Heart Disease Now.* 2007
· Sinatra ST. *Metabolic Cardiology.* 2011
Congestive Heart Failure (CHF)

- **Coenzyme Q 10**
  - Best to monitor levels and achieve a plasma Co Q 10 level of at least 2.5 mcg/ml, preferably 3.5 mcg/ml (Ann Intern Med. 2000. 133. 745-746).
  - Most published trials of Co Q 10 in CHF are positive, and of 3 negative ones, one did not measure Co Q 10 levels and the other two measured and reported low levels in the treatment group.
  - In 7 patients with symptomatic CHF despite an average of 450 mg/day of ubiquinone, the patients were switched to ubiquinol, average dose 580 mg/day, and plasma total Co Q 10 levels increased from 1.6 mcg/ml to 6.5 mcg/ml, EF increased from 22% to 39%, and symptoms improved (Biofactors. 2008. 52. 435-441).
  - In the Q-SYMBIO study, a 2 year RCT of 420 patients with NYHA class III or IV heart failure, those treated with 100 mg three times a day had lower all-cause mortality (p=0.01), cardiovascular mortality (p=0.02), and hospitalization for heart failure (p=0.05). The primary outcome measure was a composite of major adverse cardiovascular events, and significantly fewer of the treatment patients reached the primary endpoint (p=0.003) [Mortensen SA et al. Eur J Heart Failure. 2013. 15. S20].
• Fish oil
  - In a RCT (GISSI-HF trial) of 7046 patients with symptomatic heart failure of any cause, omega 3 fatty acids at a dose of 1 gram daily reduced mortality (p=0.04), with a NNT of 56 patients for 3.9 years to save one life (Lancet. 2008. 372. 1223-1230).
  - A prospective cohort study of 2735 US adults in 4 communities (Cardiovascular Health Study) showed that higher plasma omega 3 levels at baseline were associated with a lower incidence of CHF, based on 10 years of follow up (Ann Intern Med. 2011. 155. 160-170).
  - In a 12 month RCT of 133 patients with nonischemic cardiomyopathy in which the treatment group received 5 gm/day (prescription) Lovaza® for one month, and then 2 gm/day for the remainder of the trial, the active treatment group showed a significant improvement in exercise capacity (p < 0.002) and NYHA functional class (p < 0.001). In addition, the EF increased 10.4% in the active-treatment group as compared with a 5% decline in the placebo group (p < 0.001), and the rate of hospitalization for heart failure was 80.5% lower in the active treatment group (5.9% vs. 30.3%, p < 0.0002) [J Am Coll Cardiol. 2011. 57. 870-879].
CHF (cont.)

- Hawthorn ½ teaspoon 2-3 times/day or 120-240 mg three times/day
  - A systematic review of 8 RCT's (433 patients) of hawthorn in class II CHF showed improvements in subjective symptoms and exercise tolerance. These trials were of variable methodological quality, mostly 8 weeks or less in duration (Fortschr Med. 1996. 114. 27-29).
  - A meta-analysis of 13 trials, 8 of which evaluated the effect on maximal work load, and 5 of which evaluated the effect on symptoms, found significant benefit with regard to both of the above endpoints; adverse effects were generally mild and transient (Am J Med. 2003. 114. 665-674).
  - Negative published trials too.
CHF (cont.)

• L-carnitine
  – In a study of 472 European patients, 9 gm iv for 5 days, followed by 6 gm per day orally for the next 12 months was associated with improved EF, LV size, and a lower incidence of CHF death (JACC. 1995. 26. 380-387).
  – A RCT in 80 patients with NYHA Class III/IV showed that those who received 2 gm/day L-carnitine had a lower mortality rate at a mean follow up of 33 months (Am Heart J. 2000. 139. S120-S123).

• Magnesium 400-800 mg a day (Sinatra)
  – In a one year RCT of 79 patients with severe CHF (NYS Class IV), those randomized to receive magnesium orotate (2 gm tid for one month, followed by 1 gm tid for the remaining 11 months) had a survival rate of 76% vs. 52% in the placebo group (p<0.05). Furthermore, symptoms improved in 38% of those receiving magnesium, none in the placebo arm (p<0.01) [Int J Cardiol. 2009. 131.293-295].
CHF (cont.)

- Ribose 5 gm tid with carbohydrate meal for 3 weeks, then if patients respond favorably, decrease the dose to 5 gm bid
  - Beneficial in a 3 week crossover RCT of 15 patients, with improvements reported in quality of life, exercise tolerance, and echocardiographic measures of diastolic function (Eur J Heart Fail. 2003. 5. 615-619).
  - Maintains $VO_{2\text{max}}$, when compared to placebo in NYHA Class II/III CHF patients (J Mol Cell Cardiol. 2005. 38. 820).
  - Improves Doppler MPI (index) and ventilatory efficiency while preserving $VO_{2\text{max}}$, when compared to placebo in NYHA Class II/III CHF patients (JACC. 2005. 45. 185A)

- Micronutrient supplementation – a 9 month RCT of 30 patients found a 5.3% increase in mean EF ($p<0.05$) and significant improvement in quality of life scores ($p<0.05$) [Eur Heart J. 2005. 26. 2238-2244].
Depression

- Inositol - sugar alcohol located primarily in cell membranes, hypothesized to act via the intracellular phosphatidyl inositol second messenger cycle, serving as a second messenger for 5-HT-2 receptors (Natural Medications for Psychiatric Disorders. 2002. Pgs 110 and 115).
  - Full dose is 2 teaspoons (6 grams) twice a day in juice.
  - James Greenblatt, MD recommends starting with ½ teaspoon (1.4 grams) three times a day and slowly titrating dose up, as rapid dose titration sometimes associated with GI discomfort.
  - **BEWARE** those with low histamine levels may get worse.

