Webinars
Series of scientific webinars that provide a forum for discourse on scientific issues.
- Live and On-Demand
- Case Conferences
- Journal Clubs
- Grand Rounds
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Online Courses
Evidence-based online courses on a variety of children's environmental health topics.
- Interactive and Self-Paced
- CE Available

Resource Catalog
Fact sheets, journal publications, reports, and other resources for parents, community members, patients and healthcare professionals
- Topics included: Air Quality, Pesticides, Natural Disasters, BPA, Mold, Lead, Mercury
Herbal Toxicity.

Susan C Smolinske, PharmD, DABAT.
Objectives

- Understand the DSHEA regulation and amendments
- Discuss contamination and quality issues with herbal supplements
- Know the herbs most likely to cause Type I allergic reactions
- Describe the liver toxicity from pennyroyal and kava kava
- Describe the CNS toxicity from alpha lipoic acid
- Explain several toxicological problems with *Ginkgo biloba*
How are herbals regulated?

- DSHEA 1994
- Labeling Rules
- Good manufacturing practices
- Adverse event reporting rules (15 days to report)
- Medical-Legal implications
Animal, Mineral, or Vegetable?

Chlorine dioxide
Functional Foods
“Phoods”

Total caffeine 80-> 500 mg/can

33% of adolescents are frequent consumers
Functional Foods
Functional Foods

choline, alpha-ketoglutaric acid, acetyl-L-carnitine, ginkgo, *Bacopa monniera*, gotu kola, eleuthero, phytosterols

It has been estimated that 12 to 68% of parents utilize CAM to treat children with ADHD.
FDA published Guidelines to industry in 2000. Any product promoted as a street drug alternative is considered an unapproved new drug and is misbranded. They are NOT considered dietary supplements.
Epidemiology

- 344% increase in human exposures reported to PCCs from 1990 to 1997
  - 138% increase in herbal consumption
  - 1990: 1,239
  - 2003: 24,412
  - 10-year average: 21,154
- Most in children < 6 years
- Serious outcomes in 4.5%
- 3 deaths from homeopathic products
Problem list with herbal medicines

- Heavy metal contamination
- Drug adulteration
- Microbial contamination
- Insect “contamination”
- Environmental contamination
- Misidentification
- Carcinogenic
Homeopathic remedies

- Regulated by FDA, not part of DSHEA
  - Acrodynia in infant from 6X mercuric sulfide
  - Thallium poisoning in adult
  - 3 cases arsenic toxicity from 1X products
  - Current concerns over Hyland’s Teething tablets
  - Arsenic in 2 of 6 homeopathic products tested
  - 23% of Indian products had undeclared steroids
Weight Loss, Erectile Dysfunction, Sports Performance lead the list of adulteration

- Weight Loss: sibutramine, bumetanide, fenfluramine, furosemide, orlistat, phenolphthalein, phentermine, phenytoin, rimonabant, sertraline
  - Sibutramine withdrawn due to risk of stroke/MI
Weight Loss, Erectile Dysfunction, Sports Performance lead the list of adulteration

- Erectile Dysfunction: sildenafil, tadalafil, and vardenafil and more than 120 synthetic analogs
- Multiple analogs in same supplement
Weight Loss, Erectile Dysfunction, Sports Performance lead the list of adulteration

- Sports Performance: designer anabolics, androstenedione, methandienone, testosterone esters, androst-4-ene-3β-17β-diol, boldenone, prostanozol, methasterone, andostatrienedione, clenbuterol
Clenbuterol and the Internet Entrepreneurs

- Two brothers own an internet business selling their own brand of PED
- They “test” each product by taking one capsule each and noting effects to be used in marketing
- Chinese salesmen sells them a new product and they ingest it (after he’s gone back home)
- They present to ED 2 hours later with palpitations and SOB
- Both diagnosed with acute cardiomyopathy with EF around 20
- They require propranolol therapy for a week
- Samples found to contain high dose of clenbuterol
- Chinese salesmen tells them it was supposed to be clomiphene
Dimethylamylamine (1,3-dimethylamylamine, DMAA) is an oral sympathomimetic agent also known as geranamine, methylhexanamine, and pentyamine.

