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:

<table>
<thead>
<tr>
<th>Organization</th>
<th>Support</th>
<th>Role</th>
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<tbody>
<tr>
<td>Nordic Naturals</td>
<td>Donated drug and placebo for clinical trial</td>
<td>Clinical investigator</td>
</tr>
<tr>
<td>heckel medizintechnik GmbH</td>
<td>Donated Whole Body Hyperthermia device for clinical trial</td>
<td>Clinical investigator</td>
</tr>
<tr>
<td>Harvard Blog</td>
<td>Writing honoraria</td>
<td>Author of blog article</td>
</tr>
<tr>
<td>Peerpoint Medical Education</td>
<td>Speaker Fee</td>
<td>Online course faculty speaker</td>
</tr>
<tr>
<td>MGH Clinical Trials Network and Institute (CTNI)</td>
<td>Salary support through CTNI from multiple pharmaceutical companies and NIMH</td>
<td>Clinical Rater and Director of Education</td>
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</table>
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 US children used CAM practices and products (NIH, 2010)
  - About $33.9 billion out-of-pocket cost
- Global market expected to grow from $209 billion in 2017 to $373 billion in 2025
- Easy access, good tolerability
- Used by many who don’t respond to standard therapies
- Limited research, few rigorous studies
- “Natural” does NOT mean “safe”
- Toxicity, adverse effects, interactions
- Different preparations/purity
- Insurance does not cover them
Natural Antidepressants

- **St John’s Wort**: ~40 clinical trials; monotherapy effective for depression; dosed at 900-1800 mg/day; watch out for photophobia and drug-drug interactions; don’t combine with SSRIs (serotonin syndrome); little data on breastfeeding

- **SAMe**: ~45 clinical trials; effective for depression as monotherapy and augmentation; dosed at 400-1600 mg/day (sometimes up to 3200 mg/day); no interactions; GI upset common; safe to combine with other medications; little data in pregnancy

- **Omega-3**: >30 trials in depression as monotherapy and augmentation; a few trials in bipolar disorder; best for depression or depressed phase of bipolar; dosed at 1-2 g/day (EPA:DHA = 3:2 preferred); safe combined with other meds; recent evidence suggests 4 g/day may be effective in inflammatory depression; probably safe in pregnancy
Natural Anxiolytic-Hypnotics

- **Kava**: >12 studies; effective for generalized anxiety; doses from 60-300 mg/day; recent negative 16-week study in N=171 with GAD, 120 mg bid (Sarris et al, 2020); cases of liver toxicity/death, but recent evidence suggests safety; use with caution and preferably for short periods

- **Valerian**: >35 studies; recent meta-analyses less supportive; effective for insomnia; doses from 450-600 mg at bedtime; few toxicity concerns; apparently safe in pregnancy and in elderly but caution advised

- **Melatonin**: ~20 studies, 2 strong meta-analyses; effective for insomnia, particularly if circadian disturbance-based; dosed at 0.3-5.0 mg/day; start low and increase gradually; some concerns about toxicity in immunosuppressed individuals; prolonged-release form (2mg) effective in elderly; effective in children
For Multiple Indications: N-Acetyl-Cysteine (NAC)

“Mitochondrial Modulator”

http://people.eku.edu/ritchisong/301notes1.htm

http://science-quest.wikispaces.com/
NAC: Mechanisms

• Increases glutathione (GSH) synthesis, which reduces oxidative stress in mitochondrial electron transport chain
• Protects brain cells
• May have activity similar to lithium and valproate
NAC in Bipolar Disorder, SCZ, MDD

• Berk et al, 2008
  – 6-month double-blind placebo-controlled trial
  – N=76, 2 g/day + TAU
  – Improvements on most rating scales in NAC group compared with placebo group

• Zheng et al, 2018
  – Meta analysis of 6 studies of schizophrenia, bipolar disorder, MDD
  – Best results for schizophrenia, not for BIP, MDD
NAC in Bipolar Depression

• Berk et al, 2019
  – N= 181, bipolar depression
  – 2 g/d NAC vs. 2 g/d NAC + combination nutraceutical (CT) vs. PBO augmentation; 20 weeks
  – No significant differences except CGI in CT

• Ellegaard et al, 2019
  – N=80, bipolar depression
  – Adjunctive NAC 3 g/d vs PBO; 20 weeks
  – No significant difference from PBO
NAC in PTSD/SUD and OCD

