Natural Medications for Psychiatric Disorders

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Disclosures

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Objectives

• To understand the evidence base for efficacy of 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

• In 2007, 38% of adults and 12% of children used CAM practices and products in the past year (NIH, 2010)
  – about $33.9 billion out-of-pocket cost
• Easy access, good tolerability
• Used by many who don’t respond 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
  – Better tolerability/lower discontinuation for SJW
  – Limited data on severe depression
  – Poor reporting of adverse effects, particularly rare ones

• Mechanisms
  – Hypericin and hyperforin 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 when combined with SSRIs
  – SJW has mild MAOI activity
• Induces CYP-3A4 expression; reduces activity of drugs
  – Warfarin, cyclosporin, oral contraceptives, theophylline, fenprocoumon, digoxin, indinavir, camptosar, zolpidem, irinotecam, olanzapine...
  – Caution in HIV, cancer, transplant
• Preliminary evidence suggests safety in pregnancy, but caution advised
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

- > 50 clinical trials (PO, IM, IV): SAMe 200-3200 mg/d
  - SAMe > placebo; SAMe ≈ TCA
  - One major meta-analysis (Hardy et al, 2002)
  - New systematic review (Sharma et al, 2017)
- 1 comparison with SSRI (Mischoulon et al, 2014)
  - N=189; 12 weeks; SAMe (1600-3200 mg/d) vs Escitalopram vs Placebo
  - SAMe ≈ Esc ≈ PBO
  - Men may respond better than women (Sarris et al, 2015)
SAMe: Efficacy Trials (contd)

• 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
  – Mischoulon et al, unpubl.; combining SAMe + escitalopram produces better results than either treatment alone or placebo
SAMe: Recommendations

- Results encouraging at 400-3200 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 G-protein signaling inhibition, neuronal membrane stabilization, anti-inflammatory effects...

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

Eicosapentaenoic acid (EPA; 20:5, n-3)
Omega-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)
  - EPA may be more effective in people who are overweight and/or have elevated inflammation (Mischoulon et al, 2015, Rapaport et al, 2017)
  - Study in progress to examine preventive effects in older people (Okereke et al, VITAL-D)
Omega-3: Efficacy (contd)

- 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, 2012)
- Psychotic disorders? (Peet et al, 2001)
  - Preventive effects? (Pawełczyk et al, 2015)
- Borderline Personality Disorder? (Zanarini et al, 2003)
- Depression in children and adolescents (Trebatchá et al, 2017)
- Some benefit in Attention Deficit Disorders (Tan et al, 2016)
- Little evidence in dementia (Burckhardt et al, 2016)
Omega-3: Efficacy (contd)

- Data overall difficult to interpret
- Several meta-analyses show mixed results
- Heterogeneity among studies in mood disorders
  - omega-3 preparations, doses, study design
- No published head to head studies with different preparations
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 (Begtrup et al, 2017) but caution still advised (Gross et al, 2017)
- Benefit to expectant mothers, fetus, and infants
  - Neural development, allergy prevention
  - Safe upper limit in pregnancy unknown
Rhodiola Rosea

• Grows 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
Rhodiola: Efficacy

- Studied in Russia and Scandinavia for > 40 years
- 4 controlled trials support antidepressant, anxiolytic, cognitive benefits (Iovieno and Mischoulon, 2011; Hung et al, 2011)
- Other studies less encouraging
  - Rhodiola 340mg vs sertraline 50mg vs placebo did not separate, but rhodiola better tolerated (Mao et al, 2015)
  - Not effective for self-reported anxiety, stress, cognition, and other mood symptoms (Cropley et al, 2015)
- 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

• Side effects uncommon and mild
  – Allergy, irritability, insomnia, fatigue, and unpleasant sensations, especially at high doses
  – Best on empty stomach, >30 min before meals, early in day
  – May interfere with sleep or cause vivid dreams

• Few interactions reported with other drugs
  – Combined with TCAs; reduces TCA side effects
  – Mild serotonin syndrome with paroxetine (Maniscalco et al, 2015)

