An Appraisal of Over Looked Analgesic Drug Interactions—Deadly Podiatric Implications

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Thank you

Science & Management Symposium

Learning Objectives

• Recognize the potential for Analgesic-Drug Interactions.
• List the known Analgesic-Drug Interactions as reported in the medical literature
• Recognize the main reasons for caution with prescribing Analgesic Medications and the potential of drug interactions, OTC interactions, herbal interactions, illegal drug interactions, and social behavior and possible interactions.
• Know the principles for clinical coping with Analgesic-Drug Interactions and Analgesic and Social Behaviors.
Variety of Foot Pathologies

Analgesic Prescribing in Podiatry

The unpleasant and subjective sensation resulting from a noxious sensory stimulus defines the phenomenon of pain.

The podiatric physician is no stranger to the difficulties in achieving optimal pain therapy. Podiatric physicians must develop analgesic regimens to treat patients with acute, chronic, and postoperative pain. (2006)

The topic of pain management remains a minor component of the formal education and training of residents and physicians in the United States.

Misguided attitudes concerning acute and chronic pain management, in addition to reservations about the legal aspects of pain management, often translate into a "fear of the unknown" when it comes to narcotic prescribing. (2010)

Pharmacologic Strategies

• Nonopioid Analgesics and Prostaglandin Inhibition
• Opioid Analgesics
• Adjuvant Analgesics
The U.S. Food and Drug Administration (FDA) is strengthening an existing label warning that non-aspirin nonsteroidal anti-inflammatory drugs (NSAIDs) increase the chance of a heart attack or stroke.

More than 98 million nonsteroidal anti-inflammatory drugs (NSAIDs) prescriptions in 2012.

NSAIDs have accounted more than 70 million prescriptions and 30 billion purchases. NSAIDs are also among the most inappropriate prescribed inappropriately to older Americans.

It is estimated that the United States consumes 80 percent of the global opioid supply.

According to the U.S. Food and Drug Administration (FDA), more than 50 million Americans were prescribed some type of narcotic pain medication in 2011, which represents a nearly 100 percent increase in narcotic pain medication prescriptions since 2008.
### Long-Acting Opioid Analgesics

- Avinza (Morphine ER)
- Dolorphine (Methadone)
- Embeda (Morphine/Naltrexone)
- Hysingla (Hydrocodone)
- MS Contin
- Opana (Oxymorphone)
- Targiniq (Oxycodone/Naloxone)
- Butrans (Buprenorphine transdermal)
- Duragesic
- Exalgo (Hydromorphone)
- Kadian (Morphine)
- Nucynta (Tapentadol)
- Oxycontin
- Zohydro (Hydrocodone ER)

### Patient Disclosure about Supplement 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.

### The Problem of Patient Disclosure

- Many patients do not consider herbal compounds and OTCs to be medications and **DO NOT** convey use of these agents at the time of surgery
- Belief that herbs are natural and must be entirely safe or OTCs cannot harm *Energy Drinks contain Herbal Supplements*
- Fear how the healthcare provider would respond to self-medication of social behaviors
- Fear that their physician may be prejudice
Evidence for Drug Interactions

- Case reports
- Lab studies
  - Define mechanisms
    - Recent interest in CYP450 induction
    - Not necessarily borne out in trials
    - Pharmacovigilance 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

Medical Practice Implications

- Patient-physician communication is of pivotal importance in medical practice, and the use of OTCs, Herbs, Energy Drinks, and Social Behaviors are important topics of conversation.
- Kaye et al. found that more than 70% of patients failed to disclose their herbal medicines during preoperative assessment.
- “don’t ask-don’t tell”

Potential Drug Interactions with NSAID Analgesics

- Oral anticoagulants:
  - Increase oral warfarin activity
- Lithium-toxicity
- Antihypertensive agents:
  - Antagonized
- Digital-nephrocis clearance
- Valproate with ASA
- Oxidation of VPA-toxicity
- 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
### Analgesic Drug Interaction Chart

