Dangerous Liaisons:
Drug-drug, drug-nutrient interactions
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Disclosure
• No real or potential conflict of interest to disclose
• No off-label, experimental or investigational use of drugs or devices will be presented.

Objectives
• Having completed the learning activities, the participant will be able to:
  – Identify mechanisms of common drug-drug, drug-nutrient interactions.
  – Describe commonly encountered and potential hazardous drug-drug, drug-nutrient interactions.
  – Develop strategies to avoid the above-mentioned interactions.

How do drug interactions occur?
• Drug-drug
• Drug-food
• Drug-herb

Pharmacodynamics (PD)
• Study of biochemical and physiological effects of drugs
  – What the drug does to the body and/or disease

Is this what you...
• ...think about when considering drug interactions?
Pharmacodynamics
True or false?
• The pharmacodynamic profile of a medication is unchanged over the lifespan.

Pharmacokinetics (PK)
• What the body does to the drug
• Includes
  – Absorption
  – Distribution
  – Biotransformation (metabolism)
  – Excretion of drugs

Pharmacokinetics
True or false?
• Age and gender significantly impact a medication’s pharmacokinetics.

Case Example of PD Drug Interaction
• 38-year-old woman
  – Propranolol for migraine headache prophylaxis
    • β₁, β₂ blockade
  – Develops acute bronchitis with bronchospasm
  • “The albuterol is not doing anything.”
    • β₂ agonism (activation)

What is etiology of the problem?
Receptor site blockage prevents receptor site activation.

Bronchodilator in β-blockade
• Ipratropium bromide (Atrovent®)
  – Acts at cholinergic receptor sites
  – Onset of action=1 h
  – Duration of action=4–6 h
• Monitor carefully during 3–5 half-lives (T½) of beta blocker withdrawal
Chemical/Pharmacokinetic DI

- 62-year-old woman with long-standing hypothyroidism
  - On levothyroxine 0.1 mg daily
  - TSH=1.2 mcg/mL
  - Placed on iron after significant intraop bleed
    - TSH=10.3 mcg/mL (0.3–4.0 mcg/mL)

Levothyroxine (LT4) Interactions

- Iron
- Calcium
- Aluminum
- Soy milk
- Sucralfate
- Formation of inactive drug compound
  - Separate ≥2 h
  - Empty stomach
  - Same time each day

Great Resource

- Dietary Supplement Fact Sheet
  - https://ods.od.nih.gov/factsheets/Calcium-HealthProfessional/

Inactivation of Antimicrobial Effect via Chelation

- 60–70% reduction in -floxacin dose
  - When taken with metals such as iron, calcium (potential with dairy products), magnesium, aluminum
  - Separate in stomach from metals by ≥2 hours
  - Source: http://www.drugs.com/pro/cipro.html

Iron Ingestion and Levothyroxine Therapy

Ferrous sulfate effect on TSH levels in patients with hypothyroidism

<table>
<thead>
<tr>
<th>TSH Level, μIU/mL</th>
<th>Before Ingestion</th>
<th>After Ingestion</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1.2 mcg/mL</td>
<td>10.3 mcg/mL</td>
</tr>
</tbody>
</table>

P<0.001

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True or false?
The warning about drug interaction potential when taken metals and cations extends to all antimicrobials with the -floxacin suffix.

Are other antimicrobials similarly impacted?
- Tetracycline forms including doxycycline, minocycline
  - When taken with metals such as iron, calcium (potential with dairy products), magnesium, aluminum
  - Separate in stomach from metals by ≥2 hours
  - Source: http://www.accessdata.fda.gov/drugsatfda_docs/label/2008/05795s005lbl.pdf

Examples
Medications Labeled to Take with Food
- To avoid GI upset
  - Amoxicillin/clavulanate
  - NSAIDs
  - Iron forms
    - Recognizing that there will be some iron dose lost, best taken on an empty stomach but many will not tolerate