• Back et al, 2016
  – Veterans with current PTSD and SUD (N=35)
  – Double-blind RCT: NAC 2400 mg/d vs PBO; 8 weeks
  – Significant reduction of PTSD symptoms and drug cravings; good tolerability

• OCD: One case report, one case series, one RCT
  – Afshar et al, 2013
    – NAC 2400 mg/d + SSRI; 12 wks; YBOCS drop 28→17
    – Cohen d 1.31, full response in 10/19 NAC subjects
For Multiple Indications: Inositol

- Sugar alcohol, structural isomer of glucose, located primarily within cell membranes
- Present in beans, grains, nuts, and many fruits. Average adult consumes 1 g/day
- Also called Vitamin B8
- Vital in second messenger system for numerous neurotransmitter receptors
Mechanisms of Action

1. Involved in synthesis of membrane phospholipids
2. Precursor in phosphatidylinositol (PI) cycle
Efficacy

- 6 clinical trials for depression (5 PBO-controlled)
  - 1 monotherapy, 5 augmentation
  - 2 MDD, 1 unipolar + bipolar depression, the rest bipolar depression
  - Inositol > placebo in 3 of 5 controlled studies
  - Small samples; significance reached in only one study
- Also effective for panic disorder, OCD, bulimia nervosa
- Possible broad spectrum of action similar to SSRIs
- Negative in schizophrenia, ADHD, Alzheimer's, autism, ECT-induced cognitive impairment
Safety and Tolerability

- Side effects: mild increases in plasma glucose, gas, nausea, sleep disturbance, dizziness, headache
- Case reports of mania in bipolar depression
- No reported toxicity or drug-drug interactions
- Not recommended for pregnant women, given risk of inducing uterine contractions
- Recommended doses between 6-20 g/d, usually 12 g/d divided 2-4X/day
For Multiple Indications: Rhodiola Rosea

- Found in mountains of Europe and Asia
- Used for centuries in traditional medicine of Asia, Scandinavia, 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, sexual dysf.
Efficacy and Mechanisms

• Studied in Russia and Scandinavia for >40 years
  – Most reports not yet translated to English

• Multiple active ingredients
  – Adaptogenics (rosavins, tyrosol), antioxidants (flavonoids), monoamine modulation, MAO-A and B inhibition, opioid-like effects

• ≥4 controlled trials support efficacy in depression and anxiety as well as cognition
  – Doses from 100-680 mg/day
Recent RCT of Rhodiola for MDD

• Mild-to moderate MDD; N=100; 12 weeks
  – Group A: Sertraline (‘high dose’) + PBO
  – Group B: Sertraline and Rhodiola 600 mg/day
  – Group C: Sertraline + Rhodiola 300 mg/day

• All groups had statistically significant reduction in HAM-D, BDI, and CGI
  – Improvement was significantly greater for group B versus groups C and A

• Higher doses of Rhodiola may be best

Safety and Tolerability

• SFX mild, uncommon
  – Allergy, irritability, fatigue, unpleasant sensations, especially at high doses
  – Insomnia/vivid dreams; take early in day
  – Best on empty stomach, before meals

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

• No data on pregnancy or bipolar cycling
  – Use with caution
For Dementia: Ginkgo Biloba

- Cognition enhancer; slows cognitive decline
- Approx. 30 studies in Alzheimer’s, 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; Liu et al, 2019)
- 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)
Clinical Recommendations

- Suggested dose = 120-240 mg/day
- Best started early; full assessment may require 1 year
- No data on longer-term impact
- May alleviate antidepressant-induced sexual dysfunction
- Side effects: mild GI upset, headache, irritability, dizziness, seizures in epileptics
- Inhibits platelet activating factor (PAF); may cause bleeding in patients on anticoagulants or having surgery
  - No increased risk of bleeding, based on hemostatic outcomes in meta-analysis of 18 trials (Kellermann et al, 2011)
  - PAF inhibition may increase risk of bleeding in pregnancy; risk to breastfeeding infants unknown
For Cognition: Carotenoids

- Astaxanthin and Lutein
- Found in algae, other plants
- Neuroprotective
  - Antioxidants
  - Reduce cytotoxic substance release
  - Promote neurogenesis and cell plasticity
Astaxanthin Efficacy

**Satoh et al 2009**
- Open Study: N= 127 males ages 50-69
- AX 4-20 mg/day; 4 weeks (safety) → n=10 with age-related forgetfulness: 12 mg/day for 12 weeks (efficacy)
- Improvement in cognitive tests compared to own baseline

