

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

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Objectives

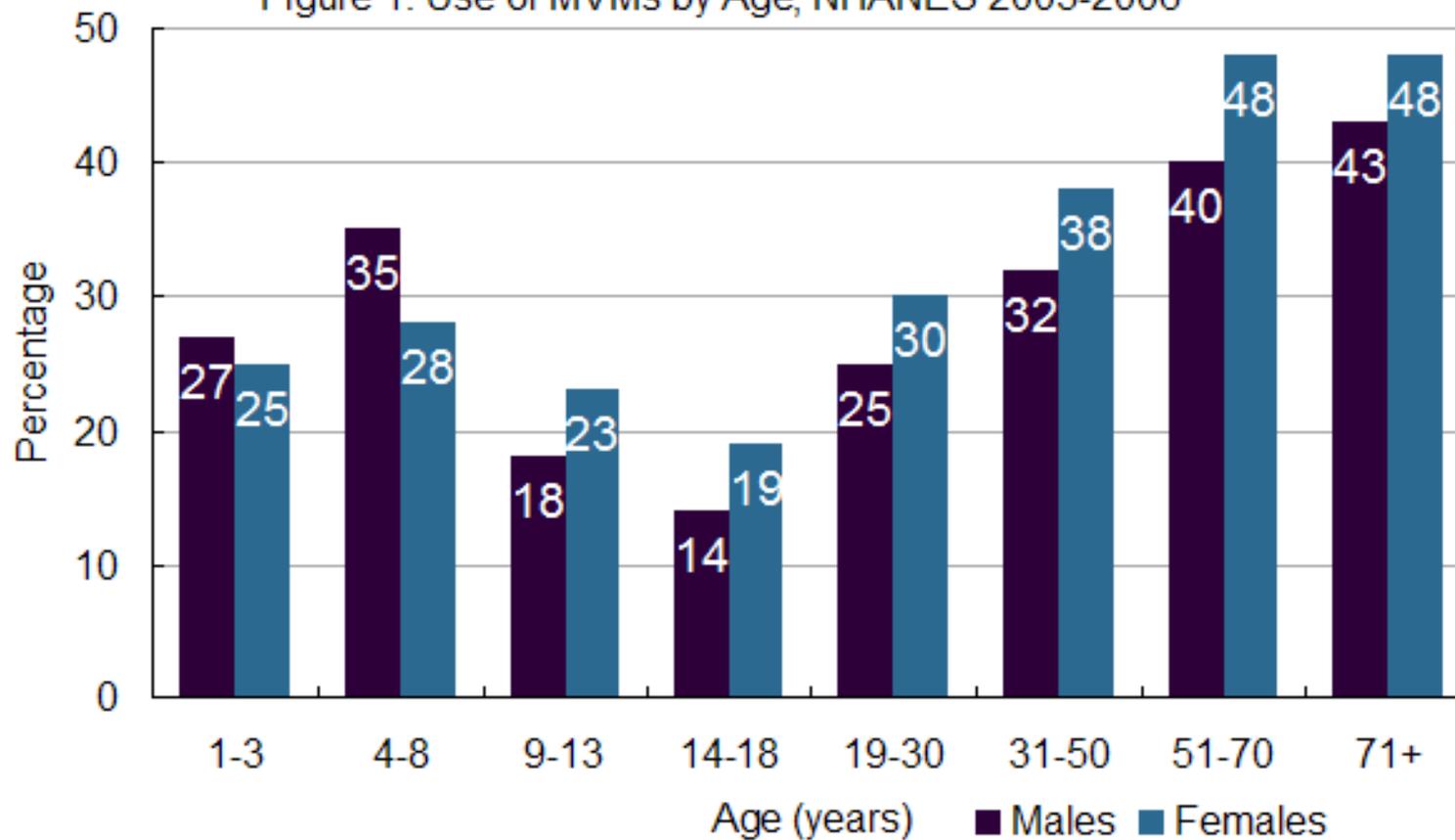
- Review commonly used non-prescription remedies for psychiatric illness
- Explore available data on efficacy, tolerability, and safety
- Show guidelines for integrating safe, efficacious complementary therapies into the psychiatric toolbox