<table>
<thead>
<tr>
<th>Prescribed Drug</th>
<th>Drugs Involved with Drug Interaction</th>
<th>Explanation of Drug Interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>NSAIDS</td>
<td>Antihypertensive Drugs</td>
<td>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.</td>
</tr>
<tr>
<td></td>
<td>Warfarin (Coumadin)</td>
<td>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.</td>
</tr>
<tr>
<td></td>
<td>Bisphosphonates (Fosmax)</td>
<td>NSAIDs enhance GI toxicity of Bisphosphonates used for Osteoporosis. No concern if NSAIDs used short term (5-7 days).</td>
</tr>
<tr>
<td></td>
<td>Methotrexate (Rheumatrex)</td>
<td>Increase serum levels of Methotrexate leading to systemic toxicity (Stomatitis).</td>
</tr>
<tr>
<td></td>
<td>Lithium</td>
<td>Lithium excretion is reduced and blood toxicity may develop in 5 to 10 days of NSAID therapy.</td>
</tr>
<tr>
<td></td>
<td>SSRIs Antidepressants</td>
<td>Enhance Risk of GI bleeding — SSRI may deplete platelets (Serotonin required for aggregation). No evidence of concern from short term use (5-7 days).</td>
</tr>
<tr>
<td></td>
<td>Ibuprofen Aspirin</td>
<td>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.</td>
</tr>
<tr>
<td></td>
<td>Acetaminophen Ethanol</td>
<td>Chronic use of alcohol increases likelihood of Hepatotoxicity. Reduce the daily Acetaminophen consumption from 4 grams to 2 grams.</td>
</tr>
<tr>
<td></td>
<td>Carbamazepine (Tegretol)</td>
<td>Increased metabolism of acetaminophen decreasing analgesic effect of Acetaminophen.</td>
</tr>
<tr>
<td></td>
<td>Phenytoin (Dilantin)</td>
<td>Increasing metabolites that are hepatotoxic.</td>
</tr>
<tr>
<td></td>
<td>Opioids Sedatives - Anxiolytics</td>
<td>Profound sedation and respiratory depression may occur with any class of drug with sedative effect.</td>
</tr>
<tr>
<td></td>
<td>Codeine or Hydrocodone SSRIs Antidepressants</td>
<td>These medications inhibit the prodrug conversion to active morphine derivative; thus decrease Bupropion and reduce analgesic effect.</td>
</tr>
<tr>
<td></td>
<td>Meperidine MAO Inhibitors</td>
<td>Mechanism of interaction is unclear, but hypertensive crisis, seizures, coma have been reported with this combination.</td>
</tr>
<tr>
<td></td>
<td>Tapentadol MAO Inhibitors</td>
<td>Contraindicated.</td>
</tr>
</tbody>
</table>

### Smoking Overview

- Nearly 18 of every 100 U.S. adults aged 18 years or older (17.8%) currently smoke cigarettes. This means an estimated 42.1 million adults in the United States currently smoke cigarettes.
- Cigarette smoking is the leading cause of preventable disease and death in the United States, accounting for more than 480,000 deaths every year, or 1 of every 5 deaths.
- More than 16 million Americans live with a smoking-related disease.
- Current smoking has declined from nearly 21 of every 100 adults (20.9%) in 2005 to nearly 18 of every 100 adults (17.8%) in 2013.

### Appraisal of Potential Drug Interactions

- Recognizing the existence of drug interactions with cigarette smoking can empower a clinician with knowledge to avoid dangerous interactions that may result in hazardous, negative patient outcomes.
- Cigarette smoking use can reduce the efficiency of certain drugs or make drug therapy more unpredictable.
Smoking and Drug Interactions

Clinical Base Literature

Cigarettes are Drugs

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 Consumption

Prevalence of Drinking: According to the 2015 National Survey on Drug Use and Health (NSDUH), 86.4 percent of people ages 18 or older reported that they drank alcohol at some point in their lifetime; 56.0 percent reported that they drank in the past year; 56.0 percent reported that they drank in the past month.

Prevalence of Binge Drinking and Heavy Alcohol Use: In 2015, 26.9 percent of people ages 18 or older reported that they engaged in binge drinking in the past month; 7.0 percent reported that they engaged in heavy alcohol use in the past month. (See sidebar below for definitions of binge drinking and heavy alcohol use.)

In 2013, of the 72,559 liver disease deaths among individuals ages 12 and older, 45.8 percent involved alcohol. Among males, 48.5 percent of the 46,368 liver disease deaths involved alcohol. Among females, 41.8 percent of the 26,191 liver disease deaths involved alcohol.
Alcohol and Analgesic 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 enhance the sedative effects of both substances, increasing the risk of death from overdose.