- The exact mechanism of action of DMAA is unknown but it is likely that DMAA is an indirect sympathomimetic agent that exerts its effects on the release or reuptake of norepinephrine.
- It was removed from the market in 1983 but was reintroduced in 2006 as a dietary supplement (trade name "Geranamine") with claims it was a constituent of oil from geranium flowers. Studies supporting these claims have since been deemed flawed. In 2012, the FDA designated DMAA-containing products illegal and potential health risks and that safety data are limited.

Dimethylbutylamine (1,3-dimethylbutylamine, DMBA) is an analog of DMAA

- It was initially claimed to be a degradation constituent of Pouchong tea, but the quantities present suggest deliberate adulteration. Three patients who reported adverse effects to DMBA had a sensation of rushing and akathisia.
**Weight Loss sympathomimetic ingredients**

- *N,α*-diethylphenylethylamine (DEPEA), a methamphetamine analog, has been found in dietary supplements labeled as extracts of dendrobium orchid.

- Alpha-ethylphenylethylamine (AEPEA) is a metabolite of DEPEA and has similar activity.

- Beta-methylphenylethylamine (BMPEA) is a positional isomer of epinephrine, and has been found in dietary supplements that imply it is a constituent of *Acacia rigidula*
• 14 of 15 ayurvedic samples contained *Aspergillus flavus*-derived aflatoxin (mean 1 ug/g)
• adrenal cortex extract
  • 68% of 69 HIV patients had injection site abscess
  • Subsequently 7 more patients
  • product contained *Mycobacterium abscessus*
• Kombucha tea: *Candida, Penicillum*
• American ginseng
  • treated with *Burkholderia cepacia* to control leaf blight
• Solgar Digestive aid-*Salmonella*
FDA warned distributors of glandular products  
11/14/2000

Risk of nv-Creutzfeldt-Jakob

- highest risk with brain, spinal cord
- medium with ileum, spleen, pineal gland, pituitary gland, lymph nodes, tonsil, placenta, adrenal gland, proximal colon, dura mater, CSF

Mad Cow
Environmental contamination

- Tested 22 brands
- 17 Panax ginseng
- 4 American ginseng
- One had only .589\% ginsenosides (<2\% minimum)
- Only 9 met quality/purity standard
- 8 had unacceptable quintozene, hexachlorobenzene, up to 20x allowed
- 2 had lead > 3 ug/serving
Misidentification

- *Aristolochia* labeled as *Stephania*
- *Petasites* labeled as coltsfoot
- *Digitalis lanata* labeled as plantain
- THP labeled as *Polygala chinensis*
- Chinese silk vine labeled as ginseng
- Podophyllum labeled as *Clematis*
Jin Bu Huan

- Contains L-tetrahydropalmitine (L-THP)
- 1993: 3 children bradycardia, coma, respiratory depression after 7, 17, 60 tabs
  - Analysis showed 28.2 mg pure L-THP per tab
- 1993: 2 adults with acute hepatic injury
The 1997 plantain story

- 23 yo heart block
- 6000 lb imported from Germany to USA
- 150 distributors
- Lanatosides
  - Both digitoxin, digoxin
  - Digitoxin differs
    - 95-100% bioavailable
    - Half life 168 hours
    - Enterohepatic recirculation
    - Lower binding to fab
Quality
Carcinogenic herbs

- Aristolochic acid
  - high association with urothelial cancer
- Tannins
  - *Krameria, Acacia, yerba mate, mormon tea, Arctostaphylos uva ursi, Ephedra viridis, Myrica cerifera*
- Safrole
  - sassafras tea, herbal Ecstasy
  - banned by FDA as food additive in 1960
  - hepatocarcinogen, potent enzyme inhibitor
    - “safrole was reacted with aqueous HBr, and the impure reaction product reacted with alcoholic methylamine to produce MDMA in an unstated yield.”
# Carcinogenic/Mutagenic herbs

- **DHEA**
  - 14 of 16 rats given high-dose DHEA developed liver cancer
  - Case control study of 20,000 found increased risk of ovarian cancer with increased levels of DHEA

- **Anthraquinone laxatives**
  - senna, cascara, rhubarb

- **Angelica (dong quai)**

- **Astragalus**
  - Mutagenic in Ames test

- **Calamus**
  - Strong mutagen
  - Isoasarone in oil

- **Soy isoflavones**
  - Stimulate existing tumors
  - Antagonize tamoxifen
More problems with herbals