**Katagiri et al 2012**
- RCT: N=96 subjects with age-related forgetfulness
- AX 6-12 mg/day vs PBO for 12 weeks
- AX subjects showed better cognitive performance (NS)
- Excellent tolerability, no AEs

**Evidence should be considered preliminary**
Lutein Efficacy

- Review of five lutein studies (8-12 mg/day)
- 10 mg lutein per day for twelve months:
  - selective improvement of visual episodic memory in young and middle-aged adults
  - inhibition in some middle-aged and older adults
- Limitations: Small samples (N=40-100), healthy individuals only
- Evidence considered preliminary

Recreational Drugs as Therapeutic Interventions: Kratom

- Tropical Southeast Asian evergreen tree in coffee family
- Used in traditional medicines
  - Chewed to relieve musculoskeletal pain and increase energy, appetite, mood, and sexual desire
- Sometimes mixed with caffeine or codeine
- Often used as an alternative to opioids, replacement or abstinence
Kratom: Mechanisms

- Key psychoactives are mitragynine and 7-hydroxymitragynine (7-HMG)
- About 17 mg of mitragynine in 20 leaves
- Opioid properties, stimulant-like effects
- Onset typically in 5-10 minutes and lasts for 2-5 hours
Kratom: Safety

- SFX: nausea, vomiting, and constipation, withdrawal...respiratory depression, seizure, addiction, and psychosis, tachycardia and HTN, trouble sleeping...liver toxicity...death
- Between 2011 and 2017, 44 kratom-related deaths, most involved multiple drugs
- 9 deaths in Sweden in 2011-2012 with a mixture of kratom + opioids
- Salmonella contamination in some kratom products
Kratom: Current Status and Recommendations

• Controlled substance in 16 countries
• FDA says no evidence of safety or efficacy for any condition
  – Considers it opioid
  – Banned importing/manufacturing as a dietary supplement
• Caution recommended, especially in people with h/o opioid use disorders
Cannabidiol (CBD)

- Cannabinoid constituent of cannabis
- Inhaled in cannabis smoke, vapor, aerosol spray; oral forms available
- Often supplied as oil containing only CBD (no THC), a full-plant CBD-dominant hemp extract oil, capsules, dried cannabis, or liquid solution
- Sold openly in most states
CBD: Applications

• Multiple sclerosis pain: Nabiximols (Sativex) oral aerosolized mist containing CBD + THC
  – Each spray delivers 2.7 mg THC + 2.5 mg CBD
  – Approved in Canada since 2005; also in Sweden

• Epilepsy: numerous clinical trials show CBD effective for certain childhood epilepsy disorders
  – Oral cannabidiol solution (Epidiolex) FDA-approved in June 2018 for Lennox-Gastaut syndrome and Dravet syndrome
  – 10-20 mg/Kg/day

• Limited data on other indications
Cannabis Products: Systematic Review

• Possible reduction of social anxiety
• Mixed (mainly positive) evidence for adjunctive use in schizophrenia
• Limited evidence in insomnia and PTSD
• No evidence of benefit for depression from high THC therapeutics or for CBD in mania
• Some potential efficacy for an oral cannabinoid/terpene combination in ADHD.

CBD: Mechanisms

- Indirect antagonist for CB1 and CB2 receptors
  - Potentiates THC by increasing CB1 receptor density or through other CB1 receptor-related mechanisms
- Interacts with G protein-coupled receptors
- Serotonin 5-HT1A receptor partial agonist
  - Antidepressant, anxiolytic effects?
- Allosteric modulator of μ- and δ-opioid receptors
CBD: Safety

• Common Side Effects
  – sleepiness
  – decreased appetite
  – diarrhea
  – fatigue
  – malaise
  – weakness
  – insomnia

• No intoxicating effects as with THC
CBD Recommendations

• Caution with high-THC formulations
  – esp. in youth, and anxiety or psychotic disorders
• Slow titration
• Regular assessment
• Caution in cardiovascular, respiratory disorders, pregnancy and breast-feeding
• Consider occupational safety as well

