
Natural Therapies in the Management of Psychiatric Disorders:

An Update on the Scientific Literature on the Use of
Dietary Supplements, Vitamins, and Medical Foods

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Financial Disclosures

Speaking Bureau:

- Allergan
- Janssen
- Intracellular


No conflict of interest in this presentation

Learning Objectives and Topic Outline





- Define dietary supplements and their regulation
- Review current trends in supplement use
- Learn how educate yourself and patients in safe supplement use
- Understand quality issues and risks of supplements
- Review literature on common supplements in mental health disorders
- Identify best supplement educational resources
- Discuss the legal and ethical risks of recommending/selling supplements

Why the growing use of non-conventional therapies?

- Prescription medicine side effects
- Cost of seeing a HCP and getting treatment
- Concern over long term effects of medicines
- Increased publicity over lack of benefit of conventional therapies
- High profile personalities advocating non-traditional therapies
- Stigma of treatment
- Perception of supplements as benign, safe, and a more “natural” approach to preventing or treating illness



Using Alternative Therapies

<p>WHO reports 80% of people in world rely on herbs to manage health issues</p> 	<p>In US, 1/3 have used a natural remedy at least once for a health condition</p> 	<p>20,000 medical plants have been identified, 1100 well researched, and 250 species are used for obtaining modern drugs</p> 	<p>Holistic-treating the entire person, not just the symptom, disease, or condition</p> 
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Definition of Dietary Supplement

- A vitamin, mineral, herb or other botanical, amino acid, a dietary substance used to supplement the diet, or is a concentrate, metabolite, constituent, extract or combination thereof
- Orally administered
- Labeled as a dietary supplement
- And is not a conventional food, antibiotic, drug, or investigational new drug.
- Complies with all related regulations (NLEA, etc)

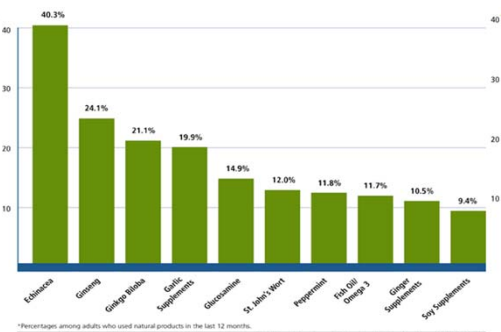
Dietary Supplement Health and Education Act (1994)

CRN Survey-2014

- 10,000 people surveyed
- 68% of reported taking supplements on a regular basis
- 97% use vitamin/mineral supplements
 - 75% multivitamins
 - 30% Vit D
 - 24% Calcium, Vit C
 - 21% B/B complex
- Specialty supplements- 19% Omega 3, 10% probiotics
- 26% Herbs/Botanicals—10% green tea
- 19% Sports/Weight Management

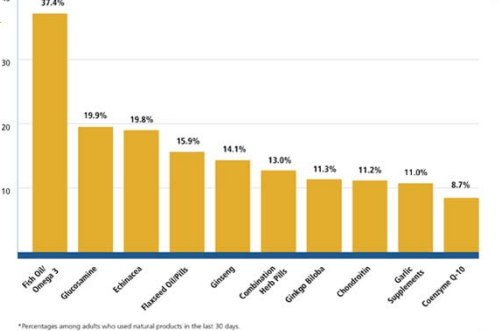
WWW.CRNUSA.ORG

10 Most Common Natural Products among Adults -2002



**Percentages among adults who used natural products in the last 12 months.
Source: Barnes R, Powell-Grier L, McFann K, Nahri R. CDC Advance Data Report #343. Complementary and Alternative Medicine Use Among Adults: United States, 2002. May 2004.

10 Most Common Natural Products among Adults -2007



**Percentages among adults who used natural products in the last 30 days.
Source: Barnes PK, Bloom B, Nahri R. CDC National Health Statistics Report #112. Complementary and Alternative Medicine Use Among Adults and Children: United States, 2007. December 2008.

CRN Survey

69%
of supplement users say their physician has talked to them about the **BENEFITS** of taking supplements

55%
of supplement users identify medical doctors/physicians as a **TRUSTED SOURCE** for reliable information on supplements

1 Polypharmacy—Time to Get Beyond Numbers. Steinman M. JAMA Int Med. Published online March 21, 2016.
2 Nondisclosure of Complementary and Alternative Medicine Use to Primary Care Physicians: Findings from the 2012 National Health Interview Survey. Jou J, Johnson PJ. JAMA Int Med. Published online March 21, 2016.

