Definitions

- National Center for Complementary and Alternative Medicine (NCCAM) defines CAM as
  - “a group of diverse medical and health care systems, practices, and products that are not generally considered part of “conventional” medicine”

- four categories of CAM:
  - mind-body medicine
  - manipulative or body-based practices
  - natural products or biologically based medicines
  - other practices
Regulation

- National Health Interview Survey (NHIS) 2007
  - 17.7% of Americans (N=87,500) had used a nonvitamin/nonmineral natural product

- Dietary Supplement Health and Education Act (DSHEA) of 1994
  - No need to demonstrate safety or efficacy
  - Can't specify a certain disease that the supplement treats

Omega-3 fatty acids (Ω3)
Omega-3 fatty acids & Depression

- ↓ Ω3 in depressed individuals (Maes et al, 1999)
- ↓ fish consumption w/ ↑ suicidal ideation (Tanskanen et al. 2001)
- meta-analyses in general adult populations
  - actual diagnosis of depression predicted better response to Ω3 (Appleton et al, 2010)

Ω3 & late-life depression

- RCT 42 depressed older females in Italian SNF showed improvement in depression (GDS) & quality of life (SF-36) x2 months (Rondanelli et al 2011)
- RCT 4,116 of older adults with hx MI showed no benefit from Ω3 on GDS scores X 40 mo
  - Majority were NOT clinically depressed (GDS 1.2-1.4)
- In a subsample (n=36) who were receiving an antidepressant, Ω3 improved depressive symptoms
**Ω3 & late-life depression conclusions**

- Data for Ω-3 supplementation in late-life depression are mixed, however severity of depression appears to predict response
  - Various dosages
    - 1000-2000mg Qday
  - Various proportions of EPA to DHA
    - >60% EPA more beneficial for depression
  - Unblinding effect of fishy aftertaste

**Ω3 & cognitive disorders**

- Anti-oxidant & anti-inflammatory effects
- Improvement of cerebral blood flow
- Reduction in amyloid plaque formation
- Animals fed low DHA diet showed cognitive impairment
- Animals fed enriched DHA diet showed improvement in learning ability

(Fotuhi et al, 2009)
Fish consumption & incidence of dementia

- 47% reduction in dementia over 9 yrs w/ ↑plasma DHA compared to ↓DHA (RR 0.53, CI 0.29-0.97) (Framingham study)

- 1 serving of seafood/wk ↓risk of dementia by 44% (RR 0.56, CI 0.47-0.93) over 7 years (PAQUID study)

- Consumption of fish 2-3x/week ↓dementia by 1/2 (HR 0.54, CI 0.35-0.85) over 4 years in APOE-4 non-carriers (Three-City cohort Study)

Ω3 supplementation & prevention of cognitive impairment: RCTs

- Cochrane database (June 2012)
  - 3 RCTs, N=4,080
  - Alpha Omega Trial (Geleijnse et al 2012) N=2,911 (MI)
  - OPAL Study (Dangour et al, 2010) N=867 X2yrs
  - MEMO Study (van de Rest, 2008) N=302 X 26mo

- Omega-3 does not prevent cognitively normal older individuals from developing dementia
**Ω3 & cognitive impairment: RCTs**

- Omega-3 benefits very mild AD (MMSE >27)
  Attention & delayed recall: N=32, X6months (Freund-Levi et al, 2006)

- Omega-3 benefits MCI
  - Attention: N=39, X90days (Kotani et al. 2006)
  - Verbal fluency & Depression: N=50, X6months (Sinn et al, 2012)

**Ω3 & adverse effects**

- GI distress/fishy aftertaste

- Safe up to 3 grams/day
  - Excessive bleeding
  - Raise LDL

(Kuhn & Winston, 2008)
(Dacks et al. 2013)
Ω3 & cognition conclusions

- Discrepancies between epidemiologic studies & RCTs in the prevention of dementia
- Ω3 might provide a modest benefit on cognitive decline in those with MCI or very early AD
- Ω3 do not treat moderate-advanced dementia

Ω3 & cognition conclusions

- Mixed results of Ω3 supplementation is multifactorial
  - Those with low levels of DHA may respond better to supplementation
  - APOE-4 non-carriers appear to respond better than APOE-4 carriers
  - DHA more helpful than EPA for cognition
  - Duration of intervention varies

(Dacks et al, 2012)
St. John’s Wort (SJW)

SJW & Depression

- In Europe: numerous large positive trials comparing SJW to placebo & standard antidepressants
  - meta-analysis (23 randomized trials)
    - outpatients
    - mild-to-moderate depression
  - 300-1000mg extract per day

