Drug Interactions: 
Let me count the ways

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Objectives

At the conclusion of this continuing education lesson, the participant will be able to:

• Discuss the two major clinical outcomes of drug interactions with other substances.
• Describe the mechanisms for pharmacokinetic drug interactions at the level of absorption, distribution, metabolism and elimination.
• List three drugs that may have altered metabolism due to cigarette smoking, alcohol consumption or grapefruit juice.
• Identify a number of pharmacodynamic drug interactions that may occur as a result of additive effects between drugs or between drugs and dietary supplements.
How Common are Drug Interactions?

Estimates of Drug-Drug Interactions (DDIs) varies according to:

- **Populations studied**
  - hospitalized, outpatient, elderly, CA, HIV, etc
- **Method of data collection and analysis**
- **Types of interactions selected for inclusion**
  - theoretical vs. documented
  - moderate vs. life threatening

### 2003 study
- 2.2% to 30% in hospitalized patients
- 9.2% to 70.3% in ambulatory patients
  - highest estimates frequently include theoretical interactions in addition to documented interactions

### 2004 study
- prescription drug claims data from 2 large health plans, in ambulatory pts, estimated to average about 6.5% per year.

### 2007 study
- 0.05% of ER visits, 0.6% of the hospital admissions and 0.1% of the re-hospitalizations caused by ADRs from DDIs.

### 2008 study
- Sample of community-dwelling older adults (> 55 yrs old) 4% of individuals was potentially at risk for a major drug-drug interaction.
Identifying Potentially Major Drug Interactions

No current standard for rating drug interactions. ▲▲▲

Some interactions can be very severe but are rare or uncommon.

Some interactions are common but are not life-threatening.

Drugs most likely to be involved in interactions are:

- Those with a narrow margin between the therapeutic and toxic dose
- Those requiring careful dosage control (TDM)
- Those which either induce or inhibit liver cytochrome P450 enzymes

Most likely classes:
- Anticonvulsants (1st generation)
- Antibiotics (just by sheer volume)
- Antiretrovirals
- Cardiac drugs (warfarin, amiodarone, dig, verapamil)
Two Basic Outcomes of Drug Interactions

**This one:**
Interaction *increases the toxicity* of a drug resulting in an ADR that hurts or kills the patient
- or -
**That one:**
Interaction *diminishes the therapeutic benefit* of a drug, allowing for disease progression and/or death

Classic Examples of Deadly Combinations

<table>
<thead>
<tr>
<th>Combination</th>
<th>Mechanism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Emycin + Seldane</td>
<td>Arrhythmia (TdP)</td>
</tr>
<tr>
<td>Nizoral + Propulsid</td>
<td>Arrhythmia (TdP)</td>
</tr>
<tr>
<td>Baycol + Lopid</td>
<td>Rhabdomyolysis</td>
</tr>
<tr>
<td>MAOI’ s + Tyramine</td>
<td>Hypertensive crisis</td>
</tr>
<tr>
<td>CNS depressants</td>
<td>Respiratory depression</td>
</tr>
<tr>
<td>(Benzos + Etoh, etc.)</td>
<td></td>
</tr>
<tr>
<td>Viagra + Nitroglycerin</td>
<td>Hypotension</td>
</tr>
</tbody>
</table>
### Types of Drug Interactions

#### Pharmacodynamic Interactions

<table>
<thead>
<tr>
<th>Additive / synergistic</th>
<th>Antagonistic</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pharmacological</strong> in nature</td>
<td></td>
</tr>
<tr>
<td>Two or more drugs working directly on the same target / system</td>
<td></td>
</tr>
<tr>
<td>eg., two CNS depressants</td>
<td></td>
</tr>
<tr>
<td><strong>Physiological</strong> in nature</td>
<td></td>
</tr>
<tr>
<td>Two drugs working on different physiologic processes but ultimately increasing risk of toxicity from one or both drugs</td>
<td></td>
</tr>
<tr>
<td>eg., digoxin and furosemide</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Antagonistic</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pharmacological</strong> in nature</td>
</tr>
<tr>
<td>Classic receptor antagonism</td>
</tr>
<tr>
<td>eg., Naloxone / morphine</td>
</tr>
<tr>
<td><strong>Physiological</strong> in nature</td>
</tr>
<tr>
<td>opposing physiologic processes</td>
</tr>
<tr>
<td>eg., NSAIDs and ACEIs on renal blood flow</td>
</tr>
</tbody>
</table>