- Omega 3 supplementation - a meta-analysis of 10 RCT’s of at least 4 weeks duration identified a significant antidepressant effect, but the quality of the individual studies was variable, and the size often small (J Clin Psychiatry. 2007. 68. 1056-1061).
Depression (cont.)

• Rhodiola – in a 6 week, 3 arm RCT of 89 patients with HAM D scores at baseline between 21 and 31, those receiving 340 mg/day and 680 mg/day improved significantly more than those on placebo (Nordic J Psychiatry. 2007. 61. 343-348).

• SAMe - 200-800 mg twice a day, ideally on an empty stomach. Start with 200 mg bid and increase dose by 200-400 mg per week until response noted.
  - Stimulating antidepressant.
  - 60-70% response rate in open trials, sometimes within 5-10 days.
  - A meta-analysis in 2002, done by Hardy, commissioned by the Agency for Health Care Research and Quality (AHRQ), identified 28 acceptable studies of SAMe versus antidepressant or placebo, and found that SAMe was superior to placebo and equally effective/possibly superior to prescription antidepressants.
Depression (cont.)

- St. John’s wort 450 mg bid of a product standardized to 0.3% hypericium
  - A Cochrane review of St John’s wort for major depression examined 29 studies and almost 5500 adults and concluded that "...the hypericum extracts tested in the included trials (a) are superior to placebo in patients with major depression; (b) are similarly effective as standard antidepressants; (c) and have fewer side effects than standard antidepressants" (Cochrane Database Syst Rev. 2008 (4): CD000448).
  - A systematic review found that St John’s wort was more effective than placebo and as effective as standard therapy with better tolerability (Linde K. Forsch Komplementmed. 2009. 16. 146-155).
  - Increases amount of REM sleep.
  - BEWARE of drug interactions.
Depression (cont.)

- Vitamin D – data is mixed
  - In a one year RCT of obese and overweight subjects, those randomized to 20,000 – 40,000 IU/week supplementation with Vitamin D showed significant improvement in BDI scores (J Intern Med. 2008. 264. 599-609).
  - Negative RCT – 6 month RCT of 231 participants randomized to 40,000 IU vitamin D3 vs. placebo (even though the vitamin D group’s vitamin D levels rose from 19 ng/ml to a mean level of 59 ng/ml) [Kjaergaard M et al. Br J Psychiatry. Epub 7/12/12].

- 5-HTP 50 - 400 mg daily, either in a single dose (usually at bedtime) or split dosing
  - Cochrane review in 2002 concluded that the evidence is of insufficient quality to be conclusive with regard to clinical benefit (Cochrane Database Syst Rev. 2002. CD003198).
Depression (cont.)

- Bright light therapy - defined as > 4 days of > 3000 lux-hr. Typically, bright-light therapy involves sitting in front of a 10,000 lux light box for 20-30 minutes in the morning.
  - A 2004 Cochrane Review noted that light therapy is most effective when administered in the first week of treatment, in the morning, and in sleep deprivation responders (Cochrane Database Syst Rev. 2004. CD004050).
  - A meta-analysis was done of all RCTs in PubMed from 1975-2003. This meta-analysis was done at the request of the APA Council on Research. Only 13% of studies (23 of 173) met predefined inclusion criteria. Data on 127 adult patients in 3 RCTs shows that bright-light therapy reduced symptom severity more than placebo for nonseasonal depression. Additional data on 360 adult patients in 8 RCTs with SAD also showed benefit for bright light therapy (Am J Psychiatry. 2005. 162. 656-662).
  - The editorial accompanying the abstract of this article in ACP Journal Club suggests that if more data for bright-light therapy shows similar results, this could be offered as first-line treatment, as an alternative to psychotherapy or pharmacological therapy.
Depression (cont.)

• Acupuncture

• Exercise – Cochrane review of 23 RCTs in 2009 showed benefit, and a systematic review and meta-analysis of 90 RCTs showed benefit.

• Tai Chi - in a study in which a weekly Tai Chi exercise class was combined with standard treatment, those in the Tai Chi group showed greater improvement in level of depression, quality of life, memory, and cognition (*Am J Geriatr Psychiatry.* 2011. 19. 839-850).

Diabetes – lifestyle interventions

- Lifestyle interventions are associated with a decreased risk of progression to diabetes, based on based on 6 studies. In these studies, the pooled RR of progression to DM is 0.55 (Selph S et al. Screening for Type 2 Diabetes Mellitus: A Systematic Review for the U.S. Preventive Services Task Force. Ann Intern Med. 2015; 162:765-776). The citations for the individual studies are as follows
  - 23 year follow up data: Lancet Diabetes Endocrinol. 2014. 2. 474-480.
Diabetes – lifestyle interventions (cont.)

• RCTs done in 3 countries show that diet and exercise reduce risk of developing type II diabetes by 40-60% (CDC Working Group. Primary prevention of type II diabetes by lifestyle intervention: implications for health policy. *Ann Intern Med.* 2004. 140. 950-957). This was confirmed in a systematic review and meta-analysis of 17 studies of 8084 individuals, which showed the magnitude of benefit of diet and exercise was similar to that of prescription drugs, with a NNT of 5-10 (*BMJ.* 2007. 334. 299).