Dietary Supplement Regulation

- Dietary Supplement Health and Education Act 1994
 - Testing on safety and efficacy of supplements is in the hands of the manufacturer.
 - The FDA is not required to approve these products, and by law, companies can selectively provide information to FDA and consumers.
 - The 1994 Dietary Supplement Act does not require that dietary supplements be shown to be safe or effective before they are marketed.
 - If a product is suspected to be unsafe, the FDA must investigate before they can take the product off the market.
- Dietary Supplement and Nonprescription Drug Consumer Protection Act (2006)
 - Require manufacturers to notify FDA about serious AEs

Changes to Current FDA Regulation

- **Dietary Supplement Labeling Act 2013**
 - Manufacturers no longer evade stricter safety requirements by simply re-categorizing their products. Companies must register their dietary supplement products with the FDA
 - Directs FDA to research dietary supplement ingredients that could potentially cause serious health problems, drug interactions, contraindications, or potential risks to subgroups such as children and pregnant or breastfeeding women.
 - Any such severe hazards would have to appear as a warning on the dietary supplement label.
- The FDA does not scrutinize a dietary supplement before it enters the marketplace but is permitted to restrict a substance if it poses a "significant and unreasonable risk"

Supplement Promotion Guidelines

- Disease claims are not permitted such as "reduces the stiffness of arthritis" but "supports the immune system" is permitted
- A product name that implies an effect on a disease, e.g. "Hepatocure" would constitute a disease claim, but names such as "Cardiohealth" or "Heart Tabs" would not.
- Can make health-maintenance claims ("maintains a healthy circulatory system"); other non-disease claims ("for muscle enhancement," "helps you relax,"); and claims for common, minor symptoms associated with pregnancy, menopause, or other life stages (e.g., "for common symptoms of PMS," "for hot flashes")
- May make misleading statements such as "vitamin A is essential to good eye function"

cGMP-CURRENT

- "The manufacturer is thus responsible for ensuring that the ingredients used in the production of a dietary supplement are such that they produce a product consistently meeting cGMPs"
<http://www.fda.gov/Food/GuidanceRegulation/CGMP/ucm173996.htm>
- In 2012, FDA inspected 361 dietary supplement facilities
- About 70% received notice of cGMP deficiencies (253/361)
- Average number of observed deficiencies/audit: Seven
- Most common: failure keeping a recipe, verifying ingredients, sanitation.

<https://www.naturalproductsinsider.com/news/2013/05/fda-gmp-inspectors-cite-70-of-dietary-supplement.aspx>

ADULTERATION AND CONTAMINATION

- Posadzki et al (2013) published an overview of 26 systematic reviews
- Most Common Contaminants: Dust, pollens, insects, rodents, parasites, microbes, fungi, mold, toxins, pesticides, toxic heavy metals and/or prescription drugs
- Most Severe Adverse Events: Agranulocytosis, meningitis, multi-organ failure, perinatal stroke, arsenic, lead or mercury poisoning, malignancies or carcinomas, hepatic encephalopathy, hepatorenal syndrome, nephrotoxicity, rhabdomyolysis, metabolic acidosis, renal or liver failure, cerebral edema, coma, intracerebral hemorrhage, and death
- Incidence highest in traditional Indian and Chinese herbal products/medicines

Contamination and adulteration of herbal medicinal products (HMPs): an overview of systematic reviews. Posadzki, P., Watson, L. & Ernst, E. Eur J Clin Pharmacol (2013) 69: 295.

Who is Minding the Store?



Ingredients are Sold in Supplements in US



How Are Products Stored?



What Does GMP Certification Really Mean?



What Are the Primary Sources of Dietary Supplement Recommendations?



Accuracy in the Media?



Cease and Desist Controversy- NY Attorney General Office 2015

- NY AG commissioned testing of supplements from GNC, Target, Walgreens, and Wal-Mart
- Echinacea, garlic, ginkgo, ginseng, St Johns Wort, and valerian
- Only 21% contained DNA from plants listed on label
- Wal-Mart-least amount at 4%
- Cease and desist letters and significant press attention
- DNA barcoding not reliable –esp in extracts
- Should use with microscopy and validated chemical methods
- Many of the products when retested did show product listed

1. A.G. Schneiderman Asks Major Retailers to Halt Sales of Certain Herbal Supplements as DNA Tests Fail to Detect Plant Materials Listed on Majority of Products Tested [press release]. Albany, NY: New York Attorney General's Office; February 3, 2015. Available at: www.ag.ny.gov/press-release/ag-schneiderman-asks-major-retailers-halt-sales-certain-herbal-supplements-dna-tests