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Pharmacokinetic Interactions

- **Absorption**
  - Altered gastric emptying, GI motility
  - Altered stomach pH
  - Chelation or adsorption
  - Altered Intestinal / hepatic transporters

- **Distribution**
  - Displacement of protein binding

- **Metabolism**
  - Enzyme induction / inhibition

- **Renal Excretion**
  - Inhibition of drug transporters

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Chemical Interactions

**Chelation**

- **IRON**
  - Tetracyclines
  - Quinolones
  - Bisphosphonates
  - Penicillamine
  - Levothyroxine
  - Levodopa

- **CALCIUM**
  - Tetracyclines
  - Quinolones
  - Bisphosphonates
  - Levothyroxine

Prevents Systemic Absorption
Chemical Interactions

Adsorption (Bile Acid Resins)

- Warfarin
- Thiazides
- Furosemide
- Propranolol
- Thyroxine
- Digoxin
- ASA / NSAIDs
- Fat Sol Vitamins A, D, E, K

Pharmacokinetic Interactions
Pharmacokinetic Interactions

**Effect of pH on passive diffusion**

*Henderson–Hasselbalch in action*

\[
\text{pH} = \text{pK}_a + \log \frac{[A^-]}{[HA]}
\]

Gut Lumen

\(\text{pH 1 - 3}\)

\(A^{-}\)

\(A^{+}\)

Interstitial Fluid

Acidic Drug

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Pharmacokinetic Interactions

**Absorption**

Drugs or liquids that *increase* gastric pH

- PPIs
- H-2 Antagonists
- Antacids

may *decrease* rate or amount of absorption:

- ketoconazole
- itraconazole
- cefpodoxime
- ampicillin esters
- delavirdine
- indinavir
- atazanavir
- nelfinavir

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**Pharmacokinetic Interactions**

**Distribution**

- Drugs that have a high affinity for serum albumen can compete for protein binding sites in circulating plasma.
- Combining two or more drugs that are highly protein bound can lead to displacement of one or both of the drugs and cause increased levels of “free” (the active form) of drug.
- Generally not clinically significant: however, in cases where one or more drugs have a “narrow therapeutic index” the possibility of serious interactions increases.
- Also, may be more likely in those with low albumin (elderly, liver disease, alcoholics).

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**Competition for Protein Binding**

[Diagram showing competition for protein binding]
Competition for Protein Binding

Blood Vessel

Free drug

Bound drug

Serum Albumin

Tissue

100% increase in “active” drug concentrations
Potential interactions between drugs that are highly protein bound

- warfarin
- NSAIDs, COX2’s
- digoxin
- ceftriaxone
- lorazepam
- phenytoin
- valproic acid
- lamotrigine

Cytochrome P450 Drug Interactions

Probably the most common source of pharmacokinetic drug interactions

Two mechanisms for interactions

- Induction
- Inhibition
CYP450 Induction

- reversible increase in enzyme concentration resulting from administration of certain drugs
- potential to increase rate of the "inducing" drug’s breakdown
- may increase the metabolism of other drugs taken concurrently

