

Recent Advances in Natural Therapies

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Disclosures

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Objectives

- To understand the evidence base for natural therapies in psychiatry
- To identify the risks and benefits of various natural treatments in psychiatry
- To be able to educate patients in purchasing natural products in both over-the-counter and prescription forms

Pros and Cons of Natural Remedies

- More than 70% of the world uses complementary therapies
- Easy access, good tolerability
- Used by many who have not responded to standard therapies
- Limited research/systematic studies
- Effectiveness unclear
- “Natural” does NOT mean “safe”
- Toxicity, adverse effects, interactions
- Different preparations/purity
- Insurance does not cover them
- Limited clinician and consumer education

St. John's Wort (SJW, Hypericum Perforatum)



SJW: Evidence

- About 40 published trials; 26 placebo-controlled; 14 with std antidepressant active comparators; various systematic reviews and meta-analyses
 - Short duration; often no standardized diagnostic instruments; varied severity
 - SJW > PBO; SJW = low-dose TCA, esp. for mild-moderate depression
 - Benefits in atypical depression (Mannel et al, 2010), PMS (Canning et al, 2010); no benefit in Minor Depression (Rapaport et al, 2011)
 - Inconsistent evidence in comparisons against newer antidepressants
 - About 13 trials comparing SJW to SSRIs ; 2-3 Cochrane reviews
 - SJW = SSRIs; SJW > PBO
 - No benefit for ADD, anxiety, OCD (Weber et al, 2008; Sarris et al, 2013)

SJW: Mechanism of Action and Safety

- Hypericin, hyperforin, adhyperforin key ingredients
 - Interaction with cytokine production and HPA axis?
 - Hyperforin may help in Alzheimer's (Griffith et al, 2010)
- Generally safe
 - Usual side effects: dry mouth, dizziness, constipation
 - Watch out for: phototoxicity, cycling to mania, interactions
 - Serotonin syndrome with SSRIs (SJW has MAOI activity)
 - Risk of cataracts?
 - Colic, drowsiness, lethargy in breastfed infants
 - Low birth weight from in utero exposure in animal studies
 - No fetal malformations in one human study

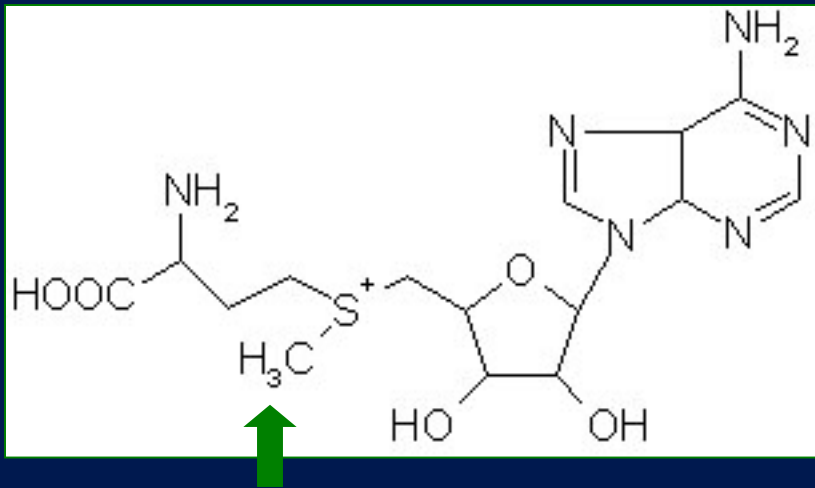
SJW: Major Drug-Drug Interactions

- Warfarin
- Cyclosporin
- Oral contraceptives
- Theophylline
- Fenprocoumon
- Digoxin
- Indinavir
- Camptosar
- Zolpidem
- Irinotecan
- Olanzapine
- SJW induces CYP-3A4 expression
- Reduces therapeutic activity of other drugs
- Caution required in
 - HIV+ patients
 - Cancer patients
 - Transplant patients