• HOWEVER, in the Look AHEAD trial, a 16-center RCT of 5145 overweight or obese patients with type II diabetes, the intensive lifestyle intervention was successful with regard to weight loss (7.9% difference between the two groups at 1 year), waist circumference, SBP and HbA1c, but at a median follow up of 9.6 years, the trial was prematurely terminated based on a lack of effect on cardiovascular outcomes (*N Engl J Med.* 2013. 369. 145-154 and editorial 189-190 and cited in Update in Endocrinology. *Ann Intern Med.* 2014. 160. 785-790).
Diabetes – behavioral intervention

• A 1 year RCT of 222 adults with poorly controlled diabetes (49% type I) at Joslin diabetes center showed a significantly greater improvement in HbA1c (0.8% drop at 3 months and 0.7% drop at 6 months) in the behavioral intervention group than in the educator-led attention control group (0.4% drop at 3 months and 0.37% drop at 6 months) and in the unlimited individual nurse and dietician education sessions individual control group (0.4% drop at 3 months and 0.24% drop at 6 months). The structured behavioral intervention was a 5-session, manual-based, educator-led structured group intervention which used cognitive behavioral strategies, for a total of 10 hours of interactive education (Arch Intern Med. 2011. 171. 1990-1999 and Invited Commentary 1999-2000).
Diabetes – magnesium intake

• Cross-sectional analysis of 11,686 women over age 45 in the Women’s Health Study suggests that magnesium intake is inversely associated with systemic inflammation and prevalence of metabolic syndrome (Diabetes Care. 2005. 28. 1438-1444).

• Data from 4637 young adults in the CARDIA Study without metabolic syndrome or diabetes at baseline showed a 30% reduction in metabolic syndrome at 15 years of follow-up in those in the highest quartile of magnesium intake compared those in the lowest quartile of magnesium intake, based on food frequency questionnaires (Circulation. 2006. 113. 1675-1682).

• Benefit based on a meta-analysis (Arch Intern Med. 2007. 167. 956-965).

• A meta-analysis of 13 prospective cohort studies (n=536,318) showed an inverse relationship between diabetes risk and magnesium intake, with each 100 mg increase in intake associated with a 14% lower relative risk of developing diabetes (Diabetes Care. 2011. 34. 2116-2222).
Diabetes - supplements

• Alpha lipoic acid
  - A meta-analysis of four large RCTs which included 716 diabetics who received 600 mg iv 5 days per week for 3 weeks and 542 diabetics who received placebo showed that the 53% of the treatment group responded with a decrease in symptom scores, compared with 37% of the placebo group (Diabet Med. 2004. 21. 114-121).

• Chromium picolinate 200-500 mcg twice a day – appears to work as an insulin sensitizer, by binding to an oligopeptide which then binds to the insulin receptor, increasing the activity of tyrosine kinase, amplifying the action of insulin. May be synergistic with biotin.
  - 500 mcg bid associated with a 2% decrease in HbA1c in a 4 month RCT of 180 Chinese subjects (Diabetes. 1997. 46. 1786-1791). Note a review (Alt Med Alert. 2006. 9. 78-82) states that 500 mcg bid is the dose of elemental chromium and that the above cited study actually used 4000 mcg chromium picolinate twice a day.
  - Meta-analysis – 20 RCTs were identified and 15 (n=618) deemed suitable for meta-analysis. Chromium did not alter the glucose or insulin levels in the 425 healthy volunteers; results inconclusive for the group of 193 diabetics because the only trial that showed benefit was the large (n=155) Chinese study (1997) cited above.
Diabetes – supplements (cont.)

- Magnesium - in a 6 month RCT of 52 overweight, insulin resistant, nondiabetic individuals, those randomized to 345 mg daily of Mg showed 7% improvement in FBS and improvement in 2 out of 3 markers of insulin sensitivity (Diabetes Obes Metab. 2011. 13. 281-284).

- Multivitamin - in a one year RCT of 130 community-dwelling adults over age 45, within the subgroup of 51 diabetics, 93% in the placebo group but only 17% in the multivitamin group became ill during the study (Ann Intern Med. 2003. 138. 365-371).
Diabetes - herbs

- Berberine - 1 gram daily lowered HbA1c from 7.5% to 6.6% in a 3 month multicenter RCT in 116 diabetics with dyslipidemia, and also significantly lowered triglycerides and LDL (J Clin Endocrinol Metab. 2008. 93. 2559-2565). Widely used in China.

- Bitter melon (Momordica charantia) [IMCJ. 2008. 7(1). 21-24].
  - A systematic review of 8 clinical trials noted promising results, but methodological flaws in all of the studies (J Clin Epidemiol. 2007. 60. 554-559).
  - In a 24 week crossover trial of 27 adults with type II DM, those consuming 1 glass of bitter melon tea tid (containing 3 grams of dried ground bitter melon brewed in 650 ml of hot water for 5 minutes) showed a mean decrease in HbA1c of 0.63% and FBS of 2.96 mg/dl, compared to those who consumed Lipton tea. Loose stools more common in the bitter melon group (Phil J Internal Medicine. 2001. 39. 213-216).
Diabetes – herbs (cont.)

• Cinnamon
  – As of 2009, Natural Medicine Comprehensive Database reports five clinical trials, with two showing some reduction of fasting blood glucose levels, but three show no effect on HbA1c.
  – In a 12 week RCT of 58 patients administered 500 mg at breakfast, 1 gm at lunch, and 500 mg at dinner, the mean HbA1c decreased in the cinnamon group ($p<0.005$) [Diabet Med. 2010. 27. 1159-1167].

• Gurmar (Gymnema sylvestre)
  – Early clinical trial data limited and methodologically flawed.
  – Benefit seen in a 60 day open label trial of 11 patients – mean fasting glucose improved dramatically and insulin levels and C-peptide levels increased – dose was 1 gram per day of a high molecular weight extract (Om Santal Adivasi) [Phytother Res. 2010. 24. 1370-1376].
Diabetes – complementary modalities

• Ayurvedic medicine – in a 6 month RCT of 60 adult patients, a combination of exercise, Ayurvedic diet, meditation instruction, and an Ayurvedic herb supplement (MA 471) was associated with statistically significant improvements in HbA1c and fasting glucose (Altern Ther Health Med. 2006. 12 [5]. 24-30).