- Fleeting product ingredients
- Ineffective standardization
- Delay in seeking treatment
- Toxic components
- Adverse reactions
- Hypersensitivity reactions
- Highly toxic herbs
- Interactions
Standardization

- Ginseng: 15-fold variation in ginsenosides
- Eleuthero: 43-fold variation in eleutherosides
- St John’s wort: hypericin varied 0-109% for capsules, 31-80% for tablets
  - Consumerlab.com
  - National Nutritional Foods Association
  - NSF International Certification program
  - USP Dietary Supplement Verification program
Delay in seeking treatment

- 11 y.o. with aplastic anemia: Nepal pill
  - analysis negative
- 15 y.o. with CML: chiropractor
  - successful bone marrow transplant
- 19 y.o. with diabetes: Echinacea
  - persistent vegetative state
- 15 y.o. with Hodgkin’s: Astragalus
  - progressed from IIA to IIB
- 9 y.o. with brain tumor: shark cartilage
  - Death
- 23-m.o. with brain tumor: homeopathic treatment
  - Court ordered evaluation; progressed beyond help
Toxic components Blue-Green algae

- Upper Lake Klamath
- Aphanizomenon flos-aquae
  - aphantoxin: similar to saxitoxin, tetrodotoxin
    - cell injury due to intracellular calcium flux
- Microcystis
  - hepatotoxic
Microcystin

- Cell Tech products all had a small amount of microcystin
- Has t1/2 of 10 wks
- 116 hemodialysis patients in Brazil with microcystin toxicity from contaminated dialysis fluids
Adverse reactions - Allergic

- **Echinacea**
  - 23 cases
  - 3 anaphylaxis
  - 10 asthma
  - 10 urticaria, edema
  - 20% atopics + SPT
  - Recurrent erythema nodosum

- **Anaphylaxis**
  - Kombucha
  - St John’s wort
  - bee pollen/royal jelly (22 cases)
  - chamomile
  - capsaicin

- **Ginkgo biloba**
  - 13 of 14 samples had ginkgolic acid
  - > 16-733 WHO limit
  - related to urushiol
  - 1 case of SJS

- **Passiflora**
  - allergic vasculitis

- **100 species of Compositae family**
Allergic reactions to homeopathic

- Rhus toxicodendron: contact dermatitis
- Nat mur: erythroderma
- Immunostimulant combo: erythroderma
- Combo weight loss: morbilliform rash
- Grass pollen: anaphylaxis
- Mandragora: anaphylaxis
Highly Toxic Herbs—Liver

**Toxic hepatitis**
- Black Cohosh (number one cause)
- Chaparral (cholestatic jaundice)
- Germander (*Teucrium chamaedrys*)
  - >30 cases, CYP3A metabolism of furano-neo-clerodane diterpinoids to electrophilic metabolites that deplete thiols
- Jin bu Huan (tetrahydropalmatine)
- *Ephedra* species
- *Packera candidissima*
- Syo-saikoto-to
- kava kava
- bee pollen
- hydrazine sulfate
- Kombucha tea (usnic acid)
Highly Toxic Herbs - Liver

- pennyroyal
- lobelia, parguay tea, podophyllum, rue, sassafras, scullcap, Pau d’arco, *Dictamnus dasycarpus*, senna, *Crotolaria*
- Neem oil (Reye’s like syndrome in infants)

**Hepatic veno-occlusive disease**
- pyrrolizidine alkaloids
- arterial hypertension, RVH, abdominal pain, ascites, hepatomegaly, transaminitis
- Borago, coltsfoot, comfrey, *Petasites, Senecio*
Pennyroyal toxicity

- Member of mint family
- Oil contains pulegone
- Pulegone metabolized by P450 to menthofuran then reactive metabolite
- Covalent binding to liver cells, depletes glutathione
Pennyroyal toxicity

• 1 oz caused fatal centrilobular necrosis
• tea fatal in 16 m.o.
• multiorgan failure
  • renal failure
  • pulmonary hemorrhage
  • seizures, coma, paresthesias (0.5 to 1 tsp)
  • shock, DIC
Usnic Acid

