

*Drug Interactions: A Podiatric
Assistance Program*

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APMA

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Thank you



Learning Objectives

Recognize the potential for Drug-Drug Interactions.

- List the known Drug-Drug Interactions as reported in the medical literature
- Discuss the probability and occurrence of drug-drug interactions as supported by clinical based evidence.
- Identify relative clinical drug interactions within the scope of our practice setting as found in the literature.
- Discuss methods to avoid potential drug interactions and adverse drug reactions within the our patient population.

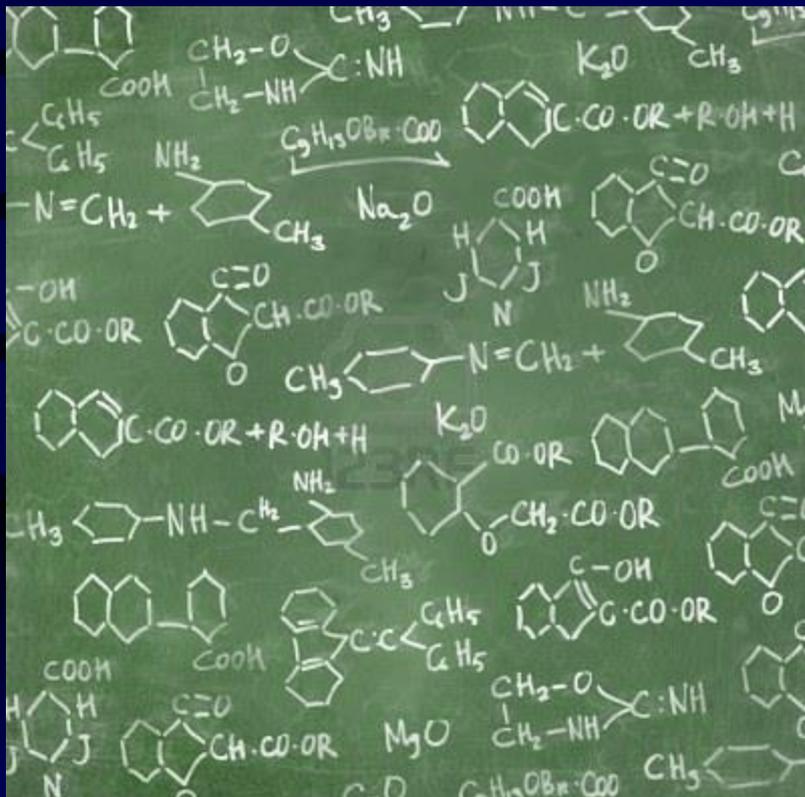
Introduction

- Drug interactions are considered a category of drug misadventures. (ADR)
- Some drugs interact with other drugs, food or drink, tobacco products, alcohol consumption, and botanicals or herbal products.
- The effect on the medication by these variables can result in increase or decrease activity.

History

- The scientific field of drug-drug interactions is relatively new.
- Fifty-years ago the first major symposium on drug interactions was held in Britain.
- The relatively recent discoveries of cytochrome P-450 isozymes and ATP binding cassette transporters have revolutionized the field.

The Heart of Drug Interactions



Prescribers' Knowledge of Drug Interactions

- Only five published studies as of 2017 (n=1901) evaluate prescriber's knowledge.
- Assessing causality is difficult.
- Important to consider the results of published literature in addition to personal clinical experience when making decisions about drug interactions in individual patients.
- Pharmacists can be helpful resources.