• Biofeedback-assisted relaxation – RCT of 30 patients, 10 sessions biofeedback versus 3 sessions education. Benefit persisted for 3 months – lower glucose and HbA1c (Diabetes Care. 2005. 28. 2145-2149).

Diabetes – complementary modalities

• Meditation (Mindfulness Based Stress Reduction) – BP and HbA1c improved significantly from baseline in a one month pilot study of 11 adults (Altern Ther Health Med. 2007. 13. 36).

• Qi gong - HbA1c improved significantly in a four month RCT of 26 adults (Diabetes Care. 2002. 25. 241).

• Yoga – in a 6 month pilot study of 80 patients, regular yoga was associated with an improvement in blood glucose control, with effects evident after one month (Altern Ther Health Med. 2014. 20[6]. 24-26).
Hypercholesterolemia

• Polymeal (also referred to as Portfolio Diet) – reduces LDL by 29-35% (Endocrinol Metab Clin North Am. 2009. 38. 45-78).
Hypercholesterolemia (cont.)

• Berberine – 500 mg two or three times a day
  – Lowers LDL by extending the half-life of the LDL receptor messenger RNA, a mechanism of action which is complementary to the mechanism of action of red yeast rice and statin medications. Berberine also is used to treat metabolic syndrome and diabetes. Berberine lowers LDL and triglycerides (Alt Ther Health Med. 2015. 21[suppl 2]. 40-44).
  – A systematic review and meta-analysis of RCTs (n=874) shows that berberine lowers LDL 25 mg/dl more than placebo (Planta Med. 2013. 79. 437-446).

• Garlic 300 mg 3 times a day – mixed results in meta-analyses
Hypercholesterolemia (cont.)

• Guggulipid
  - This is a standardized extract of the herb *Commiphora mukul*, used in India for 2000 years.
  - A systematic review identified 7 RCTs, 2 of intermediate quality and 5 of high quality, and 6 of the 7 trials showed efficacy greater than placebo (*Alt Ther Health Med.* 2007. 13[4]. 22-28).

• Psyllium (Metamucil)
  - A meta-analysis of 5 studies using a total of 10.2 grams per day of psyllium seed husk as an adjunct to Step I AHA diet found that psyllium was associated with significant reductions in total cholesterol and LDL cholesterol (*Am J Clin Nutr.* 2000. 71. 472-479).
Hypercholesterolemia (cont.)

• Policosinol
  - Studies show a 15% to 25% decrease in total cholesterol, 20% to 30% decrease in LDL cholesterol, and 5% to 15% increase in HDL cholesterol (Alternative Medicine Alert. 2004. 7. 37-41). The lipid lowering effect is believed to be dose-dependent.
  - Seven RCT's comparing policosanol to prescription statins found similar effectiveness. The limitation of this data is that all but two studies were done by a single research group in Cuba.
  - However, a 12 week RCT (following a 6 week open-label placebo and diet run-in phase) of 143 patients with hypercholesterolemia or combined hyperlipidemia randomized to either placebo, 10 mg/day policosanol, 20 mg/day, 40 mg/day, or 80 mg/day found no benefit beyond that of placebo at any dose. This trial was done in Germany, but nonetheless used Cuban policosanol (JAMA. 2006. 295. 2262-2269).
  - Another negative trial was a 12 week trial of 20 mg daily (British J Nutr. 2006. 95. 968-975).
Hypercholesterolemia (cont.)

- Red yeast rice
  - A meta-analysis of 93 trials concludes that red yeast rice lowers total cholesterol, LDL cholesterol, and triglyceride levels, with magnitude of benefit similar to that of statin medications (Liu JP et al. Chin Med. 2006. 1. 4).
  - Quality concerns
    - Some brands are contaminated with citrinin, a mycotoxin which is nephrotoxic in animals. In a published study, 4 of 12 products tested had elevated levels of citrinin (Arch Intern Med. 2010. 170. 1722-1727).
    - Variability in total monacolins – these are the compounds which inhibit HMG-CoA reductase, and 14 distinct compounds are present in red yeast rice. In a published study of 12 products, total monacolin content varied from 0.31 to 11.15 mg/600 mg capsule (Arch Intern Med. 2010. 170. 1722-1727).
Hypertension

• Comprehensive lifestyle approach (PREMIER trial) – in a large RCT, patients who increased physical activity, lost weight, and decreased sodium and alcohol intake showed dramatic reductions in BP values (*J Clin Hypertens.* 2004. 6. 383-390).

• Combination neutraceutical – in a RCT of 42 patients with HTN, administration of a combination neutraceutical daily (Vitamin C 1 gram, grape seed extract 150 mg, magnesium ascorbate 87 mg, vitamin B6 100 mg, vitamin D3 2000 IU, biotin 2 mg, and taurine 6 gram) was associated with a drop in SBP from 144 mm Hg at baseline to 131 mm Hg at 2 weeks and 128 mm Hg at 4 weeks; as well as a drop in DBP from 92 mm Hg at baseline to 82 mm Hg at week 2 to 81 mm Hg at week 4. Week 6 results not reported due to loss of participants (Houston MC and Sparks WS. *IMCJ.* 2013. 12[3]. 22-29).
Hypertension (cont.)

• Coenzyme Q 10
  - A meta-analysis of 12 trials (n=362), including 3 RCTs, one crossover study, and 8 open-label trials reported that SBP reduction ranged from 11 – 17 mm Hg with Co Q 10, and DBP reduction ranged from 8.2 – 10 mm Hg (J Human Hypertens. 2007. 21. 297-306).
  - A systematic review of 8 trials of variable quality, and using Co Q 10 at variable doses, 100-225 mg daily, found a mean decrease in systolic blood pressure of 16 mm Hg and a mean decrease in diastolic blood pressure of 10 mm Hg. (Biofactors. 2003. 18. 91-100).