- FDA warning 11/2001
- Multiple cases liver failure, ages 20-32yr
- 2 wks to 3 months
  - Norephedrine (PPA), caffeine, yohimbine, T2, sodium usniate
- Class action lawsuit
- One case of liver failure needing transplant with usnic acid alone
- Phenol found in lichens
Kava kava toxicity

- >25 cases of liver toxicity
  - Hepatitis
  - Cirrhosis
  - Liver failure
  - 4 transplants
Kava Kava

- faster growing varieties of kava were cultivated and that there was an increase in the use of parts of the plant other than the traditional kava root, such as stem peelings
- Kavalactone content in standardized extracts are 30 times more than that
- piperidine alkaloid pipermethystine has been considered to be responsible for alleged hepatotoxicity of Kava products of the traditional aqueous extract
- pipermethystine is absent from all root and stem extracts. Leaves of *P. methysticum* contain 0.2% pipermethystine
Recommendations for Kava use

- (1) use of a noble kava cultivar, at least 5 years old at time of harvest, (2) use of peeled and dried rhizomes and roots not exposed to light (3) aqueous extraction (to avoid pipermethystine), and (4) dosage recommendation of ≤250mg kavalactones per day for medicinal use.
Liver Toxicity Related to Herbs

- Oregon Health Science University
  - 2002 study of candidates for liver transplant
  - 10 of 20 patients were taking hepatotoxic herbal supplement with kava or others
    - Ephedra, kava, chaparral, skullcap, dandelion root implicated
  - 7 of 10 was only explanation
  - Herbal toxicity more common now than APAP/viral
- 474 cases (in approx 10,000 users) in Japan from Chinese weight loss herbals adulterated with N-nitroso-fenfluramine
Highly Toxic Herbs-Kidney

- Aristolochic acid: more than 100 cases
- Glycyrrhizin (licorice)
  - Fanconi syndrome
- Ephedra-kidney stones
- white cohosh (*Actaea*)
- Carambola juice (star fruit)
  - two cases of oxalate nephropathy reported
- Horse chestnut (IV)
- Cat’s Claw: 1 case
Aristolochia species
“Virginia snakeroot”

- progressive interstitial renal fibrosis, renal pelvic carcinoma
- P450, peroxidase forms aristolactam, then DNA adducts
- 2 patients in US
- FDA found in 18/34 products sold in US
- *Stephania, Clematis* misidentification
Highly Toxic Herbs-Kidney

- Heavy metals
  - chromium picolinate: 1 case RF, 1 case interstitial nephritis
  - cadmium (as contaminant of Chinese herb)
  - Germanium: > 30 cases renal failure
Alpha Lipoic acid (aka thioctic acid)

- coenzyme involved in carbohydrate metabolism
- most common use is diabetic neuropathy
- 20-month-old boy presented 4 hours after ingestion of 2400 mg (226 mg/kg) with nausea, vomiting, lethargy, and involuntary movements onset < 1 hour of ingestion.
- Status epilepticus resolved in 48 hours with treatment. He awoke in the next few days and was discharged on day 5 (Karaarslan, 2013).
Wormwood
*Artemisia absinthium*

- Absinthism
  - hallucinations
  - tremors, seizures
  - paralysis
  - chronic ingestion
  - essential oil contains thujone
    - structural isomer of camphor
Wormwood

- 1800s blue-green beverage popular
  - Absinthe liqueur
- Oil available as “aromatherapy”
- Ingestion of 10 ml resulted in seizures, rhabdomyolysis, and renal failure
Highly Toxic Herbs - Heart

- Aconitum (Monkshood) - most common
- *Ephedra* (ma huang)
- *Passiflora* - prolonged QTc
- *Tripterygium wilfordii*
  - most common herbal poisoning in China
  - hypovolemic shock, cardiac damage
  - aplastic anemia
- licorice - torsades de pointes (hypokalemia)
- Scotch broom
- Squirting cucumber
Ma huang (\textit{Ephedra} species)

- Ma huang contains:
  - ephedrine
  - pseudoephedrine
  - Norephedrine (PPA)
  - methylephedrine
- peak levels delayed compared to Rx
  - 3.9 hrs vs 1.7 hrs
- \(\alpha_1, \beta_1, \beta_2\) stimulant
  - both direct and indirect
  - also releases dopamine
Ma huang (Ephedra species)