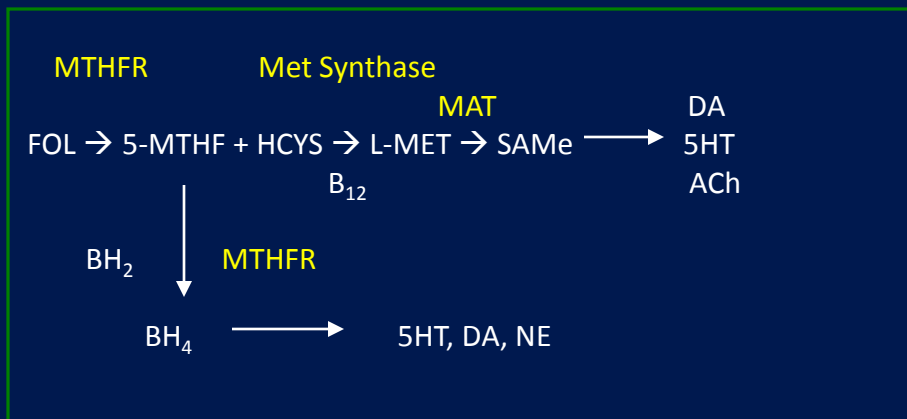
SJW: Recommendations

- Results encouraging but inconsistent
- Probably best for mild-moderate depression
- Do not combine with SSRIs
- Suggested dose: 300-1800 mg/day
 - Usually dosed 2-3 X /day
 - Different preparations may vary in potency

S-Adenosylmethionine (SAMe)



- Antidepressant
- Methyl donor
- Present in all living things
- Needed for neurotransmitter synthesis
- Depends on folate and B12 levels
- MTHFR polymorphisms may affect synthesis of neurotransmitters



SAMe: Efficacy Trials in Depression

- > 45 randomized clinical trials (PO, IM, IV): SAMe 200-1600 mg/d
- 8 placebo-controlled studies (N ~ 40-100)
 - SAMe > placebo in 6 studies; SAMe = placebo in 2 studies
- 8 comparison studies with TCAs
 - SAMe = TCA in 6 studies; SAMe > imipramine in 1 study
- 1 comparison with SSRI (Mischoulon et al, 2014)
 - N=189; 12 weeks; SAMe vs Escitalopram vs Placebo
 - Benefit in all 3 treatment arms (5-6 point drop on HAM-D)
 - No significant differences between treatment groups
 - Possible advantage for SAMe in subanalysis of one site (Sarris et al, 2014)

SAMe: Augmentation

- Combined safely with TCAs; may accelerate action (Alvarez et al, 1987, Berlanga et al, 1992)
- Combined successfully with SSRIs, SNRIs
- Alpert et al, 2004; n = 30 SSRI partial and NR; 6 weeks
 - Augmentation with SAMe 800-1600 mg/d
 - Response rate 50%; remission rate 43%
- Papakostas et al, 2010; n=73 SRI NR; 6 weeks
 - Augmentation with SAMe 800 mg bid or PBO
 - SAMe: Response=36.1%; remission= 25.8%
 - PBO: Response=17.6%; remission= 11.7%
 - Possible benefit in male sexual function (Dording et al, 2011)

SAMe: Recommendations

- Results encouraging at 400-1600 mg/day
- Side effects: insomnia, anorexia, constipation, nausea, dry mouth, sweating, dizziness, anxiety
- Mania or hypomania in bipolar depression
- Decreased methylation and SAMe levels in pregnancy
 - Benefits in pregnant women with intrahepatic cholestasis
 - Theoretical benefit in pregnancy; limited safety data
- Expensive (\$0.75-1.25 for a 400 mg tablet)

