Nutraceuticals, Part 3: Vitamins, Hormones, and Other Chemicals

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Objectives

- Review commonly used non-prescription remedies for psychiatric illness
- Explore available data on efficacy, tolerability, and safety
- Show guidelines for integrating safe, efficacious complementary therapies into the psychiatric toolbox
Vitamins: “shotgun” vs. “laser” approach

- evidence is poor that daily multivitamins convey overall health benefit
- evidence is increasing that targeted, rational use of specific vitamins is useful in certain situations
- evidence is increasing that some vitamin use has the potential to cause harm
US MULTIVITAMIN USE BY AGE

Figure 1: Use of MVMs by Age, NHANES 2003-2006

National Health and Nutrition Examination Survey
Multivitamins in Europe and the US

- MVM use more frequent among:
  - Women, and children of women who take MVM’s
  - The elderly
  - Those with higher education, higher incomes, healthier lifestyles and diets, lower BMI
- This population has a better overall diet which could decrease vitamin effect.

Multivitamins in Europe and the US

- 161,808 postmenopausal women followed for a median of 8 years*
  - 41% took MVM’s
- 182,099 men and women aged 45-75 over an average of 11 years in HI and CA
  - 48% men, 52% women took MVM’s
- NO ASSOCIATION with risk of cardiovascular disease, incidence of cancer, total mortality


Randomized, controlled study of MVM’s

- Physician’s Health Study: 14,641 male US physicians age 50 and up
- Centrum Silver vs placebo, median 11.2 yr
  - No effect of vitamins on major cardiovascular events, stroke, or CV death
  - 8% lower incidence of cancers in vitamin group (but prostate CA same); **but overall cancer mortality same**

Limits of MVM studies

- no randomized, controlled study of a more representational group with baseline nutritional parameters
- unclear if vitamins would be of benefit in less well-nourished populations
Targeted supplementation: neural tube defect prevention

- 1817 women with a previous affected pregnancy, planning to become pregnant again
- randomized to receive 4 mg folate, folate + multivitamin, multivitamin only, or placebo
- study was stopped because of major benefit from folate (RR of having affected child = 0.28)

TARGETED SUPPLEMENTATION: AGE-RELATED MACULAR

Subject Degeneration with varying degrees of age-related MD, received vitamins or placebo

- Vitamin C (500mg)
- Vitamin E (30 mg)
- Beta-carotene (6 mg)
- Selenium (100 mcg)
- Zinc (20 mg)

- Average follow up 6.3 years
- Vitamin group had less vision loss

TARGETED SUPPLEMENTATION: BREASTFED INFANTS AND VITAMIN D

- Human milk has a vitamin D concentration of 25 IU per liter or less
  - Recommended vitamin D intake for infants = 400 IU/day
- Babies spend less time outdoors than they used to, they cover up with clothes more, and some are even wearing sunscreen...
- Not enough UV (290-315nm) light exposure for conversion of provitamin to previtamin
TARGETED SUPPLEMENTATION: BREASTFED INFANTS AND VITAMIN D

- rickets has been seen in breastfed infants

- AAP recommends that breastfed infants, and those consuming less than a liter of formula per day, receive oral vitamin D (drops)
  - infant formula now contains around 500 mg/liter
UNEXPECTED RISKS: LUNG CANCER

- Beta-carotene and vitamin A supplements associated with 18\% and 28\% increased risk of lung cancer
  - *Finnish smokers, 5 to 8 year follow up
  - **Smokers, former smokers, and asbestos-exposed people


ANTIOXIDANT SUPPLEMENT META-ANALYSIS

- 68 randomized trials, pooled n= 232,606
- Relative risk of all-cause mortality was examined
- beta-carotene, vitamin A, and vitamin E given singly or combined with other antioxidant supplements significantly increased mortality

Bjelakovic G et al. Mortality in Randomized Trials of Antioxidant Supplements for Primary and Secondary Prevention Systematic Review and Meta-analysis
JAMA, February 28, 2007—Vol 297, No. 8
UNEXPECTED RISKS: PROSTATE CANCER

- SELECT trial started in 2001 to determine if selenium and vitamin E could prevent prostate Ca
  - >400 sites, 35,000 men over 50
  - Selenium (200 mcg), selenium + vitamin E (400 mg), vitamin E alone, or placebo
- Intended to last 12 years, but the blind was broken in 2008

Kristal A et al. *Baseline Selenium Status and Effects of Selenium and Vitamin E Supplementation on Prostate Cancer Risk*. Journal of the National Cancer Institute, February 2014
UNEXPECTED RISKS: PROSTATE CANCER

- Men with *high baseline selenium* at the start of the trial who received selenium had a 91% increased risk of developing a high grade prostate Ca

