Recent Advances in Natural Therapies

David Mischoulon, MD, PhD
Director of Research
Depression Clinical and Research Program
Massachusetts General Hospital
Associate Professor of Psychiatry
Harvard Medical School
Disclosures

Research support from Bowman Family Foundation, Fisher Wallace, Nordic Naturals, Methylation Sciences, Inc. (MSI), and PharmoRx Therapeutics

Honoraria for consulting, speaking, and writing from Pamlab, and the Massachusetts General Hospital Psychiatry Academy

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
• Effectiveness unclear
• “Natural” does NOT mean “safe”
• Toxicity, adverse effects, interactions
• Different preparations/purity
• Insurance does not cover them
• Limited clinician and consumer education
St. John’s Wort
(SJW, Hypericum Perforatum)
SJW: Evidence

• About 40 published trials; 26 placebo-controlled; 14 with std antidepressant active comparators; various systematic reviews and meta-analyses
  – Short duration; often no standardized diagnostic instruments; varied severity
  – SJW > PBO; SJW = low-dose TCA, esp. for mild-moderate depression
  – Benefits in atypical depression (Mannel et al, 2010), PMS (Canning et al, 2010); no benefit in Minor Depression (Rapaport et al, 2011)
  – Inconsistent evidence in comparisons against newer antidepressants
    • About 13 trials comparing SJW to SSRIs ; 2-3 Cochrane reviews
    • SJW = SSRIs; SJW > PBO
  – No benefit for ADD, anxiety, OCD (Weber et al, 2008; Sarris et al, 2013)
SJW: Mechanism of Action and Safety

- Hypericin, hyperforin, adhyperforin key ingredients
  - Interaction with cytokine production and HPA axis?
  - Hyperforin may help in Alzheimer’s (Griffith et al, 2010)

- Generally safe
  - Usual side effects: dry mouth, dizziness, constipation
  - Watch out for: phototoxicity, cycling to mania, interactions
  - Serotonin syndrome with SSRIs (SJW has MAOI activity)
  - Risk of cataracts?
  - Colic, drowsiness, lethargy in breastfed infants
  - Low birth weight from in utero exposure in animal studies
  - No fetal malformations in one human study
**SJW: Major Drug-Drug Interactions**

- Warfarin
- Cyclosporin
- Oral contraceptives
- Theophylline
- Fenprocoumon
- Digoxin
- Indinavir
- Camptosar
- Zolpidem
- Irinotecam
- Olanzapine

- SJW induces CYP-3A4 expression
- Reduces therapeutic activity of other drugs
- Caution required in
  - HIV+ patients
  - Cancer patients
  - Transplant patients
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
- Present in all living things
- Needed for neurotransmitter synthesis
- Depends on folate and B12 levels
- MTHFR polymorphisms may affect synthesis of neurotransmitters
SAMe: Efficacy Trials in Depression

- > 45 randomized clinical trials (PO, IM, IV): SAMe 200-1600 mg/d
- 8 placebo-controlled studies (N ~ 40-100)
  - SAMe > placebo in 6 studies; SAMe = placebo in 2 studies
- 8 comparison studies with TCAs
  - SAMe = TCA in 6 studies; SAMe > imipramine in 1 study
- 1 comparison with SSRI (Mischoulon et al, 2014)
  - N=189; 12 weeks; SAMe vs Escitalopram vs Placebo
  - Benefit in all 3 treatment arms (5-6 point drop on HAM-D)
  - No significant differences between treatment groups
  - Possible advantage for SAMe in subanalysis of one site (Sarris et al, 2014)
SAMe: Augmentation

• Combined safely with TCAs; may accelerate action (Alvarez et al, 1987, Berlanga et al, 1992)

• Combined successfully with SSRIs, SNRIs

• Alpert et al, 2004; n = 30 SSRI partial and NR; 6 weeks
  – Augmentation with SAMe 800-1600 mg/d
  – Response rate 50%; remission rate 43%

• Papakostas et al, 2010; n=73 SRI NR; 6 weeks
  – Augmentation with SAMe 800 mg bid or PBO
  – SAMe: Response=36.1%; remission= 25.8%
  – PBO: Response=17.6%; remission= 11.7%
  – Possible benefit in male sexual function (Dording et al, 2011)
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)
L-methylfolate (Deplin)

L-methylfolate vs. Synthetic Folic Acid

Bypasses polymorphisms

L-methylfolate

Dihydrofolate (Dietary Folate)

Tetrahydrofolate

10-formyl-THF

5, 10 Methylenyl THF

5, 10 Methylene THF

L-methylfolate

DHF Reductase

MTHFD1 Polymorphism

MTHFR C→T Polymorphism

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
- L-methylfolate 15 mg/day vs placebo
- Two 30-day treatment phases using sequential parallel comparison design (SPCD)

(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)
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)](image)

![Eicosapentaenoic acid (EPA; 20:5, n-3)](image)
Omega-3 Fatty Acids: Efficacy

• > 30 RCTs in depression, mostly adjunct omega-3
  – EPA and EPA+DHA combos used most often; 1-2g/day
  – Possible advantage in obese patients with high inflammation?
• Mixed evidence for DHA (Marangell et al, 2003; Mischoulon et al, 2008)
  – Protective effect against suicide? (Lewis et al, 2011)
• 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, in press)
  – Benefit from flax oil (ALA) in pedi bipolar? (Gracious et al, 2010)
• Weaker results in borderline PD, schizophrenia (Zanarini et al, 2003; Peet et al, 2001)
Omega-3s: Recommendations