• Dark chocolate- a meta-analysis of 5 RCTs involving a total of 173 subjects showed a drop in BP of 4.7/2.8 mm Hg associated with cocoa consumption. Median duration of studies was 2 weeks (Arch Intern Med. 2007. 167. 626-634).
Hypertension (cont.)

- Garlic
  - A meta-analysis of 8 RCTs (N=415) of Kwai® garlic showed reductions in BP of 7.7/5.0 mm Hg (J Hypertens. 1994. 12. 463-468).
  - However, a 2001 meta-analysis identified 23 RCTs and reported that only 4 showed statistically significant reductions in BP (Arch Intern Med. 2001. 161. 813-824).

- Magnesium - a meta-analysis of RCTs found that oral magnesium supplementation resulted in small overall reductions in BP in a dose dependent manner in hypertensive patients (Am J Hypertens. 2002. 15. 691-696).

- Pomegranate juice - in a RCT of 19 patients with asymptomatic carotid artery disease, 50 ml daily for a year was also associated with a drop in systolic blood pressure from 174 mm Hg at baseline to 153 mm Hg at 12 months (Clin Nutr. 2004. 23. 423-433).
Hypertension (cont.)

- **Pycnogenol®**
  - In a 12 week RCT of 48 type 2 diabetics with moderate HTN, those in the Pycnogenol group (125 mg bid) were able to reduce dose of Rx ACE (Zibadi S et al).
  - In an open label 12 week trial of 24 healthy subjects, benefit reported using a combination of 480 mg pine bark extract with 240 mg vitamin C (*Phytother Res.* 2003. 17. 490-494).
  - In a 12 week study, those administered Pycnogenol were able to reduce dose of nifedipine (*Life Sci.* 2004. 74. 855-862).
  - NEGATIVE STUDY – a 12 week RCT of 130 subjects with increased cardiovascular risk showed that 200 mg daily of pine bark extract was safe but was not associated with improvement in cardiovascular risk factors (*Arch Intern Med.* 2010. 170. 1541-1550).
  - NEGATIVE STUDY – an 8 week crossover RCT in patients with stable CAD showed improvement in endothelial function, but no change in BP (*Eur Heart J.* 2012. 33. 1589-1597).
Hypertension (cont.)

- **Soy**
  - A RCT of 40 men and women showed that soy milk 500 ml bid, as compared with cow's milk 500 ml bid, was associated with a 17/12 mm Hg decrease in BP (J Nutr. 2002. 132. 1900-1902).
  - A 8 week crossover RCT of 60 healthy postmenopausal women found that substituting soy nuts (25 gm of soy protein per day) lowered SBP 9.9% and DBP 6.6% in hypertensive (SBP > 140) women; lowered SBP 5.2% and DBP 2.9% in normotensive (SBP < 120) women (Arch Intern Med. 2007. 167. 1060-1067).

- **Vitamin D**
  - An 8 week RCT of 148 women, mean age 74, all with 25-OH vitamin D levels less than 20 ng/mL, showed a greater reduction in systolic blood pressure in those administered 800 IU vitamin D + 1200 mg calcium daily, as compared with those administered only the 1200 mg calcium (J Clin Endocrinol Metabol. 2001. 86. 1633-1637).
  - An 8 week RCT of 42 individuals with HTN and vitamin D deficiency showed that 50,000 IU weekly vitamin D3 significantly lowered systolic, diastolic, and mean arterial BP (Mozaffari-Khosravi H et al. Blood Press Monit. Epub 10/27/14).
Hypertension (cont.)

• Device-guided breathing (i.e. RESPeRATE®) - review article (Am J Med. 2015. 128. 567-570) concludes that the level of evidence is “B.” The citation is a systematic review and meta-analysis (J Hypertens. 2012. 30. 852-860).

• Meditation – a review article (Am J Med. 2015. 128. 567-570) concludes that the level of evidence for Transcendental Meditation (TM) is “B” and the level of evidence for “other meditation techniques” is “C.” The citation for TM is a meta-analysis (Am J Hypertens. 2008. 21. 310-316).
Hypothyroidism – Hashimoto’s

- Consider a gluten free diet and anecdotally 10-20% will report an improved quality of life, and occasionally a significant drip in antithyroglobulin or anti TPO antibody titers.

- Selenium
  - 200 mcg daily decreases thyroid autoantibodies (Thyroid. 2007. 17. 609-612).
  - In a 12 month study of 76 patients with autoimmune thyroiditis, sodium selenite 80 mcg daily was associated with a mean 30% drop in TPO antibody titers at 12 months in the treatment group (p=0.001), with 5 patients in the treatment group becoming TPO antibody negative (Clin Endocrin. 2010. 73. 535-539).
Hypothyroidism – toxic metals

- Heavy metal exposure is linked to thyroid disease – cadmium (Environ Health Perspect. 1999. 107. 843-849), mercury (Biol Trace Elem Res. 2008. 126. 1-12), and lead (Environ Res. 2008. 107. 380-392) – thus, consider heavy metal provocation testing, and treatment (medical food which induces metallothionein, zeololites, or chelation therapy) if body burden is identified upon provocation testing.
Hypothyroidism:
Levothyroxine versus dessicated thyroid extract (Armour®)

- In a crossover 16 week RCT of 70 patients with primary hypothyroidism, overall symptoms and neurocognitive measurements did not differ between the two groups. However, in a few patients, substitution of dessicated thyroid extract for levothyroxine was associated with weight loss – these patients presumably have a (rare) deiodinase polymorphism which is associated with a decreased T4 to T3 conversion in the brain (J Clin Endocrinol Metab. 2013. 98. 1982-1990 as cited in Update in Endocrinology. Ann Intern Med. 2014. 160. 785-790).

