

Idaho Society of Health-System Pharmacists

Challenges with naturopathic products and alternative medicine

Kaitlyn Holyfield PharmD, Heather Walser Pharm D,
Marina Izzi PharmD,
PGY1 Pharmacy Practice Residents
Boise Veterans Affairs Medical Center
September 29, 2018



Disclosures

- No conflicts of interest to disclose
- Please note that the safety and efficacy of any products discussed have not been evaluated by the FDA

Learning Objectives

- Define complementary and alternative medicine (CAM)
- Discuss challenges associated with CAM
- Understand potential risks, such as adverse events and drug-herb interactions, that could occur with herbal product use
- Demonstrate the ability to discuss natural medicine with patients including challenges that may impact patient care

DEFINING COMPLEMENTARY AND ALTERNATIVE MEDICINE

What is Complementary and Alternative Medicine (CAM)?

- Definition
 - A group of diverse medical and health care systems, practices, and products that are not presently considered to be part of conventional medicine

Complementary, Alternative, or Integrative Health: What's in a Name? National Center for Complementary and Integrative Health. August 09, 2018 <https://nccih.nih.gov/health/integrative-health>

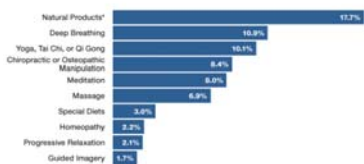
Examples of Alternative Medicine

- Natural Products
 - Herbal supplements
 - Vitamins and minerals
 - Probiotics
 - Homeopathy
- Mind and Body Practices
 - Yoga
 - Tai Chi
 - Chiropractic care
 - Meditation
 - Massage
 - Acupuncture

Complementary, Alternative, or Integrative Health: What's in a Name? National Center for Complementary and Integrative Health. August 09, 2018 <https://nccih.nih.gov/health/integrative-health>

2012 National Health Interview Survey Findings

10 most common complementary health approaches among adults—2012

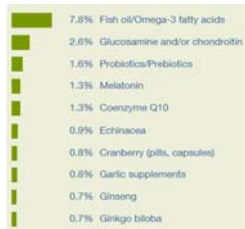


About 59 million Americans spend up to \$30.2 billion a year.

Clarke TC, Black LI, Stussman BJ, Barnes PM, Nahin RL. Trends in the use of complementary health approaches among adults: United States, 2002–2012. National health statistics reports; no 79. Hyattsville, MD: National Center for Health Statistics. 2015.

Most Used Natural Products

There are over 55,000 natural products available



Clarke TC, Black LI, Stussman BJ, Barnes PM, Nahin RL. Trends in the use of complementary health approaches among adults: United States, 2002–2012. National health statistics reports; no 79. Hyattsville, MD: National Center for Health Statistics. 2015.

CHALLENGES WITH CAM: STANDARDIZATION

What do people believe?

General Public

- 68% of Americans believe the government requires herbal manufacturers to report potential adverse effects or dangers
- 58% believe government agencies must approve herbal products before they can be sold
- 55% believe the manufacturers cannot make claims for safety or efficacy of supplements without firm scientific evidence

Medical Residents

- Approximately 33% of internal medicine residents surveyed believed that dietary supplements require FDA approval

Harris Poll: Health Care News 2002, December 23 Volume 2, Issue 23
Ashar BH, Rice TN, Sisson SD. Physicians' understanding of the regulation of dietary supplements. Arch Intern Med 2007;167:966-9.

Regulation of Herbal Products

- In 1994 the Dietary Supplement Health and Education Act (DSHEA) classified herbal products as "dietary supplements"
 - Can be produced, sold, and marketed without first demonstrating safety and efficacy
- **Manufacturers** of dietary supplements are responsible for ensuring that their products are safe and that the label information is truthful and not misleading
- FDA has the regulatory burden of proving a dietary supplement is unsafe

Bent S. Herbal Medicine in the United States: Review of Efficacy, Safety, and Regulation: Grand Rounds at University of California, San Francisco Medical Center. Journal of General Internal Medicine. 2008;23(6):854-859.