- Men with *low baseline selenium* levels who received vitamin E *alone* had a 63% increased risk of prostate Ca, and a 111% increased risk of high-grade prostate Ca
  - Vitamin E + selenium did not cause increased risk in the low baseline selenium group: *did selenium protect from effects of vitamin E?*

Kristal A et al. *Baseline Selenium Status and Effects of Selenium and Vitamin E Supplementation on Prostate Cancer Risk*. Journal of the National Cancer Institute, February 2014
Figure 2a: Cumulative Incidence of Prostate Cancer, Vitamin E vs. Placebo

Cumulative Cases (Placebo) vs. Cumulative Cases (Vit E)

Year 1 to Year 9
VITAMINS AND THE BRAIN

- Examine vitamins, minerals and hormones which may have utility in treating mental illnesses
- Recall biochemistry of these vitamins’ metabolic cycles
- Understand how deficiency states may contribute to mental illness
B VITAMINS

- B1 (thiamine)
- B2 (riboflavin)
- B6 (pyridoxine)
- B9 (folate)
- B12 (cyanocobalamin)
B1 (THIAMINE)

- Essential for glucose metabolism, synthesis of GABA, acetylcholine
- Deficiency starves brain of energy
- Also leads to increase in free radicals, pro-inflammatory cytokines, and dysfunction of BBB
- Alcohol impairs absorption at the brush border membrane of the jejunum
  - parenteral administration of thiamine is needed for alcoholic patients
Thiamine Metabolism in Mammalian Cells: TPP, thiamine pyrophosphate; PDHC, pyruvate dehydrogenase complex; α-KGDH, α-ketoglutarate dehydrogenase; BCKDH, branched chain α-keto acid dehydrogenase.

OTHER B VITAMIN DEFICIENCIES

- Decreased DNA synthesis and repair
- Inhibition of catecholamine synthesis
- Increased homocysteine levels
- Increased free radicals → DNA damage,
- Other cytotoxic effects
Vitamins B2, B6, B9, and B12 directly impact the functioning of the methylation cycle. Deficiencies pertain to brain function, as neurotransmitters, myelin, and active glutathione are dependent on one-carbon metabolism.
INCREASED HOMOCYSTEINE LEVELS

- Associated with risk of cardiovascular disease, stroke, and thrombosis
- Elderly depressed patients with higher homocysteine levels scored lower on cognitive screening tests than younger depressed patients and elderly depressed patients with lower homocysteine levels
B vitamins and neurogenrative function in the elderly

- Low levels of B6, B12, and folate are associated with worse memory and non-verbal abstract thinking in non-demented patients
FOLATE (B9)

- In 2682 Finnish men, those in lowest one-third of folate consumption had 67% increased chance of depression*
- A meta-analysis of 11 studies found low folate levels correlated with depression**
- Low folate levels associated with poor response to antidepressant rx


FOLATE (B9)

- Good evidence for folate as an effective adjunctive therapy for depression in women (but not men) when folate 500 mcg/d was added to fluoxetine
  - regardless of baseline folate levels
  - RDA for folate 400 mcg/d

FOlate and MTHFR Polymorphisms

- *MTHFR* (methylene tetrahydrofolate reductase) C677T polymorphism is associated with
  - Major depression (OR=1.36)
  - Schizophrenia (OR=1.44)
  - Bipolar disorder (OR=1.82)
- Treatment: high dose folate, L-methylfolate

FOolate, B12, AND PERNICIOUS ANEMIA

- Megaloblastic anemia can be caused by B12 and/or folate deficiency
  - Inhibition of DNA synthesis during cell cycle
  - Continued cell growth without division (mitosis)
- If there is a B12 deficiency and only folate is given, many physical symptoms will disappear but neurologic damage will continue
  - Subacute combined degeneration of the spinal cord
  - Confusion, psychosis
B12 (cyanocobalamin) main roles

In low B12 states, there is excess accumulation of methylmalonyl co-A: a probable cause of neurotoxicity
PYRIDOXINE (B6)

- A cofactor in the tryptophan-serotonin pathway
- B6 was observed to reverse oral contraceptive-related depression in the 1970’s
- This led to consideration as a treatment for other ‘hormone-driven’ mood states
- 50-100 mg/day can be helpful for PMDD
  - avoid higher doses: peripheral neuropathy
  - also: good evidence for modest effect in PMDD with Ca 1200 mg/d, Mg 200-360 mg/d, and Vitamin E 400 IU/d
PYRIDOXINE ( B6 )

- A 2005 meta-analysis did not find B6 generally effective in major depression, but noted that if studies on pre-menopausal women were considered separately, *there was sufficient evidence to warrant further study*.

