MASSACHUSETTS GENERAL HOSPITAL
PSYCHIATRY ACADEMY

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:

Organization	Support	Role
Nordic Naturals	Donated drug and placebo for clinical trial	Clinical investigator
heckel medizintechnik GmbH	Donated Whole Body Hyperthermia device for clinical trial	Clinical investigator
Harvard Blog	Writing honoraria	Author of blog article
Peerpoint Medical Education	Speaker Fee	Online course faculty speaker
MGH Clinical Trials Network and Institute (CTNI)	Salary support through CTNI from multiple pharmaceutical companies and NIMH	Clinical Rater and Director of Education

Objectives

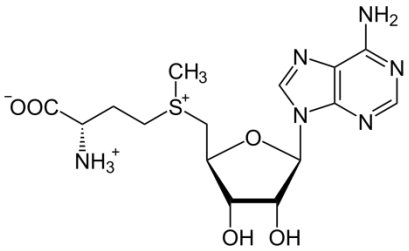
- To understand the evidence base for efficacy of natural therapies in psychiatry
- To identify the risks and benefits of various natural treatments in psychiatry
- To be able to educate patients in purchasing natural products in both over-the-counter and prescription forms

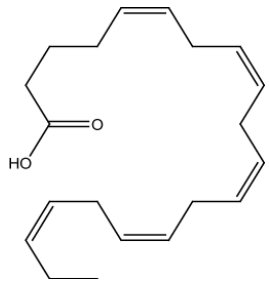
Pros and Cons of Natural Remedies

- 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



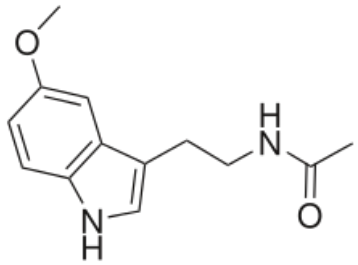


Natural Anxiolytic-Hypnotics

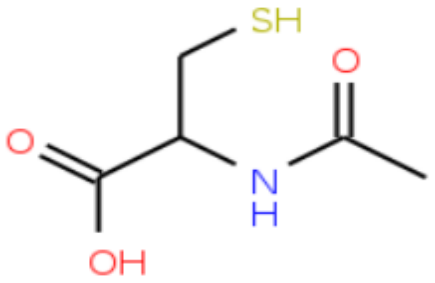
- **Kava**: >12 studies; effective for generalized anxiety; doses from 60-300 mg/day; recent negative 16-week study in N=171 with GAD, 120 mg bid (Sarris et al, 2020); cases of liver toxicity/death, but recent evidence suggests safety; use with caution and preferably for short periods

- **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

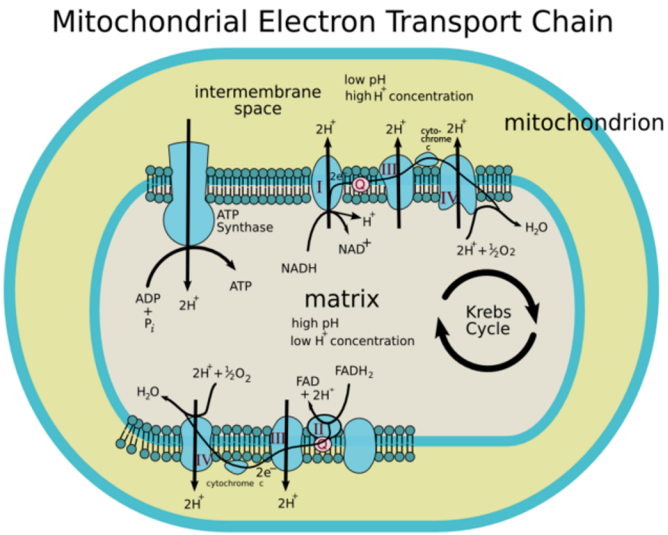
- **Melatonin**: ~20 studies, 2 strong meta-analyses; effective for insomnia, particularly if circadian disturbance-based; dosed at 0.3-5.0 mg/day; start low and increase gradually; some concerns about toxicity in immunosuppressed individuals; prolonged-release form (2mg) effective in elderly; effective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



