Integrative Medicine and Psychiatry

David Kiefer, MD
May, 2009

David Kiefer, MD

- Bastyr, UW, UA, Group Health, 45th
- Fellow: Program in Integrative Medicine (Andrew Weil, MD)
- Residency in Family Medicine, Seattle, Washington
- MD, BS at University of Wisconsin-Madison
- Research interests: ethnobotany, herbal medicine
Disclosure

• Financial relationship with a commercial interest
• Dr. Dave’s Omega-3 Foods LLC

Our goals today

• Dietary supplements for common psych d/o
  – SJW
  – SAMe
  – Omega-3’s
  – Ginkgo
  – Ginseng + Rhodiola
  – Herbal sedatives (lavender, chamomile, valerian, kava)
• Cases
A huge topic

• Integrative Medicine
  – www.integrativemedicine.arizona.edu

• Collaboration with and/or Rx with:
  – Lifestyle changes (exercise, diet)
  – Acupuncture, mind-body medicine, spirt

Integrative Medicine

• Main tenets
  – Is healing-oriented medicine
  – Takes account of the whole person (body, mind, spirit, emotion)
  – Emphasizes the therapeutic relationship
  – Makes use of all appropriate therapies, both conventional and complementary/alternative: “the best of the best”
Integrative Medicine intake

• Of course, we want to cover the “normal” questions:
  • Chief complaint(s)
  • History of present illness
  • Past medical history (hospitalizations, operations, serious illnesses, accidents)
  • Family history
  • Social history (smoke, drink)

Integrative Medicine intake

• Let’s down to business:
  – What is your main source of stress?
  – What was your childhood like?
  – What do you do for exercise? Relaxation?
  – Do you take any herbs, vitamins, or other supplements?
  – What have been your life-changing events?
  – Do you consider yourself spiritual?
U.S. Trends: 2004 Sales

- Garlic
- Echinacea
- Saw palmetto
- Soy
- Ginkgo
- Black cohosh

- Ginseng
- Cranberry
- St. John’s wort
- Milk thistle

The Natural Foods Merchandiser, 2004

Echinacea

- Be a good botanist
  - Purple coneflower
  - *Echinacea pallida*, *E. pallida* var. *angustifolia*, *E. purpurea*

- Detecting purity
  - Organoleptic:
    - “tingle”…absent in *E. pallida*
  - Standardization….later
Echinacea

- Plant parts to use?
  - Above-ground parts (leaves, stems, flowers)
  - Roots (rhizomes, tubers, etc.)

Echinacea spp.

- *In vitro* and animal studies
  - macrophage phagocytosis, stimulates monocytes, NK cells, and pmns cells.
  - Increase antibody responses, interleukin level, TNF, interferon

- Phytochemicals
  - Polysaccharides
  - Glycoproteins
  - Alkylamides (tingle)
**Echinacea: Clinical trials**

- **URIs: Prevent or Treat?**
- *Echinacea angustifolia* root extract: 437 adults
  - Prevention (day -7-0) and treatment (day 0-5)
- Dried pressed *E. purpurea* juice of the above-ground plant parts
  - 707 URIs in 407 children ages 2-11: No diff.
  - 80 adults: cold from 9→6 days
- Dried, whole-plant, unrefined echinacea capsule (50% *E. purpurea*, 50% *E. angustifolia*)
  - College students, n = 148: No difference
**Echinacea: Clinical trials**

- Meta-analyses (Cochrane)
  - positive results in the treatment of the common cold early in its course
  - inability to make specific recommendations regarding the use of echinacea given the significant heterogeneity in research trials
    - The form and species of plant used
    - The large variation in the methodological quality of the research conducted.

**Echinacea summary**

- Know your species
- Form matters
- Patient population matters
- Treatment vs. preventive
Where do I look for information?

• Books (but: out of date quickly)
  – Rational Phytotherapy (Varro Tyler)
  – Herbs of Choice (Varro Tyler)
  – German E Commission Monographs
  – Pocket Guide (Lane Johnson)
  – The ABC Clinical Guide to Herbs (Mark Blumenthal)

Where do I look for information?

• Journals
  – Economic Botany
  – HerbalGram
  – Journal of Ethnopharmacology
  – Journal of Herbal Pharmacotherapy
  – Phytomedicine: international journal of phytotherapy and phytopharmacology
Where do I look for information?