2. O'Connor A. New York Attorney General Targets Supplements at Major Retailers. New York Times. February 3, 2015. Available at: http://www.blogs.nytimes.com/2015/02/03/new-york-attorney-general-targets-supplements-at-major-retailers/?_r=0

3. O'Connor A. What's in Those Supplements? New York Times. February 3, 2015. Available at: <http://www.blogs.nytimes.com/2015/02/03/sidebar-what-in-those-supplements/>

Use of Non-Conventional Therapies In Psychiatric Disorders

Prevalence of Supplement Use in Psychiatric Disorders

- Those with psychiatric disorders are more likely to use non-conventional therapies than general population
- Nearly 30% with GAD, mood swings, or psychosis have used non-conventional therapies
- Approximately 66% have used non-conventional with conventional therapies
- 90% of those have seen a psychiatrist or other MHP

Use of Supplements in Anxiety Disorders

- Survey of 1004 adults
- Ages 18–75 who met DSM-IV criteria for Generalized Anxiety Disorder (GAD), Panic Disorder, Social Anxiety Disorder, or Post-Traumatic Stress Disorder.
- 43% use of a variety of CAM treatments; older and more educated, multiple conditions

Psychosomatics 2012 May-June 53 (3): 266-272
Mantani R, Cimino A. A primer of complementary and alternative medicine and its relevance in the treatment of mental health problems. Psychiatr Q. 2002;73(4):367-381.

Clinical Pearls

- Ask your patients the right way about supplement use-create a safe zone
- Many supplements, especially botanicals, contain multiple compounds, many of which have different effects
- Don't believe everything you read or hear
- Always read the labels
- Know the manufacturer and the distributor of the supplement
- Don't treat a symptom with a supplement-supplements should be part of a balanced lifestyle
- Above all, do no harm

Depression and Complementary Therapy

- Omega 3
- St John's Wort
- SAMe
- Saffron
- 5-HTP
- Vit B12
- Vit D
- Vit B6, Mg, Zinc

Omega-3 in Depression

- Omega 3 most widely used non-vitamin supplement used in US-adults and children
- Diets high in omega 3 have lower rates of MDD, BP, and perinatal depression
- Factory farming, substituting animal fats for vegetable oils, and increases use of soy/corn has lowered omega 3 to 6 ratio from 1:1 -4:1.2 to 10:1-20:1.2
- Hard to assess diet intake as predictor of response to supplementation
- No reliable data for monotherapy use in MDD
- Signal but inconclusive data on adjunctive tx in MDD

Not All Omegas Are The Same

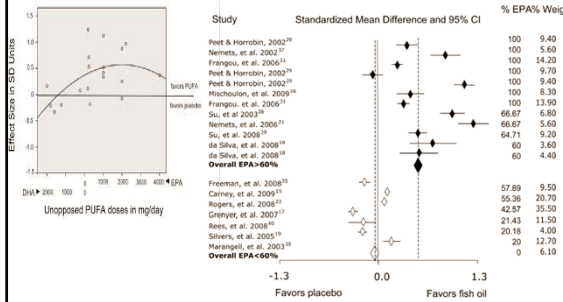
- EPA (eicosapentaenoic acid) affects endothelial function, anti-inflammatory
- DHA (docosahexaenoic acid)-regulates signaling and functioning in cell membrane/neuronal tissue
- EPA benefits independent of DHA (? Anti-inflammatory vs. correction of membrane DHA deficiencies).
- Response to EPA greater with increased pretreatment biomarkers of inflammation. DHA and EPA less effective with low inflammation.
- Omega 6 crucial for brain development but contradictory evidence that it benefits mood. Possible risk of increased inflammation.
- Short chain (ALA)- plant based-not easily converted

Omega-3 Studies in Depression

- 5 DB, PLC as mono therapy in MDD (1 in pregnancy, 1 in children)-showed benefit
- 4 studies showed no benefit
- 7 studies as adjunctive tx with mixed results
- Dosing ranges from 1-9 g/d; High EPA doses or ratio to DHA yield better results; no benefit seen above 1-2 g/d
- Omega 3 supplementation with antidepressants demonstrate an effect size of 0.61.

Sublette et al Meta-analysis of Effects of EPA. J Clin Psych 2011

EPA Dosing in Depression




Sublette et al Meta-analysis of Effects of EPA. J Clin Psych 2011

Omega-3 Summary

- Appropriate to recommend 1 gram a day of EPA (DHA doses not clear-possible competition for same site)
- No evidence that EPA monotherapy outperforms combination
- Higher inflammation may predict benefit
- 2006-APA adopted AHA for consumption of fish 2 times a week and supplementation 1-9 gram
- 3 grams or greater require physician monitoring due to bleeding risk
- Low fat diets may be contraindicated in psychiatric patients.

