Drug Interactions

Andrea Trescot, MD

Adverse Drug Reactions (ADRs)

• In 1994 alone, there were over 2.2 million cases of serious ADRs
  – 106,000 fatalities due to ADRs
• Many ADRs are due to preventable drug interactions
  – The overall prevalence of drug interactions is 50 to 60%
  – About 7% of hospitalizations are due to drug interaction
Drug Interactions

• Drug interactions may present as:
  – Enhanced efficacy
  – Increased toxicity
  – Lack of efficacy
• Drugs with a long half life may still have an effect long after the drug has been administered

Overview of Drug Interactions

• Drug-drug interactions
• Drug-food/beverage interactions
• Drug-herb interactions
• Drug-condition interaction
Drug-Drug Interactions

• Multiple prescriptions
  – Polypharmacy increases the risk of interactions
• Multiple physicians
  – Lack of communication
  – Incomplete medication lists
• Prescription vs OTC
  – Patients don’t report OTC use
    • Embarrassed
    • “I didn’t think it was important”

Drug-Drug Interaction

• Duplication
• Alteration
  – Absorption
  – Distribution
  – Metabolism
  – Excretion
• Receptor interactions
  – Activity receptors
  – Excretion receptors
Duplication

- When two drugs with the similar effects are taken, their therapeutic effects and side effects may be intensified
  - Cold remedies and sleep aids may both contain diphenhydramine
  - Multiple analgesics may contain acetaminophen which may lead to liver toxicity
  - Multiple medications may have sedation side effects which can be additive

Alteration

One drug may alter the way the body absorbs, distributes, metabolizes, excretes another drug
Absorbsion

• Food
  – Some medicines should be taken on an empty stomach
    • bisphosphonoids
• Dietary fiber
  – Pectin will slow down the absorption of acetaminophen
  – Oatmeal will decrease the absorption of digoxin
• Antacids
  – can increase absorption of antibiotics, heart medicine, or thyroid medications by up to 90%

Absorbsion

• High fat meals will slow GI transit, leading to the potential for increased absorption
• Changes in gastric pH can alter absorption
  – H2 blockers, PPI
  – Antacids
  – Total parenteral nutrition
Distribution

- Distribution is dependent on
  - Permeation properties
    - Acidic vs basic
    - Lipophilic vs hydrophilic
  - Blood flow to tissues
    - Brain vs muscle vs fat
  - Plasma and tissue uptake
    - Protein binding vs receptor binding
- Body fat
  - For the antibiotic daptomycin, the absolute volume of distribution and total clearance of the drug were higher in obese patients
    - Total body weight vs lean body weight

Metabolism

- Glucose-6-phosphate dehydrogenase (G6PD) deficiency
  - Most common human enzyme deficiency
  - Affects approximately 400 million people worldwide
  - Over 400 variant alleles
    - X chromosome
  - Patients can not handle oxidative drugs
    - Causes hemolytic anemia
<table>
<thead>
<tr>
<th>ANALGESICS/ANTIPYRETICS</th>
<th>ANTIMALARIALS</th>
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<tbody>
<tr>
<td>acetanilid</td>
<td>chloroquine</td>
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<tr>
<td>acetophenetidin (phenacetin)</td>
<td>hydroxychloroquine</td>
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<td>amidopyrine (aminopyrine)</td>
<td>mepacrine (quinacrine)</td>
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<td>antipyrine</td>
<td>_pamaquine</td>
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<td>aspirin</td>
<td>pentaquine</td>
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<td>phenacetin</td>
<td>primaquine</td>
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<td>pyramidone</td>
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<table>
<thead>
<tr>
<th>MISCELLANEOUS</th>
<th>naphthalene</th>
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<tbody>
<tr>
<td>alpha-methyldopa</td>
<td>naphthalene</td>
</tr>
<tr>
<td>ascorbic acid</td>
<td>niridazole</td>
</tr>
<tr>
<td>dimercaprol (BAL)</td>
<td>phenylhydrazine</td>
</tr>
<tr>
<td>hydralazine</td>
<td>pyridium</td>
</tr>
<tr>
<td>mestranol</td>
<td>quinine</td>
</tr>
<tr>
<td>methylene blue</td>
<td>toluidine blue</td>
</tr>
<tr>
<td>nalidixic acid</td>
<td>trinitrotoluene</td>
</tr>
<tr>
<td></td>
<td>urate oxidase</td>
</tr>
<tr>
<td></td>
<td>vitamin K (water soluble)</td>
</tr>
</tbody>
</table>
Glucuronidation