Examples
Medications Labeled to Take with Food (continued)
- To enhance drug absorption
  - Nitrofurantoin (Macrodantin®, Macrobid®)
    - 200–400% increase in drug absorbed due to delayed emptying, increased time to dissolve
  - Sertraline (Zoloft®)
    - ~33% increase in dose absorbed when taken with food
    - Source: http://www.globalrph.com/drugfoodrxn.htm

Examples
Medications Labeled to Take with Food (continued)
- To minimize risk of adverse effect
  - Carvedilol (Coreg®), alpha-beta blocker
    - Take with food in immediate-release formulation to slow absorption and minimize risk of orthostasis
    - Source: http://www.globalrph.com/drugfoodrxn.htm
Drug-food Interactions: Potential for Decreased Drug Absorption

- Enteral feedings
  - Contains Ca+, other metals, protein
- Binds to components of feeding
  - Potential
    - Decreased absorption
    - Chelation

Medications Given with Enteral Feedings

- Phenytoin suspension
  - 71.6% dose absorption reduction with continuous feeding
    - If continuous feeding required
      - Increase dose accordingly.
    - Alternative
      - Hold feeding for 2 h before and 2 h after phenytoin dose; flush feeding tube with 60 mL water after phenytoin dose.

Medications Given with Enteral Feedings (continued)

- FQ antimicrobials
  - 27–67% reduction in mean bioavailability
    - Increased risk of treatment failure
  - Optimally, hold feeding for 1 h before and 2 h after FQ dose; flush feeding tube with 60 mL water after FQ dose.
    - Might not apply to moxifloxacin
    - Avoid use of liquid ciprofloxacin due to tube occlusion risk.

With drug-drug interactions, what drugs are most worrisome?

- Narrow therapeutic index (NTI) vs. wide therapeutic index (WTI) medications

What is a drug’s therapeutic index?

- Drug’s therapeutic index
  - Ratio of dose that produces toxicity to the dose that produces clinically desired or effective response in a population of individuals

How is drug’s therapeutic index calculated?

- TD50
  - Dose of drug that causes a toxic response in 50% of population
- ED50
  - Dose of drug that is therapeutically effective in 50% of population
- Therapeutic index = TD50/ED50
Narrow Therapeutic Index (NTI) Medications

Defined: Any pharmaceutical which has a <2-fold difference between the minimum toxic concentration and minimum effective blood concentration.

NTI Medications
How can you tell?

• Need to check a therapeutic level?
  – Of the medication?
  • Theophylline, digoxin, TCA (when given in full antidepressant dose), carbamazepine
  – Of the medication’s effect?
  • Levothyroxine (TSH), warfarin (INR), heparin (PTT)

Wide Therapeutic Index (WTI) Medications

• Typically
  – Have wide dose ranges
  • Fluoxetine 10–80 mg
  • Atorvastatin 10–80 mg
  – No requirement for periodic drug monitoring of the medication

What does the body want to do to drugs?

• Hang on to these foreign substances?
• Get rid of the “invader” as quickly as possible?

Biotransformation

• Metabolism (biotransformation)
  – The process by which the body modifies or alters the chemical structure of the drug
  • Often to allow for urinary excretion
  – Prodrug (inactive compound) is transformed to active metabolite.

Lipophilic vs. Hydrophilic

• Most drugs are designed to be lipophilic to allow for absorption and cell membrane penetration.
• These products must be changed to a hydrophilic metabolite to allow for excretion.
CYP450 Drug Metabolism

- The major process in which drugs are converted from lipophilic to hydrophilic.
- This is also a common source of drug-drug interactions.

Biotransformation Sites via CYP450

- Liver
- Kidney
- Placenta
- Lung
- Plasma
- Intestinal mucosa

Cytochromes P450 (CYP)

- Important to drug metabolism
  - CYP1A2
  - CYP2C9
  - CYP2C19
  - CYP2D6
  - CYP2E1
  - CYP3A4
- A source of pharmacokinetic DI

Proportion of Medications Metabolized by Select CYP450 Isoenzymes

CYP3A4

CYP2C9/19

CYP2D6

CYP2C9

CYP1A2


CYP450 Drug-metabolizing Isoenzymes: A Potential Source of Drug-drug Interactions