Standardization issues

- An herbal supplement may contain dozens of compounds
- All ingredients may not be listed on the label
- An herbal supplement may not contain the correct plant species or the correct part of the plant
- The amounts of the ingredients may be lower or higher than the label states
- Variability in how the plant is grown, stored, and processed

Boullata JJ, Nace AM. Safety issues with herbal medicine. Pharmacotherapy 2000;20:257-69

Selecting an Herbal Product

- Non-profit independent testing services
 - NSF International
 - USP
 - Consumer Lab
- Products that meet criteria may carry a seal indicating that they have been verified for purity, identity, and potency



Stussman BJ et al. Wellness-related use of common complementary health approaches among adults: United States, 2012. National health statistics reports; no 85. Hyattsville, MD: National Center for Health Statistics. 2015

CHALLENGES WITH CAM: LIMITED EVIDENCE

Evidence of Efficacy

- Of the top 10 herbs used in the US only 50% have scientific evidence of efficacy
- Studies on herbal products often have poor methodology, inconsistent outcome measures, different preparations of the herb, and conflicting results
- Indications are based on word of mouth or traditional and cultural uses

Bent S. Herbal Medicine in the United States: Review of Efficacy, Safety, and Regulation: Grand Rounds at University of California, San Francisco Medical Center. *Journal of General Internal Medicine*. 2008;23(6):854-859.

CHALLENGES WITH CAM:
SAFETY

Safety Concerns

- Chinese herb *Aristolochia*
 - Found in some weight loss supplements
 - 105 cases in Belgium of interstitial fibrosis of kidneys
 - Led to renal failure and urothelial carcinoma
- Germander
 - Capsules sold in France for weight control
 - >30 cases of acute liver failure, at least 1 fatality
- 23,000 ER visits/year due to ADRs from supplements
 - Weight loss, Energy products: 72% of ADRs
 - Cardiovascular effects

Ernst E. Harmless herbs? A review of the recent literature (1998) *American Journal of Medicine*, 104 (2), pp. 170-178.
Geller AI et al. Emergency Department Visits for Adverse Events Related to Dietary Supplements *N Engl J Med* 2015;373:1531-40

Toxicity

- Nephrotoxicity
- Hepatotoxicity
- Cardiotoxicity
- Teratogenicity
- Carcinogenic

Ernst E. Harmless herbs? A review of the recent literature (1998) *American Journal of Medicine*, 104 (2), pp. 170-178.

Drug Interactions

- Interactions between alternative medicine and prescription medications are under researched
- Drug-Herb interactions can cause serious adverse effects, some which can be life-threatening
- Examples
 - Blood thinners
 - Aspirin, warfarin, ginkgo, vitamin E
 - St. John's Wort may reduce efficacy of medications for
 - Heart disease
 - Depression
 - Contraception
 - Seizures
 - Cancer

Tips for Dietary Supplement Users. U.S. Food and Drug Administration 02/23/2018
<https://www.fda.gov/food/dietarysupplements/usingdietarysupplements/ucm110567.html>

Common CYP Metabolites

CYP3A4	CYP2D6	CYP1A2
Alprazolam (Xanax)	Acetaminophen	Theophylline
Amiodarone	Carvedilol	Clozapine
Statins	Codeine	Mirtazapine
Fentanyl, oxycodone	Fluoxetine	Ropinirole
Colchicine	Amphetamine	
Carbamazepine		

Horn JR, Hansten PD. Get to Know an Enzyme: CYP1A2. Pharmacy Times. November 01, 2007
 Physician Guidelines: Drugs Metabolized by Cytochrome P450's. Genelex Corporation. 2005
 Horn JR, Hansten PD. Drug Interactions with CYP3A4: An Update. Pharmacy Times. December 16, 2015

Contamination

- Most commonly an issue in products marketed for weight loss, sexual health, athletic performance, and body-building
- Can contain toxic substances
 - Lead, arsenic, mercury, belladonna
- Can contain undeclared pharmaceuticals
 - Aspirin, corticosteroids, diazepam, ephedrine, theophylline

Ernst E. Harmless herbs? A review of the recent literature (1998) *American Journal of Medicine*, 104 (2), pp. 170-178.

High-Risk Patients

- Patients with chronic health conditions
 - Cardiovascular disease
 - Hypertension
 - Diabetes
 - Mental health conditions
- Elderly
- Children
- Pregnant or Nursing
- Patients taking high-risk medications
 - Blood thinners
 - HIV medication
 - Anti-rejection medications
- Surgical Candidates

Tips for Dietary Supplement Users. U.S. Food and Drug Administration 02/23/2018
<https://www.fda.gov/food/dietarysupplements/usingdietarysupplements/ucm110567.html>

5 THINGS TO CONSIDER BEFORE TAKING A DIETARY SUPPLEMENT

Dietary supplements include ingredients such as vitamins, minerals, herbs, and amino acids. Dietary supplements can help you get the nutrients you need to maintain health.