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

• Clearest indication for asthenic or lethargic conditions secondary to intense physical or intellectual strain

• Adaptogenic activity and monoamine modulation suggests promising antidepressant

• R. rosea plus SSRIs or SNRIs might diminish antidepressant side-effects
  – Poor memory, sexual dysfunction, weight gain
  – But use with caution, watch for serotonin syndrome

• More controlled studies are warranted
Vitamin Supplements

• Broad spectrum micronutrients for the treatment of a range of problems

• >30 positive RCTs on various mental health conditions
  – Stress, low mood, anxiety, ADHD, autism
  – Heterogeneity of doses and ingredients.

• Some negative trials studied people not meeting DSM criteria for a psychiatric disorder (e.g. BDI scores below 10)
Vitamin Supplements (contd)

• EmpowerPlus
  • About 40 trace minerals, vitamins, inositol
  • Legal controversies over claims
    – Mostly settled in favor of manufacturer
• >30 publications on EMP (or variations)
• 3 more RCTs recently completed (Rucklidge et al)
  – May clarify efficacy questions
• Mega-Vitamin Therapies (>200% of RDAs) have been marketed as a “cure“
  – Need to watch out for hypervitaminosis
L-methylfolate (Deplin)

L-methylfolate vs. Synthetic Folic Acid

Bypasses any polymorphisms


www.mghcme.org
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
• Added L-methylfolate 15 mg/day vs placebo

(Papakostas et al, 2012)
Mean change from baseline was significantly greater with L-methylfolate 15 mg/day than with placebo.

- HDRS-17: p=0.05
- HDRS-28: p=0.017
- QIDS-SR: p=0.04
- CGI-S: p=0.01
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)
Valerian (Valeriana Officinalis)

- Used as a drug for over 1000 years
- Popular worldwide as sedative and mild hypnotic
- Contains GABA-ergic compounds (valepotriates and sesquiterpenes)
Valerian: Efficacy

• More than 40 controlled trials
  – Healthy subjects and symptomatic individuals
• 7 studies suggest comparable efficacy to BDZs, with fewer side effects and no tolerance
• Meta-analyses less supportive (Fernandez-San-Martin et al, 2010; Nunes et al, 2011; Sarris et al, 2011)
• Beneficial in children and the elderly (Muller et al, 2006; Glass et al, 2003)
• Benefit in menopausal women (Taavoni et al, 2011)
• Possible benefit in OCD (Pakseresht et al, 2011)
• Powerful smell hindered controlled studies
Valerian: Dosing and Safety

• Recommended doses are 450-600 mg approximately 2 hours before bedtime
  – No added benefit from higher doses
  – Promotes natural sleep after several weeks
  – No AM hangover
  – Safe in overdose, no interactions

• Headaches and GI complaints are common

• Toxic reactions (rare)
  – Blurry vision, dystonias, hepatotoxicity, withdrawal and delirium (one case)
Valerian: Recommendations

• Valerian appears 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

• Retrospective studies suggest safety in pregnancy, but use with caution
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: Efficacy

• Various meta-analyses

• Auld et al (2011)
  – 12 double or single-blind RCTs
  – Melatonin > placebo at reducing sleep onset latency, delayed sleep phase syndrome, regulating sleep-wake patterns in blind

• Ferracioli-Oda et al (2013)
  – 19 trials showed benefit in sleep onset latency, total sleep time and overall sleep quality
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
- 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
• Contains flavonoids and terpene lactones
• Stabilizes neuronal membranes, scavenges free radicals
• Meta-analyses and systematic reviews suggest efficacy (Weinmann et al, 2010; Brondino et al, 2013; Hashiguchi et al, 2015)
• 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
- Better for Alzheimer’s than vascular dementias
- Best started early; 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)
  - Recent meta-analysis of 18 trials did not find increased risk of bleeding, based on hemostatic outcomes (Kellermann et al, 2011)
  - 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!