St John's Wort in Depression

- Hypericum perforatum, yellow flowering plant indigenous to Europe
- Dosing 300-1800mg; usually TID-typical dose 900mg
- Known also as **Tipton's weed, rosin rose, goatweed, chase-devil, or Klamath weed**
- Antidepressant, antibacterial, and anti-inflammatory
- Name comes from its traditional flowering and harvesting on St John's Day, June 24th
- Chemical components-hypericin,pseudohypericin, and hyperforin
- Germany's Commission E supports use and describes mechanism of action as inhibitor of neurotransmitter reuptake.



Mech of Action of St John's Wort

May inhibit cytokine production on IL-6, ILB, dec CRH, reducing cortisol; may also inhibit reuptake SHT, NE, DA

Hypericin

Hyperforin

5% extract > effect than 0.5% in depression

Possible increase in monoamines and glutamate via uptake inhibition

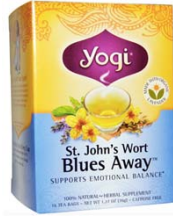
St John's Wort Studies in Depression

- Cochrane Summary 2009-review 29 studies in 5489 subjects for 4-12 weeks vs. PLC or other ADT
- Generally used in mild to moderate depression, better results in German-speaking countries where prescribed by physician
- Some smaller studies may have been overly optimistic and flawed affecting results
- Typically effective, similar results to ADT, fewer side effects than ADT
- Two studies, both sponsored by NCCAM and NIMH
 - Neither St. John's Wort vs. Zoloft decreased symptoms of minor depression better than a placebo (2011).
 - No more effective than placebo in treating major depression of moderate severity (2012).

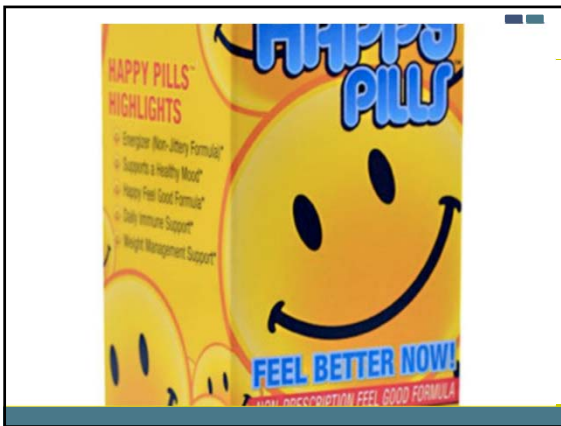
[http://www.cochrane.org/CD000448/DEPRESS_st.-johns-wort-for-treating-depression.](http://www.cochrane.org/CD000448/DEPRESS_st.-johns-wort-for-treating-depression)

Safety and St John's Wort

- Taking St. John's wort can affect other prescription medicines
 - Strong CYP 3A4 inducer; PGP
 - Antidepressants and some antipsychotics
 - Birth control pills
 - Cyclosporine
 - Digoxin
 - Some HIV, cancer, transplant medications
 - Warfarin, other blood thinners
- Sensitivity to sunlight
- Increased anxiety due to stimulant properties
- Upset stomach
- Serotonin syndrome with other ADT, migraine meds, etc



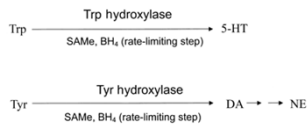
<http://nccam.nih.gov/health/stjohnswort/sjw-and-depression.htm>



Nutrition Facts		
Amount Per Serving		% Daily value
Serving Size :	2 Capsules	
Serving per Container :	30	
Proprietary Blend	502mg	
St. Johns Wort		
Caffeine Anhydrous		
5 Hydroxytryptophan		
N Acetyl Tyrosine		
S Adenocetyl Methionine		
Huperzine A		
Vitamin D	1200IU	300
Thiamin (B1)	50mg	3333
Niacin (B3)	25mg	125
Vitamin B6	40mg	2000

S-Adenosyl-L-Methionine (SAME)

- One of the best studied natural therapies
- Naturally occurring substance produced in mammals from L-methionine and adenosine triphosphate (using B12 and folate)
- Not a plant extract, vitamin, or mineral
- Major donor of methyl group in brain needed to synthesize hormones, neurotransmitters (NE, SHT, DA), nucleic acids, and phospholipids
- Low SAME detected in CSF of depressed persons