SJW vs placebo Cochrane database (2009)

- 17 trials SJW vs standard antidepressants
- SJW is superior to placebo
- SJW is comparable to standard antidepressants
- 29 trials
- N=5,489
- SJW has fewer s/e than standard antidepressants

SJW & Geriatrics

- RCT
  - N=149
  - 6 weeks
  - SJW (400mg BID) vs fluoxetine (10mg BID)
  - mild-moderately depressed older adults
  - equivalent efficacy (HAMD decreased by ½)

Harrer et al. (1999).
SJW & Geriatric depression

- RCT
  - Mixed age adults (18-70 years)
  - N=100
  - LI160 (600mg Qday)
  - 8 weeks
  - atypical depression
  - Improvement in depressive symptoms on PHQ-9


SJW adverse effects

- Well-tolerated & safe when used alone
- Better tolerated than older antidepressants
- Side effects
  - HA
  - GI upset
  - Fatigue
  - Restlessness
  - Dizziness
  - Dry mouth
  - Anorgasmia
  - Photoxicity (at 2-3grams/day)
  - Mania

SJW & adverse effects

- Dangerous drug-drug interactions
  - Inducer CYP450 3A4 & 2C19
    - ↓ Alprazolam, amitriptyline, digoxin, coumadin, methadone, clopidogrel
    - ↓ Simvastain, atorvastatin
    - ↓ cyclosporin & tacrolimus
    - ↓ Nifedipine, verapamil
    - ↓ nevirapine, indinavir
  - Can cause 5-HT syndrome
    - Caution w/ co-administration w/ SSRIs, SNRIs buspirone
    - Debatable MAOI

(Borrelli & Izzo 2009)

Conclusions SJW & depression

- SJW is an effective treatment for depression
- SJW is sometimes better tolerated than SSRIs
- There are multiple drug-drug interactions to advise patients of when taking SJW w/ other meds
- Standard extract is recommended
Ginkgo biloba

Ginkgo biloba & Cognitive disorders

- Clinical effects
  - scavenging free radicals
  - ↓ oxidative stress
  - ↓ neural damage
  - ↓ platelet aggregation
Ginkgo & prevention of dementia

- Ginkgo evaluation of memory (GEM) study
  - RCT multisite trial X5 yrs
  - N=3,072
  - 75yrs +
  - Normal cognition & MCI
  - Ginkgo 120mg BID
  - Results: no significant difference between placebo & ginkgo in developing dementia

(Dekosky et al. 2008)

Ginkgo biloba & treatment of dementia

- Cochrane database 2009 (studies 1979-2008)
  - 36 trials, randomized, double-blind studies
    - Most were short in duration (9 of which lasted 6 months in duration)
    - Combined N=2,016 patients
    - Ginkgo has inconsistent & unreliable effects for treatment of dementia or cognitive impairment
Ginkgo biloba vs placebo

- RCT 52 week
- N=309
- 1.4 point ADAS-cog

Lebars et al, 1997)

Adverse effects of Ginkgo biloba

- Alter seizure threshold
- Headaches
- Minimal transient GI s/e
- Dizziness
- Bleeding risk
  - PT/INR

(Kuhn & Winston 2008)
Ginkgo Conclusions

- Ginkgo does not prevent dementia in most epidemiologic studies of cognitively normal individuals or those with MCI

- However, the RCTs are mixed for ginkgo treating dementia & the studies supporting an effect are modest at best

SAMe

(S-adenosyl-L-methionine)
SAMe
Background

- Naturally occurring compound in the body
- Methyl-group donor that maintains nerve cell membranes
- Necessary co-factor for the synthesis of 5-HT, NE, DA
- ↓ CSF levels of SAMe in depressed patients
- ↑ SAMe in response to treatment

Bottiglieri et al. 1990; (Paul et al. 2004); (Mischoulon et al. 2002)

SAMe & depression

- Most studies use parenteral formulations
- Meta-analysis in general adult age populations
  - SAMe superior to placebo (5 out of 6 studies)
    - N=402
    - Global Effect size 17-38%
  - SAMe equivalent to TCAs
    - N= 86
    - Global Effect size 7%

(Bressa. 1994)
**SAMe & depression**

- Open trial of 30 mixed-aged adults (18-75yrs) supports SAMe as an augmentation strategy with SSRI/venlafaxine X 6 weeks
- 8 point drop on HAMD

**SAMe & depression**

- RCT of oral SAMe
  - N=73
  - Mixed age 18-80y/o
  - 6 weeks duration
  - Augmenting agent to SSRI/SNRI

(Alper et al. 2004)

(Papakostas et al. 2010)
SAMe & depression RCT

- Oral SAMe shows superior results to placebo over 6 wks as an augmentation strategy
- 36% vs 17% response rate

(Papakostas et al. 2010).

