Food, Supplement and Drug Interactions

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Disclosure

• Tieraona Low Dog, MD has nothing to disclose.

• This talk will not discuss off-label and/or investigational use of pharmaceuticals or devices not yet approved by the FDA.

Objectives

• Participants will be aware of the complex underlying mechanisms responsible for drug-food-supplement interactions.

• Participants will be able to identify five potential food, supplement and drug interactions/nutrient depletions and how they can affect clinical outcomes.

Key Points

• Drugs may alter nutrient intake, digestion, availability, absorption, storage, metabolism, and excretion.

• A drug interaction occurs when either the pharmacokinetics or pharmacodynamics of one drug is altered by the administration of food, a dietary supplement or another drug.

• Drug interactions can be difficult to predict given the complex underlying mechanism of metabolism and excretion.

“Variability is the law of life, and as no two faces are the same, so no two bodies are alike, and no two individuals react alike and behave alike under the abnormal conditions which we know as disease...”

Sir William Osler (1849-1919)
Examples Drug-Drug Contraindications

- Ketorolac with NSAIDs
  - Can increase GI and renal toxicity
- Cidofovir with liposomal foscarin
  - Increases risk of nephrotoxicity
- Monoamine oxidase inhibitors with serotonergic agents
  - Increases the risk of serotonin syndrome (14-day washout)
- Simvastatin, lovastatin, atorvastatin with itraconazole and ritonavir
  - Increases risk of myotoxicity
- Sildenafil with nitrates
  - Risk of severe hypotension

Examples Drug-Supplement Interactions

- Potassium and potassium sparing diuretics, NSAIDs, ACE inhibitors, caution beta blockers
  - Risk of hyperkalemia and renal toxicity
- Zinc, Mg, Ca and tetracycline drugs (not doxycycline)
  - Chelation reduces absorption of both, separate intake or discontinue during short-term therapy
- Calcium and levothyroxine
  - Chelation reduces absorption of both, separate intake (am/pm dosing)

Juice and Drug Interactions

- Cranberry juice does NOT interact with warfarin in human studies.
- Grapefruit juice DOES interact with numerous drugs in human studies, some clinically relevant
  - Carbamazepine, pimozide, anti-arrhythmics, calcium channel blockers, lovastatin, simvastatin and atorvastatin, cisapride, tacrolimus, PDE-5 inhibitors

Tremendous Variability

- Same dose does not produce same concentration in each person
- Factors that can alter pharmacokinetic activity
  - Drug-drug interactions
  - Drug-food interactions
  - Drug-supplement interactions
  - Drug-disease interaction (altered GI, renal and/or hepatic function)
  - Pregnancy
  - Genetic variations

Most common metabolic proteins responsible for the breakdown of xenobiotics are cytochrome P450 (CYP) enzymes and most common protein responsible for transport is P-glycoprotein (Pgp).
Pharmacogenomics

Pharmacogenomics is the study of how genes affect a person's response to drugs. This relatively new field combines pharmacology and genomics to develop effective, safe medications and doses that will be tailored to a person's genetic makeup.

- It can be difficult to predict who will benefit from a medication, who will not respond at all, and who will experience negative side effects.

Pharmacogenomics

Pharmacogenomic information is contained in about 10% of labels for FDA approved drugs.

- CYP2C19 – poor metabolizers have diminished response to clopidogrel (Plavix)
- CYP2C9 – poor metabolizers caution with celecoxib (Celebrex)
- CYP2C9*2 or CYP2C9*3 alleles – increased risk of bleeding with warfarin (Coumadin)
- CYP2D6*2x2 – ultra metabolizers convert codeine to active metabolite morphine, more rapidly and completely than others – can experience overdose on typical dose.

www.fda.gov/Drugs/ScienceResearch/ResearchAreas/Pharmacogenetics/ucm083378.htm
**Warfarin**

- Mayo – first prospective study reported hospitalization rates for patients taking warfarin dropped 30% when genetic information was available to doctors when prescribing the drug.

