Natural Medications for Psychiatric Disorders

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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)

- Methyl donor (>100 rxns)
- Present in all living things
- Neurotransmitter synthesis, gene regulation, post transl. modifications, cell membrane and receptor integrity
- Depends on folate, B12 levels
- Deficiencies in MTHFR polymorphisms, depression, Alzheimer’s, Parkinson’s, HIV

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)
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 (Trebatická 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
Kratom

- Tropical evergreen tree in coffee family native to Southeast Asia
- Used in traditional medicines
  - Chewed to relieve musculoskeletal pain and increase energy, appetite, and sexual desire
  - Heal wounds, local anesthetic, coughs, GI infections
  - Workers use to prevent exhaustion, mood enhancer, painkiller
- Very bitter and generally combined with a sweetener
- Sometimes mixed with other psychoactive drugs, such as caffeine and codeine
- Not injectable
Kratom: A Survey

- Kirsten Elin Smith, PhD student
- Survey of 478 PSA users focused on the use of kratom within the past 12 months
- 21% used kratom at least once, 10% in past 12 months
- 3 kinds of users
  - "Safe" heroin alternative to help abstain; PRN when there is no opioid around
  - Casual 1-2 time users
  - Long-term replacement for opioids, incl. IV heroin
Kratom: Mechanisms

- Opioid properties and some stimulant-like effects
- Key psychoactive compounds are mitragynine and 7-hydroxymitragynine (7-HMG), > 40 compounds in leaves
- Some people take it for managing chronic pain, opioid withdrawal symptoms, or for recreational purposes
- Onset typically begins 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 occurred, with one involving kratom alone. 9 in Sweden in 2011-2012, with a mixture of kratom plus 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 opioid use disorders
Cannabidiol (CBD)

- Cannabinoid constituent of cannabis
  - One of at least 113 cannabinoids
  - Up to 40% of hemp extract
- Discovered in 1940 and initially thought not to be pharmaceutically active
- Inhaled in cannabis smoke, vapor, aerosol spray into the cheek; oral forms available
- Often supplied as oil containing only CBD as the active ingredient (no added THC or terpenes), a full-plant CBD-dominant hemp extract oil, capsules, dried cannabis, or as a prescription liquid solution
CBD: Applications

- Multiple sclerosis pain: Nabiximols (brand name Sativex) aerosolized mist for oral administration containing 1:1 CBD:THC
  - Approved in Canada since 2005; also in Sweden
- Epilepsy: numerous clinical trials show CBD effective for certain childhood epilepsy disorders
  - Oral cannabidiol solution containing sesame oil (Epidiolex) approved by FDA in June 2018 as a treatment for Lennox-Gastaut syndrome and Dravet syndrome
- Limited data on other indications
CBD: Mechanisms

• Low affinity 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 (GPRs) in caudate nucleus and putamen
• Serotonin 5-HT1A receptor partial agonist
  – antidepressant, anxiolytic, neuroprotective effects
• Allosteric modulator of μ- and δ-opioid receptors
• Peroxisome proliferator-activated receptor (PPARγ) agonism and intracellular calcium release
• Inhibition of fatty acid amide hydrolase, may increase endocannabinoids (anandamide)
CBD: Safety and Recommendations

• Common SFX
  – sleepiness, decreased appetite, diarrhea, fatigue, malaise, weakness, insomnia
• No intoxicating effects as with THC
• May oppose disordered thinking and anxiety produced by THC
• Schedule I in the US but approved for childhood epilepsy
• Sold openly in most states
• Caution recommended; long-term safety and efficacy data are needed
Phenibut

• CNS depressant with anxiolytic and hypnotic effects
  – Developed in the Soviet Union in 1960s
  – Marketed in Russia, Ukraine, Kazakhstan, and Latvia
  – Brand names: Anvifen, Fenibut, and Noofen; oral or IV

• For anxiety, sleep, asthenia, depression, alcoholism, alcohol withdrawal syndrome, PTSD, stuttering, tics, vestibular disorders, Ménière's disease, dizziness, motion sickness, anxiety before or after surgical procedures or painful diagnostic tests

• Not approved in US, most of Europe; controlled substance in Australia

• Sold on Internet as supplement and purported nootropic

• Used recreationally for euphoria, anxiolysis, increased sociability
Phenibut: Mechanisms

- GABA analogue
- GABA-B receptor agonist, similar to baclofen and γ-hydroxybutyrate (GHB)
- Potent blocker of α2δ subunit-containing voltage-dependent calcium channels (VDCCs), similarly to gabapentin and pregabalin
- Available in 250 mg tablets and as a solution of 10 mg/mL for infusion
Phenibut: Safety

- SFX: sedation, sleepiness, nausea, irritability, agitation, anxiety, dizziness, allergic skin rash, headache
- Incoordination, loss of balance, and hangovers at high doses
- CNS depression/unconsciousness with OD; no deaths reported
- Tolerance with repeated use
- Withdrawal upon discontinuation; with high dose withdrawal severe rebound anxiety, insomnia, anger, irritability, agitation, visual and auditory hallucinations, psychosis
- Contraindications: Pregnancy and breastfeeding, children <2 years of age, liver insufficiency or failure, ulcerative lesions of GI tract
Phenibut: Recommendations

- With prolonged use/high doses, risk of fatty liver disease and eosinophilia; monitor regularly
- Should not be combined with alcohol
- Because of delayed onset of effects, first-time users often mistakenly take an additional dose of phenibut in the belief that the initial dose did not work
- Recreational users usually take the drug orally; there are case reports of rectal and intranasal administration
  - Painful; swollen tissues
- Should be used with great caution
Kava, Valerian, Melatonin

- **Kava**: More than 12 studies; effective for generalized anxiety; doses of about 60-300 mg/day; cases of liver toxicity/death, but recent evidence suggests these were due to contamination; use with caution and preferably for short periods

- **Valerian**: More than 35 studies; recent meta-analyses less supportive; effective for insomnia; dosed at about 450-600 mg at bedtime; few toxicity concerns; apparently safe in pregnancy but caution advised

- **Melatonin**: About 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
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 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
    • drug-drug interactions can be significant!