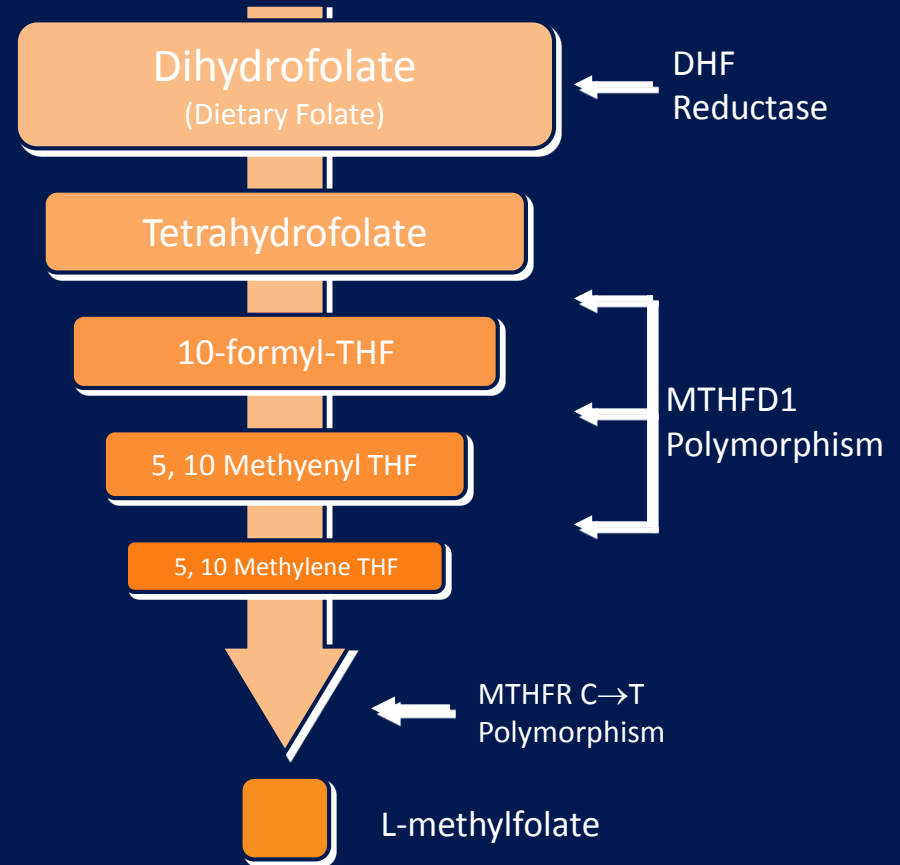
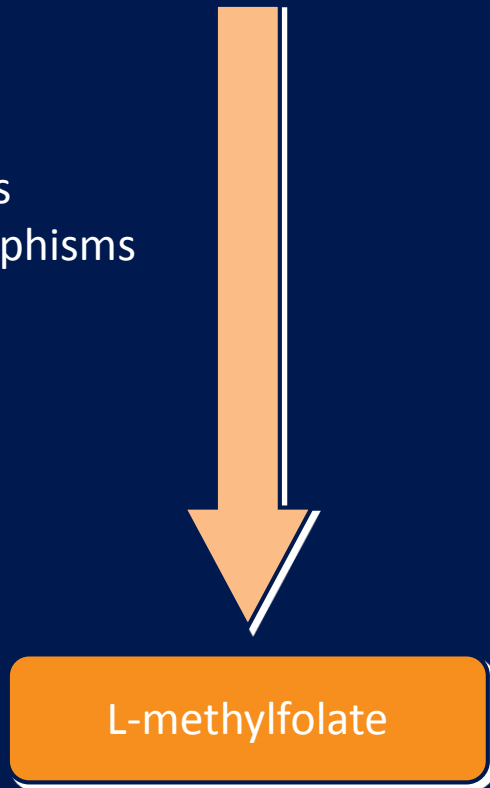
L-methylfolate (Deplin)

L-methylfolate

vs.