Dietary supplements can be good for your health by helping you get the nutrients you need to maintain health. But there are some risks, especially if you take too many or use them in addition to, or in place of, prescription medications.

CONSIDER THIS:

- 1 Ask your healthcare provider if the supplement you're considering would be safe and beneficial for you.
- 2 Remember that supplements are not permitted to be marketed for the purpose of treating, diagnosing, preventing, or curing diseases. Disease claims, such as "lowers high cholesterol" or "treats heart disease," cannot be legitimately made for dietary supplements.
- 3 When searching for information about supplements on the internet, use noncommercial sites (e.g., the National Institutes of Health, the Food and Drug Administration, the U.S. Department of Agriculture) rather than depending on information from sellers.
- 4 If claims sound too good to be true, they probably are. Be mindful of product claims such as "works better than [a prescription drug]," "totally safe," or "has "no side effects."
- 5 Be aware that the term "natural" doesn't always mean "safe."

So how can you make an informed decision for yourself about using supplements?

If you decide to take a supplement and have a bad reaction, report the reaction to FDA through one of the following:

- Contact the **Consumer Complaint Coordinator** in your area.
- File a safety report only through the **Safety Reporting Portal**.

FDA U.S. FOOD & DRUG ADMINISTRATION

CHALLENGES WITH CAM: LACK OF COMMUNICATION

Failure to Communicate

- More than 50% of CAM users do not discuss their CAM activities with their health care provider
- Most common reasons why
 - No one asked
 - Patient did not know they should discuss CAM
 - There was not enough time
- Patients may worry they will be judged or criticized for use alternative medicine

Cowan RP. CAM in the real world: You may practice evidence-based medicine, but your patients don't. *Headache*. 2014;54(6):1097-1102.
Salmonsens A, Frenkel M. How to communicate effectively about complementary, integrative and alternative medicine. *National Information Center for Complementary and Alternative Medicine*. December 4, 2015

NATURAL PRODUCTS- PAIN

Feverfew

- Common Use
 - **Migraine headache** prophylaxis, reducing fever, headaches
- Adverse effects
 - Heartburn, nausea, diarrhea or constipation
 - Long-term use: anxiety, headaches, insomnia
- Precautions
 - Allergic reactions
 - **May interact with anticoagulant/anti-platelet drugs**
 - **Avoid in pregnancy**; may cause uterine contractions



Wider B, Pittler MH, Ernst E. Feverfew for preventing migraine. *Cochrane Database Syst Rev*. 2015 Apr. 20

Glucosamine

- Common Use
 - Osteoarthritis treatment and prevention
- Adverse effects
 - Mild GI upset
 - Diarrhea or constipation
- Precautions
 - Caution with shellfish allergy
 - May increase blood glucose and increase anticoagulant effect of warfarin

Sawitzke et al. Clinical efficacy and safety of glucosamine, chondroitin sulphate, their combination, celecoxib or placebo taken to treat osteoarthritis of the knee: 2-year results from GAIT. *Annals of the Rheumatic Diseases*. 2010.

Chondroitin

- Common Use
 - Osteoarthritis
 - Cataracts
- Adverse effects
 - Mild GI upset
 - Diarrhea or constipation
- Precautions
 - May increase anticoagulant effect of warfarin

Kratom


- Common Use
 - Pain reliever
 - Mood
 - Ease opioid withdrawal
- Adverse effects
 - Nausea, vomiting, constipation
 - Loss of muscle coordination
 - Dizziness, sedation
 - Tachycardia
- Precautions
 - Increased effects with sedatives, hypnotics, and analgesics

White M. Pharmacologic and Clinical assessment of kratom. *Am J Health-Syst Pharm*. 2017

NATURAL PRODUCTS- COGNITION

Ginkgo


- Common Use
 - Improve **memory**; prevent or treat Alzheimer's disease
 - Peripheral artery disease
- Adverse effects
 - Mild GI upset, headache, dizziness, constipation or diarrhea
- Precautions
 - May increase effects of **anticoagulants**
 - Thyroid and other cancer risk has been reported
 - Do not consume seeds (contain ginkgotoxin)



Weinmann S. Effects of ginkgo biloba in dementia: systematic review and meta-analysis. BMC Geriatrics. 2010.