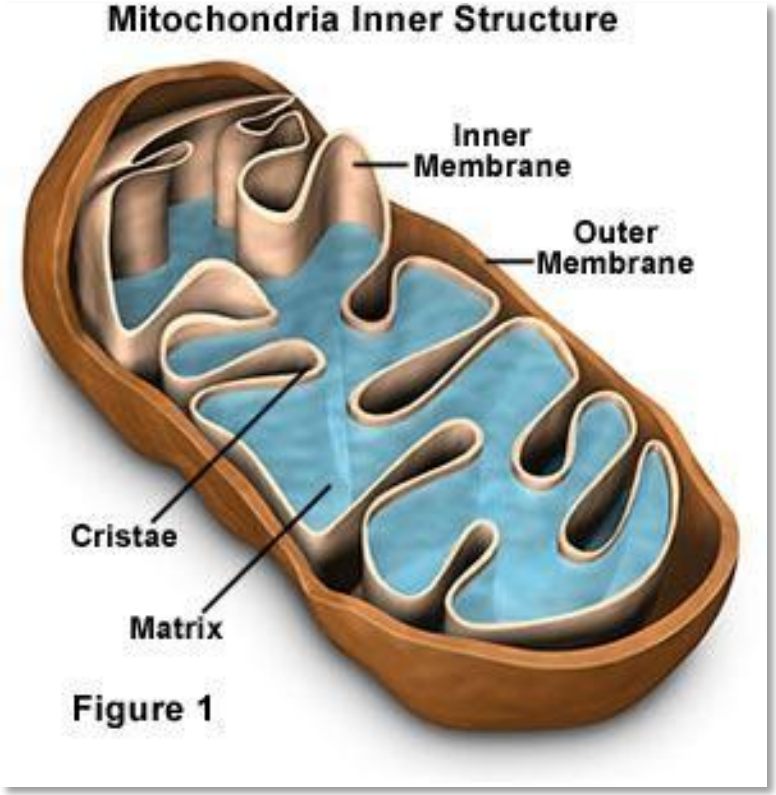
For Multiple Indications: N-Acetyl-Cysteine (NAC)



"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

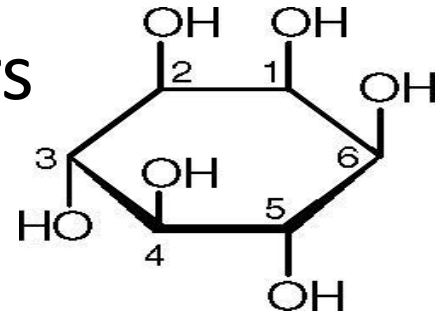
- Berk et al, 2019
  - N= 181, bipolar depression
  - 2 g/d NAC vs. 2 g/d NAC + combination nutraceutical (CT) vs. PBO augmentation; 20 weeks
  - No significant differences except CGI in CT
- Ellegaard et al, 2019
  - N=80, bipolar depression
  - Adjunctive NAC 3 g/d vs PBO; 20 weeks
  - No significant 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