Synthetic Folic Acid

Bypasses
polymorphisms

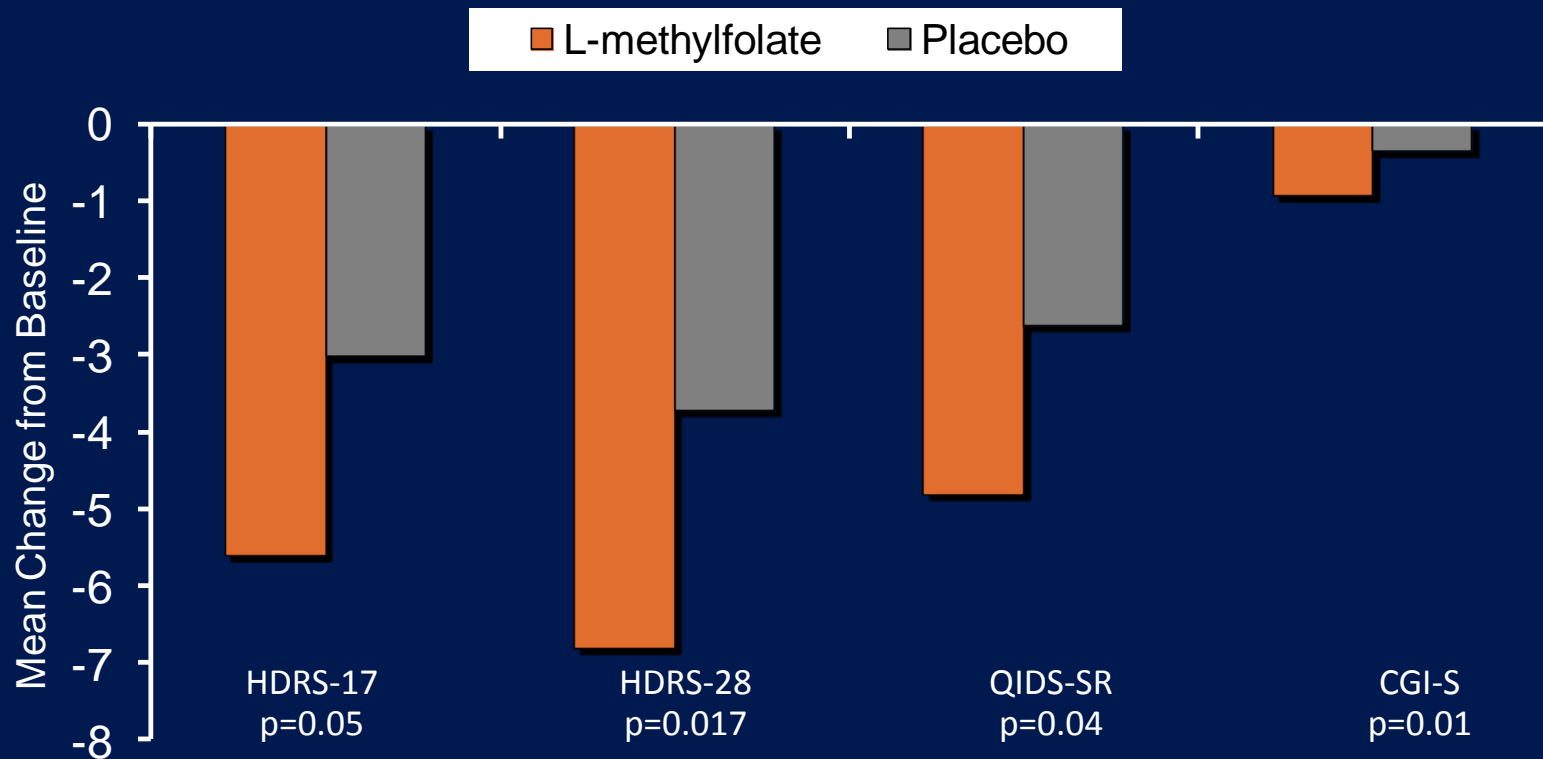


L-Methylfolate Clinical Trial in MDD

- Adults 18-65 years with MDD
- QIDS-SR ≥ 12 at screening and baseline visits
- Not responding to SSRI for ≥ 8 weeks
- Multi-center, randomized, double-blind study
- L-methylfolate 15 mg/day vs placebo
- Two 30-day treatment phases using sequential parallel comparison design (SPCD)