  *Presented at the American College of Cardiology’s 33rd annual scientific session*

- In 2010, the AMA recommended to Centers for Medicare & Medicaid Services (CMS) to establish CPT codes and reimbursement schedules which can be applied to pharmacogenetic diagnostics, especially warfarin.

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**CYP2D6**

- 7-14% of population has slow acting form; 7% super-fast form.

- 35% are carriers of a non-functional CYP2D6 allele, elevating the risk of ADRs when taking multiple drugs.

- Drugs metabolized by CYP2D6 include fluoxetine, paroxetine, venlafaxine, hydrocodone, amitriptyline, haloperidol, endosetron, metoprolol, cimetidine and tamoxifen.

- CYP2D6 responsible for activating prodrug codeine and other opioids into active forms. The analgesic activity of these drugs are therefore reduced or absent in poor metabolizers of CYP2D6.

- Women who are PM do not effectively convert prodrug tamoxifen to active metabolites and are at higher risk for RELAPSE than normal metabolizers.

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**Strong Inhibitors: CYP2D6**

- SSRIs
  - Citalopram (Celexa)
  - Fluoxetine (Prozac, Serafem)
  - Paroxetine (Paxil, Aropax)

- Other
  - Bupropion (Wellbutrin, Zyban)
  - Duloxetine (Cymbalta)
  - Terbinafine (Lamisil antifungal)
  - Quinidine (class 1 antiarrhythmic)
  - MDMA (Ecstasy)
  - Resveratrol

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**CYP phenotypic indices before and after 4 wk of daily resveratrol administration (1 g QD)**

*Chow, et al. Cancer Prev Res; 3(9) September 2010*
What About Drug Induced Nutrient Deficiencies?

- Drug-induced nutrient deficiencies are an important yet poorly appreciated category of adverse drug reactions.
- Some drugs may cause marginal nutrient deficiencies with serious consequences.
- The major risk factors for developing a drug induced nutrient deficiency is the lack of awareness by the prescribing clinician and long duration of drug therapy.

Folic Acid

- Methotrexate, pyrimethamine, pentamidine, triamterene
  - Decreased availability folate - inhibition of dihydrofolate reductase
  - Supplement with 1 mg per day (monitor)
- Sulfasalazine
  - Impaired metabolism and absorption of intestinal folate
  - Supplement with 400 - 1000 mcg per day (monitor)
- Phenytoin
  - Phenytoin can lower serum folate. Folic acid in doses of 1 mg/d or higher can lower serum levels of drug, so monitor closely.

Isoniazid

- Increased urinary excretion of pyridoxine complexed with INH
- Competitive inhibition of pyridoxal phosphate
- Impaired niacin synthesis secondary to pyridoxine deficiency
- Pyridoxine (10-50 mg/d) and niacin supplements (50-100 mg/d) during chronic therapy with INH
- Monitor 25(OH)D levels

Statins + Carnitine

- Statins have neutral effect on lipoprotein (a).
- 2000 mg/d oral L-carnitine significantly reduces Lp(a) levels, particularly in patients with type 2 diabetes.
- Statin + carnitine superior to statin monotherapy

Cardiovascular Medicines

- Thiazides and ACEI/ARB can cause excessive urinary zinc loss and zinc depletion. May explain altered sense of taste.
  - Four weeks of lisartan at 50 mg/d induced zinc deficiency in patients with hypertension. The addition of 12.5 mg/d thiazide had additive effect for zinc loss.
  - Captopril and enalapril caused significant reduction in intramonomocytic zinc levels after 6 months treatment, however, only captopril caused significant excretion of urinary zinc.

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Monitor

- Watch for signs of zinc deficiency
  - Fatigue, muscle pain, depressed mood, rough skin, inflammatory acne, increased incidence of infection, poor wound healing, reduced taste, etc
- Lab tests are often unreliable.
- If supplementing with zinc (15-30 mg/d), administer with low-dose copper (1.0-1.5 mg/d).