- Occurs primarily in the liver
- As a rule, creates a highly polar molecule that does not cross the blood-brain barrier
- Drug interactions
  - All TCAs inhibit glucuronidation of morphine
    - Nortriptyline in a non-competitive manner
    - Amitriptyline and clomipramine in a competitive or mixed manner

Metabolite Activity

- Morphine is metabolized by glucuronidation in the liver (and potentially a small amount in renal and brain tissue) to:
  - Morphine-6-Glucuronide (M6G)
  - Morphine-3-Glucuronide (M3G)
M6G

- Crosses blood brain barrier slowly
- Has a peripheral effect in inflammatory pain
- More selective for $\mu$ receptors than $\kappa$ or delta receptors
- 6 hour half life compared to 2-3 hour half life of MSO4
  - Side effects appear slowly but may be persistent
- Renally excreted
  - accumulates in renal failure
- May have effect in chronic morphine use

M3G

- More than half of each dose of morphine given systemically to rats or humans is metabolized to M3G
- Excreted in bile
- Does not bind to $\mu$ receptors
- May be excitatory and anti-analgesic, may cause myoclonus
- Indirectly activates NMDA receptors
- May be mechanism of tolerance and hyperalgia

Cytochrome P450 System

- Microsomal enzymes in the liver and gut
  - Catalyze phase I drug metabolism
    (oxidation, reduction, and hydrolysis)
- There are more than 20 CYP enzymes
  - 2C9, 2D6, and 3A4 account for 60-70% metabolism of clinically important drugs
- 58 different human genes
CYP Polymorphism
Consequences

- Drug toxicity
- Adverse drug reactions
- Extended pharmacologic effects
- Decreased effective dose
- Exacerbation of drug-drug interactions
- Metabolism by alternate deleterious pathways
- Lack of drug efficacy
- Increased drug requirement
- Lack of pro-drug effect

Metabolism

A. PM poor metabolizer, absent or greatly reduced ability to clear or activate drugs.
B. IM intermediate metabolizer. Heterozygotes for normal and reduced activity genes.
C. EM extensive metabolizer. The norm.
D. UM Ultra Metabolizer. Greatly increased activity accelerating clearance or activation
### Population Frequency of CYP Genotypes

<table>
<thead>
<tr>
<th>CYP</th>
<th>Poor metabolizer</th>
<th>Intermediate metabolizer</th>
<th>Extensive metabolizer (normal)</th>
<th>Ultra metabolizer</th>
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</thead>
<tbody>
<tr>
<td>2D6</td>
<td>10%</td>
<td>35%</td>
<td>48%</td>
<td>7%</td>
</tr>
<tr>
<td>2C9</td>
<td>4%</td>
<td>38%</td>
<td>58%</td>
<td>N/A</td>
</tr>
<tr>
<td>2C19</td>
<td>3-21%</td>
<td>N/A</td>
<td>79-97%</td>
<td>N/A</td>
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</table>

### Cytochrome P450 Inhibition in vitro

<table>
<thead>
<tr>
<th></th>
<th>3A4</th>
<th>2D6</th>
<th>1A2</th>
<th>2C19</th>
<th>2C9</th>
</tr>
</thead>
<tbody>
<tr>
<td>Escitalopram</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Citalopram</td>
<td>0</td>
<td>+</td>
<td>+</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Fluoxetine</td>
<td>++</td>
<td>+++</td>
<td>+</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>Paroxetine</td>
<td>+</td>
<td>+++</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Sertraline</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>++</td>
<td>+</td>
</tr>
</tbody>
</table>