Mean Change From Baseline

Mean change from baseline was significantly greater with L-methylfolate 15 mg/day than with placebo



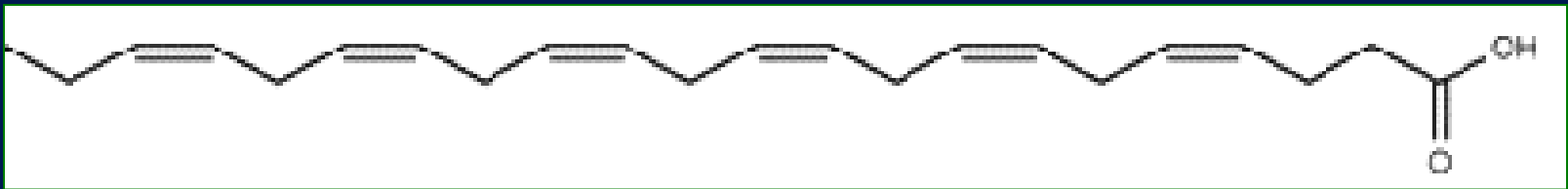
Cerefolin

- Cerefolin
 - 5.6 mg L-methylfolate (metafolin)
 - 1 mg of vitamin B12 (cyanocobalamin)
 - 50 mg of vitamin B2 (riboflavin)
 - 5 mg of vitamin B6 (pyridoxine)
- Cerefolin NAC
 - With methylcobalamin 2mg, N-acetylcysteine 600mg (increases glutathione, reduces oxidative damage)
- Approved for treatment or prevention of vitamin deficiencies (need Rx)
- Used off-label for psychiatric indications, including depression and dementia

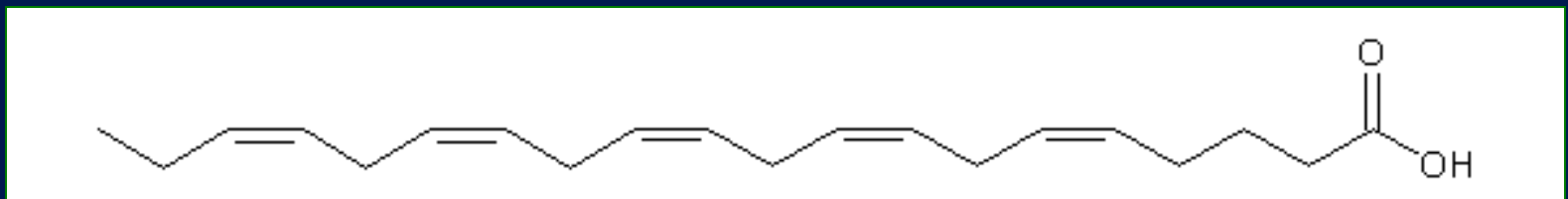
(McCadden and Hudson, 2010)

Omega-3 Fatty Acids: DHA and EPA

- Long-chain polyunsaturated omega-3 fatty acids
 - Primarily in fish oil and other marine sources
 - Mechanism may involve neuronal membrane stabilization, anti-inflammatory effects



Docosahexaenoic acid (DHA; 22:6,n-3)



Eicosapentaenoic acid (EPA; 20:5, n-3)

Omega-3 Fatty Acids: Efficacy

- > 30 RCTs in depression, mostly adjunct omega-3
 - EPA and EPA+DHA combos used most often; 1-2g/day
 - Possible advantage in obese patients with high inflammation?
- Mixed evidence for DHA (Marangell et al, 2003; Mischoulon et al, 2008)
 - Protective effect against suicide? (Lewis et al, 2011)
- Postpartum depression? (Freeman et al, 2006; Marangell et al, 2004)
- Bipolar disorder? (Stoll et al, 1999; Keck et al, 2006)
 - Best for depressed phase rather than mania (Sarris et al, in press)
 - Benefit from flax oil (ALA) in pedi bipolar? (Gracious et al, 2010)
- Weaker results in borderline PD, schizophrenia (Zanarini et al, 2003; Peet et al, 2001)

