

Nutraceuticals, Part 2: Herbs

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Objectives

- Review commonly used non-prescription remedies for psychiatric illness
- Cite available data on efficacy, tolerability, and safety
- Discuss how to integrate *safe, efficacious* complementary therapies into the psychiatric toolbox

Herbal Medicine

- Plant or plant extract used for its therapeutic properties (including spices)
- Can be ingested in plant, leaf (tea), powder, extract, tincture (usually alcohol) or infusion (oil or water) form
- Also called botanical medicine or phytomedicine

Herbal Medicine

continued

- WHO estimates that 80% of the world's population relies on herbal medicine for some part of their primary health care
- 70% of physicians in Germany *prescribe* herbals
- Many widely-used drugs started their careers as herbal medicines

Some drugs with plant origins

- Deadly nightshade -- atropine
- Poppy-- codeine
- Autumn crocus-- colchicin
- Cowage, velvetbean-- l-dopa
- Purple foxglove-- digoxin
- Chonodendron sp.-- tubocurarine
- White willow-- aspirin
- Penicillin chrysogeuum--penicillin

Herbal Medicines

- A leaf, root, seed or berry contains **MANY** compounds
- Preparation is very important
 - active ingredients may be volatile
- Freshness and storage conditions can greatly affect potency

Buyer beware

- herbal remedies are sold in the US as 'foods', not medicines
- not subject to testing for presence of active compounds, strength, or adulteration
- Some countries monitor production, adverse effects of herbs as they do prescription drugs

Buyer beware

- Impurities
 - *sildenafil and tadalafil found in 2 of 7 'herbal' erectile dysfunction products tested in 2005
 - ** dexamethasone found in 8 of 11 Chinese 'herbal' skin creams tested in 1999

*Fleshner N et al, Urology Vol. 174, 636–641, August 2005

**Ernst E. *Herbal medicines: where is the evidence?* BMJ. Aug 12, 2000; 321(7258): 395–396.

Pharmacologically Active Foods

- Some common spices and foods contain compounds which are lately being shown to have specific effects at receptors and/or membrane channels in humans and other mammals
- Findings often confirm traditional beliefs and culinary uses

In the Spice Cabinet: Ginger



Ginger (*Zingiber officianale*)

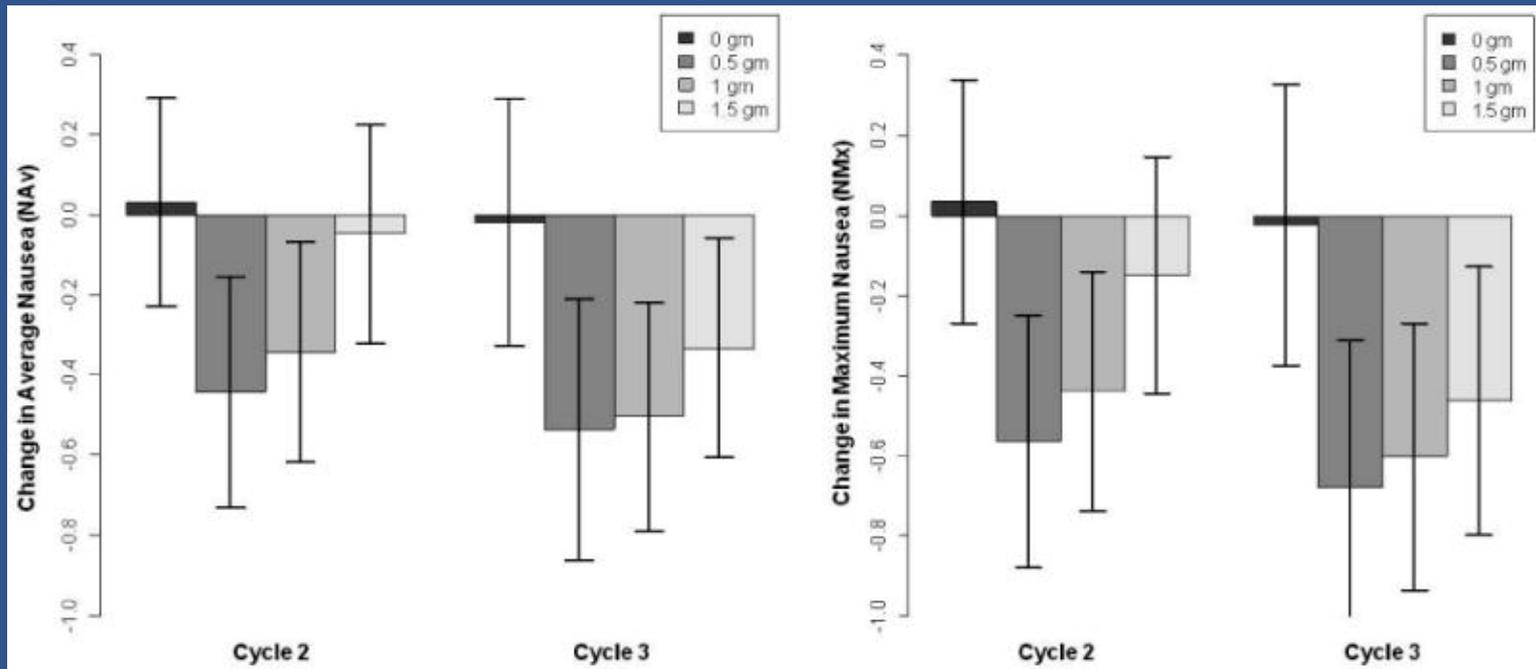
- Pale gold rhizome (fresh or powdered)
- Long used to help digestion, combat nausea, and prevent seasickness in many cultures

