Natural Medications for Psychiatric Disorders

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Disclosures

• My spouse/partner and I have the following relevant financial relationship with a commercial interest to disclose:
  – Research support from Fisher Wallace, Nordic Naturals, Methylation Sciences, Inc. (MSI), and PharmoRx Therapeutics
  – Royalties from Lippincott Williams & Wilkins for published book “Natural Medications for Psychiatric Disorders: Considering the Alternatives”
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
• “Natural” does NOT mean “safe”
• Toxicity, adverse effects, interactions
• Different preparations/purity
• Insurance does not cover them
St. John’s Wort
(SJW, Hypericum Perforatum)
St John’s Wort

- About 40 published trials; many comparisons with TCAs and SSRIs; various systematic reviews and meta-analyses
  - SJW > PBO; SJW ≈ low-dose TCA; SJW ≈ SSRIs
  - esp. for mild-moderate depression
- Mechanism
  - May interact with HPA axis to reduce cytokine production
Safety

• Mild side effects: dry mouth, dizziness, constipation
• Serious side effects: phototoxicity, cycling to mania
• Serotonin syndrome with SSRIs (SJW has mild MAOI activity)
• SJW induces CYP-3A4 expression; reduces therapeutic activity of other drugs
  – Warfarin, cyclosporin, oral contraceptives, theophylline, fenprocoumon, digoxin, indinavir, camptosar, zolpidem, irinotecam, olanzapine
  – Caution in HIV, cancer, transplant
• Preliminary evidence suggests safety in pregnancy
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
- Needed for neurotransmitter synthesis
- Depends on folate and B12 levels
- May be helpful for those with MTHFR polymorphisms
SAMe: Efficacy Trials in Depression

- > 45 randomized clinical trials (PO, IM, IV): SAMe 200-1600 mg/d
  - SAMe > placebo; SAMe ≈ TCA
- 1 comparison with SSRI (Mischoulon et al, 2014)
  - N=189; 12 weeks; SAMe (up to 3200 mg/d) vs Escitalopram vs Placebo
  - SAMe ≈ Esc ≈ PBO
- Combined successfully with TCAs, SSRIs, SNRIs
  - Alpert et al, 2004; N = 30 SSRI NR; 6 weeks; SAMe 800-1600 mg/d
  - Papakostas et al, 2010; N = 73 SSRI/SNRI NR; 6 weeks; SAMe 800 mg bid or PBO; significant advantage for SAMe
- Recommended doses 400-3200 mg/day
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)
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)
Efficacy

- > 30 RCTs in depression, mostly adjunctive omega-3
  - EPA and EPA+DHA combos used most often; 1-2 g/day
  - Recommended ≥60% EPA in combinations (Sublette et al, 2011)
- Limited evidence for DHA (Marangell et al, 2003; Mischoulon et al, 2008; Lewis et al, 2011)
- Postpartum depression? (Freeman at 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, 2012)
EPA vs DHA vs PBO (Mischoulon et al, 2015)

- N=196 with MDD; MGH and Emory University
- EPA 1000mg/day or DHA 1000mg/day or PBO; 8wks
- Significant improvement in HAM-D-17, QIDS-SR, and CGI-S, but neither active treatment reached statistical significance compared to placebo (P > 0.05)
- Response rates 40-50% for each arm; remission ~30%; no significant differences between groups
- Do baseline levels of markers human c-Reactive Protein (hsCRP), Interleukin-6 (IL-6), Interleukin-1 Receptor Antagonist (IL-1RA), Leptin, and Adiponectin impact on response?
Inflammatory Biomarkers and O3
(Rapaport et al, 2015)

• No markers: smaller response to EPA than PBO
• 4-5 markers: ES=-1.11 (EPA > placebo; HAMD drop of 11 vs 5 points)
• ≥ 1 marker: overweight, elevated CRP, leptin, IL-6, IL-1Ra, decreased adiponectin
• EPA may benefit individuals with ≥ 2 markers
• New study examines depressed patients with obesity and elevated inflammatory status at baseline to enhance signal detection
Omega-3s: Recommendations

- Depression: Preferably 1-2 g/day of EPA/DHA combo, with ≥ 60% EPA (Sublette et al, 2011)

- Bipolar disorder: high doses (6-10 g/day)?
  - Watch for cycling!

- Side effects include stomach upset, fishy taste; risk of bleeding may have been exaggerated

- Benefit to expectant mothers, fetus, and infants
  - Neural development, allergy prevention
  - Safe upper limit in pregnancy unknown
Rhodiola Rosea

• Found at high altitudes in mountainous regions of Europe and Asia
• “Golden root” or “Arctic root”
• Used for centuries in traditional medicine of Asia, Scandinavia, and Eastern Europe
• “Adaptogen” -- increases resistance to chemical, biological, and physical stressors
  – Stimulates nervous system
  – Enhances physical and mental performance
  – Prevents altitude sickness
  – Alleviates fatigue, stress, depression, impotence
Efficacy

- Studied in Russia and Scandinavia for more than 40 years
- Most studies not yet translated to English
- Literature generally supports adaptogenic properties
- Remedy for asthenic or lethargic conditions secondary to intense physical or intellectual strain
- 4 controlled trials support efficacy in depression and anxiety as well as cognition
- Doses used from 100-680 mg/day
- Adaptogenics (rosavins, tyrosol), antioxidants (flavonoids), monoamine modulation, MAO-A and B inhibition, opioid-like effects
Safety and Tolerability