- Databases/Internet
  - Free
    - Longwood Herbal Task Force
    - Sloan-Kettering (www.mskcc.org/mskcc/html/11570.cfm)
    - Bastyr University (www.bastyr.edu): Library, Resources, HerbMedPro
  - Charge
    - Natural Standard
    - Natural Medicines Comprehensive Database

Pocket Guide to Herbal Remedies (Johnson L., 2002)

- For depression…
  - Three listed
- For sedatives….
  - 15 species listed, Latin name
  - Don’t recognize any of them
Herbal Medicine use

- Evidence
  - Traditional use
  - DBRCT (meta-analyses): Level A Evidence
- Psychological
  - Anxiety/insomnia
  - Depression
  - General well being (memory)

Chamomile

- What is its species name?
- How do you dose it?
  - Kids, adults
- Adverse effects?
- Name in Spanish?
Manzanilla

- *Matricaria recutita*
- Asteraceae
- Volatile oils (such as bisabolol) and the flavonoids (such as apigenin)
- Flower infusion
- Tablespoon of flowers steeped in a covered cup of hot water for 10’
- Several times a day

Herbs for anxiety

- Chamomile
- Skullcap
- Hops
- Lavender
- Valerian
- Kava kava

- For each, know:
  - Dose
  - Plant part
  - Form
  - Side effects

- For example…
Herbal medicine forms

• Raw herb
  – Eat
  – Infusion (pour hot water over herb)
  – Decoction (boil)
• Tinctures (alcohol, glycerin)
• Standardized extracts (capsule)
• Drinks, combination products, etc.

Show and tell
Dietary supplements for depression

- St. John’s wort
- SAMe
- 5-HTP
- Omega-3's

St. John’s wort

- *Hypericum perforatum*
- Dried above-ground parts
- Standardization: 0.14-0.3% hypericin, 2-5% hyperforin
- Doses used in the clinical trials 500-1800 mg/d
- Mild-moderate depression
Common Adverse Effects: 5 categories

- Ephedra and ephedrine containing dietary supplements (Banned)
- Plants containing pyrrolizidine alkaloids (PA)
  - Heliotropium (heliotrope), Senecio (gordolobo), Crotalaria, Symphytum (comfrey)
  - Senecio and Crotalaria: Jamaica, bush tea.
- Adverse herb-drug interactions
- Plant products with contaminants (i.e., heavy metals)...TCM
- Accidental ingestion of ornamental plants or essential oils

Common Adverse Effects: 5 categories

- Ephedra and ephedrine containing dietary supplements
- Plants containing pyrrolizidine alkaloids (PA)
- Adverse herb-drug interactions
- Plant products with contaminants (i.e., heavy metals)...TCM
- Accidental ingestion of ornamental plants or essential oils
Herb-drug interactions

- Warfarin: most reported clinically significant herb-drug interaction
- Narrow therapeutic ranges
  - digoxin, theophylline, and phenytoin
- More carefully monitored by healthcare professionals
  - more likely to be reported

Herb-drug interactions (St. John’s wort)

- A case report (Ruschitzka, 2000)
  - Two heart transplant patients stable on cyclosporine began to experience cellular rejection after taking St. John’s wort
- Eleven case reports and two case series (Ernst, 2002)
  - Decreased cyclosporine blood levels
  - Several cases of transplant rejection
Herb-drug interactions

- Inhibition, induction, or substrates of cytochrome P450 (CYP)
- CYP3A4 isoform
  - High levels in the intestines and liver
  - Involved in the metabolism of 50% of the clinically used drugs
- St. John’s wort: potent inducer
  - Cyclosporine, Digoxin, SSRIs, Other 3A4 substrates

P-gps and SJW

- St. John’s wort: induces p-gp activity by increasing the number of p-gps available
- Reduces the bioavailability of some oral medications by eliminating the drug via efflux mechanisms.
- P-gps decrease serum concentrations of certain drug and may lead to organ rejection in the case of cyclosporine or an increased viral load with certain HIV medications
Be careful

RISK

BENEFIT

Evidence

Two others

- SAMe
- 5-HTP

- What is it
- Mech of Action
- Dose
- Studies?
- Adverse Effects

- Bottom line
Omega-3

- We don’t eat enough
  - We eat too many foods (meats, seed oils) with omega-6 fatty acids
  - Ratio (6:3) used to be 2:1, now 10-20:1
  - Inflammation (pain), heart disease
- Omega-3’s can help
  - Arthritis
  - Heart disease
  - Brain development (Alzheimer’s)
  - Others?

