Snakes in the Grass:
Herb-Drug Interactions You Need to Know

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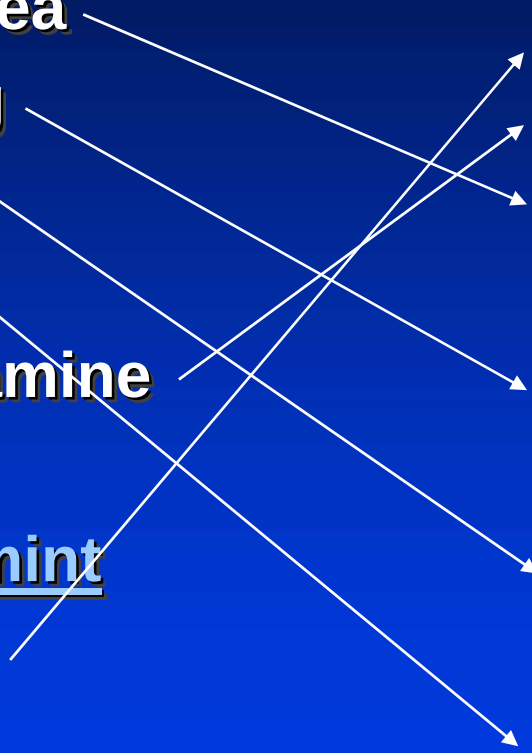
Learning Objectives

1. Develop practical approach to reviewing information on popular dietary supplements (DS)
2. Recognize common and/or serious drug-herb interactions
2. Be able to communicate with patients regarding issues related to use of DS

Top 10 Herbs 2002 vs. 2007

1. Echinacea
2. Ginseng
3. Ginkgo
4. Garlic
5. Glucosamine
6. SJW
7. Peppermint
8. Fish Oil
9. Ginger
10. Soy



1. Fish oil
2. Glucosamine
3. Echinacea
4. Flaxseed
5. Ginseng
6. Combination
7. Ginkgo
8. Chondroitin
9. Garlic
10. Coenzyme Q10

Herb-Drug Interactions

- St. John's wort and Drug Metabolism
  - Induces
    - Cytochrome P450 enzyme system
    - CYP3A4 subenzyme system
    - Intestinal P-glycoprotein
  - Metabolism of many common drugs

Glue 1999, Lee 2006,
Bell 2007, Schwarz 2007

Herb-Drug Interactions

- **St. John's wort and Drug Metabolism**
  - Antiretrovirals - Cyclosporin
  - Warfarin - Digoxin
  - Oral contraceptives - Theophylline
  - Tritptans - SSRI's
  - Anticonvulsants

Piscitelli 2000, Ruschitzka 2000, Nebel 1999, Mueller 2006, Madabushi 2006

Herb-Drug Interactions

St. John's Wort

- **Serotonin Syndrome**
  - Tremor, GI upset, HA, restlessness, myalgia, altered MS
  - Several reported cases
    - Nefazodone, paroxetine , sertraline, trazodone
  - Mechanism?

Martin 1996, Miller 1998, Gordon 1998, Lantz 1999, Beckman 2000

Herb-Drug Interactions

Kava (*Piper Methysticum*)

“Coma from the Health Food Store: Interaction between Kava and Alprazolam”

Almeida, Ann IM, 1996

Herb-Drug Interactions

Kava (*Piper Methysticum*)

- **Potentiation of CNS agents**
  - Alcohol
  - Antidepressants
  - Barbiturates
- **Decreased effectiveness**
  - Levodopa

Jamieson 1990, Bone 1994,
Brinker 1998, Pepping 1999

Herb-Drug Interactions
Kava (*Piper Methysticum*)

- **Kava hepatotoxicity**
  - N = 26 patients (20 German, 6 Swiss)
  - Co-medication 22/25
  - Liver disease 13/26
    - (e.g. PBC, autoimmune hepatitis, EBV)
  - Causality unable to assess, excluded - 16
  - Causality unlikely - 2
  - 7/8 exceeded dose/duration recs.

Teschke, 2008

Herb-Drug Interactions
Ginkgo (*Ginkgo biloba*)

- **Anticoagulant interactions**
  - Ginkgolide B
    - Inhibitor of platelet-activating factor (PAF)
    - Blocks binding of PAF to receptor

Chung, Lancet 1987

Herb-Drug Interactions
Ginkgo

- **Bleeding complications**
  - Spontaneous bilateral subdural hematomas
  - Subarachnoid hemorrhage
  - Spontaneous hyphema
  - Increased bleeding time

Rowin, Neuro 1996
Rosenblatt, NEJM 1997
Vale, Lancet 1998

Herb-Drug Interactions
Ginkgo

- **Trazodone**
  - Case report
    - Elderly patient w/ Alzheimer's
    - Added trazodone to ginkgo > coma ensued
  - Mechanism
    - ? Enhanced Cytochrome P450 (CYP3A4)
    - Increased metabolism to active metabolite

Galluzzi, 2000

Herb-Drug Interactions

Ginseng

- **Case Report**
  - Asian ginseng (Ginsana™)
  - 47 yo man, stable INR 3-4 (mech. valve)
  - 2 wks of Ginsana, INR fell to 1.5
  - Returned to normal 2 weeks after d/c'ed

Janetzky, Am J Health Syst Pharm 1997

Herb-Drug Interactions

Ginseng

- **U of Chicago**
  - RCT, n= 20 young healthy volunteers
  - 4-week study
    - Warfarin
    - Warfarin + ginseng
  - Peak INR, plasma warfarin; INR AUC –decreased