Alpert and Mischoulon Natural Medications for Psychiatric Disorders 2002

SAMe

- Nearly 40 clinical trials, mostly small Ns, poorly controlled
- Dose ranges 200 to 1600mg
- Some studies showed faster onset of action, 2 studies SAMe showed faster onset of action than tricyclic alone
- Usually well tolerated, few AEs; middle insomnia, dec appetite, constipation, nausea, dry mouth; mania reported in bipolar pts
- Older studies may have failed due to dissolution and stability
- Most early positive trials were with IV preparations
- Meta-analysis dosage up to 1600mg/day; usually 400mg doses suggested by distributors



SAMe-Recent Studies

- Sarris et al-DB, RCT of 107 non-remitted depressed outpts on antidepressants received 800mg SAMe vs placebo.
- Authors looked at response predictors including genotypes such as COMT, red cell folate, homocysteine, or BDNF.
- Response rates 54.3% SAMe vs 50.0% in placebo, Remission 43.5% vs 38.3%
- Cochrane review (2016)- 8 DB, RCT-934 patients
 - No difference in SAMe vs IMI vs escitalopram
 - Better than placebo when added to SSRI-low quality
 - No difference between SAMe vs placebo alone-low quality
 - Fewer side effects than IMI-similar to other antidepressants

Sarris J, Byrne GJ, Bousman C, Stough C, Murphy J, MacDonald P, Adams L, Nazareth S, Oliver G, Cribb L, Savage K, Menon R, Chamoh S, Berk M, Ng C, Mischoulon D. Eur Neuropsychopharmacol. 2018 Oct;28(10):1126-1136. doi: 10.1016/j.euroneuro.2018.07.098. Epub 2018 Aug 14.

Saffron in Major Depression

- Spice derived from flower *Crocus sativus*
- First cultivated in Greece; 90% now produced in Iran
- Minoans reported therapeutic uses in 1500BC
- Cleopatra used in her baths to enhance lovemaking
- Great variety of quality and strengths based on styles
- Mechanism Theories
 - May increase 5HT via reuptake inhibition, mech unknown, shown in animal studies
 - Crocetin, crocins, and safranil may protect against reactive radical O2 species and proinflammatory cytokins



Meta-Analysis of Saffron in Major Depression

- Ages >18, randomized studies, either placebo control or antidepressant comparison
- Of 21 studies, only 5 met criteria for review
- Trials ranged from 6-8 weeks, HAM-D>18, 30mg dose
- 2 studies of saffron vs plc showed large effect size
- 3 studies vs ADT (fluoxetine or IMI) both groups improved, no diff observed, >AEs in IMI group
- Common adverse effects-headache, nausea, anxiety, decreased appetite
- Saffron was effective for short term use
- Doses 20mg BID-30mg TID

Hausenblas et al J of Integrative Medicine Nov 2013

Turmeric/Saffron Combination in Adjunctive Tx Major Depression

- No studies of either greater than 8 weeks
- High dose, combination tx, for 12 weeks, 1 week placebo run in
- N=123, single site, IDS-SR30 >18, allowed to stay on antidepressant if stable dose >4 weeks
- Placebo vs curcumin 500mg vs 1000 mg curcumin vs 500 mg curcumin +30 mg saffron
- All groups improved but placebo only improved through wk 4
- 13% (plc) vs 28 % (high dose curcumin) vs 27% (low dose) v-s 31% (combo) decrease-not stat sig
- Sub analysis showed atypical depression (N=34) improved p<0.007 and anxiety measure p<0.009
- Curcumin beneficial on anxiety and depression but no difference adding saffron or higher dose curcumin
- Only significant AE trend of increased loose stool and spicy after taste in both curcumin groups
- Limitations: self reported scales, ? underpowered to detect differences

Logreest AL, Drummond PG. Efficacy of Turmeric/Saffron Combination for the Treatment of Major Depression: A Randomized, double-blind, placebo-controlled study. J Affect Disorder 2017; 207:188-196

5-HTP in Depression

5-Hydroxytryptophan

- Chemical by-product of the protein building block L-tryptophan.
- Produced commercially from the seeds of an African plant (*Griffonia simplicifolia*).
- Amino acid used in synthesis of NT, 5HT, and melatonin

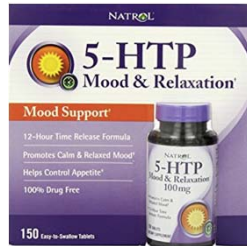
Cochrane Review

- 108 trials were reviewed; only 2 met standards for review
- Total of 64 subjects; 5-HTP >placebo for depression
- Conclusion-insufficient data to make a claim of safety and efficacy
- Dose range 50-300mg (some studies as high as 3000mg???)

