DRUG-SUPPLEMENT INTERACTIONS AND NUTRIENT DEPLETIONS

Awareness of Drug-Supplement Interactions and Nutrient Depletions with Common Medications

Samuel Mathis, MD
Assistant Professor
UTMB Health
Disclosure

- Dr. Mathis has disclosed that he has no actual or potential conflict of interest in relation to this topic.
Goals

By the end of this activity, participants should be better able to:

1. Review the mechanisms of drug-nutrient interactions and drug-nutrient depletions.
2. Discuss various drug nutrient interactions.
3. Explore possible drug nutrient depletions.
4. Increase the frequency of physician-patient dietary supplement discussions during office visits and utilize discussions with patients due to non-disclosure of supplements.
Audience Question 1

What percentage of U.S. adults with chronic disease use dietary supplements?

1. 0-20%
2. 20-40%
3. 40-60%
4. 60-80%
Why is this important?

- ~50% of adult patients use dietary supplements
- 25% of patient’s do not inform their physician of their supplement use.\(^1\)
- Missing the main ingredient\(^2\)
  - *No FDA testing requirements*\(^3\)
  - *Mixed with medications/supplements*
  - *Label does not have to be true*
- Lack of solid research
  - *Mostly case reports on adverse reactions*
  - *No RCTs*
Understanding Drug-Supplement Interactions

■ Pharmacodynamics:
  – Synergistic vs. Antagonistic interactions
  – Either increases or diminished the effect

■ Pharmacokinetic\(^6\)
  – Absorption
  – Distribution
  – Metabolism
  – Excretion
Audience Question 2

Mrs. Smith is a 67 y/o female with PMH of HTN, HLD, DM 2 that is controlled with rosvuastatin, lisinopril, and metformin. She reports that she does take some supplements and has recently started a new grapefruit juice protocol she heard about from a TV doctor. Since starting juicing she has noted increased muscle cramps and wants to stop her statin because her friend said that they cause muscle cramps. You inform her that the juice is likely causing this reaction through what pathway?

1. CYP450 3A4 enzyme blockage in the liver decreasing metabolism of the statin
2. CYP450 3A4 enzyme blockage in the intestines causing increased absorption of statin
3. Mercaptan competitively preferentially cleared by renal tubules, decreasing excretion of statin
4. The grapefruit juice tasted so good she forgot she took her medicine and has been taking an extra dose
Grapefruit

- Most studied dietary supplement
- Interacts on CYP450 3A4 in the intestines.
- Interactions:
  - Calcium Channel Blockers
  - Angiotensin II Receptor Blockers
  - Beta Blockers
  - Antiarrhythmics
  - Anti-cancer agents
  - Statins

- Use it to our benefit?
  - Increases simvastatin/lovastatin levels by 260%
Foods:

- **Food as Medicine**
- Numerous Food/Drug interaction possibilities\(^7\)
  - *Milk*: Ca\(^{2+}\) & Casein bind with tetracyclines and fluoroquinolones to reduce amount absorbed.\(^8\)
  - *Dark Leafy Greens*:
    - Potassium – Increased concentrations if taken with ACE Inhibitors
    - Vitamin K – Decreased INR with Warfarin
  - *Tyramine containing foods (matured cheese, red wine, yogurt, salami)*
    - Hypertensive crises if taken with MAOIs.
Coca-Cola

- Increased max concentration of ibuprofen if taken with Coca-Cola.\textsuperscript{10}
- Recommend decrease amount or frequency of ibuprofen
- Study in rabbits
## Warfarin

### Increase INR

- Acarbose
- Allopurinol
- Antibiotics
- Levothyroxine
- **Vitamin E**
- Statins
- SSRI Antidepressants
- Antipsychotics
- Diabetes medications
- Influenza vaccine
- EtOH

### Decrease INR

- Barbiturates
- Phenobarbital
- Phenytoin
- Rifampin
- **St. John’s Wort**
- Azathioprine
- Carbamazepine
- Coenzyme Q10
- Colestipol
- Estrogens
- Green Tea
- Ginseng