Discontinue "inducing" drug

initiate "inducing" drug

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**CYP450 Induction**

**Systemic Circulation**

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**Portal vein**

**CYP450 Induction**

**Substrates**
- Calcium Channel Blockers: amlodipine, diltiazem, verapamil, others
- Statins: lovastatin, simvastatin, atorvastatin
- Protease Inhibitors: indinavir, nelfinavir, ritonavir, saquinavir
- PDE5 Inhibitors: sildenafil, tadalafil, vardenafil
- Benzodiazepines: alprazolam, midazolam, triazolam
- Hypnotics: zolpidem, eszopiclone
- Opioids: methadone, oxycodone, buprenorphine
- Miscellaneous: buspirone, trazadone, estradiol, progesterone, ziprasidone, cyclosporine, warfarin (R)

**Inducers**
- phenytoin
- rifampin
- carbamazepine
- pioglitazone
- efavirenz
- nevirapine
- St. John’s wort

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### CYP450 Induction

<table>
<thead>
<tr>
<th>Substrates</th>
<th>Inducers</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CYP1A2</strong></td>
<td>Interactions potentially leading to sub-therapeutic drug levels</td>
</tr>
<tr>
<td><strong>CYP2E1</strong></td>
<td>Interactions potentially leading to toxicity</td>
</tr>
<tr>
<td>Antipsychotics</td>
<td>rifampin, omeprazole, broccoli, brussel sprouts, cabbage, char-grilled meat, tobacco smoke</td>
</tr>
<tr>
<td>Antidepressants</td>
<td>Ethyl alcohol, Whisky, Scotch, Bourbon, Vodka, Gin, Wine, Beer</td>
</tr>
<tr>
<td>Miscellaneous</td>
<td>Acetaminophen, ethanol, isoniazid</td>
</tr>
</tbody>
</table>

**CYP1A2 Substrates**
- Antipsychotics: clozapine, olanzapine
- Antidepressants: duloxetine, mirtazapine, clomipramine
- Miscellaneous: frovatriptan, ropinirole, tizanidine, warfarin(R), caffeine, theophylline

**CYP2E1 Substrates**
- Anesthetics: enflurane, halothane, isoflurane
- Miscellaneous: acetaminophen, ethanol, isoniazid

**Pharmacology ONE**
**Acetaminophen Toxicity**

- Glucuronide
- Sulfate
- Glutathione
- Overdose
- CYP2E1
- Alcohol Induces

**Inhibition of Drug Metabolism**

- Due to two drugs competing for the same enzyme
- Drug with greater affinity typically wins!
- Some drugs get into active site and are slow to dissociate
- Drug that is not metabolized can build up to toxic levels
Cytochrome P450 Inhibition

Competition for Enzyme by Substrates

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CYP450 Inhibition

Substrates

Calcium Channel Blockers
antidopamine, diltiazem, verapamil others

Statins
lovastatin, simvastatin, atorvastatin

Protease Inhibitors
Indinavir, ritonavir, saquinavir

PDE5 Inhibitors
sildenafil, tadalafil, vardenafil

Benzodiazepines
alprazolam, midazolam, triazolam

Hypnotics
zolpidem, eszopiclone

Opioids
methadone, oxycodone, buprenorphine

Miscellaneous
bupropion
trazadone
estradiol, progesterone
zopiclone
cyclosporine
warfarin (R)

Inhibitors
clarithromycin
erythromycin
ketoconazole
itraconazole
fluconazole
ritonavir
verapamil
amiodarone
cyclosporine
furancoumarins (grapefruit juice)

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The Grapefruit Juice Story

- Grapefruit juice contains dihydroxybergamottin - a "suicide" inhibitor of CYP3A4.
- It destroys some of the CYP3A4 in the small intestine, and the body must make new CYP3A4 to reestablish normal activity.
- The effect of grapefruit juice on CYP3A4 can last long after it passes through the small intestine and is eliminated from the body.
- Therefore: one cannot avoid the grapefruit juice ~ drug interactions by staggering juice consumption and drug administration.