Diuretics

<table>
<thead>
<tr>
<th>Drug Category</th>
<th>Nutrient Depletion</th>
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</thead>
<tbody>
<tr>
<td>Loop diuretics</td>
<td>Calcium, magnesium, potassium, thiamine, vitamin B6 and vitamin C</td>
</tr>
<tr>
<td>Potassium sparing diuretics</td>
<td>Calcium, folic acid, zinc</td>
</tr>
<tr>
<td>Thiazide diuretics</td>
<td>Magnesium, potassium, zinc, coenzyme Q10</td>
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</tbody>
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Clinically significant:
- Potassium sparing diuretics increase risk for hyperkalemia and cause loss of calcium, folic acid and zinc.
- Thiazides and loop diuretics cause dramatic loss of magnesium, which can adversely impact blood pressure, glucose control and heart rhythm.
- Thiazides cause retention of calcium, cautious with supplementation.

Chronic Use of Loop Diuretics

- Nutrient depletion of thiamine can worsen heart failure with long-term use of loop diuretics
  - Supplement 100 mg/d if on high-dose loop diuretics to improve hemodynamic function. Can monitor erythrocyte transketolase activity.
  - Magnesium: supplement 300-600 mg/d if renal function okay.
  - Monitor serum magnesium or erythrocyte magnesium periodically.
  - Calcium: supplement aggressively if hypocalcemia is suspected of aggravating heart failure.
  - HOWEVER, calcium supplementation + digoxin can increase cardiac arrhythmias in CHF.
  - Potassium: monitor every 2-4 weeks until stable and if dose changes, if stable check every 2-4 months.

Thiazides, Magnesium and Calcium

- 242 healthy individuals given 50 mg/d hydrochlorothiazide for 1-3 weeks.
  - Roughly 20% developed hypomagnesemia.
- Calcium supplementation + thiazides can increase risk for hypercalcemia.

Calcium

- Glucocorticoids
  - Calcium malabsorption and calciuria
- Diuretics (loop diuretics)
  - Increased urinary calcium excretion
- Ensure adequate calcium and vitamin D intake

Seizure Medications and Vitamin D

- Phenytoin, phenobarbital, carbamazepine, valproate
  - Increased metabolism of vitamin D to inactive metabolites
  - Increased risk of osteoporosis and fracture.
  - Monitor vitamin D levels

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### Ulcer/GERD Medications

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<tr>
<td>Proton pump inhibitors</td>
<td>Magnesium, iron, calcium, vitamin B12, folic acid</td>
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<tr>
<td></td>
<td>vitamin C, vitamin D (?), zinc, vitamin A (?), vitamin</td>
</tr>
<tr>
<td></td>
<td>E (7)</td>
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<tr>
<td>H2 antagonists</td>
<td>folic acid</td>
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</tbody>
</table>

- There were 118.5 million prescriptions for PPIs in 2010 with roughly $11.4 billion in sales. These numbers do not include over-the-counter sales for PPIs.
- Magnesium is essential for the regulation of fluid balance, bone health, and nerve function.
- Magnesium has anti-arrhythmic properties.
- Nurses Health Study (88,375 women) found that for every 0.25-mg/dL increment in plasma magnesium — there was a 41% lower risk of sudden cardiac death. Chiuve, et al. Am J Clin Nutr. 2011;94(2):253-60.

### FDA Safety Advisory March 2, 2011

- FDA issued a MedWatch warning and label change for PPIs due to low magnesium levels associated with long-term use.
- "Those taking medications, generally more than one year, may end up with low magnesium, which can put them at risk for seizures, irregular heartbeats, and muscle spasms.
- "In approximately one-quarter of the cases reviewed, magnesium supplementation did not improve low serum magnesium levels and PPI had to be discontinued.
- "Check magnesium levels before and periodically during treatment."


### Magnesium & Sudden Cardiac Death

- Magnesium has anti-arrhythmic properties.
- Nurses Health Study (88,375 women) found that for every 0.25-mg/dL increment in plasma magnesium — there was a 41% lower risk of sudden cardiac death.