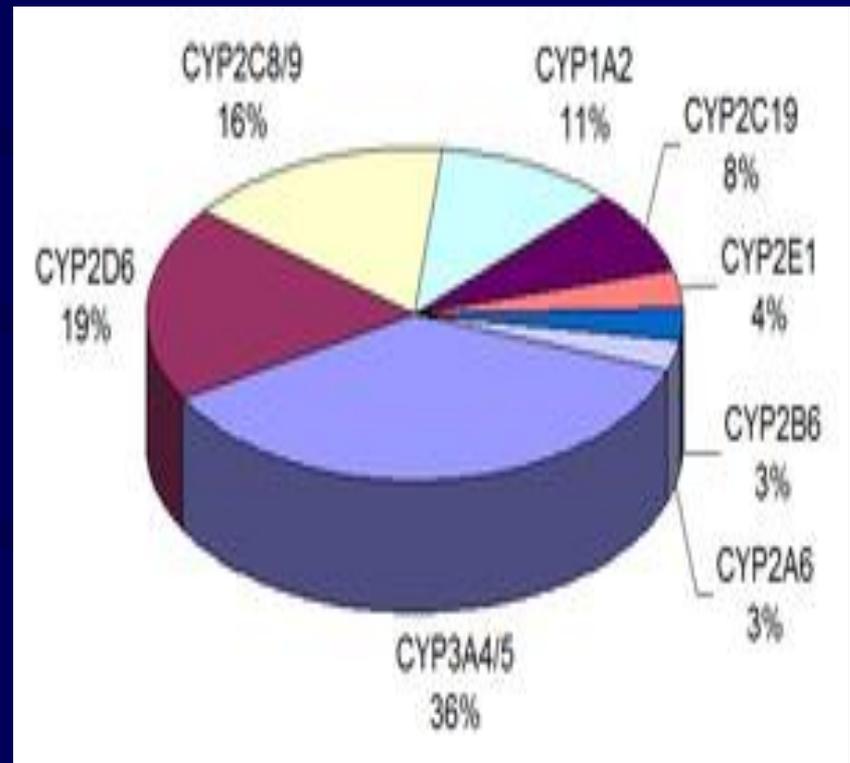
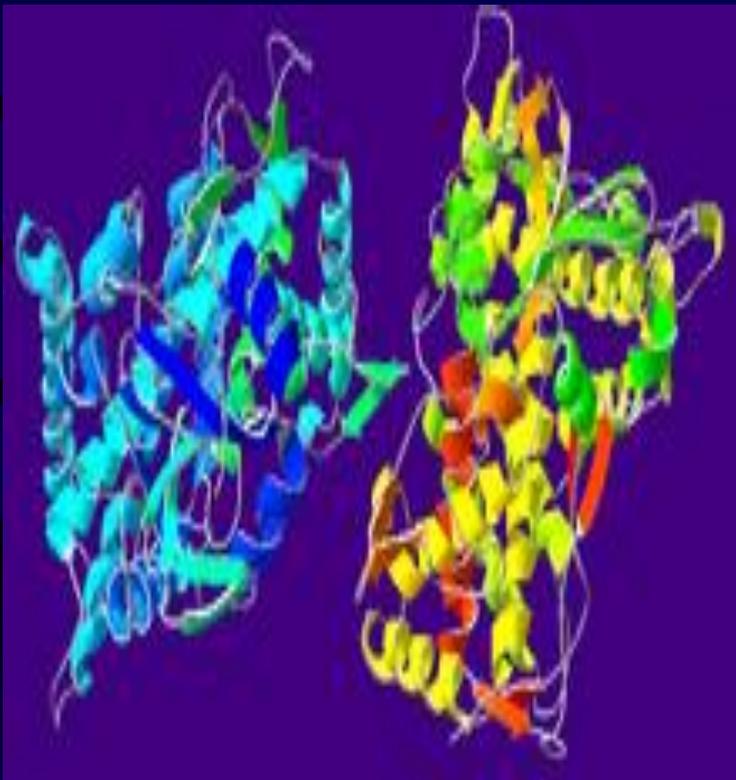
Drug-Drug Interaction Mechanisms

- Pharmacokinetic and Pharmacodynamic
- Pharmacokinetic- Inhibition of Absorption, Enzyme Inhibition Increasing Risk of Toxicity, Enzyme Inhibitors and Induction resulting in Reduce Drug Effect, Enzyme Induction resulting in Toxic Metabolites, Altered Renal Elimination
- Pharmacodynamic-Additive or Antagonistic Pharmacodynamic Effects.

Drug-Drug Interaction Mechanisms

- It is important to remember that even if a drug is not metabolized by a specific CYP enzyme, it can affect the metabolism of other drugs through that pathway.
- Drug interaction potential is recognized as an important consideration in the evaluation of a new molecular entity.