CYP450 Inhibition

### Substrates

- **Antidepressants**: fluoxetine, paroxetine, venlafaxine, duloxetine, amitriptyline, clomipramine, desipramine, imipramine
- **Antipsychotics**: risperidone, haloperidol, perphenazine
- **Beta Blockers**: carvedilol, metoprolol, timolol
- **Opioids**: tramadol, tapentadol, codeine
- **Miscellaneous**: atomoxetine, dextromethorphan, tamoxifen

### Inhibitors

- paroxetine
- fluoxetine
- bupropion
- ritonavir
- terbinafine
- amiodarone
- quinidine
CYP450 Inhibition

**Substrates**

- **Pro-drug Substrates** (need activation by CYP2D6)
  - codeine
    - diminished analgesia
  - tamoxifen
    - decreased protection

**Inhibitors**

- paroxetine
- fluoxetine
- bupropion
- ritonavir
- terbinafine
- amiodarone
- quinidine

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CYP2D6

Interactions potentially leading to **Subtherapeutic** drug levels

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CYP2C9

Interactions potentially leading to **Toxic** drug levels

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**Substrates**

- Miscellaneous
  - phenytoin
  - warfarin(S)
  - sulfamethoxazole
- NSAIDs
  - diclofenac, ibuprofen, meloxicam, naproxin
- Oral Hypoglycemic Agents
  - glyburide, glipizide, glimepiride
- Angiotensin II Blockers
  - losartan, irbesartan, valsartan, candesartan

**Inhibitors**

- fluconazole
- amiodarone
- ketoconazole
- voriconazole
- miconazole
- sulfamethoxazole
- gemfibrozil
CYP450 Inhibition

**Substrates**
- PPIs: lansoprazole, omeprazole, esomeprazole, pantoprazole, rabeprazole
- Miscellaneous: clopidogrel, citalopram, escitalopram, phenytoin, warfarin (R), voriconazole

**Inhibitors**
- Omeprazole
- Esomeprazole
- Lansoprazole
- Pantoprazole
- Rabeprazole
- Cimetidine
- Fluoxetine
- Ketoconazole

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CYP2C19

Interactions potentially leading to **Toxic** drug levels

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CYP2C19

Interactions potentially leading to **Subtherapeutic** drug levels

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**CYP2C19**

2 steps

- Omeprazole ≥ Esomeprazole = Lansoprazole >> Rabeprazole, Pantoprazole

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Platelet

- ADP
- P2Y12 receptor

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CYP450 Inhibition

**Substrates**
- Antipsychotics: clozapine, olanzapine
- Antidepressants: duloxetine, mirtazapine, chlorimipramine
- Miscellaneous: furosemide, meprobamate, tizandine, warfarin(R), caffeine, theophylline

**Inhibitors**
- fluvoxamine
- ciprofloxacin
- cimetidine

P-gp Drug Transporters

- into the gut
- into urine
- into bile
- out of the brain
- out of the gonads
- out of other organs

P-glycoprotein

To Portal System

Out through bowel
P-gp Drug Transporters

**Substrates**
digoxin
doxepin
doxorubicin
doxorubicin
fexofenadine
digoxin
indinavir
indinavir
rotinavir
rotinavir
vincristine
vincristine
morphine
morphine
loperamide
loperamide
cyclosporine
cyclosporine
colchicine
colchicine
paclitaxel
paclitaxel
verapamil
verapamil

dabigatran

**Inhibitors**
amiodarone
clarithromycin
erthyromycin
cyclosporine
diltiazem
indinavir
itraconazole
ketoconazole
amiodarone
clarithromycin
erthyromycin
cyclosporine
indinavir
itraconazole
ciclosporine
Dabigatran

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Pharmacokinetic Interactions
Renal Elimination

- When one drug slows the elimination of another
- Few Interactions noted at this level.
- Potential for competition at renal drug transporters

Renal Transporters “Active Secretion”

- Anionic transporter (OAT)
  - furosemide, thiazides
  - penicillins
  - NSAIDs
  - methotrexate
  - probenecid