Omega-3’s

- Depression and pregnancy (3.4 g qd)
- 5X amount of EPA
Omega-3’s

- Plants: LNA
  - flaxseed oil (8.5 g/Tbsp), flaxseeds (2.2 g/Tbsp), canola oil (1.3 g/Tbsp), soybean oil (0.9 g/Tbsp), English walnuts (0.7 g/Tbsp), and olive oil (0.1 g/Tbsp).
- Marine: EPA, DHA
  - cold-water fish (herring, sardines, salmon, mackerel, tuna, and halibut)
  - 15 g of mackerel or herring provides about 400 mg of n-3 fatty acids

Not all omega-3’s are the same

[Diagram showing the conversion of ALA to EPA and DHA]

- Dark green vegetables, walnuts, freshly ground flax seeds, and other plant foods supply ALA.
- ALA converts to EPA and DHA.
- EPA and DHA supply intermediate molecules (like DHA).
- DHA and EPA supply cold water fish, fish oil, fresh seaweed, clean animal foods (like free range chicken, eggs, and grass fed beef).
- ALA can convert back to DHA and EPA.
Fish

Certain fish

• Herring
• Sardines
• Salmon
• Mackerel
• Tuna
• Halibut
Omega-3 recommendation

- 1000-4000 milligrams daily of DHA + EPA
- General health
  - AHA: 2 servings of fish per week
- Secondary prevention
  - 1000 mg DHA+EPA daily
- Hypertriglyceridemia
  - 3000-4000mg DHA+EPA daily
  - 30% reduction in TG

General well-being

- Multi-factorial
- Traditional medical systems
  - CAM = Cross-cultural medicine?
- Tonics
  - Hair?
Herbal Tonics

• The perfect integrative medicine topic
  – EBM
  – Interactive
  – Cross-cultural

• Five definitions
  – See your sheet

Some cultural examples

• An example: China
  – 932 plants used, 79 (8.5%) are listed as a tonic
  – Other names:
    • Activate support
    • Cardiac tonic
    • Healing
    • Invigorates
    • Lung tonics
    • Post-partum protective medicine
Why might another country have so many plants with such “different” uses?

• Diverse ethnobotanical and anthropological methods (i.e. plant use descriptions)
• Some areas may emphasize preventive medicine and overall general health (i.e. Ayurveda)
• Lack of research

Cross-cultural take-home messages

• Knowledge of the cross-cultural adaptogen use may help clinicians and researchers to
  – better understand patients’ behavior
  – begin to guide them towards effective treatment options
  – develop future research into beliefs about health and healing, or the prevalence of traditional medical practices in different populations
Anyway…let’s talk about one tonic

• “Doc, I am taking ginseng.”
• “What kind of ginseng are you taking?”
• “I don’t know. The guy in the store gave me this…”
  – Whole root
  – Extract

Be a good botanist

• Ginseng
  – Asian ginseng (*Panax ginseng*, Family Araliaceae)
  – American ginseng (*Panax quinquefolius*, Family Araliaceae)
  – Siberian ginseng (*Eleutherococcus senticosus*, Family Araliaceae), now called “Eleuthero”
Problem with common names

• The synonym phenomenon

Applying research to patients

• Study 1
  – Korean ginseng, in doses of 100 mg and 200 mg for eight weeks, improved fasting blood sugar, elevated mood, and improved psychophysical performance (on a numbered diagram test) in 36 people with newly-diagnosed non-insulin-dependent diabetes. The 200 mg dose also improved HbA$_{1C}$ values.
Applying research to patients

• Study 2
  – In 112 healthy subjects over 40 years old, 400 mg of one standardized ginseng product (Gerimax®) over eight weeks led to better and faster simple reactions and abstract thinking, though there was no change in concentration, memory, or subjective experience (Level A Evidence/RCT)

Applying research to patients

• Studies 3a and 3b
  – Two small studies using 200 mg a day of G115 for eight weeks in young, healthy subjects showed an improvement on certain psychomotor functions (i.e. better attention, processing, and auditory reaction time), social functioning and mental health, though some of the effects present at week four disappeared by week eight (n=30 and n=32)
Applying research to patients

• Study 4
  – One study randomized 384 post-menopausal women to receive placebo or ginseng for 16 weeks; improvements in three subsets of a Psychological General Well-Being index were observed

Applying research to patients

• Studies 5a and 5b
  – Even a single 400 mg dose of ginseng improved the cognitive performance of healthy, young volunteers (n=20) in one small study, showing improved secondary memory performance, speed of performing memory tasks, and the accuracy of attentional tasks. However, another study showed no effect on positive affect, negative affect, or total mood disturbance in 83 young, healthy subjects treated with 200-400 mg of G115 for 8 weeks.
Applying research to patients

• Study 6
  – One study in 227 people demonstrated the enhancement of anti-influenza polyvalent vaccine efficacy with 100 mg of extract G115 administered daily for 12 weeks; there was significantly less influenza or common cold, higher anti-body titers and higher natural killer cell activity levels in the ginseng-treated group.