**Note:**
- **Acarbose**: Metformin and other diabetes medications may increase or decrease INR depending on the dosage and individual response.
- **St. John’s Wort**: Can significantly alter INR, requiring close monitoring.
- **Ginseng**: May increase INR, but its effect can vary widely among individuals.
Mrs. Smith returns to you a few months later complaining of depressive symptoms. PHQ-9 score is 21 and she reports this is having significant impact on her competitive ballroom dancing. You recommend starting an antidepressant, which she is open to, but she suddenly remembers some integrative therapies she has read about that may also help. Which of the following IS NOT an appropriate adjunctive to her SSRI?

1. Regular exercise and a healthy diet
2. Adding 3,000mg of Fish oil daily
3. Adding 300mg St. John’s Wort daily
4. Visiting her local acupuncturist for relaxation therapy
St. John’s Wort (*Hypericum Perforatum*)

- Natural antidepressant
- Induces CYP3A4 and P-glycoprotein\textsuperscript{11}
- Few case studies showing serotonin syndrome if taken with SSRIs\textsuperscript{12}
- May cause decreased absorption of digoxin
- Breakthrough bleeding with oral contraceptives
- High doses to cause interaction\textsuperscript{13}
- Avoid concurrent use with prescription and OTC medications
- May worsen photosensitivity with antibiotics
Ginseng (American/Asian)

- American Ginseng (panax quinquefolius)
  - May cause small decrease in INR.

- Asian Ginseng (panax ginseng)\textsuperscript{11, 12}
  - Root used for concentration, mood, memory, general well-being.
  - Induce CYP3A4: Decrease CCB, chemo, HIV, statins, and antidepressant medications
  - Warfarin: Decreased INR\textsuperscript{13}
  - Phenelzine (MAOI): Mania,\textsuperscript{14} headache, tremors
  - Alcohol: Increased clearance in mice.\textsuperscript{12}
Goldenseal

- Used for URIs, UTIs, allergies, bleeding, infections, fatigue, etc.
- No great human trials for interactions
- Known to inhibit CYP2D6 & CYP3A4\(^{11}\)
  - Responsible for over half of all metabolized drugs
- Recommend against use as no good trials for or against it
Ginkgo Biloba

- Used for: Improved cognition, blood flow
- No obvious interactions with metabolism
- Interactions
  - ASA, warfarin, anticoagulants: Increased bleeding (case studies)\(^{11}\)
  - Thiazides: One case of elevated BP\(^{12}\)
- Caution if taking other supplements or medications with antiplatelet or anticoagulant effects
Green Tea Extract

- “Jesus and Green Tea”
- Conflicting results In vitro vs. human clinical trials
- May inhibit drug transporters\textsuperscript{11}
  - $OATP1A1/OATP1A2$
  - Involved in transport of statins, fluoroquinolones, beta blockers, antiretrovirals
- Green Tea vs. Extract
Milk Thistle (Silybum Marianum)

- Used to help boost liver function
- CYP2C9
  - *Involved with losartan, warfarin, phenytoin, diazepam*
  - *Depends on individuals genotype*¹⁵
Low Risk Supplements

- Cranberry
- Black Cohosh
- Curcumin
- Saw Palmetto
- Valerian\textsuperscript{11}
Drug Nutrient Depletions
Mrs. Smith comes to see you with a new complaint of fatigue. She reports that 2 months ago, her GI started her on a medication for her reflux. On physical exam, she appears slightly pale which prompts a CBC. Her CBC shows WBC 6.8 x10^9L, Hgb of 10.4g/dL, Hct 30.3% with an MCV of 115, PLT 165,000/mcL. You suspect the anemia is caused by what nutritional deficiency?