*Williams A et al. The role for vitamin B-6 as treatment for depression: a systematic review Family Practice (October 2005) 22 (5): 532-537*
VITAMIN D3  
(CHOLECALCIFEROL)

- Enhances intestinal absorption of calcium, iron, magnesium, phosphate, and zinc
- Controls expression of hundreds of genes involved in cell differentiation, proliferation
- Is a potent immunomodulator
- Increases myocardial contractility
VITAMIN D3
(CHOLECALCIFEROL)

- low levels associated with:
  - 30-50% increased risk of incident colon, prostate, and breast cancers
  - increased CHF risk
  - higher inflammatory factors (C-reactive protein, interleukin 2)
VITAMIN D3 (CHOLECALCIFEROL)

- low levels associated with depression and worse cognitive performance in:
  - older adults
  - fibromyalgia patients
- in one study, vitamin D was *more effective than light therapy* for SAD
- as general treatment for depression, mixed results
OXYTOCIN

- Hormone synthesized in hypothalamus
- Important in mother-infant bonding, pair-bonding, sexual behavior
- Small studies have explored its use in:
  - autism, social anxiety, postnatal depression, OCD, schizophrenia, borderline PD, PTSD
- Only the autism studies show significant effect size

Bakermans-Kranenburg M and van Ijzendoorn M. Sniffing around oxytocin: review and meta-analyses of trials in healthy and clinical groups with implications for pharmaco-therapy Translational Psychiatry (2013) 3, e258
OXYTOCIN AND AUTISM STUDIES

- ASD adults given oxytocin (IN) looked more at faces/eyes and chose the responsive player in a ball-toss task more often  n= 13
- ASD adults given oxytocin (IV infusion) showed significant reduction in repetitive behaviors  n= 15
- ASD adults given oxytocin (IV infusion) showed improvement in affective speech comprehension (happy, sad, indifferent, neutral)  n= 15
MELATONIN
MELATONIN

- ‘Natural’, ‘animal’, or ‘bovine’ melatonin is extracted from pineal glands of cattle
- ‘Synthetic’ or ‘pharmacy grade’ melatonin has no animal ingredients
- Widely used for many problems
- Sleep, ADHD, depression, others
Melatonin and primary insomnia: 2013 meta-analysis

- Studies included in meta-analysis used between 0.1 mg and 5 mg melatonin at HS
- Significantly improves sleep in subjects with primary sleep disorders
  - Reduces sleep latency (time to fall asleep)
  - Increases total sleep time
  - Improves sleep quality

MELATONIN AND INSOMNIA

- Effect size is smaller than that for benzodiazepines
  - But no evidence for the development of tolerance
    - In contrast to benzos
  - Most efficacious at higher doses (3-5 mg) over longer periods

Melatonin and the circadian ‘clock’

- Jet lag: can be useful for adult travelers
  - crossing 5 or more time zones
- More effective for *easterly* travel
- Timing is important- take at dark on the day of travel and for a few days after travel
- Shift work? evidence is less strong that melatonin improves quality of sleep or wakefulness at work
Sidetrack: shift work tolerance

- Shift work (work that occurs between 7 pm and 6 am) is associated with higher rates of type II DM, cardiovascular disease, and some cancers.

- Factors associated with better tolerance of shift work include: young age, low ‘morningness’, high extraversion, internal locus of control.

SAM-E, 5-HTP
in depression

- SAM-e: moderately good data on efficacy in depression, but effective dose is not well established
  - it can trigger mania in susceptible individuals
- 5-HTP: crosses BBB, and is freely converted to serotonin
  - 2011 meta-analysis did not find it effective
  - 5-HTP alone is contraindicated for long-term use
  - It competes for the same enzyme that converts L-dopa to dopamine → dopamine depletion
ZINC IN ADHD?

- A meta-analysis of studies in 2012 found only 3 studies that were randomized and controlled, and results were mixed.
MAGNESIUM

- Low Mg levels cause n-methyl d-aspartate (NMDA)-coupled Ca channels to be biased toward opening, leading to neuronal injury.
- Higher magnesium diet is associated with lower depression incidence.
- There is some evidence supporting Mg supplements for depression in diabetics.
“URBAN LEGENDS”?

- no evidence that B vitamins (especially B12) work as hangover prevention/cure
- in a large meta-analysis, Vitamin C did not reduce incidence of colds in the general population
  - may be preventive for those doing intense physical training in subarctic conditions
- if Vitamin C taken regularly, colds may be of slightly shorter duration

Hemila H et al. Vitamin C for preventing and treating the common cold. Cochrane Database Syst Rev. 2013 Jan 31
SUMMARY

- People who can afford to take multivitamins are not likely to benefit.
- Studies are lacking on the effect of multivitamins on people with poor diets with baseline deficiency states.
- Supplementation has risks, and should be discussed with a medical provider.
- Eat fruits and vegetables, whole grains, eggs, and lean meat (or other protein).