- Depression: Probably 1-2 g/day of an EPA/DHA combo is best, with ≥ 60% EPA (Sublette et al, 2011)
  - Possible advantage for EPA (Mozaffari-Khosravi et al, 2013; Mischoulon et al, in press)
- Bipolar disorder: high doses (6-10 g/day)?
  - But watch for cycling!
- Side effects include stomach upset, fishy taste, risk of bleeding when combined with anticoagulants
- Benefit to expectant mothers, fetus, and infants, particularly for neural development, allergy prevention
  - Safe upper limit in pregnancy unknown
Vayacog (Lipicogen)

- Phosphatidylserine (PS)
  - Important in cell membrane function
  - Cognitive decline with decreased brain PS-DHA
- Lipicogen (DHA-enriched PS) 310mg
  - PS 100mg; DHA 19.5mg; EPA 6.5mg
- Vakhapova et al, 2010, 2014; N=157; 15 weeks
  - 300mg/d vs PBO; + 15wk follow-up at 100mg/d
  - PS-DHA associated with significant improvement in sustained attention and memory recognition; maintained in continuation
Vayarin (Lipirinen)

- Prescription medical food for lipid imbalances associated with attention deficit hyperactivity disorder (ADHD) in children

- Lipirinen
  - Phosphatidylserine (PS): 150 mg
  - Eicosapentaenoic acid (EPA): 43 mg
  - Docosahexaenoic acid (DHA): 17 mg
Vayarin

• Manor et al, 2011
• 15-week double-blind, randomized, placebo-controlled study in 200 children with ADHD
• Significant advantage for Vayarin in Conners’ rating scales and child health questionnaire scores
• Benefit in hyperactive/impulsive behavior, mood, behavior-dysregulation
• 15-week open-label extension during which all children received Vayarin
• Well tolerated, no significant side effects
Kava (Piper Methysticum)

• Anxiolytic, anticonvulsant, and muscle relaxant (kavapyrones)
• More than 12 studies, mostly RCTs
• Similar efficacy to venlafaxine, buspirone, opipramol (sigma antagonist)
• Effective for mild anxiety, not for panic attacks (Sarris et al, 2011)
• Antidepressant effect? (Sarris et al, 2009)
Kava: Adverse Effects

• Common mild side effects
  - Stomach upset, headaches, dizziness

• Toxic reactions with high doses, prolonged use
  - Unsteadiness, hair loss, visual problems, respiratory problems, kava dermopathy
  - 78 cases of severe liver toxicity; 36 cases of hepatitis; cirrhosis; 11 cases of liver failure requiring transplant; 4 deaths → banned in parts of Europe
  - Most were taking high doses for long periods or concurrently with other hepatotoxic medications
  - Toxicity may be due to hepatotoxic molds if long period between harvest and preparation (Teschke et al, 2011)
Kava: Recommendations

• Suggested doses 60-300 mg/day
  – Potency and efficacy may vary

• Avoid kava if:
  – History of liver disease, alcohol use, concurrent medications with potential liver toxicity
  – Pregnant or breastfeeding

• Use only under physician supervision

• Monitor liver enzymes regularly

• Use for 1-3 months at most
Valerian (Valeriana Officinalis)

- Used as a drug for over 1000 years
- “Valere” (Latin) = “in good health”
- “Baldrian” (German)
- Popular worldwide as sedative and mild hypnotic
- Popular among Hispanics
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: Ingredients and Mechanisms

• Monoterpenes and sesquiterpenes
• Iridoids and valepotriates
• Alkaloids, amino acids (esp. GABA)
• Active ingredients may function like BDZ
  – Direct GABA-ergic activity
  – Decrease GABA breakdown
• Changes in sleep architecture
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
Valerian: Adverse Effects

- Headaches and GI complaints are common
- No hangover effect in AM
- Reportedly safe in overdose, no interactions
  - Has been combined with SJW with good results
- Toxic reactions (rare): Blurry vision, dystonias, hepatotoxicity, withdrawal and delirium (one case)
- Some preparations may contain mutagens
- Unclear safety in pregnancy
  - Studies suggest no adverse effects, but data are limited
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)
- Few studies in psychiatric populations per se
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
Ginkgo Biloba

• Cognition enhancer
• May slow down cognitive decline in dementia
• Approx. 30 studies; some methodological problems
• Stabilizes neuronal membranes, scavenges free radicals
• Meta-analyses suggest efficacy (Weinmann et al, 2010; Brondino et al, 2013)
• Mixed results in young healthy people (Stough et al, 2001; Persson et al, 2003)
• Benefit in healthy middle aged people (Kaschel, 2011)
• Discouraging data on preventive effects (Andrade et al, 2009)
Ginkgo vs. Cholinesterase Inhibitors

• Placebo-controlled RCT of ginkgo (160 mg) vs. donepezil (5 mg) in Alzheimer’s disease (Mazza et al, 2006); n = 60; 24 weeks; Equivalent

• RCT of ginkgo (240 mg) vs. donepezil (5-10 mg) vs. combination of both in Alzheimer’s disease (Yancheva et al, 2009); n = 96; 22 weeks; Equivalent, advantage and better tolerability for combination

• RCT Ginkgo biloba (120 mg) vs. rivastigmine (4.5 mg); n=56; 24-weeks (Nasab et al, 2012); Riv > Ginkgo

• Donepezil + antiox Formula F (incl. Ginkgo) > Dpz+PBO (Cornelli, 2010)

• Meta-analyses of different studies of Ginkgo and ChE Inh
  – Each > placebo; ChE Inh > Ginkgo; Ginkgo more tolerable
  – Combination > monotherapy (Canevelli et al, 2014)
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 too many side effects
  - But they are often the most difficult to treat
- Be careful with patients on multiple medications
  - Drug-drug interactions can be significant!