Shaw K, Turner J, Del Mar C. Tryptophan and 5-hydroxytryptophan for depression. *Cochrane Database Syst Rev* 2001;(3)

5 HTP in Depression-Risks

- Potentially fatal Eosinophilia-Myalgia Syndrome associated with L-tryptophan-most likely a contaminant in manufacturing
- Possible drug interactions with other SSRI and other 5HT drugs
- Increased risk of seizures in Down's Syndrome
- Possible side effects:
 - Heartburn
 - Stomach pain
 - Nausea, vomiting
 - Diarrhea
 - Drowsiness
 - Sexual problems
 - Muscle problems



Inositol

- Sugar alcohol (similar to glucose), located in cell membranes, typical human consumption approx. 1 gram a day
- Barkai et al-low levels of inositol in CSF of depressed patients
- May work through a second messenger system affecting cell signaling; possibly bypassing first messengers such as 5-HT, NE
- Lithium may inhibit inositol-1-monophosphatase decreasing inositol levels
- Depression
 - 27 subject completed trial, monotherapy
 - Doses 12 grams
 - No change in 2 weeks, sig change HAM-D in 4 weeks
 - 27 pt study as add on to SSRI-no benefit
 - 42 pt study in SSRI non-responders after 3 weeks-no benefit
- Few side effects-flatulence, inc glucose levels, nausea, sleepiness

Vitamin Therapy and Depression



Vitamin D

- Receptors in amygdala, may be neuroprotective and pro-cognitive
- Higher rates of Vit D Deficiency in depression
- Review of 7 (N=3200) of effect of vitamin D supplementation on depression was small and not clinically meaningful.
- Re-analysis suggested vitamin D may help patients with clinically significant depression, particularly when combined with traditional ADT

Vitamin B12

- Involved in DNA synthesis, homocysteine formation, and synthesis of S-adenosylmethionine
- Vegetarians, Gastric bypass, H2 blockers, age, heavy alcohol use, IBS/Crohns, associated with low B12 levels
- Low levels assoc with depression; lower levels assoc with poorer response to antidepressants; no evidence B12 helps depression if levels normal
- Depression/Dementia- may have normal serum levels but low CSF

Vitamin Therapy and Depression



Vit B6

- Cofactor in synthesis of dopamine, NE, GABA, 5-HT
- Low P5P doubled risk of depression in elderly
- 50mg improved depression/irritability/fatigue in PMS

Magnesium

- Low levels associated with depression and neuropsychiatric symptoms
- Magnesium as effective as Imipramine but better tolerated in depressed elderly with T2DM; IMI higher drop out rate
- Risks with medical conditions, medications, and OD-may affect heart rhythm, BP, and could be fatal

Zinc

- Modulates glutamate, lower Zinc levels shown in depression
- In a DB, placebo controlled trial, Zinc + antidepressant showed a greater reduction in depression scores than antidepressant alone-

Nutraceuticals May Be Effective Adjuncts to Antidepressants



- Meta-Analysis of 40 studies up to December 2015
- 31 double blind, placebo controlled; 4-8 weeks, mean sample 63 subjects
- Variety of open label antidepressants used, mainly SSRIs
- Positive effect 68% of trials
- Positive replicated studies for **SAME, methylfolate, omega-3 (mainly EPA), and Vitamin D**
- Mixed results with **Zinc, folic acid, Vitamin C, tryptophan**
- No benefit from inositol
- Mechanistic therapies range from altering neurotransmitters and/or receptors, glutathione antioxidant activity, cell membrane fluidity, and anti-inflammation

J Sarris, J Murphy, D Mischoulon, G Papakostas, M Fava, M Berk, C Ng. Adjunctive Nutraceuticals for Depression: A Systematic Review and Meta-Analyses. Published online April 26, 2016.
<https://doi.org/10.1176/appi.ajp.2016.15091228>

Depression-Summary

St. Johns Wort

- Dosing around 300mg TID; probably ok if few medical problems or concomitant medications, mild depression

SAMe

- Safe, 800-1600mg in divided doses

5-HTP

- Probably ok, caution with SSRIs, dosing 50mg 1-3 times a day

Omega-3

- Why not? EPA 1-2 grams a day

Optimize Mg, B12, Vit D, Zinc, and Folic acid/Methyfolate

Natural Therapies in Anxiety/Insomnia

1 Kava-kava

2 Valerian

3 Passion Flower

4 Magnesium

5 Inositol

Kava Extract in Anxiety

- Used as ceremonial and recreational drink in Oceania
- Roots are ground into a pulp
- Kava (*Piper methysticum*)
 - Member of pepper family native to S Pacific
 - Active ingredients are alpha-pyrone and kavalactones
 - Targets GABA receptors
- Possible abuse potential at supratherapeutic doses
- Suggested dose range 100-200mg
- Reports of liver toxicity
 - Most reports are incomplete and inconclusive
 - 50-100 cases in literature
 - Many be related to other components of kava, not the kavalactones
 - Some cases led to liver transplant and death