- 15-20% of the population has a polymorphism of the D2 enzyme which converts T4 to T3, as per an interview with Antonio Bianco, division chief of Endocrinology at Rush Medical Center (IMCJ. 2014. 13[3]. 20-22).
Insomnia

• Cognitive behavioral therapy - a systematic review of 20 RCTs (n=1162) shows that “CBT is an effective treatment for adults with chronic insomnia with meaningful effect sizes.” Mean time to fall asleep was 19 min less in the CBT group and total time sleeping was 26 min longer in the CBT group (Ann Intern Med. 2015. 163. 191-204 and editorial 236-237).

• Exercise – as effective as benzodiazepines in some studies

• Sleep hygiene
Insomnia - supplements

- Casein tryptic hydrosylate (75-225 mg/day, standardized to 2.2% casein decapeptide) has an affinity for GABA receptors. In a one month RCT of 32 men and women, those who received 150 mg of milk peptides reported 50% improvement in sleep quality and 30% less time to fall asleep (The Open Sleep Journal. 2009. 2. 26-32).

- Valerian 600 mg aqueous (labeling often suggests lower dose, but higher dose may be needed for efficacy), but odor of the herb may be an issue in regard to tolerance. Enhances deep sleep.
  - In a one month RCT of 100 postmenopausal women with sleep disturbance, those who received two capsules at bedtime, containing valerian 160 mg and lemon balm 80 mg showed improvement in quality of sleep (Complement Ther Clin Pract. 2013. 19. 193-196).
  - Valerian 530 mg twice a day beneficial in a 4 week RCT of menopausal women (Menopause. 2011. 18. 951-955).

- Many supplements with evidence of efficacy for anxiety may have efficacy in insomnia.
Insomnia – complementary modalities


- Tai Chi - effective in a 16 week study of 112 healthy older adults (Sleep. 2008. 31. 1001-1008).

- White noise – sound machines beneficial based on a Consumer Reports 2012 survey. See ‘Products – Sound Machines’ below

Menopause

- Acupuncture – published data is mixed

- Exercise
  - Observational studies show that women who exercise regularly are less likely than sedentary women to experience severe hot flashes (Acta Obstet Gynecol Scand. 2000. 79. 286-292; Maturitas. 2005. 52. 374-385).
  - In one study of 793 women age 55-56 who had reached natural menopause, the relative risk for severe hot flashes was 0.26 in the highly physically active women, versus those with little or no exercise (Maturitas. 1998. 29. 139).
Menopause (cont.)

• Paced respiration (slow, deep breathing) - shown effective in 2 controlled trials.
  - In one trial of 33 postmenopausal women, paced respiration training for 4 months significantly reduced the frequency of hot flashes by 39% (p<0.02) compared to control groups with progressive muscle relaxation or nontherapeutic alpha-wave EEG biofeedback (*Am J Obstet Gynecol.* 1992, 167, 436-439).
  - In another trial with 24 postmenopausal women with >5 hot flashes per day, those assigned to paced respiration had a 44% decrease in hot flashes (p<0.001) compared to biofeedback controls who had no change in hot flash frequency (*Menopause.* 1995. 2. 211-218).

• Relaxation response technique - A 7 week RCT with 45 women (33 completed the study) who were experiencing > 5 hot flashes daily, in which the treatment group practiced the relaxation response 20 minutes daily and the control group charted symptoms, showed no change in the frequency of hot flashes in either group, but a decrease in intensity of hot flashes only in the relaxation group [p<0.05] (*J Psychosom Obstet Gynaecol.* 1996. 17. 202-207).
Menopause (cont.)

- Black cohosh
  - Initially thought to contain phytoestrogens, but current consensus is that it does NOT have estrogenic activity; benefit may be mediated via an effect on the hypothalamus.
  - Clinical trial data – Mixed. A meta-analysis of 9 RCTs reported that 6 showed improvement in the black cohosh group, with overall improvement in symptoms of 26% as compared with placebo, but with significant heterogeneity between trials (*Alt Ther Health Med.* 2010. 16[1]. 36-44).
  - Safety in women with a personal or family history of breast cancer is unknown, with conflicting published data.
Menopause (cont.)

- DHEA - negative Cochrane review: A Cochrane review of 28 RCTs of postmenopausal women and 66 RCTs of perimenopausal women concluded that in symptomatic perimenopausal or postmenopausal women, DHEA did not improve menopausal symptoms and was associated with increased androgenic side effects (Cochrane Database Syst Rev. 2015. CD011066).


- Fish oil – mixed results
Menopause (cont.)


- Hops (Humulus lupulus) – mixed results


- Maca (Lepidium peruvianum) specifically from the highlands of Peru. Several positive RCTs (Int J Biomedical Sci. 2006. 2. 360-374; Int J Biomedical Sci. 2006. 2. 375-394; Menopause. 2008. 15. 1157-1162).
Menopause (cont.)


- Red clover (Alt Med Alert. 2008. 11. 90-93). Contains isoflavones, which are phytoestrogens. Clinical trial data – Mixed. Unknown whether long term use may be harmful in terms of a possible estrogenic effect on the uterus and the breast.

- Siberian rhubarb (Rheum rhaponticum) root extract – used widely in Germany since 1993. Several positive RCTs; a limitation of the ‘independent’ RCTs showing efficacy is that both have been carried out by the same contract research organization (Guest Editorial. Alt Ther Health Med. 2009. 15[1]. 24-34).
Menopause (cont.)