Omega-3s: Recommendations

- Depression: Probably 1-2 g/day of an EPA/DHA combo is best, with $\geq 60\%$ EPA (Sublette et al, 2011)
 - Possible advantage for EPA (Mozaffari-Khosravi et al, 2013; Mischoulon et al, in press)
- Bipolar disorder: high doses (6-10 g/day)?
 - But watch for cycling!
- Side effects include stomach upset, fishy taste, risk of bleeding when combined with anticoagulants
- Benefit to expectant mothers, fetus, and infants, particularly for neural development, allergy prevention
 - Safe upper limit in pregnancy unknown

Vayacog (Lipicogen)

- Phosphatidylserine (PS)
 - Important in cell membrane function
 - Cognitive decline with decreased brain PS-DHA
- Lipicogen (DHA-enriched PS) 310mg
 - PS 100mg; DHA 19.5mg; EPA 6.5mg
- Vakhapova et al, 2010, 2014; N=157; 15 weeks
 - 300mg/d vs PBO; + 15wk follow-up at 100mg/d
 - PS-DHA associated with significant improvement in sustained attention and memory recognition; maintained in continuation

Vayarin (Lipirinen)

- Prescription medical food for lipid imbalances associated with attention deficit hyperactivity disorder (ADHD) in children
- Lipirinen
 - Phosphatidylserine (PS): 150 mg
 - Eicosapentaenoic acid (EPA): 43 mg
 - Docosahexaenoic acid (DHA): 17 mg

Vayarin

- Manor et al, 2011
- 15-week double-blind, randomized, placebo-controlled study in 200 children with ADHD
- Significant advantage for Vayarin in Conners' rating scales and child health questionnaire scores
- Benefit in hyperactive/impulsive behavior, mood, behavior-dysregulation
- 15-week open-label extension during which all children received Vayarin
- Well tolerated, no significant side effects

Kava (Piper Methysticum)



- Anxiolytic, anticonvulsant, and muscle relaxant (kavapyrones)
- More than 12 studies, mostly RCTs
- Similar efficacy to venlafaxine, buspirone, opipramol (sigma antagonist)
- Effective for mild anxiety, not for panic attacks (Sarris et al, 2011)
- Antidepressant effect? (Sarris et al, 2009)

Kava: Adverse Effects

- Common mild side effects
 - Stomach upset, headaches, dizziness
- Toxic reactions with high doses, prolonged use
 - Unsteadiness, hair loss, visual problems, respiratory problems, kava dermatopathy
 - 78 cases of severe liver toxicity; 36 cases of hepatitis; cirrhosis; 11 cases of liver failure requiring transplant ; 4 deaths → banned in parts of Europe
 - Most were taking high doses for long periods or concurrently with other hepatotoxic medications
 - Toxicity may be due to hepatotoxic molds if long period between harvest and preparation (Teschke et al, 2011)

Kava: Recommendations

- Suggested doses 60-300 mg/day
 - Potency and efficacy may vary
- Avoid kava if:
 - History of liver disease, alcohol use, concurrent medications with potential liver toxicity
 - Pregnant or breastfeeding
- Use only under physician supervision
- Monitor liver enzymes regularly
- Use for 1-3 months at most

Valerian (Valeriana Officinalis)



- Used as a drug for over 1000 years
- “Valere” (Latin) = “in good health”
- “Baldrian” (German)
- Popular worldwide as sedative and mild hypnotic
- Popular among Hispanics

Valerian: Efficacy

- About 37 controlled trials, incl. 29 RCTs
 - Healthy subjects and symptomatic individuals
- 7 studies suggest comparable efficacy to BDZs, with fewer side effects and no tolerance
- Beneficial in children and the elderly
- Beneficial in menopausal women (Taavoni et al, 2011)
- Meta-analysis of 18 trials suggest lack of objective evidence of efficacy (Fernandez-San-Martin et al, 2010)
- Powerful smell a problem for controlled studies