Yuan 2004

Herb-Drug Interactions

Ginseng

- **Phenelzine**
  - 42 yo woman – manic-like sxs
    - Decr. sleep, optimism, inviting strangers to her house, irritability, hallucinations
  - 64 yo woman
    - Tremor, headache

Shader 1985, Jones 1987

Herb-Drug Interactions

- **CYP1A2**

  kava, feverfew, echinacea, SJW, ginkgo
- **CYP2C19**

  kava, feverfew, devil's claw, ginkgo
- **CYP2C9**

  kava, feverfew, devil's claw, ginkgo, SJW
- **CYP2D6**

  pomegranate, kava, ginseng, black cohosh,
- **CYP3A4**

  pomegranate, feverfew, devil's claw, valerian

Herb-Drug Interactions

- **CYP1A2**

  Amitriptyline, clozapine, diazepam, fluvoxamine, olanzapine
- **CYP2C19**

  Amitriptyline, citalopram, diazepam
- **CYP2C9**

  Amitriptyline, diazepam
- **CYP2D6**

  Amitriptyline, clozapine, desipramine, fluoxetine, olanzapine, paroxetine, trazodone, venlafaxine
- **CYP3A4**

  Fluoxetine, triazolam

Herb-Drug Interactions

- **Possible bleeding complications**
  - Ginkgo (*Ginkoba biloba*)
  - Ginger (*Zingiber officinale*)
  - Garlic (*Allium sativum*)
  - Feverfew (*Tanacetum parthenium*)
  - Dong quai (*Angelica sinensis*)

Herb-Drug Interactions

- **Documented warfarin Interactions**
  - Danshen (*Salvia miltiorrhiza*)
  - Devil's claw (*Harpagophytum procumbens*)
  - Green tea (*Camellia sinensis*)
  - Ginseng (*Panax ginseng*)
  - Papain (*Carica papaya*)

Herb-Drug Interactions

Documented warfarin Interactions

- **Green tea (*Camellia sinensis*)**
  - **Case report**
    - **44 yo man w/ mech valve, began green tea**
    - **INR fell to 1.37**
    - **Drinking 1/2 to 1 gallon tea/day!**

Taylor, Ann Pharmacother. 1999

Herbs and the FDA

Dietary Supplement Health and Education Act, 1994

- Reclassified herbs as “dietary supplements”
- Separate classification from either food or drugs
- Can be marketed with suggested dosages
- Not required to undergo pre-market testing for
  - Safety
  - Efficacy

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Adulterants in Asian Patent Medicines

component of what are called traditional Chinese medicines. Asian patent medicines comprise multiple products, including herbs, plants, animal parts, and minerals, which are formulated into tablets, pills, or liquids for ease of use. ve gained acceptance by the American public as a form of alternative medicine. However, many patent medicines manufactured in Asian countries contain toxic ingredients, such as heavy metals, as well as prescription drugs or dentified on the label.[1,2] Some have caused serious illness in unsuspecting consumers.[3,4]

Food and Drug Branch, initiated a study to screen imported Asian patent medicines for undeclared pharmaceuticals and heavy-metal contamination, using gas chromatography–mass spectrometry and atomic-absorption methods. Our se for these products; educate the public, the herbal industry, and the medical community about the potential danger of Asian patent medicines; and provide objective information about toxicity.

ollected from California retail herbal stores, 14 had labels that declared pharmaceutical ingredients, and 3 had insufficient sample amounts. Of the remaining 243 products, 17 (7 percent) contained undeclared pharmaceuticals. The drine, chlorpheniramine, methyltestosterone, and phenacetin. A total of 251 products were analyzed for lead, arsenic, and mercury; 9 other samples, including the 3 noted above, were insufficient for this analysis. Twenty-four products

"Of the 260 products we investigated, at least 83 (32 percent) contained undeclared pharmaceuticals or heavy metals"

Richard J. Ko, Pharm.D., Ph.D.
California Dept of Health Services

mayo

FDA and Good Manufacturing Practices

DS must be manufactured consistently:

- Identity
- Strength
- Purity
- Composition

- **Effective**
  - 6/08 for large companies
  - 6/09 for companies with <500 employees
  - 6/10 for companies with < 20 employees

Herb-Drug Interactions

- **Scope of the issue**
  - N = 804 outpatients from 6 clinics
  - 122 (15%) used herbal therapies
    - 85 potential AI in 49 pts (40%)
    - 12 possible AI in 8 pts (7%)
      - severity scores were rated as mild
      - 8 cases of hypoglycemia

Bush 2007

Herb-Drug Interactions

- **Scope of the issue**
  - One year (2006) Poison Control Center
    - Total calls 75,390
    - Dietary supplement calls 275
      - 163 asymptomatic/ info requests
      - 112 symptomatic
  - Caffeine 47%, yohimbine 18% of sympt. cases

Haller 2008

Herb-Drug Interactions

- **Scope of the issue**
  - N = 1795 Mayo Clinic patients, 6 specialty clinics
    - 40% used DS
    - 107 potential interactions
  - 68% of potential interactions.
    - garlic, valerian, kava, ginkgo, and St John's wort
  - 94% of potential interactions.
    - antithrombotics, antidepressants, antidiabetic agents
  - No serious adverse events

Sood 2008

Herb-Drug Interactions

- **Health Care Team**
  - Patients may be reluctant to discuss use
    - Fear of censure
    - Different beliefs re: herbs
  - Non-judgmental questions critical
  - Easy access information

Herb-Drug Interactions

- **Patients…**
  - If you decide to use a treatment:
    - Determine the effect sought
    - Discontinue if not achieved
    - Record and save therapy information
  - If meeting a need…
    - Partner w/ health care team to watch for adverse effects

Questions???

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