- Cationic Transporter (OCT)
  - metformin
  - contrast media (iodinated)
  - cimetidine
  - amiloride
  - morphine
  - procainamide
  - quinidine
Pharmacodynamic Interactions

Additive Drug-Drug Interactions

Combining CNS depressants

Opioids
Antihistamines (1st generation)
Tricyclic antidepressants (3rd)
Antipsychotics
Alcohol
Benzodiazepines
Z-hypnotics
Barbiturates
Muscle relaxants

Sedation, confusion, ataxia, amnesia, respiratory depression, coma, death

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### Additive Drug-Drug Interactions

#### Combining vasodilators or antihypertensives

- **ACEI**
- **ARB**
- **Diuretics**
- **CCBs**
- **B-Blockers**
- **Thiazides**

- **Nitroglycerin**
- **PDE-5 Inhibitors**
- **DHP-CCBs**
- **Alpha blockers**

**Hypotension Syncope MI**

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#### ACEIs, ARBs, Direct Renin Inhibitors

+ potassium-sparing diuretics  
  (spironolactone, triamterene, amiloride)

  + potassium Supplements  
    trimethoprim

**Hyperkalemia**
Additive Drug-Drug Interactions

Combining serotonin enhancing drugs
- SSRIs
- SNRIs
- trazadone
- mirtazepine
- lithium
- selegiline
- dextromethorphan
- tramadol, tapentadol, methadone
  - triptans

Serotonin syndrome

Additive Drug-Drug Interactions

Antiplatelet Drugs
- Aspirin
- NSAIDs
- clopidogrel
ticagrelor

Anticoagulants
- warfarin
- heparin, LMWH,
  Factor Xa inhibitors

Misc
- Some cephalosporins
  (SSRIs ???)

Hemorrhage
**Additive Drug-Drug Interactions**

Combining drugs that increase QT interval

- clarithromycin
- erythromycin
- quinidine
- procainamide
- disopyramide
- amiodarone
- chlorpromazine
- thioridazine
- haloperidol
- ziprasidone

**Torsades de Pointes**
Fatal Arrhythmia

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**Additive Drug-Drug Interactions**

- Metformin
- Corticosteroids
- Alcohol
- NRTIs (HIV)

**Lactic Acidosis**
Additive Drug-Drug Interactions

Combining Drugs with Anticholinergic Side Effects

- Overactive bladder drugs,
- Centrally-acting anticholinergics
- Antiemetics
- Antispasmodics
- Respiratory anticholinergics
- Sedating antihistamines
- Tricyclic antidepressants
- Antipsychotics
- Opioids
- Clonidine

Constipation, Dry mouth, Urinary Retention, Confusion, Tachycardia

Additive Drug-Drug Interactions

- Statins
- Niacin
- Fibrates
- NRTIs (nukes)
- Alcohol (acute or chronic)
- glucocorticoids
- Antimalarials
- Phenothiazines

Myopathy, Rhabdomyolysis
Summary

Limiting Drug Interactions

Don't rely on memory to determine which drugs interact
- There are many commercial drug interaction programs available

Recognize patient and drug-related risks for interactions
- Acute medical conditions (fever, infection, dehydration)
- Age extremes (very young, elderly)
- Documented renal or hepatic impairment
- Multiple medications / multiple prescribers,
- Narrow therapeutic range drugs
- Drugs with very long half-lives
Limiting Drug Interactions

Remember not all drugs in a class interact the same way
Macrolides: Emycin and clarithromycin inhibit CYP3A4; azithromycin does not
Statins: Simvastatin, lovastatin, atorvastatin cleared by CYP3A4
SSRIs: Fluoxetine and paroxetine inhibitors of CYP2D6, others not

Appreciate the time-course or sequence of administration for drug interactions
Half-lives, drug accumulation, CYP induction lag, INR lag, irreversible inhibitors (i.e., grapefruit)

Don't assume similar magnitude of interactions for all pts
Genetic variability (pharmacogenetics)

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Thanks for listening!

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Alan