Ginger and nausea

- RDBPC study of effect of ginger on chemotherapy-induced nausea
- Equivalent of 250 mg ginger root was mixed with olive oil and double-encapsulated
- Each subject received 3 capsules twice daily: 3 placebo caps, or 1 ginger cap and 2 placebos, or 2 ginger caps and 1 placebo, or 3 ginger caps (n=576)

Ginger reduces severity of acute chemotherapy-induced nausea

The boxplots represent the mean change in average nausea severity (NAv in left panel) and maximum nausea severity (NMx in right panel) for each treatment arm (i.e., ginger dose) on Day 1 of chemotherapy (i.e., acute CIN). Each shaded bar is a different treatment arm. All doses of ginger significantly reduced nausea severity on Day 1 of chemotherapy compared to placebo. The largest reduction in acute nausea occurred with 0.5g and 1.0g of ginger daily. Although Study Cycle 3 appears to show a greater reduction in nausea, there was no significant difference in mean nausea change between the two study cycles.



In the Spice Cabinet: Cinnamon



Cinnamon: it's complicated

- The ground bark of different plants is sold as cinnamon, and these have different properties
 - *Cinnamomum verum* (also called *C. zeylanicum*)
 - *Cinnamomum cassia*
- *C. verum* is 4 to 5 times more expensive, so most cinnamon sold is *C. cassia*

Cinnamon: it's complicated

continued

- C. cassia contains much more coumarin, which is banned as a food *additive* by the FDA due to hepatotoxicity
 - C. verum contains very little coumarin
- Most studies of 'cinnamon' and glucose metabolism have used use C. cassia

Cinnamon and Type II DM

- In vitro, increases insulin receptor kinase activity, glycogen synthesis
- Meta-analysis of 10 RCT's, *patients with Type II DM*
- 120 mg – 6gm/day for 4 to 18 weeks
 - Reduced total cholesterol, triglyceride
 - Reduced fasting glucose
 - but no significant effect on A1c levels

In the Spice Cabinet: Turmeric



Turmeric (*Curcuma longa*)

- Deep yellow rhizome (powdered)
 - Important component of many curries
 - Widely used throughout the Indian sub-continent, the Middle East, North Africa
- Contains curcuminoids
 - Subject of much research on possible anticancer, anti-inflammatory, antioxidant, antiviral effects

Turmeric and C-reactive protein

- Meta-analysis of 6 trials
- Compared to placebo, curcuminoid was associated with significant reduction in C-reactive protein

Turmeric and Alzheimer's

- Various mechanisms have been identified by which curcumin *may* be helpful in Alzheimer's dementia
 - it may help macrophages clear amyloid plaques
 - inhibits transcription of inflammatory cytokines
 - inducer of hemoxygenase, which is protective against oxidative stress

Mishra S, Palanivelu K. The effect of curcumin (turmeric) on Alzheimer's disease: An overview. Ann Indian Acad Neurol

Turmeric and cancer

- Curcumin has anti-proliferative effect on multiple cancers
- Mostly animal studies, human dosage not established
- Effects on mutagenesis, oncogene expression, cell cycle regulation, apoptosis, metastasis

Wilken et al. *Curcumin: A review of anti-cancer properties and therapeutic activity in head and neck squamous cell carcinoma* Molecular Cancer 2011,

Saffron (*Crocus sativus*)



Saffron in depression

- 3 trials using saffron vs. antidepressants
- 5, six-week RCT's
 - 2 trials used 30-90 mg saffron vs. placebo
- Significant improvement over placebo on HAMD
- Saffron response equivalent to imipramine and fluoxetine

Sarris J et al. *Herbal medicine for depression, anxiety, and insomnia: a review of psychopharmacology and clinical evidence*
Eur Neuropsychopharm Vol 21, No 12, 841-860, Dec 2011

Depression: St. John's Wort
(Hypericum perforatum)