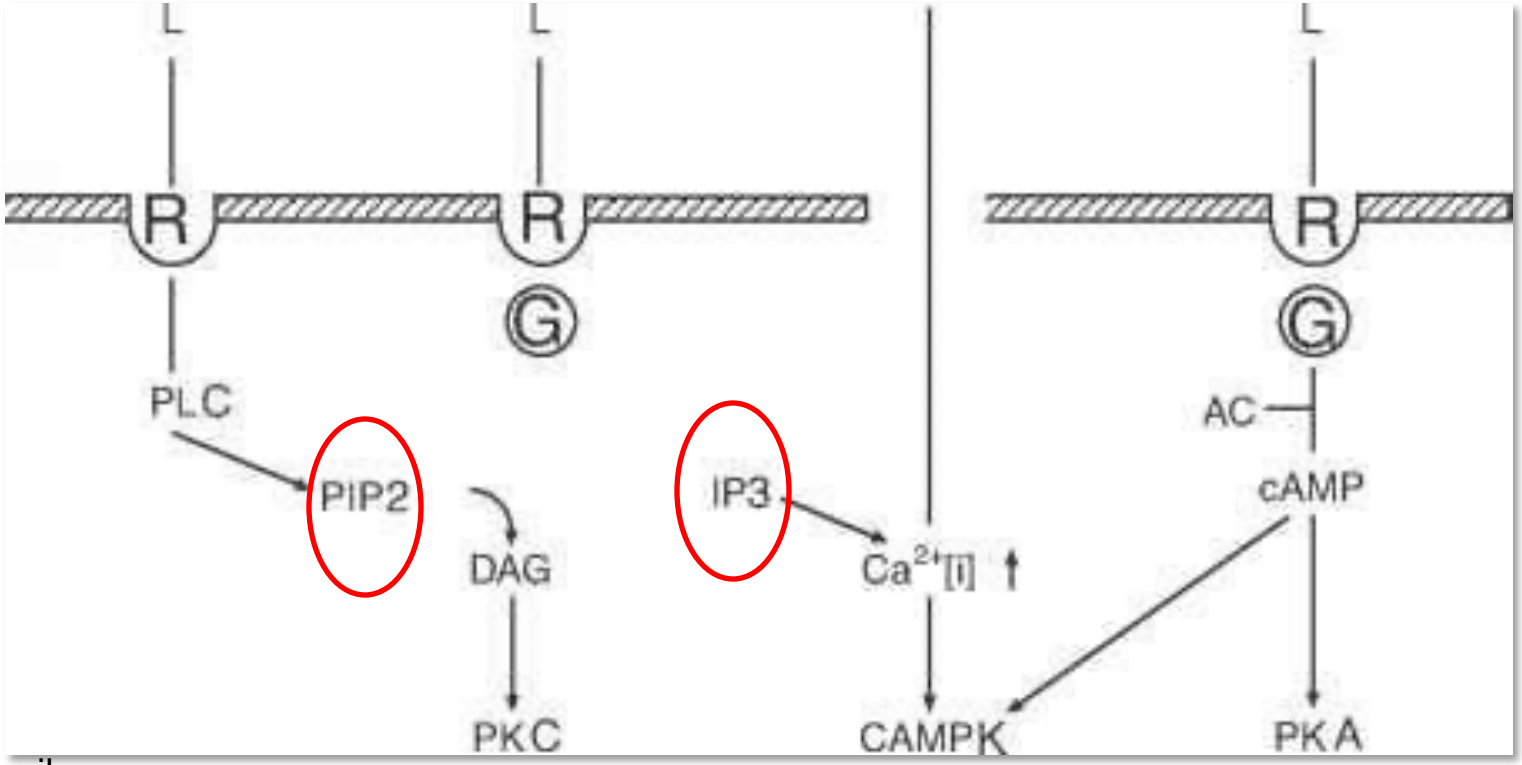
For Multiple Indications: Inositol

- 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



www.johnnysilva.com

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

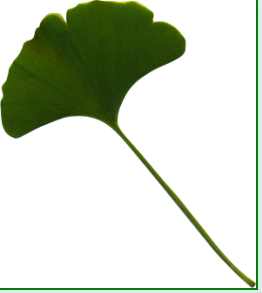
Recent RCT of Rhodiola for MDD

- 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

Gao et al. J Affect Disord 2020; 265:99-103.