### CARDIA Trial

- NIH funded 20 year study of 4,497 Americans (18–30 years old) with no diabetes at baseline were prospectively examined for incident diabetes based on quintiles of magnesium intake.
- Magnesium favorably effects inflammation and insulin resistance and reduces onset of diabetes.
- Study found that magnesium intake was inversely associated with inflammatory markers (hs-CRP, IL-6, fibrinogen) and fasting insulin levels.


### PPI and Fracture

- FDA reviewed seven published studies, six of which reported an increased risk of fractures of the hip, wrist, and spine with the use of PPIs.
- FDA concluded patients at highest risk for fractures are those taking high doses of prescription PPIs and/or taking PPI for one year or more.
- Prescription PPI label now required to include warning.
- "Observational study showed current PPI use increased fracture in patients on bisphosphonates. "Reasonable grounds for discouraging the use of PPIs to control upper gastrointestinal tract complaints in patients treated with oral bisphosphonates.""


**PPI and Iron**

- PPI reduces absorption of non-heme iron. Gastric HCl acts to promote optimum absorption by reducing ferric iron to the more soluble ferrous form. Gastric pH < 2.5 needed to solubilize and absorb non-heme iron.
- High gastric pH may also retard clinical response to iron supplementation.


**Diabetic Medications**

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<tr>
<td>Sulfonylureas</td>
<td>Coenzyme Q10</td>
</tr>
<tr>
<td>Biguanides</td>
<td>Folic acid, vitamin B12</td>
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- Chronic metformin use results in vitamin B12 deficiency in 30% of patients.
- Diabetics taking metformin had half the serum levels of vitamin B12 of those not taking metformin; 31% had levels significantly below normal. They also had more advanced neuropathy.

Bell DS. South Med J 2010 Mar;103(3):265-7

**Proton Pump Inhibitors - Iron**

- 98 patients on chronic PPI therapy, at baseline, demographics and hematologic indices similar to controls.
- After adjusting for confounders odds ratio of decreasing hemoglobin by 1 g/dl was 5.03 and decreasing hematocrit by 3% was 5.46.


- 50 patients on omeprazole for 4 years with Fe-deficiency anemia (no blood loss, no chronic disease) at 3 months follow-up on ferrous sulfate.
- Only 16% had normal response with Hgb levels (rise of >2 g/dl)
- Iron-deficient patients taking PPIs may have to be treated with high dose iron therapy or intravenous iron therapy.

Aphra JH H, et al. Am J Ther 2010; Dec 3

**Vitamin B12**

- According to the Institute of Medicine:
  - “Since 10 - 30% of older people may malabsorb food-bound B12, it is advisable for those older than 50 to meet their RDA (2.4 mcg) mainly by consuming foods fortified with B12 or by taking a B12-containing supplement.”
  - B12 levels checked every 5 years starting at age 50 - serum level = 350 pg/ml
  - Can check methylmalonic acid if equivocal B12 levels

**Take Home Messages**

- Tremendous variability in an individual’s ability to metabolize medication.
  - Age, renal/hepatic/GI illness, pregnancy
- Dietary supplements can interact with CYP450 enzymes and/or p-glycoprotein and adversely affect metabolism of medication.
  - Difficult to predict – monitor closely.
- Numerous drugs are associated with loss of micronutrients, which can be clinically significant.
  - Supplement when appropriate, monitor when necessary and stay on top of drug information data for those you typically prescribe.

Resource:
- Herb, Nutrient, and Drug Interactions: Clinical Implications and Therapeutic Strategies; Stargrove M, McKee D, Treasure J.
- Herb-Drug Interactions in Oncology, 2nd edition, Cassileth B, Yeung KS, Gubili J.
- Pharmacogenomics and Personalized Medicine, Cohen, N [Ed]
- http://medicine.iupui.edu/clinpharm/ddis/ClinicalTable.asp
- The National Institute of General Medical Sciences: www.nigms.nih.gov/Initiatives/PGRN/Background/pgrn_faq.htm