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



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

*Neuhouser M et al. *Multivitamin use and risk of cancer and cardiovascular disease in the Women's Health Initiative cohorts*. Arch Intern Med 2009;169:294-304

**Park S-Y et al. *Multivitamin use and the risk of mortality and cancer incidence: the Multiethnic Cohort Study*. Am J Epidemiol 2011;173:906-914

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

Age-Related Eye Disease Study Research Group. *A randomized, placebo-controlled, clinical trial of high-dose supplementation with vitamins C and E, beta carotene, and zinc for age-related macular degeneration and vision loss: AREDS report no. 8.* Arch Ophthalmol 2001;119:1417-1436

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

*Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study Group. *The effect of vitamin E and beta carotene on the incidence of lung cancer and other cancers among male smokers.* N Engl J Med 1994;330:1029-1035

**Omenn G et al. *Effects of a combination of beta carotene and vitamin A on lung cancer and cardiovascular disease.* N Engl J Med 1996;334:1150-1155

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

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

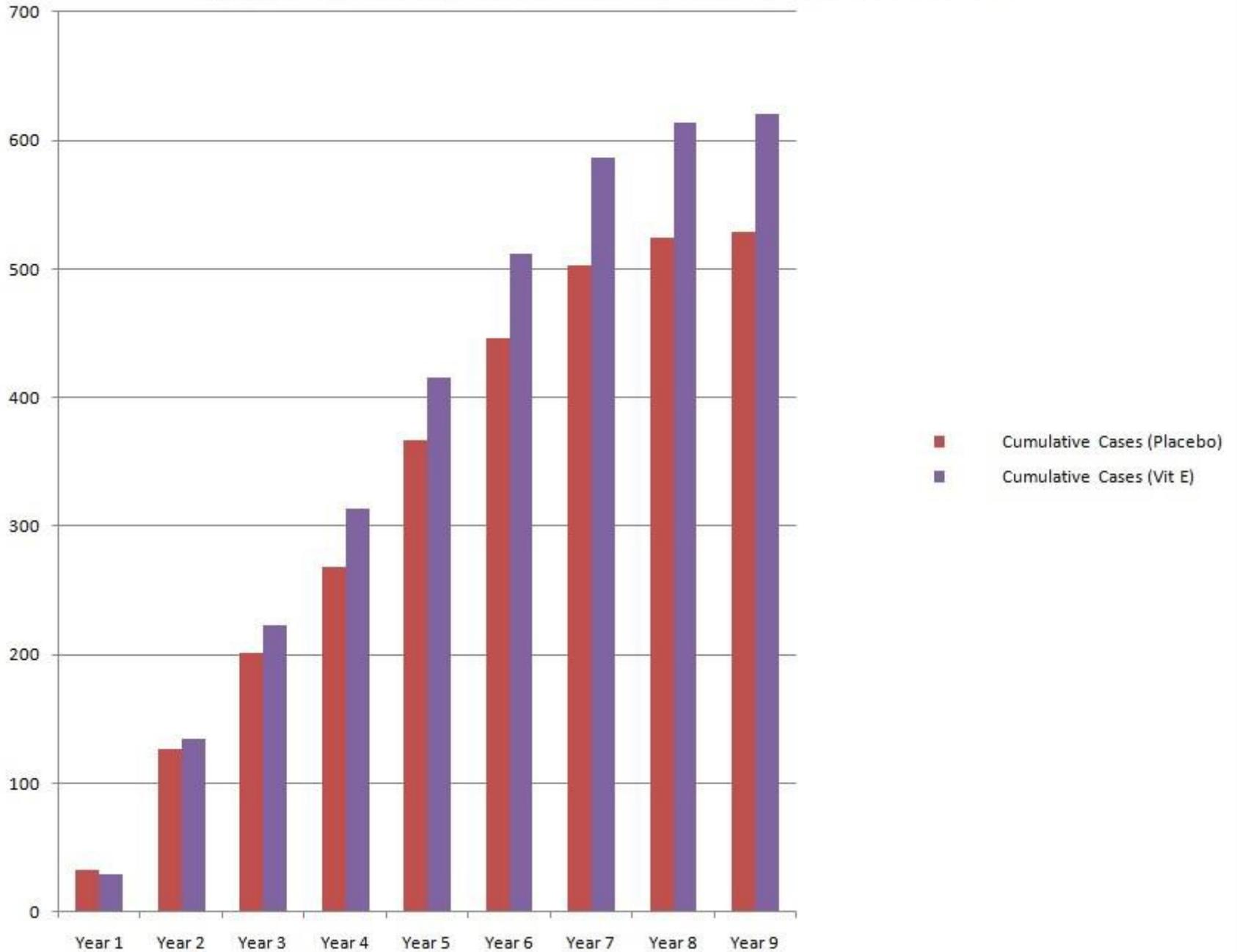
Kristal A et al. *Baseline Selenium Status and Effects of Selenium and Vitamin E Supplementation on Prostate Cancer Risk*. Journal of the National Cancer Institute, February 2014