Valerian: Ingredients and Mechanisms

- Monoterpenes and sesquiterpenes
- Iridoids and valepotriates
- Alkaloids, amino acids (esp. GABA)
- Active ingredients may function like BDZ
 - Direct GABA-ergic activity
 - Decrease GABA breakdown
- Changes in sleep architecture

Valerian: Dosing

- Recommended doses are 450-600 mg approximately 2 hours before bedtime
- No apparent increased benefit from higher doses
- Valerian may not be optimal for acute treatment of insomnia; its value may be in the promotion of natural sleep after several weeks of use

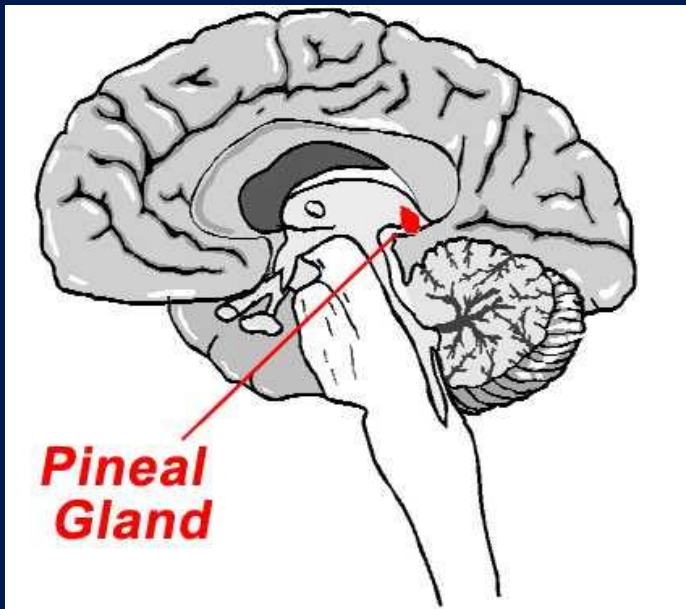
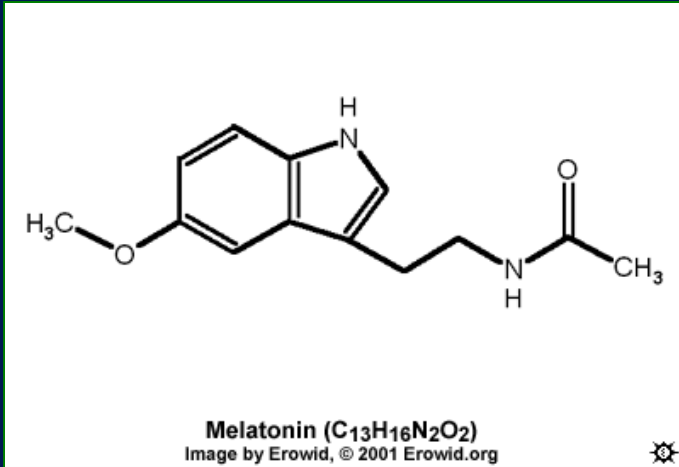
Valerian: Adverse Effects

- Headaches and GI complaints are common
- No hangover effect in AM
- Reportedly safe in overdose, no interactions
 - Has been combined with SJW with good results
- Toxic reactions (rare): Blurry vision, dystonias, hepatotoxicity, withdrawal and delirium (one case)
- Some preparations may contain mutagens
- Unclear safety in pregnancy
 - Studies suggest no adverse effects, but data are limited

Valerian: Recommendations

- Valerian appears to be a promising hypnotic
- Decreases sleep latency, improves sleep quality
- May work as well as BDZs, though not ideal for acute treatment of insomnia
- No dependence or daytime drowsiness
- Safe in children and elderly