Ginseng

- Common Use
 - **Adaptogen**– increasing “wellness” and stamina
- Adverse effects
 - **Insomnia**, tachycardia, palpitations, edema, diarrhea
- Precautions
 - May increase effects of **anticoagulants and hypoglycemic drugs**
 - Often combined with caffeine in weight loss products
 - Don't confuse Panax ginseng with Siberian ginseng




Yakoot M, Salem A, Helmy S. Effect of Memo, a natural formula combination, on Mini-Mental State Examination scores in patients with mild cognitive impairment. Clin Interv Aging 2013

NATURAL PRODUCTS- DEPRESSION

St. John's Wort

- Common Use
 - Depression, anxiety, mood disorders
- Adverse effects
 - Photosensitivity, GI upset, insomnia, dry mouth, anxiety, sexual dysfunction
- Precautions
 - May decrease blood levels of several drugs
 - Inadequately diagnosed and treated depression can be dangerous; use only under medical supervision



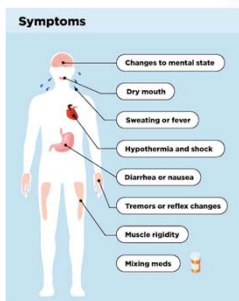
Melzer, J., Brignoli, R., Keck, M. E., and Saller, R. A hypericum extract in the treatment of depressive symptoms in outpatients: an open study. Forsch. Komplementmed. 2010;17(1):7-14

St. John's Wort Interactions

- May decrease levels of
 - Birth control pills
 - Cyclosporine
 - Anti-seizure drugs
 - Anti-retroviral drugs
 - Warfarin

St. John's Wort Interactions

- Serotonin Syndrome
 - SSRIs, SNRIs
 - Monoamine oxidase inhibitors
 - Triptans
 - Tramadol
 - Linezolid



S-Adenosyl-L-Methionine (SAME)

- Common Use
 - Depression, anxiety
 - Heart disease
 - Fibromyalgia
- Adverse effects
 - GI upset
 - Dry mouth
 - Headache
- Precautions
 - Serotonin syndrome

NATURAL PRODUCTS- SLEEP

Valerian

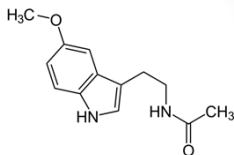
- Common Use
 - Insomnia
 - Anxiety
- Adverse effects
 - Headache, dizziness, GI upset
 - Tiredness the next morning
- Precautions
 - May potentiate the activity of other GABA-ergic drugs (BZs, EtOH)— don't use in combination
 - Don't use more than 4-6 weeks



Salter, S. and Brownie, S. Treating primary insomnia - the efficacy of valerian and hops. Aust.Fam.Physician 2010

Melatonin

- Common Use
 - Insomnia
 - Jet lag
- Adverse effects
 - Daytime drowsiness, headache, dizziness
- Precautions
 - Avoid melatonin from animal sources due to potential for contamination (synthetic is preferred)
 - Use in caution in patients with history of seizures, bleeding disorders and transplant recipients



Salter, S. and Brownie, S. Treating primary insomnia - the efficacy of valerian and hops. Aust.Fam.Physician 2010

NATURAL PRODUCTS-
CARDIOVASCULAR HEALTH

Fish Oil

- Common Use
 - Lipid Control
 - Coronary artery disease
- Adverse effects
 - Generally Recognized as Safe (GRAS)
 - Fishy aftertaste
- Precautions
 - Allergy to fish/shellfish
 - May increase anticoagulant effect > 3 grams/day



Garlic

- Common Use
 - Lipid Control
 - Blood Pressure
- Adverse effects
 - Generally Recognized as Safe (GRAS)
 - Breath/body odor
- Precautions
 - May increase anticoagulant effect
 - Can reduce efficacy of oral contraception



Red Yeast Rice

- Common Use
 - Lipid Control
- Adverse effects
 - Similar to that of statins
- Precautions
 - Duplication of therapy with statins
 - Watch liver function



Coenzyme Q10

- Common Use
 - Congestive heart failure
 - Blood pressure
 - Statin-induced myopathy
- Adverse effects
 - Generally well-tolerated
 - Can minimize GI ADEs by dividing doses > 100mg
- Precautions
 - Structurally related to Vitamin K → warfarin DDI



NATURAL PRODUCTS- WEIGHT LOSS

Bitter Orange

- Common Use
 - Weight loss
- Adverse effects
 - Generally recognized as safe in amounts commonly found in food
 - Risk for cardiovascular toxicity
- Precautions
 - Can prolong QT interval and cause an arrhythmia
 - Inhibits CYP 3A4