- Vasoconstriction
- 47% of cases had cardiovascular toxicity
- MI, stroke, sudden cardiac death, myocarditis, HTN
  - hypertension single most frequent ADR
  - tachycardia, palpitations
- caffeine is synergistic
- exercise may increase risk
Citrus aurantium (bitter orange)

- Phenylephrine isomer (Synephrine)
- Potent alpha stimulant
- N-methyltryptamine
- 1 death from MI
- Animal data suggest prolonged QRS, ventricular dysrhythmias
Toxic Herbs-Gastrointestinal

- Podophyllum (mayapple)
- Dieter’s teas
- Grapefruit seed extract
  - esophageal mucosal lesions (2 cases)
  - swollen tongue with abrasions (2 cases)
- Milk thistle
  - abdominal pain, diarrhea, weakness, collapse
- Kombucha “retch factor”
Kombucha “mushroom”

- Fermented yeast product in sugar, black tea
  - *Candida, penicillum*
  - Alcohol .5%, glucuronic acid, hyaluronic acid, lactic acid, heparin, usnic acid, chondroitin, caffeine (if made with caffeinated tea)
  - Cutaneous anthrax
    - 20 cases in Iran
    - Good growth medium
Kombucha “mushroom”

- Gastroenteritis with more than 4 oz per day
- hepatitis
- allergic reactions
- 2 severe cases in Iowa
  - lactic acidosis
  - DIC, death in 1 case
  - pulmonary edema
  - 4-12 oz for 2 months

Kombucha art
Toxic Herbs-Hematologic

- **Salviae multiorrhizae** (cinnabar root, danshen)
  - anticoagulant
- **Horse chestnut**
  - antithrombin activity
  - hydroxycoumarin
  - aesculin
- **Red clover** (*Trifolium pratense*)
  - anticoagulant coumarins
- **Cat’s Claw** (*Uncaria tomentosa*)
  - Increases PT
- **Saw palmetto**
  - intra-op hemorrhage
- **Glucosamine**
- **Alfalfa seeds**
  - pancytopenia
  - hemolytic anemia
  - re-activation of SLE
  - L-canavanine
- **Asafetida** (*Ferula assaloetida*)
  - methemoglobinemia
Toxic Herbs-Hematologic
Inhibit Platelet Aggregation

- Anise
- Bishop’s weed
- Bogbean
- Boldo
  - boldine inhibits thromboxane A2 production
- Bromelains/Papaya
- Capsicum
- Celery
- Chamomile
- Clove
- Danshen
- Dong quai (*Angelica sinensis*)
  - ferulic acid
- Feverfew
- Garlic
- Ginger
- *Gingko biloba*
Other platelet aggregation herbs

- fenugreek
- Horseradish
- licorice
- meadowsweet
- prickly ash
- onion
- passion flower
- poplar
- quassia
- Reishi mushroom
- turmeric
- wild carrot
- wild lettuce
- willow
Gingko biloba

• gingkolide B
  • terpenoid component
  • ranged from 6.4 to 10.9%
  • potent PAF inhibitor
  • single doses of 80 mg mixed ginkgolides produced significant platelet aggregation inhibition in human volunteers
  • Systematic review found no change in coagulation
Gingko biloba

- Case reports
  - 70 y.o. iris bleeding after 40 mg bid x 1 wk + ASA 325 mg/d
  - 56-y.o. intracerebral hemorrhage 40 mg tid x 18 mo
  - 61 y.o. subarachnoid hemorrhage after 40 mg tid-qid for > 6 mo
  - 33 y.o. serious bleeding in gall bladder surgery patient
  - 60 y.o. severe postop bleed after mastectomy 375 mg tid x 8 mo
  - 33 y.o. bilateral subdural hematomas after 60 mg bid x 2 yrs
- alpha lipoic acid (IV)
- chromium picolinate
- *Gingko biloba* (WHO ADR report)
- kava kava (chronic use)
- L-arginine (IV)
- lentinan (shiitake mushroom component)
- parsley (massive amt of volatile oil)
- pokeweed
- selenium
- *Ephedra* (6 cases with FDA)
Conclusions

- Three types of herbal products are most likely to contain unlisted drugs
- There is no pre-marketing safety data
- New ADRs and interactions will surface
- Poison centers are important part of surveillance
  - FDA has < 1000 cases per yr, PCCs have > 24,000
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