- Soy
  - Many published trials, and published meta-analyses and systematic reviews, with mixed results.
  - A meta-analysis of 17 RCTs of soy isoflavones found a pooled reduction of 20.6% in frequency and 26.2% in duration of hot flashes (p<0.0001) [*Menopause*. 2012. 19. 776-790].
  - A systematic review of 13 randomized, controlled trials of soy extracts for menopausal symptoms found that there is some evidence of efficacy, but the data overall is inconclusive (*Maturitas*. 2004. 47. 1-9).
Menopause (cont.)

• St. John's wort 300 mg 3 times a day with meals. The data is mixed


• Vitamin E – negative RCT

• Vitex - no controlled trial data for symptoms of menopause.
Osteoporosis

- Alkalization of the urine – beware of risk if chronic kidney disease
  - In a RCT of 161 women with osteopenia, oral potassium citrate, 30 mEq/day, which produced systemic alkalinization, led to significant improvements in bone mineral density (J Am Soc Nephrol. 2006. 17. 3212-3222).
  - Supplementation with potassium and magnesium citrate associated in a RCT with decreased urinary excretion of calcium, increased bone density, and decreased fracture (J Clin Endocrinol Metab. 2013. 98. 207-217).
Osteoporosis (cont.)

- Tai Chi - reduces the risk of falling; data is mixed regarding prevention of osteoporosis.

- Weight bearing exercise - in a RCT of 246 women age > 65, those assigned to the 18 month exercise program showed significantly improved bone mineral density and a reduced fall risk (*Arch Intern Med.* 2010. 170. 179-185).

- Weight training – increases bone density, also increases muscle mass, so a fracture is less likely with a fall, and improves balance so that falling is less likely to occur.
Osteoporosis – nutritional factors

• Dairy - limit intake
  – Despite the advertisements for milk for osteoporosis prevention, epidemiologic and cross cultural data actually show a positive correlation between intake of milk products and osteoporotic fractures (Hippocrates. July/August 1999. 53-55).
  – A 12 year Harvard study which prospectively tracked the dietary intake and medical histories of 77,761 women showed an increased risk of osteoporotic fractures associated with increased milk consumption (Am J Pub Health. 1997. 87. 992-997).
  – In a review of 37 studies of dairy or unsupplemented dietary calcium intake in children, adolescents, and young adults, 27 studies found no relationship between dairy or dietary calcium intake and measures of bone health (Pediatrics. 2005. 115. 736-743).
Osteoporosis – nutritional factors

• Protein – moderate intake. Despite conventional wisdom that high dietary protein intake can increase urinary calcium losses and theoretically increase the risk of osteoporosis (calcium balance is detrimentally affected by an increased intake of purified proteins), published data would suggest that it is actually low protein intake, which is associated with inadequate intake of phosphorous, which can increase the risk of osteoporosis.

• Soy – plentiful intake of whole soy foods. A 4 ½ year prospective cohort study looking at the relationship between usual soy food consumption and fracture incidence in 74,942 women aged 40-70 found a statistically significant inverse relationship between soy consumption and bone fractures; the relationship also showed a dose-response relationship across quintiles of soy intake (Arch Intern Med. 2005. 165. 1890-1895).
Osteoporosis – vitamins and minerals

• Calcium + Vitamin D – dosage of supplements controversial. 300-1000 mg daily for calcium and 800 – 2000 IU daily for vitamin D.

• Magnesium - clinical trial data is limited, with small, positive studies published (Magnes Res. 1993. 6. 155-163; Nutr Rev. 1995. 53. 71-74; Biol Trace Elem Res. 2010. 133. 136-143).
Osteoporosis - strontium


- In a Commentary (*Townsend Letter*: December 2012. Page 38), Dr Alan Gaby states that the data showed that the fracture-preventing effect of strontium tended to wane in years 6-10 despite progressive increases in BMD, and this suggests that some of the new bone formed during long term high-dose strontium treatment is not of high quality.

- Note that because strontium accumulates in bone and attenuates X-rays more than calcium (strontium has a higher atomic mass), DEXA studies will overestimate BMD when patients are taking high dose strontium. **Alert the radiologist reading the DEXA scan.**
Osteoporosis – strontium (cont.)

  – Low dose – a few strontium atoms replace calcium in hydroxyapatite crystals, and appear to enhance bone quality and strength.
  – High dose – effect of pharmacological doses of strontium are thought to be mediated by adsorption of strontium onto the crystal surface (as opposed to incorporation into the crystal lattice), where the strontium promotes bone formation and inhibits bone resorption. There is some concern that long term high dose strontium in humans might cause mineralization defects, and thus in clinical practice it may be wisest to consider a dosage reduction after one year, or to treat with high doses for one year on and one year off.

• Risks: European Medicines Agency released a warning about the use of strontium ranelate - the relative risk of serious heart problems is 1.6 as compared with placebo, and strontium ranelate is associated with an increased risk of venous thromboembolism.
Osteoporosis – vitamin K

• Catalyzes a structural change in osteocalcin, a protein in bone, such that the osteocalcin attracts calcium, enhancing mineralization of bone.

• A systematic review of 13 RCTs, all longer than 6 months in duration, 7 of which reported data on fractures, found that supplementation with phytonadione (1 – 10 mg/day) and menaquinone-4 (15 – 45 mg/day) reduces bone loss, and that supplementation with menaquinone-4 is protective against fractures. These 13 trials varied in size from 20 participants to 241 participants, and some included co-supplementation with other vitamins and minerals. NOTE that most of these trials were conducted in Japanese women (Cockayne S et al. Vitamin K and the Prevention of Fractures: Systematic Review and Meta-analysis of Randomized Controlled Trials. *Arch Intern Med.* 2006. 166. 1256-1261).