Substrate

Utilizes a specific enzymatic pathway

A medication or substance that is metabolized by the isoenzyme, utilizing this enzyme in order to be modified so it can reach drug site of action and/or be eliminated
Medications
Parent Drug to Metabolite
• Amitriptyline ---> nortriptyline
• Codeine ---> morphine
• Primidone ---> phenobarbital
• Valacyclovir ---> acyclovir

Clopidogrel Activation

CYP450 Drug-metabolizing Isoenzymes:
A Potential Source of Drug-drug Interactions

<table>
<thead>
<tr>
<th>Substrate Utilizes a specific enzymatic pathway.</th>
<th>CYP450 3A4 substrates: Sildenafil (Viagra®), atorvastatin, simvastatin, venlafaxine (Effexor®), alprazolam (Xanax®), many others</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inhibitor Blocks a specific enzymatic pathway, keeps substrate from exiting.</td>
<td></td>
</tr>
<tr>
<td>Inducer Pushes the substrate out the exit pathway.</td>
<td></td>
</tr>
</tbody>
</table>

About 50% of all prescription medications are CYP450 3A4 substrates

Inhibitor
Blocks a specific enzymatic pathway, keeps substrate from exiting.

- Erythro-, clarithromycin=CYP450 3A4 inhibitors
- Concomitant use of one of these antibiotics with any of the aforementioned CYP450 3A4 substrates (sildenafil, atorvastatin, simvastatin, venlafaxine, alprazolam, many others) results in an increase in substrate levels, potentially leading to substrate-induced toxicity

Additional CYP450 3A4 Inhibitors

- Select HIV antivirals
  - Indinavir, nelfinavir, ritonavir
- Select systemic antifungals
  - Itraconazole, ketoconazole
- Grapefruit juice
- NonDHP CCB verapamil, diltiazem

-- Source: P450 Drug Interaction Table: Abbreviated “Clinically Relevant” Table, available at http://medicine.iupui.edu/clinpharm/ddis/clinicalTable.aspx
Caution:
DI of Select Statins and Clarithromycin

• “Clarithromycin significantly (p <0.001) increased the AUC and C\text{max} of all 3 statins (atorvastatin, lovastatin, simvastatin \{CYP 3A4 substrates\}), most markedly simvastatin (approximately 10-fold increase in AUC)...”


What about statin choices if one of aforementioned meds is needed?

CYP450 Substrates

- CYP450 3A4
  - Atorvastatin
  - Lovastatin
  - Simvastatin

- CYP450 2C9
  - Pitavastatin
  - Rosuvastatin

Not metabolized by CYP450
- Pravastatin

CYP1A2

- 70-year-old woman with UTI
  - On ciprofloxacin
  - CYP1A2 inhibitor

Feeling better but cannot sleep
- “The antibiotic is keeping me awake.”
- Drinks 4–5 cups (0.95–1.18 L) of coffee/d
  - Caffeine=CYP1A2 substrate

CYP450 Drug-metabolizing Isoenzymes:
A Potential Source of Drug-drug Interactions

Substrate
Utilizes a specific enzymatic pathway.
- Sildenafil (Viagra®), atorvastatin, simvastatin, venlafaxine (Effexor®), alprazolam (Xanax®), many others

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Inducer
Pushes the substrate out the exit pathway.
- St. John’s wort=CYP450 3A4 inducer

Concomitant use of St. John’s wort and 3A4 substrate can lead to reduced target drug levels and diminished therapeutic effect, possible treatment failure

Medications of particular concern include select antiretrovirals, combined oral contraceptives, and cyclosporine
CYP450 3A4 Inducer

• St. John’s wort
  – Cyclosporine
  • Result– Transplanted organ rejection
  – Digoxin
  • Decreased digoxin levels by day 10
    – Clinically relevant table of drug interactions, available at http://medicine.iupui.edu/clinpharm/ddis/main-table

“But that St. John’s wort really works…”

• ...states the 70-year-old man with heart failure who is taking digoxin.
  • Has been taking two capsules of St. John’s wort per day for the past 5 years with no evidence of loss of digoxin effect.