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



VITAMINS AND THE BRAIN

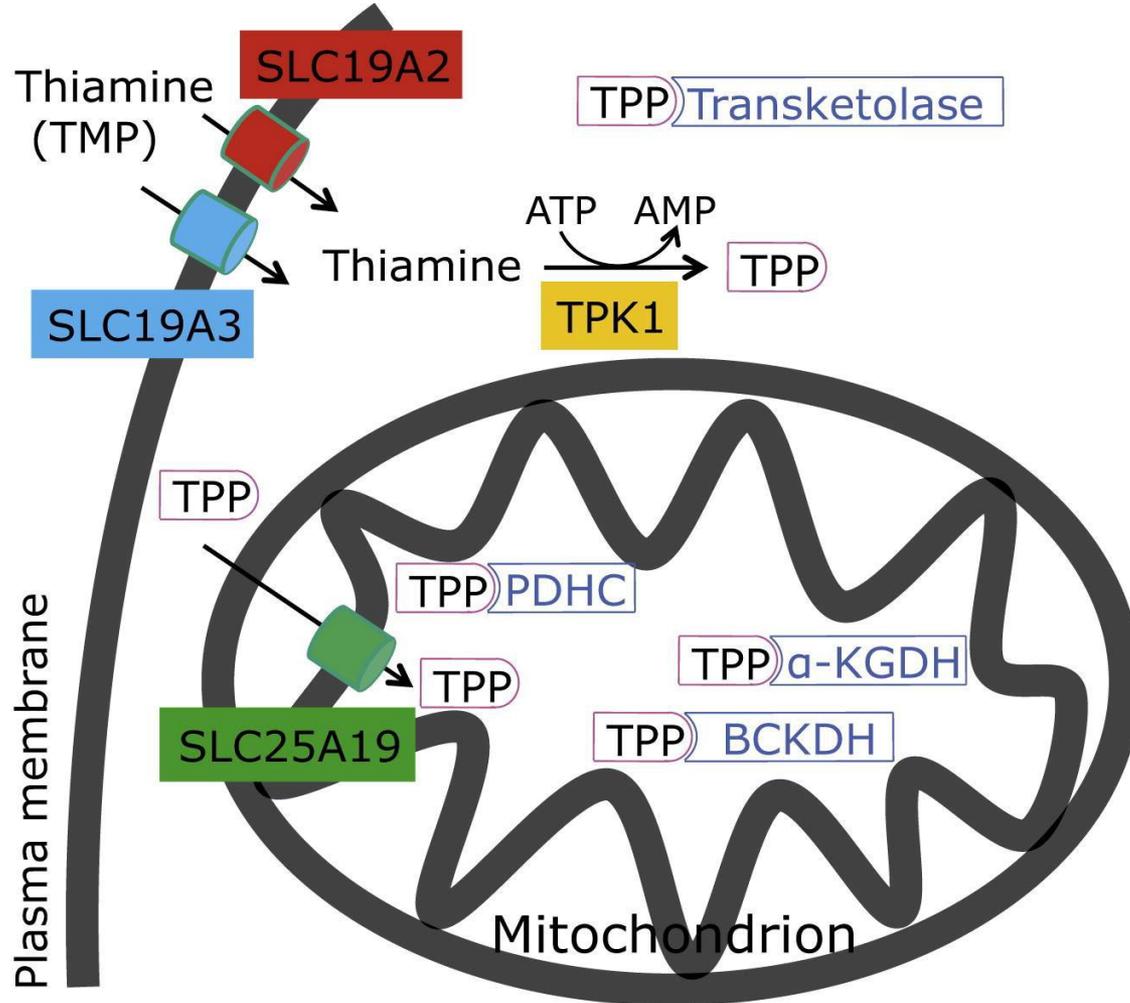
- Examine vitamins, minerals and hormones which may have utility in treating mental illnesses
- Recall biochemistry of these vitamins' metabolic cycles
- Understand how deficiency states may contribute to mental illness