Applying research to patients

• Studies 7a and 7b
  – 200 mg per day of G115 in 19 healthy adult females showed no change in physical work performance, energy metabolic responses, or directly-measured O$_2$; and, in 31 healthy males taking 200 mg or 400 mg of G115 daily for 8 weeks had no change in physiologic or psychological responses to submaximal or maximal exercise
Panax ginseng: uses

- Diabetes: one small RCT suggests a benefit for several parameters
- Psychological functioning: RCTs suggest benefit, though conflicting evidence
- Physical performance: RCTs do not show an improvement
- Immune system: RCTs suggest benefits

Panax ginseng: uses

- Standardized
  - 4% ginsenosides
  - 1.5%- 7%
- G115, 200 mg per day
**Panax ginseng**: adverse effects

- Nausea
- Diarrhea
- Headaches
- Insomnia
- Mastalgia
- Blood pressure abnormalities

**Rhodiola rosea**

- Fatigue in physicians after call
- Military cadets (Russia)
- GAD
  - Open-label trial
- Dose:
  - Standardized to rosarins, salidoside
  - 185 milligrams BID-TID
Memory loss

Ginkgo

- *Ginkgo biloba*
- Dried, green leaf
- Uses (WHO, German E):
  - Dementia
  - Intermittent claudication
  - Vertigo, tinnitus
Ginkgo biloba

- Standardized
  - the dry extract is prepared using a 35-67:1 ratio of dried leaf to final extract (generally 50:1) and standardized to 22-27% flavone glycosides and 5-7% terpene lactones
  - Egb 761 (120-240mg)

Ginkgo biloba

- Cochrane
  - Tinnitus, 2004
    - “The limited evidence did not demonstrate that Ginkgo biloba was effective for tinnitus which is a primary complaint”
  - Dementia, 2002
    - “Overall there is promising evidence of improvement in cognition and function associated with Ginkgo”
    - Dilates blood vessels, reduces clotting, modulates neurotransmitters, prevents oxidative damage to nerve cells
Common Adverse Effects:  
5 categories

• Ephedra and ephedrine containing dietary supplements
• Plants containing pyrrolizidine alkaloids (PA)
• Adverse herb-drug interactions
• Plant products with contaminants (i.e., heavy metals)
• Accidental ingestion of ornamental plants or essential oils

Let’s practice counseling on this topic

• Counsel a patient about the adverse effects of ginkgo
• 4 possibilities
  – 1) Absolutely contraindicated
  – 2) Relatively contraindicated (for who?)
  – 3) No contraindications, but lots of hesitations
  – 4) Completely safe with no known side effects
**Ginkgo biloba: Adverse effects**

- Cochrane, 2002: no different than placebo
- Ginkgolides: potent inhibitors of platelet activating factor
- Documented herb-drug interactions and AEs
  - ASA: ocular hyphema
  - Warfarin: ICH with ginkgo X 2 months
  - Bilateral subdural hematoma: 33 yo woman, 120 mg/d of ginkgo X 2 years
  - Subarachnoid hemorrhage: 61 yo man with mildly prolonged bleeding time, 120-160 mg/d ginkgo for 6 months.

**Ginkgo biloba: Adverse effects**

- Prospective, DBRCT
  - 32 young, healthy male volunteers
  - Three dosages of Egb 761 (120, 240, and 480 mg/day)
  - Hemostasis, coagulation, and fibrinolysis
  - After 14 days’ administration: no significant modification of bleeding time, platelet function, or coagulation at any dosage when compared with placebo
- “While an interaction may exist between ginkgo and anticoagulant and antiplatelet agents, bleeding risk is probably quite low in otherwise healthy individuals taking gingko”
OK, clinician…

• 4 possibilities: *Ginkgo biloba*
  – 1) Absolutely contraindicated
  – 2) Relatively contraindicated (for who?)
  – 3) No contraindications, but lots of hesitations
  – 4) Completely safe with no known side effects

Congrats

• Graduated: Herbs/supplements 101 for Psychiatry
• Uses
  – Depression, Anxiety, Well-being, Memory
• Adverse effects
• Resources
stay together
learn the flowers
go light

-Gary Snyder