Cytochrome P450 Enzymes



Drug-Drug Interaction Mechanisms

- The terms pharmacogenomics and **pharmacogenetics** tend to be used interchangeably, and a precise, consensus definition of either remains elusive.
- Pharmacogenetics is generally regarded as the study or clinical testing of genetic variation that gives rise to differing response to drugs.
- Pharmacogenomics is the broader application of genomic technologies to new drug discovery and further characterization of older drugs.

Evidence for Drug Interactions

- ▶ Case reports
- ▶ Lab studies
 - Define mechanisms
 - ▶ Recent interest in CYP450 induction
 - ▶ Not necessarily borne out in trials
 - ▶ Pharmacovigilence Model
- ▶ Human studies – interpret with caution
 - Trials using probe drugs
 - May be too short or financially biased
 - May be done on healthy population (not always)
 - Genetic polymorphisms
 - Multiple drug/herb users, elderly patients

Drug Interactions-The Swiss Cheese Model (James Reason)

Horn and Hansen Pharmacy Times March 2004 53-54

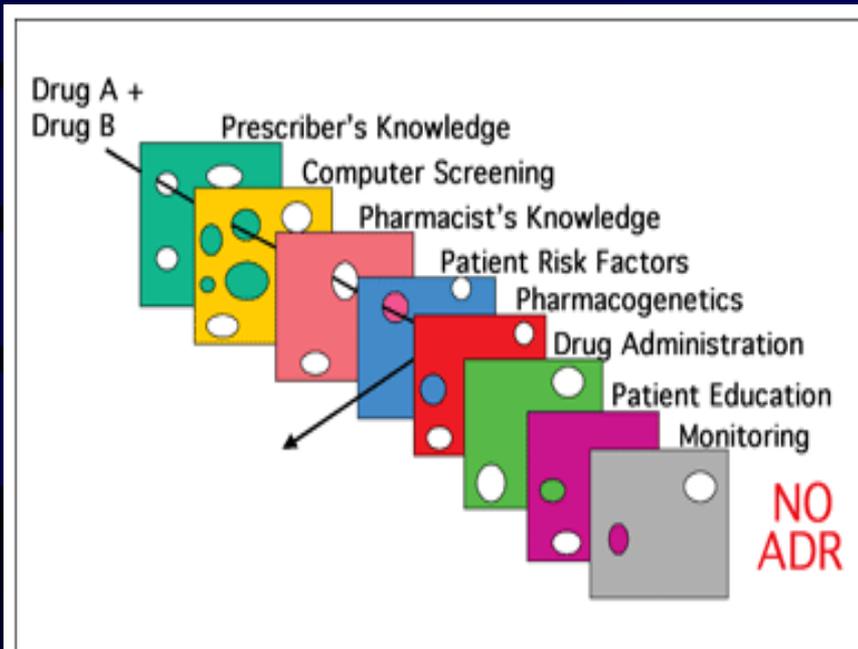


Figure 2—Usually, one of the defenses stops the drug interaction before it can produce an adverse consequence. In this case, the patient's pharmacogenetic makeup protects against an adverse event. ADR = adverse drug reaction.