Alcohol and Analgesic Drug Interactions

- Alcohol beverages or medications containing alcohol may result in rapid release and absorption of long acting opioids.
- P-gP inhibitors (quinidine) may increase absorption and exposure of morphine.

Illicit Drug Use In United States

- Prevalence: Percent of persons 12 years of age and over with any illicit drug use in the past month: 10.2% (2014)
- Percent of persons 12 years of age and over with any nonmedical use of a psychotherapeutic drug in the past month: 2.5% (2014)
- From 2000 through 2013, the age-adjusted rate for drug-poisoning deaths involving heroin nearly quadrupled from 0.7 deaths per 100,000 in 2000 to 2.7 deaths per 100,000 in 2013. Most of the increase occurred after 2010.
- The number of drug-poisoning deaths involving heroin was nearly four times higher for men (6,525 deaths) than women (1,732 deaths) in 2013.
- Marijuana is the most commonly used illicit drug (22.2 million people have used it in the past month) according to the 2015 National Survey on Drug Use and Health. Its use is more prevalent among men than women—a gender gap that widened in the years 2007 to 2014.
**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

**Herbal Use Among Americans**

Herbal medicine, also called botanical medicine or phytomedicine, refers to using a plant's seeds, berries, roots, leaves, bark, or flowers for medicinal purposes. An herb is a plant or plant part used for its scent, flavor, or therapeutic properties. Herbal medicines are one type of dietary supplement.

In December 2008, the National Center for Complementary and Integrative Health (NCCIH) and the National Center for Health Statistics (part of the Centers for Disease Control and Prevention) released new findings on Americans' use of complementary and alternative medicine (CAM).

The findings are from the 2007 National Health Interview Survey (NHIS), an annual in-person survey of Americans regarding their health- and illness-related experiences. The CAM section gathered information on 23,939 adults aged 18 years or older and 9,417 children aged 17 years and under.

**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.

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 – hyphema
- Warfarin – bilateral subdural 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 CYP3A4 and 2C9

Kava (Piper methysticum)

- One case report of coma induced by a combination of kava and alprazolam-a benzodiazepine
- Extrapyramidal 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

- 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
- Isoniazid
- Omeprazole
- SSRI (Serotonin syndrome)
- Varenicline
- Warfarin
- Ginseng
- Dugoxin
- MAO Inhibitors
- Toxicity

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**Prevalence of Energy Drink Use by Americans**

Energy drink consumption has continued to gain popularity since the 1997 debut of Red Bull, the current leader in the energy drink market. More than 500 new energy drinks were launched worldwide in 2006 and beverage companies are reaping the financial rewards of the 5.7 billion dollar energy drink industry.

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.

Energy drinks are targeted to the 18 to 35 year old consumer.

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**Energy Drinks in America**

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 in 2007 to 20,783 visits in 2011.
Common Energy Drink Ingredients

- Caffeine* 0.02 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), furosemide (Lasix), 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

Adjuvant Analgesics

• Multiple types of pain syndromes: Corticosteroids, TCAs, SSRI/SNRIs, alpha-2-adrenergic agonists (clonidine), Topical therapy (Local anesthetics).
• Neuropathic pain: Antiepileptics, NMDA receptor antagonists-Memantine, Ketamine, Dextromethorphan, Oral Na+ channel blockers, Baclofen, Calcitonin.
• Complex regional pain syndrome: Calcitonin, Clonidine, and Prazosin.
• Bone pain from cancer: Bisphosphonates, Calcitonin, Radiopharmaceuticals.
Clinical Coping

► Counteract “don’t ask–don’t tell”
  – 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

► Patients on complicated medical regimens should avoid herbs, supplements, energy drinks and illicit drugs unless carefully screened/supervised, but prioritize analgesic drugs that may have a narrow therapeutic index

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, Chondronitin,
Milk Thistle

No Specific Recommendations
Flax Seed, Coenzyme Q-10, Green Tea

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

► medscape.com/drug-interaction checker

► Natural Medicines Comprehensive Database (www.naturaldatabase.com). Subscription service.

► National Institutes of Health Dietary Supplement Fact Sheets

► MicroMedex – Altmedex. Subscription service (www.micromedex.com)
References


References


References

**Conclusions**

- Maintain a healthy skepticism when considering statements of fact about analgesic drug interactions—more than one viewpoint exists, use clinical base evidence.
- Exercise restraint in making dogmatic statements about the clinical importance of particular analgesic-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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