CYP450 1A2

• A cigarette smoker
  – Nicotine as a CYP450 1A2 inducer
• Takes theophylline
  – CYP450 1A2 substrate
• Cuts down on smoking due to a “bad cold”
  • Feels jittery and nauseated

“But that St. John’s wort really works”...

(continued)

• What advice should you give?
  A. Stop the St. John’s wort immediately.
  B. Taper the St. John’s wort over the next 2 weeks.
  C. Continue to take the St. John’s wort with certain additional advice.

35-year-old with Genetically-based Coagulopathy

• Goal INR
  – 2.5-3.5, average warfarin weekly dose=56 mg
• INR 7 d ago=3.2
• Today=5.6
• Denies
  – Increased leafy greens, new meds, extra warfarin doses, alcohol, etc.

35-year-old with Genetically-based Coagulopathy

• Admits to going away for the weekend and “smoking some weed, something I hardly ever do.”
Warfarin-Marijuana Interaction

• “Theoretically, marijuana might increase the risk of bleeding when used concomitantly with anticoagulant/antiplatelet drugs.”
  – Aspirin, clopidogrel (Plavix®) nonsteroidal anti-inflammatory drugs (NSAIDs), dalteparin (Fragmin®) enoxaparin (Lovenox®) heparin, warfarin (Coumadin®); and others.”


Marijuana Use, Drug Interaction Potential

• Potential inhibitor cytochrome P450 3A4 (CYP3A4)
  – Based on in vitro evidence
  • CYP3A4 substrates include lovastatin (Mevacor®), clarithromycin (Biaxin®), cyclosporine, diltiazem (Cardizem®), estrogens, indinavir (Crixivan®), triazolam (Halcion®), approx ~50% Rx medications


Simvastatin: When Compared to Ingestion with Water as Control

• With grapefruit juice
  – C_max and AUC increased 12.0-fold (P<0.001) and 13.5-fold (P<0.001)
  – 24 hours after last grapefruit juice
  – C_max and AUC increased 2.4-fold (P<0.01) and 2.1-fold (P<0.001)
  – 7 days after last grapefruit juice dose
  – No change

  – Source: [http://cat.inist.fr/?aModele=afficheN&cpsidt=795058](http://cat.inist.fr/?aModele=afficheN&cpsidt=795058)

CYP450 Substrates

• CYP450 3A4
  – Atorvastatin
  – Lovastatin
  – Simvastatin

• CYP450 2C9
  – Pitavastatin
  – Rosuvastatin
  – Not metabolized by CYP450
  – Pravastatin
Statin vs. Statin
LDL Lowering at Various Doses
(www.prescribersletter.com)

<table>
<thead>
<tr>
<th>Statin</th>
<th>20 mg</th>
<th>40 mg</th>
<th>80 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lova</td>
<td>29%</td>
<td>31%</td>
<td>48%</td>
</tr>
<tr>
<td>Pravachol</td>
<td>19%</td>
<td>29%</td>
<td>48%</td>
</tr>
<tr>
<td>Zocor</td>
<td>28%</td>
<td>35%</td>
<td>48%</td>
</tr>
<tr>
<td>Lescol</td>
<td>17%</td>
<td>23%</td>
<td>33%</td>
</tr>
<tr>
<td>Lipitor</td>
<td>38%</td>
<td>46%</td>
<td>51%</td>
</tr>
<tr>
<td>Crestor</td>
<td>43%</td>
<td>50%</td>
<td>53%</td>
</tr>
<tr>
<td>Livalo</td>
<td>30%</td>
<td>36%</td>
<td>45%</td>
</tr>
</tbody>
</table>

Conclusions
- Polypharmacy is a reality.
- Avoid drug interactions and you will avoid problems for you and your patients.

References

Resources for Ongoing Information, Updates
- Indiana University School of Pharmacy’s work on the most important DI
  - http://medicine.iupui.edu/clinpharm/ddis/clinical-table/
- AZCert’s website on drugs that potentially prolong the QT interval
  - http://crediblemeds.org/everyone/composite-list-all-qtdrugs/?rf=US

End of Presentation
Thank you for your time and attention.

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