B VITAMINS

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

B1 (THIAMINE)

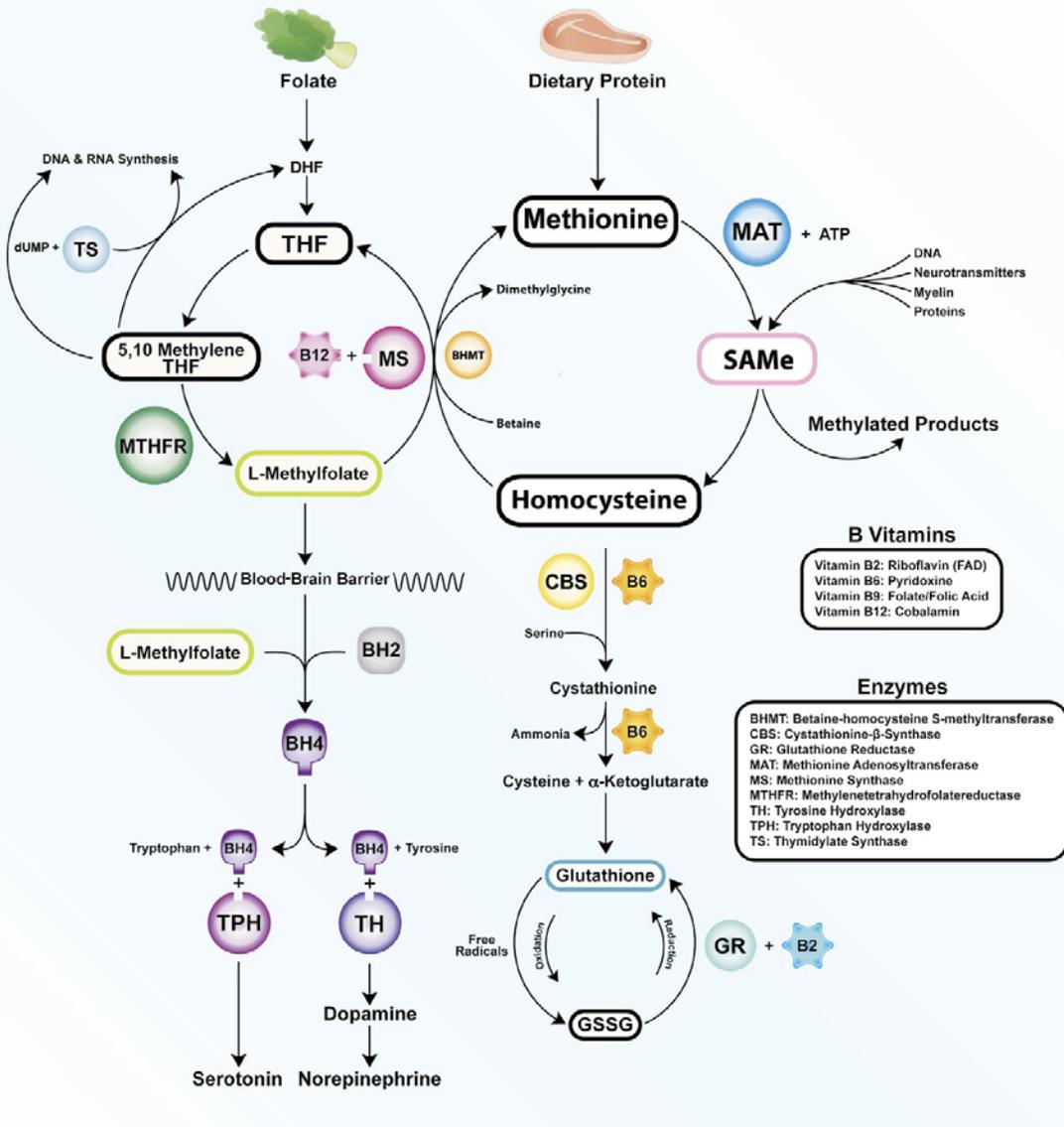
- Essential for glucose metabolism, synthesis of GABA, acetylcholine
- Deficiency starves brain of energy
- Also leads to increase in free radicals, pro-inflammatory cytokines, and dysfunction of BBB
- Alcohol impairs absorption at the brush border membrane of the jejunum
 - parenteral administration 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