CYP 1A2

<table>
<thead>
<tr>
<th>Substrates</th>
<th>Inhibitors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amitriptyline</td>
<td>Cimetidine</td>
</tr>
<tr>
<td>Imipramine</td>
<td>Ciprofloxin</td>
</tr>
<tr>
<td>Clomipramine</td>
<td>Fluvoxamine</td>
</tr>
<tr>
<td>Clozapine</td>
<td>Inducers</td>
</tr>
<tr>
<td>Caffeine</td>
<td>Insulin</td>
</tr>
<tr>
<td>Cyclobenzaprine</td>
<td>Omeprazole</td>
</tr>
<tr>
<td>Estradiol</td>
<td>Tobacco</td>
</tr>
<tr>
<td>Acetaminophen</td>
<td></td>
</tr>
<tr>
<td>Propranolol</td>
<td></td>
</tr>
<tr>
<td>Theophylline</td>
<td></td>
</tr>
<tr>
<td>Frovatriptan</td>
<td></td>
</tr>
<tr>
<td>Naratriptan</td>
<td></td>
</tr>
<tr>
<td>Zolmitriptan</td>
<td></td>
</tr>
</tbody>
</table>

CYP2D6

- Acts on one-fourth of all prescription drugs
  - SSRI, TCA
  - Beta blockers
  - Type A1 anti-arrhythmics
  - Several opioids
- 35% of the population are carriers of a nonfunctional 2D6 allele
### CYP 2D6

<table>
<thead>
<tr>
<th>Substrate</th>
<th>Inhibitors</th>
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</thead>
<tbody>
<tr>
<td>Codeine</td>
<td>Propranolol</td>
</tr>
<tr>
<td>Metoprolol</td>
<td>Tramadol</td>
</tr>
<tr>
<td>Nortriptyline</td>
<td>Timolol</td>
</tr>
<tr>
<td>Fluoxetine</td>
<td>Venlafaxine</td>
</tr>
<tr>
<td>Paroxetine</td>
<td>Risperidone</td>
</tr>
<tr>
<td>Fluvoxamine</td>
<td>Tamoxifen</td>
</tr>
<tr>
<td>Dextromethorphan</td>
<td></td>
</tr>
</tbody>
</table>

**Inducers**
- Buproprion
- Celecoxib
- Cimetidine
- Cocaine
- Dexamethasone
- Rifampin

**Substrate**
- Nortriptyline
  - Metabolized by CYP2D6
  - Poor metabolizers are homozygous for a null allele
    - Dosage 50mg/day
  - Intermediate metabolizers have one copy of normal allele
  - Extensive metabolizers have two copies
    - Dosage should be 500mg/day

Activation of Analgesics by CYP 2D6

<table>
<thead>
<tr>
<th>Drug</th>
<th>Metabolized Form</th>
<th>→ receptor binding potency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Codeine</td>
<td>Morphine</td>
<td>300-7000</td>
</tr>
<tr>
<td>Oxycodone</td>
<td>Oxymorphone</td>
<td>14-64</td>
</tr>
<tr>
<td>Hydrocodone</td>
<td>Hydromorphone</td>
<td>7-33</td>
</tr>
<tr>
<td>Dihydrocodeine</td>
<td>Dihdromorphine</td>
<td>67</td>
</tr>
</tbody>
</table>

CYP2C9

- Primary route of metabolism for NSAIDS, coumadin and phenytoin
- Also metabolizes celecoxib, tamoxifen, amitriptyline, THC, sildenafil
- 10% of the population are carriers of at least one allele for the slow-metabolizing form
  - Should be treated with half the normal dose
CYP 2C9