1. Vitamin B12 deficiency caused by proton pump inhibitor use
2. Iron deficiency caused by H2 Blocker use
3. CoQ10 deficiency caused by Bismuth subsalicylate
4. Copper deficiency caused by a zinc deficiency from proton pump inhibitor use
Acid Suppressing Medications

- **H2 Antagonists**\(^{21}\)
  - *Deplete calcium, iron, zinc, folic acid, vitamin D, vitamin B12*
  - *Recommended supplementation:*
    - Calcium citrate: 500mg/day
    - Folic Acid: 400mcg/day

- **Proton Pump Inhibitors**\(^{18}\)
  - *Deplete vitamin B12, magnesium*
  - *Recommended supplementation*
    - Vitamin B12: 25-400mcg/day
    - Magnesium: 250-400mg/day
Antihypertensives

- **Angiotensin Converting Enzyme Inhibitors**
  - *Depletes Zinc*\(^{19}\)
  - *Recommended supplementation*
    - Zinc: <30mg/day

- **Calcium Channel Blockers/ Thiazides**
  - *Deplete Potassium*
  - *Recommended supplementation*
    - Potassium: <100mg/day

- **Beta Blockers**
  - *Deplete CoQ10*
  - *Recommended supplementation*
    - CoQ10: 100-200mg/day
Diuretics

- **Loop Diuretics**
  - Depletes magnesium, potassium, zinc
  - Recommended supplementation
    - Magnesium: 250mg/day
    - Potassium: <100mg/day
    - Zinc: <30mg/day

- **Potassium-sparing diuretics**
  - Depletes folic acid
  - Recommended supplementation
    - Folic Acid: 400mcg/day
Hormonal Agents

- Contraceptives & Hormone replacement therapy (Estrogens)\textsuperscript{20}
  - *Depletes vitamin B6, folic acid, magnesium*
  - *Recommended supplementation*
    - Vitamin B6: 5mg/day
    - Folic Acid: 400mcg/day
    - Magnesium: 250-400mg/day
Psychotropics

- **SSRIs**
  - Deplete Folic Acid
  - Recommended supplementation
    - Folic Acid: 400mcg/day

- **Benzos**
  - Depletes Calcium and melatonin
  - Recommended supplementation
    - Calcium: 500-1000mg/day divided dosing

- **Antipsychotics**
  - Depletes Vitamin B2 (riboflavin)
  - Recommended supplementation
    - Multivitamin: 1/day
    - B-complex: 1/day
Audience Question 5

What supplement is recommended for all patients taking competitive inhibitors of the HMG-CoA reductase?

1. Turmeric
2. Fish Oil
3. Zinc
4. Coenzyme Q 10
Cardiac

- **Statins**\(^\text{17}\)
  - *Deplete Coenzyme Q 10*
  - *Recommended supplementation*
    - CoQ10: 100-200mg/day

- **Digoxin**
  - *Depletes calcium, magnesium, phosphorus, vitamin B1 (thiamin), potassium*
  - *Recommended supplementation*
    - Calcium: 500-1000mg/day
      - *High Calcium* → toxic reaction to digoxin
      - *Low Calcium* → interference with digoxin’s function
    - Magnesium: 250-400mg/day
    - B-complex
    - Potassium: <100mg/day
Antibiotics

- **Antibiotics**
  - Deplete folic acid, vitamin B1, vitamin B2, vitamin B6, vitamin B12, calcium, magnesium, potassium, Vitamin K
  - **Recommended supplementation**
    - B-Complex
    - Calcium: 500-1000mg/day
    - Magnesium: 250-400mg/day

- **Caution**
  - Many supplements can interfere with absorption of antibiotics.
  - Hold or take them separately
Rules for Supplements

- Best way to get nutrition is through healthy diet

- “Eat food, not too much, mostly plants.” – Michael Pollan

- Less is best
  - 3-5 supplements, no more than 10

- Consumerlab.com
  - ~$50/year

- Natural Medicines Database

- Be open
How to Talk to Patients

- “Are you taking any herbal products, supplements, or other natural remedies?”
- “Have you used any herbal products or supplements recently?”
- “Do you use any natural or nutritional supplements?”

- No judgement!
References