Weight-loss Products

- Many weight-loss products contain multiple ingredients that have not been tested in combination
- Can contain **high levels of stimulants** as well as undisclosed **prescription drugs/controlled substances**
- Messages like “magic diet pill!”, “melt your fat away!”, and “lose weight without diet or exercise!” that sound too good to be true usually are
- **Caution in elderly and patients with cardiovascular disease**

Dietary Supplements for Weight Loss. National Institutes of Health: Office of Dietary Supplements. November 1, 2017

NATURAL PRODUCTS- DIABETES

Cinnamon/ Cassia Bark


- Common Use
 - **Diabetes**
- Adverse effects
 - Generally well-tolerated
 - Hypoglycemia
- Precautions
 - Impure products can contain high levels of coumarin → **hepatotoxic**
 - Look for **USP seal!**
 - Inhibits CYP 3A4



NATURAL PRODUCTS- HORMONAL CONCERNS


Black Cohosh

- Common Use
 - Menopause
- Adverse effects
 - Estrogen and serotonin like effects
 - Hard on liver
- Precautions
 - Estrogen promotes clots!
 - CYP 2D6 inhibitor
 - Be aware of hormone sensitive disease states



Saw Palmetto

- Common Use
 - Benign prostatic hyperplasia (BPH)
- Adverse effects
 - Generally well-tolerated
- Precautions
 - Can increase bleed risk



Ginger

- Common Use
 - Morning-sickness
 - Nausea/dyspepsia
- Adverse effects
 - Generally well-tolerated
- Precautions
 - Can increase bleed risk



NATURAL PRODUCTS- RESPIRATORY HEALTH

Echinacea

- Common Use
 - Common cold
- Adverse effects
 - Generally well-tolerated
 - Likely safe if used for typical 10 day course
- Precautions
 - Related to ragweed – caution in those with sensitive seasonal allergies
 - Screen for potential DDIs (inhibits CYP1A2)



THE PATIENT INTERVIEW

Methods to Promote an Effective Patient Interview

- Open ended questions
 - What herbal products do you use?
- Neutral but engaged tone
 - Imply curiosity > judgement
 - Separate pharmacy technician hat from personal opinions
- Know your audience, ask targeted questions
 - Prompt – creams, teas, essential oils
- Get details
 - How using it, frequency, where applying
 - Essential oils that are ingested are toxic!
- Don't assume patients will tell you if you don't ask
- Treat natural products like prescriptions! Ask the same questions.

Cowan RP. CAM in the real world: You may practice evidence-based medicine, but your patients don't. *Headache*. 2014;54(6):1097-1102.

Salamonsen A, Frenkel M. How to communicate effectively about complementary, integrative and alternative medicine. National Information Center for Complementary and Alternative Medicine. December 4, 2015.

Assessment Question #1

Complementary and alternative medicine includes

- A. A group of diverse medical and health care systems, practices, and products
- B. Practices not presently considered to be part of conventional medicine
- C. Natural products such as herbal supplements, vitamins, minerals, probiotics, and homeopathy
- D. Mind and body practices such as yoga, Tai Chi, chiropractic care, meditation, massage, and acupuncture
- E. All of the above

Assessment Question #2

Medications:

- Loestrin Fe 1/20, 1 tablet QD
- B vitamin complex, 1 tablet QD
- Vitamin E 400 IU, 2 capsules QD
- Probiotic QD
- Fish oil 1000 mg QD
- Multivitamin QD
- St. John's Wort QD
- Melatonin prn for sleep

KH is a 39 year old female that despite strict adherence with her birth control pill regimen, has become pregnant. What was most likely the cause of pregnancy?

- A. Use of fish oils
- B. Use of St. John's Wort
- C. Use of melatonin
- D. Use of high-dose vitamin E

Assessment Question #3

A 55 year old female comes into the emergency room because of bothersome nose bleeds. Her medication list is as follows:

- | | | |
|-------------|----------|--------------|
| Clopidogrel | Aspirin | Rosuvastatin |
| Amlodipine | Atenolol | Gingko |
| CoQ10 | Cinnamon | Melatonin |

What natural product are you concern could increase bleed risk?

- A. Gingko
- B. Cinnamon
- C. CoQ10
- D. Melatonin

Assessment Question #4

Which statement(s) are ways to facilitate an effective patient interview? (SELECT ALL THAT APPLY)

1. I see you don't take any prescription meds, are you one of those "naturals" people?
2. What, if any, natural and herbal products do you take?
3. It sounds like you find benefit from several essential oils. How do you use them?
4. It sounds like you find benefit from several essential oils. Do you know that they have no evidence for your condition?
5. Do you drink specialty herbal or therapeutic teas?