Melatonin



- Sleep-inducing drug
- Popular with travelers who wish to reset circadian rhythm
- About 20 studies; some in children and elderly
- Prolonged-release form (2mg) effective in elderly (Luthringer et al, 2009; Wade et al, 2010; Lemoine et al, 2011)
- Few studies in psychiatric populations per se

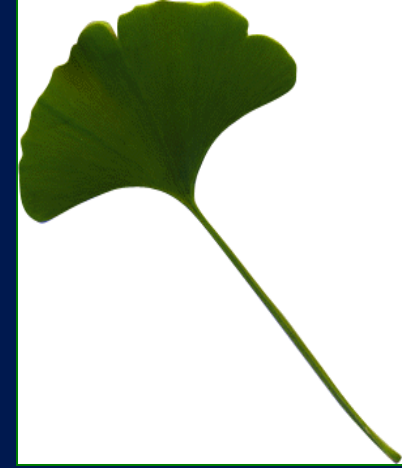
Melatonin: Mechanism and Adverse Effects

- Resets circadian rhythm and has direct sedative effect
- Adverse effects (rare)
 - Inhibition of fertility
 - Decreased sex drive
 - Lowered body temperature
 - Retinal damage
 - Immunosuppression; beware in HIV+ patients
 - Unknown risk to fetus in pregnant women

Melatonin: Recommendations

- Doses of 0.25-0.30 mg/day can decrease time it takes to fall asleep
- Commercial preparations may have up to 5 mg of melatonin
 - High doses may cause daytime sleepiness or confusion
 - Best to begin with low doses
- Potentially useful in children

Ginkgo Biloba



- Cognition enhancer
- May slow down cognitive decline in dementia
- Approx. 30 studies; some methodological problems
- Stabilizes neuronal membranes, scavenges free radicals
- Meta-analyses suggest efficacy (Weinmann et al, 2010; Brondino et al, 2013)
- Mixed results in young healthy people (Stough et al, 2001; Persson et al, 2003)
- Benefit in healthy middle aged people (Kaschel, 2011)
- Discouraging data on preventive effects (Andrade et al, 2009)

Ginkgo vs. Cholinesterase Inhibitors

- Placebo-controlled RCT of ginkgo (160 mg) vs. donepezil (5 mg) in Alzheimer's disease (Mazza et al, 2006); n = 60; 24 weeks ; **Equivalent**
- RCT of ginkgo (240 mg) vs. donepezil (5-10 mg) vs. combination of both in Alzheimer's disease (Yancheva et al, 2009); n = 96; 22 weeks; **Equivalent, advantage and better tolerability for combination**
- RCT Ginkgo biloba (120 mg) vs. rivastigmine (4.5 mg); n=56; 24-weeks (Nasab et al, 2012); **Riv > Ginkgo**
- **Donepezil + antiox Formula F (incl. Ginkgo) > Dpz+PBO** (Cornelli, 2010)
- Meta-analyses of different studies of Ginkgo and ChE Inh
 - **Each > placebo; ChE Inh > Ginkgo; Ginkgo more tolerable**
 - **Combination > monotherapy** (Canevelli et al, 2014)

Ginkgo: Recommendations

- Suggested dose = 120-240 mg/day
- Minimum 8-week course recommended; best started early
- Better for Alzheimer's than vascular dementias
- Full assessment of effect may require 1 year
 - No data on longer-term impact on illness
- May alleviate antidepressant-induced sexual dysfunction
- Side effects: mild GI upset, headache, irritability, dizziness, seizures in epileptics, bleeding in patients on anticoagulants or having surgery, via inhibition of platelet activating factor (PAF)
- PAF inhibition may increase risk of bleeding in pregnancy; risk to breastfeeding infants unknown

Conclusions: Who Should Use CAM?

- Mildly ill people with a strong interest in CAM who don't mind the cost
- People who have tried most everything else and have not responded, or had too many side effects
 - But they are often the most difficult to treat
- Be careful with patients on multiple medications
 - Drug-drug interactions can be significant!