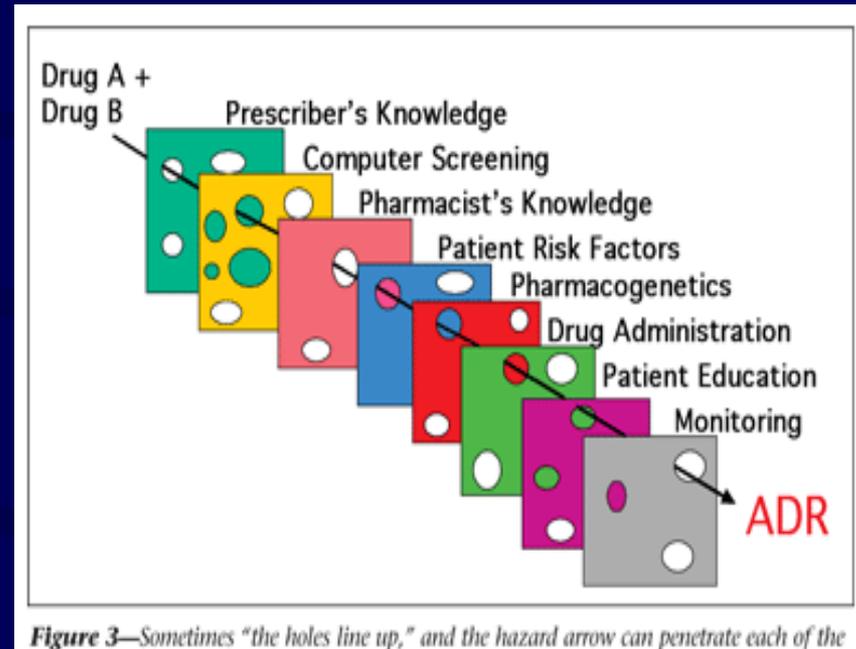


Figure 3—Sometimes "the holes line up," and the hazard arrow can penetrate each of the defenses unimpeded. Each defense also has other holes, which are called latent failures. These are gaps in the defenses that are not involved in the interaction between Drug A and Drug B, but rather would come into play with other drug interactions. As such, they are accidents waiting to happen. ADR = adverse drug reaction.

Drug-Drug Interactions for the Providers References

- The Top 100 Drug Interactions 2016 edition Hansten and Horn.
- An appraisal of Potential Drug Interactions in Cigarette Smokers and Alcohol Drinkers. Smith R.G., Journal of the American Podiatric Medical Association 2009 99 (1) 81-88.
- Illicit Drug Abuse Implications for the Podiatric Physician. Smith R.G., Podiatry Management 2009 28 (3): 171-184.
- The Use of Dietary Supplements in Diabetic Peripheral Neuropathy. Smith R.G., Podiatry Management 2009 28 (9): 195-202.
- An appraisal of Potential Drug Interactions in Dietary Supplements among the Top 200 Prescriptions of 2009. Smith R.G.
- An appraisal of Potential of Drugs effect on Bone Healing Drug Interactions in the Top 200 Prescriptions of 2016. Smith R.G., JAPMA

Patient Disclosure about Supplements and Social Behaviors Use Among Adults in US

- Non-disclosure of Herbal Supplements, OTCs, Energy Drinks, Cigarette and Ethanol use is particularly common among racial and ethnic minority groups and among non-citizens.
- Language barriers, cultural differences and limitations in access to conventional medical care may account for these differences.
- Many of these adults have cultural tradition of herbalists, and are more likely to use herbs and supplements than majority populations.

Analgesic Drug Interaction Chart

Interactions of Analgesic Drugs Commonly Used a in Podiatry Practice

Prescribed Drug	Drugs Involved with Drug Interaction	Explanation of Drug Interaction
NSAIDS	Antihypertensive Drugs	Effectiveness of most classes of antihypertensive drugs is reduced following prolonged use of most NSAIDs. If NSAIDs are required for more than 5 days, the patient's blood pressure control should be assessed.
	Warfarin (Coumadin)	Antiplatelet effects of NSAIDs may add to the anticoagulant effect of Warfarin. The primary concern is the GI erosive effects of NSAIDs may be prone to hemorrhage
	Bisphosphonates (Fosmax)	NSAIDs enhance GI toxicity of Bisphosphonates used for Osteoporosis. No concern if NSAIDs used short term (5-7 days)
	Methotrexate (Rheumatrex)	Increase serum levels of Methotrexate leading to systemic toxicity (Stomatitis)
	Lithium	Lithium excretion is reduced and blood toxicity may develop in 5 to 10 days of NSAID therapy
	SSRIs Antidepressants	Enhance Risk of GI bleeding ---SSRI may deplete Platelets (Serotonin required for aggregation) No evidence of concern from short term use (5 - 7 days)
Ibuprofen	Aspirin	Ibuprofen may block the antiplatelet action of Aspirin significance is equivocal Can be avoided with AM dose of Ibuprofen is delayed 1-2 hours following Aspirin Intake
Acetaminophen	Ethanol	Chronic use of alcohol increases likelihood of Hepatotoxicity. Reduce the daily Acetaminophen consumption from 4 grams to 2 grams