Depression: St. John's Wort

Review of 37 DBRCT's

- Trials limited to *major depression* showed only minor effect over placebo
- Trials including all depressive states showed marked efficacy, similar to SSRI's

Linde K et al. *St. John's wort for depression: Meta-analysis of randomised controlled trials* The British Journal of Psychiatry (2005) 186: 99-107

Cautions: St. John's Wort

- SJW induces cytochrome P450 enzymes
 - STRONG 3A4 : faster clearance (lower levels) of statins, some benzos and opioids, sex hormones, some antipsychotics, etc. etc.
 - MOD 2C9, 1A2 : faster clearance (lower levels) of warfarin, oral hypoglycemics, antidepressants
 - Less to no induction of 2D6
- Reports of psychosis with concomitant use of SSRI
- Sun sensitivity

St. John's Wort : What (who) is it good for?

- Mild depression
- Medically healthy people who are not taking other medications
- Medically healthy people with major depression who refuse conventional treatment

Anxiety: Kava (*Piper methysticum*)



Anxiety: Kava (*Piper methysticum*)

continued

- *Meta-analysis of 9 trials shows effect over placebo significant
- ** Inhibitor of CYP1A2, 2C9, 2C19, 2D6, 3A4, and 4A9/11
 - Higher levels of substrate drugs
- HEPATIC TOXICITY: *at least 68 cases of liver failure reported*

* Pittler and Ernst, 2003 **Mathews et al, 2002

Anxiety: Passionflower (*Passiflora*)



Anxiety: Passionflower

- may be partial GABA receptor agonist
 - *comparable to oxazepam in GAD (1 study)
- inhibits CYP3A4 : increases levels of anticoagulants, sedatives
- **case reports of prolonged QTc and runs of v. tach; nausea, vomiting, drowsiness

*Akhondzadeh et al 2001

**Fisher et al, 2000

Insomnia: Chamomile
(Matricaria chamomilia, Chamaemelum nobile)



Anxiety, Insomnia: Chamomile

- U of P study showed improvement in GAD with 220 mg chamomile extract
- U Mich study *did not* show improvement in:
 - sleep time, latency, quality, or number of wakings

Insomnia: Valerian Root
(Valeriana officinalis)



Insomnia: Valerian Root

- Possible GABA'ergic effects
- Inconclusive evidence-*may* be helpful for 'non-organic' insomnia, *may* shorten sleep latency and speed onset of slow wave sleep
- Pungent smell and taste
- Studies use around 600 mg extract dose

Insomnia: Valerian Root

continued

- In one study, bedtime use of 600 mg extract did not slow reaction time, alertness, or concentration the next morning
- Reported SE include headache, dizziness, pruritis, and GI disturbance

Not recommended
Psychosis: Rauwolfia



Psychosis: Rauwolfia *(Rauwolfia serpentina)*

- Used in India for snakebite and insanity
 - also called snakeweed
- Extract is sold by many companies for hypertension, 'mental disorder'

Rauwolfia: unintended consequences

- Reserpine *irreversibly* blocks vesicular monoamine transporters (VMAT's)
 - Loose monoamines in the cytoplasm are metabolized by MAO and COMT
- Depletion of vesicular NE, 5-HT, and DA has antihypertensive, depressant, and antipsychotic properties
 - Rebound psychosis has occurred when hypertensive patients stopped it

Pitfalls with herbal treatments

- the common belief that herbals are harmless
 - kava hepatotoxicity
- overlooked drug interaction potential
 - CYP450 issues
- unregulated content of products

Still need more evidence:

- Depression

- Borage (*Echium amoenum*)
- Roseroot (*Rhodiola rosea*)
- Lavender (*Lavandula spp.*)

- Anxiety

- Ginkgo (*Ginkgo biloba*)
- Scullcap (*Scutellaria lateriflora*)
- Passionflower

Bridging the gap

1

- To safely use plant-based treatments in 'western' medical practice, we must assess safety and efficacy
- Look for same evidence 'levels' as with pharmaceuticals
 - 1'A' : meta-analysis of RCT's

Bridging the gap

2

- If patient asks about herbal remedy
 - be sure to place the option in context with conventional treatment
 - share what you know from peer-reviewed sources
 - review side effects, quality control issues
 - document

Bridging the gap

3

- Don't be afraid to say, "I would not recommend that"
 - Severe depression and St. John's wort
- Document

Quick Lookups on Plant Based Medicines

- National Center for Complementary and Integrative Medicine (NIH)
 - <https://nccih.nih.gov/health/atoz.htm>
- Consumerlab
 - Independent company which analyzes content of supplements, vitamins, herbals
 - products off store shelves are tested for content, strength, additives
 - subscription fee (around \$35 per year)
 - www.consumerlab.com