Livertax.nih.gov/kavakava

Kava Extract in Anxiety

- Cochrane Review (2010)
 - 22 DB, PLC studies, 12 met inclusion criteria (N=700)
 - Meta analysis of 7 studies showed sig change on HAM-A but small effect size
 - AEs were mild, transient
 - Safe short term (1-24 weeks), no long term data
- Duke Study
 - 3 PLC controlled studies meta-analysis (N=64)
 - No benefit
- Case reports of coma with kava+BNZ



Connor KM, Payne V, Davidson JR. Kava in generalized anxiety disorder: three placebo-controlled trials. Int Clin Psychopharm 2006 Sep;21(5):249-53.

Other Alternative Therapies in Psychiatry

- **Valerian**
 - Used for insomnia and anxiety
 - Only one study was identified, involving 36 patients and comparing valerian with placebo and diazepam. This study found no significant differences in effectiveness between valerian and placebo, or between valerian and diazepam
- **Passiflora (passion flower)**
 - Used for treating anxiety
 - Only two studies were eligible for inclusion, involving a total of 198 participants.
 - One study showed that passiflora was as effective as benzodiazepines, with similar dropout rates between the two treatments.



Miyasaka LS, Atallah AN, Soares B 21 January 2009

Inositol Studies in Anxiety

- Panic**
 - One placebo controlled study (N=25)
 - Attacks decreased from 10 to 6 on placebo; inositol from 10 to 3.5
 - Doses 6 grams BID
 - One study-inositol vs. fluvoxamine; inositol showed greater reduction in first month, second month no difference
- Bulimia/OCD**
 - Small studies showed improvement over PLC
- Other Indications**
 - No improvement in schizophrenia, ADHD, autism, dementia



Benjamin J, Levine J, Fux M. Double-blind, placebo-controlled, crossover trial of inositol treatment for panic disorder. Am J Psych 1995 Jul;152(7):1084-6.

Mischoulon et al Natural Medications for Psychiatric Disorders 2006

Review of Evidence of CAMs in ADHD

- More than 50% of parents using CAMs but few disclose to pediatrician
- Sarris et al systematic review of CAMs-Complementary Therapies in Medicine (2011) 19, 216–227
- Reviewed only methodologically sound studies based on randomization criteria, diagnostic criteria, sample size, outcome measures, duration, and study quality.
- Of 2354 studies, 233 were RCT. Only 16 of those met quality criteria
- Nutritional medicine: Zinc, iron, omega-3, vitamin c, acetyl-L-carnitine
- Herbal medicine: ginko biloba, St. John's wort, Pinus marinus (French maritime pine bark), and Ningdong Granule (Chinese herbal formula)

Complementary Therapies in Medicine (2011) 19, 216–227

Other Alternative Tx in ADHD

St John's Wort	<ul style="list-style-type: none"> • Inhibits 5-HT, NE, and DA • Webster et al-54 children (6-17), BD/PC, negative • One positive case series, 3 subjects
Iron	<ul style="list-style-type: none"> • Low ferritin/iron assoc with ADHD symptoms • Konofal et al (2008)-23 children, iron deficient ARS improved but not Conner's • RLS improved ?helping ADHD symptoms
Magnesium	<ul style="list-style-type: none"> • Omega3 and 6 +Mg showed modest improvement but not controlled, poorly done study
Ginko biloba	<ul style="list-style-type: none"> • Case series of 6 positive, RCT of 50 children showed no change compared with MHP

L-Theanine in Alertness and Cognition

- 35 subjects give high dose 50 mg of L-theanine or placebo with caffeine. Greater inc in alpha activity
- Effect of caffeine with and without L-theanine on cognition and mood in 27 participants.
- Combination improved speed and accuracy in an attention-switching task, as well as reduced the likelihood of distraction during a memory task.
- Caffeine alone did improve alertness and accuracy
- Generally safe-main side effects relate to high tea/caffeine usage i.e. GI, nausea. May affect levels of chemotherapy agents, lipid lowering, and sedatives

Haskell CF, Kennedy DO, Milne AL, Wesnes KA, Scholley AB. The effects of L-theanine, caffeine, and their combination on cognition and mood. *Biol Psychol*. 2008;77(2):113-122.