Drug-Drug Interactions- Podiatric Implications

- Phenobarbital and fluconazole cause increase of Phenobarbital levels.
- Phenytoin and fluconazole cause increase of Phenytoin levels.
- Phenobarbital and rifampin cause decrease of Phenobarbital levels.
- Lithium plus NSAIDs increase of Lithium level (toxicity)
- Oral Contraceptives and anti-infective decrease effectiveness of oral contraceptives. (controversial with no definitive studies to demonstrate contraceptive failure)

Drug-Drug Interactions

- Amiodarone with Fluconazole or Itraconazole or Ketoconazole cause increase plasma levels of Amiodarone and possible toxicity.
- Beta-Blockers and Duloxetine (Cymbalta) may cause increase of Beta Blocker plasma concentration and Hypotension and Heart Block.

Drug-Drug Interactions

- Lovastatin or Simvastatin (Zocor) with Erythromycin or Fluconazole or Itraconazole or Ketoconazole causes an increase risk of myopathy.
- Opioid Analgesics with Enzyme Inducers increase opioid elimination (decrease relief).
- Opioid Analgesics with Antimicrobials decrease opioid elimination.

Potential Drug Interactions with NSAID Analgesics

- Oral anticoagulants-
Increase oral warfarin activity
- Lithium-toxicity
- Antihypertensive agents-
Antagonized
- Digoxin-renal clearance inhibited
- Valproate with ASA
oxidation of VPA-toxicity
- Phenytoin (Ibuprofen and ASA) Increase levels.
- MTX reduce clearance
- Insulin with Salicylates-
Possible decreased hypoglycemic effect with large doses
- Cephalosporins with ASA
possible increase bleeding risk
- Probenecid with naproxen-
reduce clearance of naproxen

Drug-Drug Interactions

(Warfarin)

- Sulfamethoxazole/trimethoprim and fluconazole inhibit the metabolism of warfarin (CYP2C9) and clearance causing hypoprothrombinemia.
- Azithromycin inhibits warfarin metabolism and elevates INRs (mechanism unknown)
- Ciprofloxacin, Clarithromycin, Erythromycin, Metronidazole all increase effect of warfarin.
- Research on the role of infection and other sources of inflammation to inhibit warfarin metabolism and increase INR values.

Smoking and Drug Interactions

Clinical Base Literature

Cigarettes are Drugs

CLINICAL PHARMACOLOGY

An Appraisal of Potential Drug Interactions in Cigarette Smokers and Alcohol Drinkers

Robert G. Smith, DPM, MSc, RPh, CPed*

Background: Many health-care providers may overlook or be unaware of most drug-to-drug interactions. Recognizing the existence of drug interactions with cigarette smoking and alcohol ingestion can empower a clinician with knowledge to avoid dangerous interactions that may result in hazardous, negative patient outcomes. Cigarette smoking and alcohol use can reduce the efficiency of certain drugs or make drug therapy more unpredictable.

Methods: This review offers the physician information regarding prescription drug interactions with cigarette smoking and alcohol use. First, mechanisms found in the medical literature of potential drug interactions in cigarette smokers and alcohol drinkers are presented. Second, the 100 most frequently prescribed medications in 2006 are reviewed regarding cigarette smoking effects and alcohol effects as cited in the medical literature. Lastly, a table of these 100 medications and any reported effects of cigarette smoking or alcohol consumption on each drug is provided.

Results: The actual number of different medications reviewed was 78. Drug interactions resulting from the effects of cigarette smoking occurred with 33.3% of the drugs (n = 26), and drug interactions resulting from the effects of alcohol consumption occurred with 76.9% of the drugs (n = 60). Finally, resource information regarding smoking cessation and alcohol abuse recovery is summarized so that physicians may empower their patients to avoid potential drug-interaction events.