• SFX uncommon and mild
  – Allergy, irritability, insomnia, fatigue, and unpleasant sensations, especially at high doses

• Best taken on an empty stomach 30 minutes before meals, early in the day
  – May interfere with sleep or cause vivid dreams

• No interactions reported with other drugs
  – Combined with TCAs; reduces TCA side effects

• No data on pregnancy or bipolar cycling
  – Use with caution
Recommendations

• Clearest indication for asthenic conditions
• Adaptogenic activity and monoamine modulation suggests promising antidepressant
  — Supported by animal and humans studies
• R. rosea plus SSRIs or SNRIs might be helpful for antidepressant side-effects
  — Poor memory, sexual dysfunction, weight gain
• More controlled studies are warranted
5-Hydroxy Tryptophan (5-HTP)

- 5- HTP is the intermediate metabolite of L-tryptophan in production of serotonin
- Western diet contains about 0.5 g of tryptophan daily; only 2–3% used in central serotonin production
- Increase in dietary tryptophan increases amount transported across the BBB and eventually transformed into serotonin
- Obtained from Griffonia simplicifolia
What happened to 5-HTP?

• Most studies conducted >20 years ago, when there was a interest in the serotonin hypothesis

• After fluoxetine and other SSRIs approved (~1987), research on 5-HTP became less compelling

• Association with the Eosinophilia-Myalgia Syndrome (1989 and 1990) after ingestion of contaminated L-tryptophan
  – 1500 cases with at least 38 deaths
  – FDA banned tryptophan
  – Later, contamination attributed to bacterial fermentation and poor filtration
  – Current manufacturing methods unlikely to produce EMS
Mechanisms of Action

• TRP hydroxylase inhibited by stress, insulin resistance, vitB6 deficiency, low magnesium
  – Results in conversion of L-TRP to kynurenine via tryptophan 2,3-dioxygenase, making L-TRP unavailable for serotonin production

• 5-HTP does not require transport molecule to enter CNS

• Melatonin, DA, NE, and beta-endorphin also increase following oral 5-HTP

• All regulate mood and sleep, may represent pathways stimulated by 5-HTP
Efficacy

• About 27 published clinical studies for depression
  – Comparisons against TCAs, augmentation, relapse prevention, combination with dopamine agonist
  – 5-HTP > placebo in 7 of 11 RCTs
  – Samples small; only 6 showed statistical significance
  – Doses from 20-3250 mg/day, majority between 200-300 mg/day
  – Responders often noticed improvement within 2 weeks
  – Meta-analyses suggest only 1-2 rigorous studies
Safety

• Most common adverse effects are gastrointestinal (nausea, vomiting, and diarrhea)
  – Dose-dependent and transient
  – May be combined with peripheral decarboxylase inhibitor (PDI) to reduce GI SFX by blocking conversion of 5-HTP to serotonin, decreases gut motility

• Less common SFX: headache, insomnia, palpitations

• Current reviews suggest no risk of EMS
Safety

- 5-HTP plus SSRI or MAOI may cause serotonin syndrome
  - hypertension, hyperthermia, flushing, hyperreflexia, dizziness, disorientation, myoclonus
- Single doses of 5-HTP (200 mg) administered to 26 patients with MDD or OCD taking fluoxetine
  - none developed signs or symptoms of serotonin syndrome
- Use with caution in patients on SSRIs or MAOIs
Recommendations

• Recommended doses from 20-3250 mg/day, often 200-300 mg/day
  – dosing frequency 3-4X/day due to relatively short half-life (4.3±2.8 hr)

• Absorption not affected by other amino acids
  – may be taken with meals

• Begin 50 mg TID with meals, titrate upward if inadequate response after 2 weeks

• 5-HTP deserves reconsideration, but more extensive clinical trials are needed
Valerian (Valeriana Officinalis)

- Used as a drug for over 1000 years
- Popular worldwide as sedative and mild hypnotic
- Contains GABA-ergic compounds
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: 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.
Safety

- Headaches and GI complaints are common
- No AM hangover
- Safe in overdose, no interactions
- Toxic reactions (rare)
  - Blurry vision, dystonias, hepatotoxicity, withdrawal and delirium (one case)
- Retrospective studies suggest safety in pregnancy
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)
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 and elderly
Ginkgo Biloba

• Cognition enhancer; slows down cognitive decline
• Approx. 30 studies in DAT, mostly supportive
• Stabilizes neuronal membranes, scavenges free radicals
• Meta-analyses suggest efficacy (Weinmann et al, 2010; Brondino et al, 2013)
• Cholinesterase inhibitors somewhat more effective but not as well tolerated; may be combined (Mazza et al, 2006; Yancheva et al, 2009; Cornelli, 2010; Nasab et al, 2012; Canevelli et al, 2014)
• No clear preventive effects (Andrade et al, 2009)
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 many side effects
  - But they are often the most difficult to treat

- Be careful with
  - Pregnant or breastfeeding women
  - Patients on multiple medications
    - drug-drug interactions can be significant!