Ramsey D and Muskin P
Vitamin deficiencies and mental health: how are they linked? Current Psychiatry 2013; Vol.12 No.1 p37-43

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 neurogenerative 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

*Tolmunen T et al. *Dietary folate and depressive symptoms are associated in middle-aged Finnish men.* J Nutr. 2003;133(10):3233-3236

**Gilbody S et al. *Is low folate a risk factor for depression? A meta-analysis and exploration of heterogeneity.* J Epidemiol Community Health. 2007;61(7):631-637

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

Coppen A, Bailey J Enhancement of the antidepressant action of fluoxetine: a randomized, placebo-controlled trial. J Affect Disord. 2009; 117 (Suppl 1)

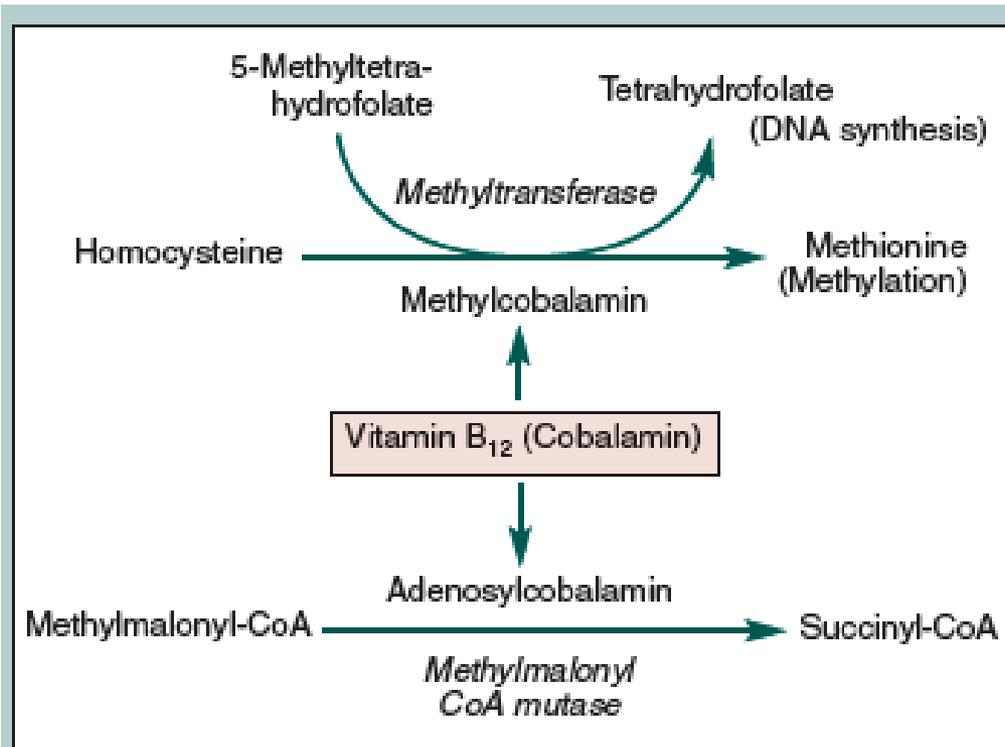
FOLATE AND MTHFR POLYMORPHISMS

- *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

FOLATE, 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

Figure 2. The Biochemical Role of Cobalamin.

Reprinted from the Centers for Disease Control and Prevention.²⁰

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 pharmacotherapy* 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 causes 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

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)