Conclusions: Cigarette smoke and alcohol may interact with medications through pharmacokinetic or pharmacodynamic mechanisms. Engaging in both of these social activities can reduce the efficiency of certain drugs or can make drug therapy unpredictable. This review offers the health-care provider information regarding potential prescription drug interactions. Empowered with this information, clinicians may assist their patients to maximize pharmacologic outcomes by avoiding these reported harmful interactions. (*J Am Podiatr Med Assoc* 99(1): 81-88, 2009)

The process of taking a patient's history is a very important one. A thorough, complete patient history will help a physician make an accurate diagnosis and develop a treatment plan. Part of such a treatment plan is the prescribing of medications. These decisions are made by the treating clinician who is empowered with a knowledge of pharmacology, medication adverse effects, and drug interactions. The physician realizes that the medication response is not always the same. A given medication may act differently depending on many patient factors. There is a need to explore critical elements of each patient to determine possible mechanisms for medication treatment failures and adverse effects.

Therefore, it is fundamental for a clinician to develop a solid foundation for good medical care when

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achieving health maintenance or treating an ill patient by fostering a comfortable evolving relationship between patient and physician. To facilitate this relationship, the provider should use permission-giving questions that allow the patient to "admit" something that he or she may not otherwise volunteer. This technique is especially crucial when interviewing a patient regarding their social history, particularly as it pertains to cigarette smoking and alcohol consumption. Clinicians who prescribe and dispense medications should appreciate the existence of drug-cigarette smoke interactions and drug-alcohol interactions that may result in medication treatment failures.

In 2004 in the United States, 28% of men and 19% of women surveyed admitted to being cigarette smokers.¹ According to the Centers for Disease Control and Prevention, alcohol consumption by adults 18 years and older in the United States at the end of



Tobacco and Drug Interactions (Cigarette Smoking)

- Hydrocodone/APAP- Decrease effect
- Oxycodone/APAP-Decrease effect
- Codeine/APAP-Decrease analgesic effect
- Propoxyphene/APAP- Increase doses needed because decrease analgesic effect.
- Lantus Insulin-Decrease Absorption
- Warfarin-Increased Clearance

Alcohol and Drug Interactions

- Alcohol is pharmacologically classified as a central nervous depressant.
- A drug interaction may occur when an individual combines depressant-type medications, such as tranquilizers or narcotic pain killers.
- Opioids and alcohol enhances the sedative effects of both substances, increasing the risk of death from overdose.

Alcohol and Drug Interactions

- Metronidazole inhibits alcohol dehydrogenase; causes severe alcohol intoxication reaction.
- Flushing, syncope, nausea, vomiting, chest pain, headache, tachycardia, anxiety, confusion.
- **Avoid alcohol**

Illicit and Analgesic Drug Interactions

- Marijuana as a partial cannabinoid agonist acts as CNS depressant.
- Heroin mu-opioid agonist acts and combined is additive CNS depression.
- Kratom (Mitragynine) mu-ka-opioid agonist combined is additive—to include Tramadol-CNS depression
- Phencyclidine-with Methadone and DM causes seizures

Illicit Drugs and Drug Interactions

- Cannabis Pharmacokinetic interactions because cannabinoids are highly protein bound (Warfarin) alter various serum levels
- Sedative medications may display added sedative effects when used in combination.
- Tricyclic Antidepressants display Pharmacodynamic alterations in outcome

Foods and Drug Interactions

- Potential Interactions Between Grapefruit Juice and CYP3A4 Substrates
- Diazepam-Midazolam causes increase plasma concentration; possible increase in sedation.
- Prednisone-Methylprednisolone causes increased plasma concentrations may increase risk of ADRs after consumption large amounts.

Foods and Drug Interactions

- Milk products (antacids) and Tetracyclines and Fluoroquinolones. Chelating occurs decreasing the drugs absorption.
- Caffeine and Fluoroquinolones interference with metabolism resulting in seizures.
- Linezolid is a reversible, nonselective inhibitor of monoamine oxidase. Therefore, linezolid has the potential for interaction with adrenergic and serotonergic agents, as well as with tyramine. However, no food-linezolid interaction has been reported so far.