• Negative trials too, though (inconsistent results in clinical trials might be due to a confounding effect of vitamin D status).
Osteoporosis - supplements

- Genistein - a 24 month RCT of 389 postmenopausal women with osteoporosis showed that genistein 54 mg/day had positive effects on BMD. Note though that 19% in the genistein group versus 8% in the placebo group discontinued treatment due to side effects, most often GI side effects with genistein (Ann Intern Med. 2007. 146. 839-847).

- Ipriflavone
  - This is a derivative of a naturally occurring class of isoflavones found mainly in soy.
  - Approved for treatment of osteoporosis in some European and Asian countries.
  - Clinical trial data to date is conflicting.

- Soy protein – clinical trial data and meta-analyses show mixed results.

Polycystic Ovarian Syndrome (PCOS)

- Diagnostic criteria – 2003 Rotterdam PCOS consensus workshop
  - at least 2 of the following 3
    - Oligo- or anovulation
    - Clinical and/or biochemical signs of hyperandrogenism
    - Polycystic ovaries
PCOS - supplements

  - As compared with myo-inositol, D-chiro-inositol had a greater impact on hyperandrogenism measurements.

• Inositol - in a RCT of 281 women, those randomized to 100 mg inositol twice a day showed improvement in ovarian function (\textit{Eur Rev Med Pharmacol Sci.} 2003. 7. 151-159).
PCOS - supplements

• Myo-inositol powder 2 grams twice a day. As compared with D-chiro-inositol, myo-inositol, had a greater impact on the metabolic profile. Citations are as follows:
  - Gynecol Endocrinol. 2007. 23. 700-703.
  - Minerva Ginecol. 2012. 64. 23-29 (in Italian).
  - Arch Gynecol Obstet. 2013. 288. 1405-1411.
  - Nat Med J. 2013. 5. 6.
PCOS - supplements

- NAC
  - 600 mg bid with Clomid® increased fertility in two well done RCT’s in women with Clomid resistant infertility (Fertil Steril. 2005. 83. 367-370; Acta Obstet Gynecol Scanda. 2007. 86. 218-222).
  - Benefits seen in a 24 week RCT of 100 women with PCOS, hirsutism, and irregular menses – those randomized to 600 mg three times a day showed significant improvements in hirsutism score, insulin sensitivity, and regularity of menses. Metformin 500 mg daily was the comparator treatment in this trial, and benefits with metformin and NAC were similar (Eur J Obstet Gynecol Reprod Biol. 2011. 159. 127-131).
  - Possible mechanism is improved insulin sensitivity (Fertil Steril. 2002. 77. 1128-1135).
Schizophrenia

- Vitamin B3 (niacin)
  - 3-6 grams daily (may increase to 30-60 grams daily).
  - As per clinical experience of Dr Abram Hoffer, use at least 1 gram three times a day for at least 5 years before judging this a treatment failure.
  - Niacin is not truly a vitamin; it is synthesized from tryptophan in humans, with 1.6% of tryptophan is converted to niacin. Hypothesized that this conversion is impaired in schizophrenics.
  - Supplementation may cause elevated transaminases, but this does NOT necessarily imply liver damage
    - No need to discontinue unless AST or ALT > 3 times upper limit of normal.
    - IF LFTs are elevated, stop niacin for 5 days and repeat – if elevated LFTs are due to true liver damage, LFTs will still be elevated, but often with niacin LFTs normalize within a few days off niacin.
    - Transaminases may be elevated secondary to methyl depletion, since niacin is a methyl acceptor – may be able to offset increases with 1.2 g lecithin bid or betaine.
Schizophrenia (cont.)

• Vitamin C - 3-40 grams daily (optimum dose is just below the laxative dose; doses as high as 100 grams have been used in cancer).
  - There is data that schizophrenic patients can metabolize ten times more vitamin C than healthy people (Int J Neuropsychiatry. 7/22/65; Biol Psychiatry. 1990. 28. 959-966).

• Glycine, D-serine, D-cycloserine - in a meta-analysis of 18 double-blind, placebo-controlled trials of glycine (n=7), D-serine (n=2), D-cycloserine (n=2) and ampakine CX516 (n=2), in addition to antipsychotics, treatment with glycine and D-serine moderately but significantly improved negative symptoms scores (Schizophrenia Research. 2005. 72. 225-234).
Schizophrenia (cont.)

• Fish oil
  – In a study of 20 chronic schizophrenics, 6 weeks of treatment with 10 grams per day of marine derived EPA led to significant improvements in negative symptoms (Lipids. 1996. 31. S163-S165).
  – A Cochrane review concludes that there is no clear evidence of benefit (Cochrane Database Syst Rev. 2006. CD001257).

• Ginkgo biloba and treatment of refractory schizophrenia – a 12 week RCT in China in which 56 patients received Haldol plus 360 mg per day of standardized extract of ginkgo and 53 patients received Haldol plus placebo showed that ginkgo increased the effectiveness of Haldol and reduced its side effects (J Clin Psychiat. 2001. 62. 878-883).
Schizophrenia (cont.)

- NAC – effective in chronic schizophrenia (average duration of 12 years) in a 6 month RCT in 140 patients administered 1 gram bid. Significant improvements were noted for negative symptoms, global functioning and abnormal movements. A qualitative review of the treatment effects identified the following patterns: the NAC group made gains in insight, self-care, social interaction, volition and stability of mood. (*Biological Psychiatry*. 2008. 64. 361-368).
  - Theoretical basis is low glutathione levels in schizophrenic brain (*Neurobio Disease*. 2006. 624-632).
  - NAC also is a glutamate receptor antagonist.
Schizophrenia (cont.)

• Resources
  – Bio Center Lab in Wichita Kansas
  – International Society for Orthomolecular Medicine/International Schizophrenia Society
  – Pfeiffer Treatment Center
  – Walsh Research Institute

• References