SAMe adverse effects

- Hypomania induction
- 5-HT syndrome
- Suicide attempt
- GI distress
- HA

(Kuhn & Winston, 2008); (Chittiva et al. 2011); (Carney et al. 1987); (Papakostas et al. 2010)
**SAMe Conclusions**

- There is evidence to support the use of oral SAMe as an antidepressant in augmentation of traditional antidepressants
  - More trials are needed for the oral SAMe before we can conclude that SAMe improves cognition outside of depression

**Vitamin B**

- Low Vit B12 & B9 (folate) are implicated in depression
  - production of monoamine neurotransmitters

- Observational studies show low B vitamins & high homocysteine are risk factors for depression in the elderly

(Beydoun et al. 2010); (Forti et al. 2010); (Tiemeier et al. 2002)
Vitamin B

- Studies evaluating an antidepressant effect of vitamins B12 & B9 are mixed
  - RCT showed no benefit from B12 & B9 supplementation in older adults with mild depressive symptoms (N=909, X6wks)
  - RCT using B12, B9 & B6 prevented depression in a group of adults who had sustained a stroke (N=273, x7yrs, ↓50%)

Walker et al. (2010); (Almeida et al. 2010)

Vitamin B

- New formulation of B9 (L-methylfolate) has antidepressant effect in adults (Tarbet et al. 2008)

- Recent RCT shows L-methylfolate 15mg is beneficial augmentation strategy in those pts with MDD & SSRI-resistance (Papakostas et al. 2012)
  - N=148
  - X 2months
  - 3 points on HAMD
Conclusions Vitamin B

- There is some data to support an antidepressant effect of vitamin B9 especially as an augmentation strategy with traditional antidepressants in general adults w/ SSRI resistant MDD

- Vitamin B12/B9 might be helpful at preventing cognitive impairment in those pts with depression & normal baseline cognition

Vitamin D

- Suicide risk associated with vitamin D deficiency (Tariq et al, 2011)

- Studies examining the impact of Vit D supplementation are mixed
  - Vit D supplementation(800 IU/day) did not improve seasonal affective disorder in 2117 elderly women (Dumville et al, 2006)
  - No benefit from Vit D (400 IU/day) in RCT of elderly women w/ depression (Bertone-Johnson, 2012)
Vitamin D

- Higher dosage supplementation might be more effective antidepressant in those with low levels of Vit D deficiency.
- RCT
  - N=441 mixed age adults 21-70y/o
  - X 1 year
  - Low Vit D levels (25(OH)D3 <40nmol/l) showed more depression
  - Vit D supplementation (40,000 IU/wk) showed improvement in depression

(Jorde et al. 2008)

Huperzine A

- Herb Huperzia serrata
- Anticholinesterase
- Antagonism NMDA
- Beneficial effects in AD
Huperzine

- Results from studies are mixed

- Multiple studies from China show huperzine being beneficial in cognition
  - Most recent RCT from China
    - Huperzine improves ADLs & MMSE in vascular dementia
    - N=79, X12 weeks

(Zhi-Qiang et al. 2012)

Huperzine

- Larger clinical trial in the US, showed less promising effects when evaluating two dosages of huperzine vs placebo in AD
  - N=210 X 16 weeks
  - Modest effect of the higher dosage of huperzine (400mcg BID) on cognitive testing
    - 2.27 point improvement ADAS-cog) X 11 weeks

(Rafi et al. 2011)
Huperzine

- Side Effects
  - Nausea
  - No long term studies have evaluated the safety of huperzine

Caprylidene

- AD shows decreased glucose metabolism
- Axona®-from coconut oil, caprylic acid, medium-chain fatty acids
  - Ketogenesis
  - RCT, n=152 AD pts
  - ADAS-cog 1.553 points after 45 days, not significant at 90 days, however when differentiated b/t APOE4 allele carriers and non-APOE4 carries there was a benefit in non-carriers

(Henderson et al 2009)
Coconut oil

- Newport Story
  - Dr. Mary Newport gave her husband coconut oil x 2 weeks, showed improvement
- Concerns increased LDL, TG, causing hypocalcemia, insulin resistance, carcinogenesis
- No data to support coconut oil in treating AD

Valerian Root

- Valerian has been associated with effects on the GABAergic system making it a feasible alternative to benzodiazepines for insomnia (Shi et al., 2014)
- Meta-analysis of eighteen RCT’s, valerian root showed an improvement in participants of general age populations in subjective measurements of sleep (Fernandez-San-Martin et al., 2010).
- In a small study (n=16) of mixed age, valerian root showed an improvement in slow wave sleep (Donath et al., 2000).
- There is a trend for valerian root as being effective for insomnia when administered for longer periods of time, such as two weeks as opposed to acute administration (Baek et al. 2014; Stevinson & Ernst 2000).
Valerian Root Side effects

- fairly well tolerated
- unpleasant odor (Kuhn & Winston), has led to unmasking the blinding effect as placebos
- exacerbation of pre-existing migraine headache and gastrointestinal effects (Donath et al., 2000),
- diarrhea (Fernandez-San martin et al, 2010)
- daytime sedation (Baek et al., 2014).