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

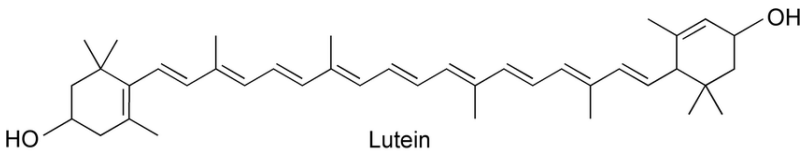
- Cognition enhancer; slows cognitive decline
- Approx. 30 studies in Alzheimer's, mostly supportive
- Contains flavonoids and terpene lactones
- Stabilizes neuronal membranes, scavenges free radicals
- Meta-analyses and systematic reviews suggest efficacy (Weinmann et al, 2010; Brondino et al, 2013; 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

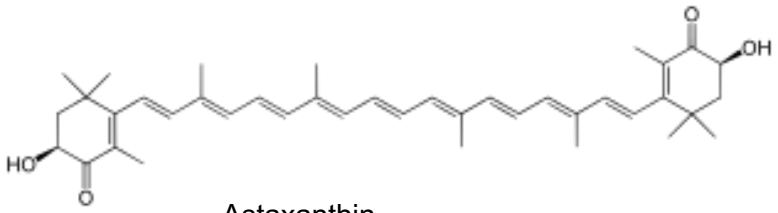
- Suggested dose = 120-240 mg/day
- Best started early; full assessment may require 1 year
- No data on longer-term impact
- May alleviate antidepressant-induced sexual dysfunction
- Side effects: mild GI upset, headache, irritability, dizziness, seizures in epileptics
- Inhibits platelet activating 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



Lutein



Astaxanthin

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

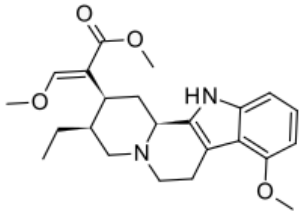
- Review of five lutein studies (8-12 mg/day)
- 10 mg lutein per day for twelve months:
  - selective improvement of visual episodic memory in young and middle-aged adults
  - inhibition in some middle-aged and older adults
- Limitations: Small samples (N=40-100), healthy individuals only
- Evidence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

Nouchi et al, Nutrients 2020; 12(3): 617. doi: 10.3390/nu12030617

Recreational Drugs as Therapeutic Interventions:

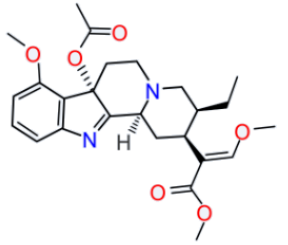
Kratom

- 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



Mitragynine

Kratom: Mechanisms



7-Acetoxymitragynine

- 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

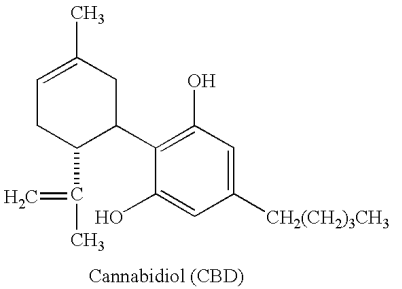
Kratom: Safety

- 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)



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.

Sarris et al. BMC Psychiatry 2020; 20:24. doi: 10.1186/s12888-019-2409-8.

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

Sarris et al. BMC Psychiatry 2020; 20:24. doi: 10.1186/s12888-019-2409-8.

Synthesis: CANMAT Recommendations

Table 3. Summary of Recommendations for Natural Health Products.

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

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

Ravindran et al, Can J Psychiatry 2016; 61: 576-587

CANMAT Recommendations (cont'd)

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

Intervention	Indication	Recommendation	Evidence	Monotherapy or Adjunctive Therapy
Exercise	Mild to moderate MDD	First line	Level 1	Monotherapy
	Moderate to severe MDD	Second line	Level 1	Adjunctive
Light therapy	Seasonal (winter) MDD	First line	Level 1	Monotherapy
	Mild to moderate nonseasonal MDD	Second line	Level 2	Monotherapy and adjunctive
Yoga	Mild to moderate MDD	Second line	Level 2	Adjunctive
Acupuncture	Mild to moderate MDD	Third line	Level 2	Adjunctive
Sleep deprivation	Moderate to severe MDD	Third line	Level 2	Adjunctive

MDD, major depressive disorder.

Ravindran et al, Can J Psychiatry 2016; 61: 576-587

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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