Herbal Medication: Potential for Adverse Interactions with Analgesics

- The incidences of hepatotoxicity and nephrotoxicity may be augmented by acetaminophen when concomitantly used with the potentially hepatotoxic herbs Echinacea, kava, and herbs containing salicylate (willow, meadowsweet), respectively.
- **The concomitant use of opioid analgesics with sedative herbs: (valerian, kava, and chamomile), may lead to increase CNS depression.**
- The analgesic effect of opioids may be inhibited by ginseng.
- St John's wort greatly reduced the plasma concentration of oral oxycodone. (2010)

May Interact with NSAIDs

- Motherwort (*Lenurus cardiaca*)
- Salai guggal (gum extract of *Boswellia serrata*) Boswellic acids “active principle”
- Bromelain {Cox inhibition activity}
- Birch bark (*Betula alba*)+ {Salicylates; Cox inhibition activity}
- Barberry(*Berberis vulgaris*) {Berberine; probably COX inhibition}
- Ginkgo and NSAIDs may display additive inhibitory effects on platelet function.

Ginkgo



- Aspirin – hyphemia
- Acetaminophen - bilateral subdural hematomas
- Warfarin - intracerebral hemorrhage case but **no** effect in 2 clinical trials
- Ibuprofen -- cerebral hemorrhage
- Valproate: 2 cases of seizures
- Trazodone – case of coma with ginkgo
- Risperidone – priapism; vasodilating effect of both substances?
- Induction of CYP2C19 – clinical trial, case report. Possible/weak effects on CYPs 3A4 and 2C9

Kava (*Piper methysticum*)



- ▶ One case report of coma induced by a combination of kava and **alprazolam**-a benzodiazepine
- ▶ Extrapramidal side effects-4 cases of **dopamine** antagonism-oral, lingual and trunk dyskinesia
- ▶ Inhibition of CYP2E1 — clinical trial
- ▶ Do not combine with alcohol, sedatives, tranquilizers or CYP2E1 substrates

St John's wort



Hypericum calycinum
Clusiaceae
Gerald D. Carr

- Many drug-drug interactions via induction of CYP 450 enzymes
- P-glycoprotein (PgP): involved in multidrug resistance, acts as a pump to remove drugs from cells
 - SJW induces; thus **removes** drugs from cells
 - Also regulates MDR-1 (multidrug resistance gene) and other drug transporters

Drug Interactions with Herbal Products

- St John's wort

- Alprazolam ↓
- Oral Contraceptives ↓
- Cyclosporine (Neoral) ↓
- Digoxin ↓
- Imatinib ↓
- Indinavir ↓
- Irinotecan ↓
- Omeprazole ↓
- SSRI (Serotonin syndrome) ↓
- Verapamil ↓
- Warfarin ↓↓↓

- Ginseng

- Digoxin ↑
- MAO Inhibitors ↑ Toxicity

Energy Drinks in American

Energy drinks have no official federal definition, but they are generally thought of as beverages with caffeine and other stimulants marketed for their energizing effect.

In the U.S., 80 percent of adults consume caffeine every day, and the average adult has a daily intake of 200 mg.

Energy drink makers are required to tell the U.S. Food and Drug Administration (FDA) about any adverse events related to their products.

Data recently obtained by the Center for Science in the Public Interest (CSPI) regarding these reports show that there have been 34 deaths linked to energy drinks since 2004, with half occurring since 2012. Of these, 22 deaths were linked to 5-Hour Energy, 11 to Monster and one to Rockstar.

A recent report published by the Substance Abuse and Mental health Administration (SAMHSA) found that the number of emergency department visits involving energy drinks doubled from 10,068 visits in 2007 to 20,783 visits in 2011.

Common Energy Drink

Ingredients

- **Caffeine*** .02 percent or less of the substance in the product to be considered safe. For example, a 12 oz. drink can have 68 mg of caffeine and still meet the .02 percent limit
- **Sugar**
- **Guarana (a plant with seeds that contain Caffeine)**
- **Yerba mate**
- **Taurine**
- **L-Carnitine**
- **5-hydroxyl tryptophan**
- **Vinpocetine**
- **Yohimbine**
- **Ginseng**
- *Energy drinks typically contain 80 to 141 mg of caffeine per 8 ounces, the equivalent of five ounces of coffee or two 12-ounce cans of caffeinated soft drink such as Mountain Dew, Coca Cola, Pepsi Cola or Dr. Pepper.

Caffeine Pharmacokinetics



Rapid (t-max 30 - 120 min) and complete absorption

- Crosses freely blood-brain, placental and testicular barrier
- No specific tissue accumulation
- Main route of metabolism in humans (70-80 %): N-3 demethylation to paraxanthine (1,7-dimethylxanthine, 17X) catalyzed by cytochrome (CYP) 1A2 in the liver.