Valerian root Conclusions

- effective at subjective markers of insomnia when given in durations spanning several weeks
- well-tolerated alternative to benzodiazepines
- Studies for valerian root have ranged from 60mg-1800mg however recommended dosages range from 450mg-600mg (Mischoulon, 2008).
Melatonin

- Cochrane review, McCleery, Cohen & Sharpley (2014) reviewed two RCT’s using melatonin in approximately two hundred individuals suffering from AD and did not find convincing evidence for support of its use for insomnia treatment.
- When other studies combined melatonin with bright light therapy, an improvement in insomnia was seen (Dowling et al., 2008; Riemersma-van der Lek et al., 2008).
- Dosages in the studies of melatonin for insomnia in AD ranged from 2.5mg-10mg however studies showing a benefit tended to use dosages from 2.5mg-5mg of extended release melatonin.
- There is evidence to support the use of melatonin when combined with BLT for insomnia in AD especially with an impact on sleep latency.
- Low dosages of melatonin can be helpful when combined with bright light therapy for those suffering from cognitive impairment and insomnia especially in terms of sleep latency.

Melatonin without cognitive impairment

- Compared to studies examining cognitively impaired individuals, there are fewer studies including cognitively intact older adults.
- Several meta-analyses examining the general adult population which may be used to extrapolate effects to the general adult population.
  - A meta-analysis of fourteen RCT’s of adults being treated with melatonin, dosages ranging from 1mg-5mg, showed the strongest effects on improvement in sleep latency among other sleep quality variables (Buscemi et al, 2012).
  - Subset analysis was performed on individuals suffering from delayed-sleep phase syndrome sleep phase disorder (Buscemi et al, 2012).
  - Another meta-analysis examining fifteen RCT’s including about seven hundred cognitively intact individuals supports melatonin in subjects suffering from shift work in that it improves sleep length (Verbeek et al., 2014).
Melatonin side effects

- Increased occurrence of urinary tract infections (17.6% compared to 2.5% placebo)
- Diarrhea and upper respiratory tract infections (Wade et al, 2014) as well as headaches, dizziness, nausea, drowsiness (Buscemi et al. 2005).
- A study examining melatonin administration in individuals with dementia showed worsening scores on depression scale but when bright light was co-administered there were no adverse mood effects (Riemersma-van der Lek et al., 2008).
- When utilized with light, caution must be exerted as melatonin has caused increased photoreceptor sensitivity in animals (Zhdanova & Friedman, 2008).
- It should be noted that the studies mentioned previously demonstrating the benefit of BLT combined with melatonin was administered during the day prior to taking melatonin.
- Melatonin has been found to decrease body temperature in larger dosages which can be problematic for older adults whose thermoregulation is often quiet fragile (Zhdanova & Friedman, 2008).

Melatonin Conclusions

- Evidence supports the use of melatonin 2mg-5mg for older adults with and without cognitive disorders when used in combination with bright light, who suffer from advanced phase sleep disorders, sleep latency difficulties or shift work disorder or AD.
- Side effects should be routinely monitored as well as use for the shortest amount of time necessary.
- Melatonin provide a non-addictive approach to improving sleep in older adults.
Who should get recommended a supplement?

- Edman & Monti (2010) framework for recommending supplements
  - Health diet as foundation
  - Evidenced base of sound rationale & mechanism
  - Positive benefit-to-risk ratio
  - Defined dosage & time frame to assess effects
  - Targeted populations
    - Pts w/ adverse or inadequate responses to medications
    - Pts who want to try natural approaches
    - Vulnerable populations that have inadequate nutrient intake

Conclusions

- Natural products & supplements should be considered medications as they have biologic effects comparable to our prescribed medications
- We can help pts avoid dangerous drug interactions & s/e if we are knowledgeable about their supplements
- We can foster rapport by addressing natural products & supplements
Acknowledgments

- Dr. Helen Lavretsky
- Dr. David Merrill
- Dr. David Sultzer