# Synthesis: CANMAT Recommendations

## Table 3. Summary of Recommendations for Natural Health Products.

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Indication</th>
<th>Recommendation</th>
<th>Evidence</th>
<th>Monotherapy or Adjunctive Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>St. John’s wort</td>
<td>Mild to moderate MDD</td>
<td>First line</td>
<td>Level 1</td>
<td>Monotherapy</td>
</tr>
<tr>
<td></td>
<td>Moderate to severe MDD</td>
<td>Second line</td>
<td>Level 2</td>
<td>Adjunctive</td>
</tr>
<tr>
<td>Omega-3</td>
<td>Mild to moderate MDD</td>
<td>Second line</td>
<td>Level 1</td>
<td>Monotherapy or adjunctive</td>
</tr>
<tr>
<td></td>
<td>Moderate to severe MDD</td>
<td>Second line</td>
<td>Level 2</td>
<td>Adjunctive</td>
</tr>
<tr>
<td>SAM-e</td>
<td>Mild to moderate MDD</td>
<td>Second line</td>
<td>Level 1</td>
<td>Adjunctive</td>
</tr>
<tr>
<td></td>
<td>Moderate to severe MDD</td>
<td>Second line</td>
<td>Level 2</td>
<td>Adjunctive</td>
</tr>
<tr>
<td>Acetyl-L-carnitine</td>
<td>Mild to moderate MDD</td>
<td>Third line</td>
<td>Level 2</td>
<td>Monotherapy</td>
</tr>
<tr>
<td>Crocus sativus (saffron)</td>
<td>Mild to moderate MDD</td>
<td>Third line</td>
<td>Level 2</td>
<td>Monotherapy or adjunctive</td>
</tr>
<tr>
<td>DHEA</td>
<td>Mild to moderate MDD</td>
<td>Third line</td>
<td>Level 2</td>
<td>Monotherapy</td>
</tr>
<tr>
<td>Folate</td>
<td>Mild to moderate MDD</td>
<td>Third line</td>
<td>Level 2</td>
<td>Adjunctive</td>
</tr>
<tr>
<td>Lavandula (lavender)</td>
<td>Mild to moderate MDD</td>
<td>Third line</td>
<td>Level 3</td>
<td>Adjunctive</td>
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<tr>
<td>Inositol</td>
<td>Mild to moderate MDD</td>
<td>Not recommended</td>
<td>Level 2</td>
<td>Adjunctive</td>
</tr>
<tr>
<td>Tryptophan</td>
<td>Mild to moderate MDD</td>
<td>Not recommended</td>
<td>Level 2</td>
<td>Adjunctive</td>
</tr>
<tr>
<td>Rhodiola rosea (rosesoot)</td>
<td>Mild to moderate MDD</td>
<td>Not recommended</td>
<td>Insufficient evidence</td>
<td>Adjunctive</td>
</tr>
</tbody>
</table>

DHEA, dehydroepiandrosterone; MDD, major depressive disorder; SAM-e, S-adenosyl-L-methionine.

# CANMAT Recommendations (cont’d)

Table 2. Summary of Recommendations for Physical and Meditative Treatments.

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Indication</th>
<th>Recommendation</th>
<th>Evidence</th>
<th>Monotherapy or Adjunctive Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exercise</td>
<td>Mild to moderate MDD</td>
<td><strong>First line</strong></td>
<td>Level 1</td>
<td>Monotherapy</td>
</tr>
<tr>
<td>Light therapy</td>
<td>Moderate to severe MDD</td>
<td><strong>First line</strong></td>
<td>Level 1</td>
<td>Adjunctive</td>
</tr>
<tr>
<td></td>
<td>Seasonal (winter) MDD</td>
<td><strong>First line</strong></td>
<td>Level 1</td>
<td>Monotherapy</td>
</tr>
<tr>
<td></td>
<td>Mild to moderate nonseasonal MDD</td>
<td><strong>Second line</strong></td>
<td>Level 2</td>
<td>Monotherapy and adjunctive</td>
</tr>
<tr>
<td>Yoga</td>
<td>Mild to moderate MDD</td>
<td><strong>Second line</strong></td>
<td>Level 2</td>
<td>Adjunctive</td>
</tr>
<tr>
<td>Acupuncture</td>
<td>Mild to moderate MDD</td>
<td><strong>Second line</strong></td>
<td>Level 2</td>
<td>Adjunctive</td>
</tr>
<tr>
<td>Sleep deprivation</td>
<td>Moderate to severe MDD</td>
<td><strong>Third line</strong></td>
<td>Level 2</td>
<td>Adjunctive</td>
</tr>
</tbody>
</table>

MDD, major depressive disorder.

Conclusions:
Who Should Use Natural Remedies?

• Mildly ill people with a strong interest in natural remedies 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
    • Beware drug-drug interactions!
Questions?

Please email me at:

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