Ginkgo Biloba in Cognitive Disorders

- From tree native to China
- Leaves and fruits used in Chinese medicine for centuries
- Extract Egb used as medicine in over 50 countries for dementia, CAD, retinal problems, tinnitus
- Need a standardized extract, leaves must be harvested at precise times
- Meta-analysis (2012) 4 randomised, controlled trials (N=1294) investigating the efficacy of Ginkgo biloba extract EGB 761(*) in elderly patients with Alzheimer or vascular dementia with neuropsychiatric features.
 - Some improvements in cognitive performance/behavioral symptoms; minimal improvements or signs of progression
- GEM study- (N=3069) over 5.8 years-120mg BID
- Not effective in lowering the overall incidence rate of dementia nor Alzheimer's disease incidence in normal elderly or elderly people with mild cognitive impairment

Int J Psychiatry Clin Pract. 2013 Nov;17 Suppl 1:8-14. doi: 10.3109/13651501.2013.814796. Epub 2013 Aug 17.
Difonzo ST, Williams JD, Fitzpatrick JJ, et al. Ginkgo biloba for Prevention of Dementia. Journal of the American Medical Association. 2008;300(15):2253-2262.

Natural Therapies in Bipolar

- Omega 3
 - Meta-analysis of RCT >4 weeks showed omega-3 improved depressive but not manic phase (p=0.029)
 - Meta-analysis showed highly stat improvement in men depression scores using random effects model (p=0.001)
- Magnesium
 - One study of 9 inpatients used 243 of elemental Mg up to 486 mg; 6/8 responded
 - 20 men, Mg added to verapamil as mood stabilizer, DB study showed improvement
 - Not enough data to warrant potential risks
- NAC
 - 75 pts, 1 gram BID in addition to their current therapy, sig benefit in mania and depression, improvement disappeared when NAC D/C'ed

Complementary Treatment in Schizophrenia

Complementary Treatment in Schizophrenia

- No independent, alternative medicine to replace conventional medicine
- Need to think about alternative as complementary
- Complementary TX may allow reduction in does, accelerate stabilization of disease, and/or treat co-morbid medical conditions

Cannabinoids

- Natural component of cannabis.
- One of 85 or more active cannabinoids
- Does not provide a “high,” not intoxicating
- May be botanic counterbalance to THC; e.g. useful for countering THC side effects like paranoia
- Sourced from hemp plant.
- Legal in most states •
- Some restrict it to children with epilepsy and other medical reasons, under 0.3% THC

CBD

- Inhibits the reuptake of serotonin, dopamine, norepinephrine, GABA, and anandamide
- Much of it's therapeutic benefit is by suppressing Fatty Acid Amide Hydrolase (FAAH)
- FAAH breaks down Anandamide
- CBD decreases psychoactive influence of THC
- CBD repeatedly administered will induce plastic changes in the brain.
- Mostly case series, small studies support the beneficial effects of CBD in anxiety, depression, PTSD, and schizophrenia.

Medical Foods in Psychiatry

Foods specially formulated and intended for the dietary management of a disease that has distinctive nutritional needs that cannot be met by normal diet alone

Does Depression, ADHD, Mild Cognitive Impairment have distinctive nutritional needs that cannot be met by normal diet?

Resources for Reviewing Integrative Medicine Therapies

- summaries.cochrane.org –The Cochrane Collaboration is an international, independent, not-for-profit organization-free
- [Nccam.nih.gov](http://nccam.nih.gov) – The National Center for Complementary and Alternative Medicine –NCCAM-free
- www.consumerlab.com – independent test results and information to help consumers and healthcare professionals identify the best quality health and nutrition products-Subscription based
- www.umm.edu/health/medical/altmed -University of Maryland-free
- <http://naturaldatabase.therapeuticresearch.com> Evidence based science on integrative, complementary and alternative therapies-subscription based
- <https://www.fullscript.com> Fullscript- Allows clinicians to “write a prescription” for preferred supplements-free/?revenue generation

Summary

- Patients are using dietary supplements, with or without your knowledge or guidance
- Dietary supplements are under-regulated, under studied, misunderstood and have poor quality control
- Physicians have an obligation to stay up-to-date about commonly used dietary supplements in their field of medicine
- There are reliable resources for consumers and health care professionals
- There are medical-legal risks and obligations in this area
- There is growing, increasingly reliable data to suggest some role for dietary supplements as a treatment option for several psychiatric conditions

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THANK YOU