Yohimbine



- Yohimbine is an alpha-blocker. It works by increasing certain chemicals in the body, which dilate the pupils of the eye. It also dilates blood vessels and increases blood flow in the penis, which helps to improve erectile function
- Caution if have a history of heart problems, kidney problems, high blood pressure, angina (chest pain), stomach or intestinal ulcers, or liver disease

Yohimbine Drug Interactions

- Some medications are changed and broken down by the liver. Yohimbine might decrease how quickly the liver breaks down some medications
- Some medications that are changed by the liver include amitriptyline (Elavil), clozapine (Clozaril), codeine, desipramine (Norpramin), dextromethorphan, donepezil (Aricept), fentanyl (Duragesic), flecainide (Tambocor), fluoxetine (Prozac), meperidine (Demerol), methadone (Dolophine), metoprolol (Lopressor, Toprol XL), olanzapine (Zyprexa), ondansetron (Zofran), tramadol (Ultram), trazodone (Desyrel), and others.

Adverse Effects of Particular Interest with Energy Drinks

- Cardiac Instability
 - Increase Heart Rate
 - Irregular Blood Pressure
- Electrolyte Disturbances
- Diuresis
- Hyperglycemia

Surgery and Podiatric Procedures

Drug interactions and physiological reactions:

CNS herbs: potential PD interactions with anesthesia:

Valerian, kava, St. John's wort (PK interaction also), lavender, passionflower, lemon balm, ashwaganda, ginseng, ephedra). Midazolam – SJW, goldenseal and possibly ginkgo PK effects but ginkgo studies are contradictory

Blood sugar – ginseng, bitter melon, chromium, fenugreek, cinnamon

Surgery and Podiatric Procedures Considerations

Anticoagulant herbs: post-op bleeding and interaction with aspirin or other NSAIDs that may cause bleeding.

Garlic, ginger, ginkgo, ginseng, feverfew.

Angelica, asafoetida, anise, astragalus, arnica, bogbean, bromelain, borage seed, capsicum, clove, curcumin, dong quai, fenugreek, fish oil, green tea, horse chestnut, juniper, licorice, meadowsweet, onion, pau d'arco, parsley, passionflower, quassia, red clover, reishi, salvia, turmeric, willow.

*Evidence Based Recommendations
Discontinuation of Natural Products*

Stop herb, supplements, energy drinks 7-14 days prior to surgery.

Fish Oil, Glucosamine, Saw Palmetto,
Ginseng, Garlic, Chondroitin,
Milk Thistle

No Specific Recommendations

Flax Seed, Coenzyme Q-10, Green Tea

Clinical Coping

- ▶ Counteract “don’t ask-don’t tell” assist the Podiatric Physician with the following:
 - Open and nonjudgmental discussion
 - Follow up herb use found in case histories
 - Explain importance of potential interactions
- ▶ ****Avoid St John’s Wort and Warfarin Interactions****
- ▶ Be watchful for patients on complicated medical regimens. Be watchful and facilitate conversations about herbs, supplements, energy drinks and illicit drugs within the scope of the Podiatric Assistant.

Checking for Herb-Supplement- Energy Drinks-Alcohol-Drug

Interactions

- ▶ *Reference.medscape.com/drug-interaction checker*
- ▶ Natural Medicines Comprehensive Database (www.naturaldatabase.com). Subscription service.
- ▶ **National Institutes of Health Dietary Supplement Fact Sheets**
http://dietary-supplements.info.nih.gov/Health_Information/Information_About_Individual_Dietary_Supplements.aspx
- ▶ Micromedex – Altmedex. Subscription service (www.micromedex.com)

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Conclusions

- Maintain a healthy skepticism when considering statements of fact about Drug-Drug interactions-more than one view point exists, use clinical base evidence
- Exercise restraint in making dogmatic statements about the clinical importance of particular social behaviors and drug interactions, especially in relationship to clinical outcome in individual patients.
- ASA recommends that all herbal medications should be discontinued 2 to 3 weeks before an elective surgical procedure.
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