<table>
<thead>
<tr>
<th>Substrates</th>
<th>Inhibitors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diclofenac</td>
<td>Fluoxetine</td>
</tr>
<tr>
<td>Ibuprofen</td>
<td>Phenytoin</td>
</tr>
<tr>
<td>Naproxen</td>
<td>Fluvastatin</td>
</tr>
<tr>
<td>Piroxicam</td>
<td>Tamoxifen</td>
</tr>
<tr>
<td>Tolbutamide</td>
<td>Warfarin</td>
</tr>
<tr>
<td>Amitriptyline</td>
<td>Sildenafil</td>
</tr>
<tr>
<td>Celecoxib</td>
<td>THC</td>
</tr>
<tr>
<td></td>
<td>Fluconazole</td>
</tr>
<tr>
<td></td>
<td>Fluvoxamine</td>
</tr>
<tr>
<td></td>
<td>Isoniazid</td>
</tr>
<tr>
<td></td>
<td>Probenicid</td>
</tr>
<tr>
<td></td>
<td>Sertraline</td>
</tr>
<tr>
<td></td>
<td>Inducers</td>
</tr>
<tr>
<td></td>
<td>Rifampin</td>
</tr>
<tr>
<td></td>
<td>Secobarbital</td>
</tr>
</tbody>
</table>

CYP3A4

- CYP3A4 is the major form of P450 in the human liver, metabolizing > 50% of all drugs.
  - All protease inhibitors (especially ritonavir) competitively inhibit this enzyme
  - Also noted interactions with SSRIs, cimetidine, antiepileptic medications, macrolide antibiotics and antimycotics
  - Many central nervous system depressants are metabolized by this system, leading to increased plasma levels and increased clinical effect
    - Fentanyl
    - Diazepam
    - Methadone
### CYP 3A4

<table>
<thead>
<tr>
<th>Substrate</th>
<th>Inhibitors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alprazolam</td>
<td>HIVantivirals</td>
</tr>
<tr>
<td>Dextromethorphan</td>
<td>Cimetidine</td>
</tr>
<tr>
<td>Midazolam</td>
<td>Erythromycin</td>
</tr>
<tr>
<td>Nifedipine</td>
<td>Grapefruit juice</td>
</tr>
<tr>
<td>Verapamil</td>
<td>Ketoconazole</td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>Verapamil</td>
</tr>
<tr>
<td>Diazepam</td>
<td>Inducers</td>
</tr>
<tr>
<td>Clonazepam</td>
<td>Modafinil</td>
</tr>
<tr>
<td>Cocaine</td>
<td>Barbitrates</td>
</tr>
<tr>
<td></td>
<td>Glucocorticoids</td>
</tr>
<tr>
<td></td>
<td>Phenytoin</td>
</tr>
<tr>
<td></td>
<td>St. Johns Wort</td>
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</tbody>
</table>

### Methadone

- **Advantages**
  - Low cost, easy to titrate
  - Long half life
  - Absence of active metabolite
  - NMDA antagonist
- **Disadvantages**
  - Stigma, multiple pills/multiple drug interactions
  - Peripheral edema, potential for arrhythmias (prolonged QT), excreted renally (decrease dose 50% in CRI)
  - Poorly tolerated initially
  - Unpredictability of blood levels and wide variation in response; difficulty calculating equipotent dose

Methadone

- Prescribed every 24 hours for prophylaxis of withdrawal
- Prescribed every 6-8 hours for pain
  - Biphasic pattern of elimination
  - Lower affinity for μ receptor compared to morphine
  - Effect is longer than the effect of naloxone
    - Potential for re-narcotization
  - Structurally unrelated to other opioids
    - Useful in patients with “morphine allergy”

Methadone

- Multiple drug interactions
  - Primarily metabolized by CYP3A4 (with 2D6 secondarily)
  - Increased metabolism (decreased blood levels):
    - Ethenyl, barbiturates, phenytoin, carbamazine, isoniazid, ritonavir
  - Decreased metabolism (increased blood levels):
    - Cimetidine, erythromycin, ciprofloxin, ketoconazole, fluoxamine
Methadone

• 2002 Interim Report of Drugs (Florida)
  – 254 deaths related to methadone
    • 31% increase compared to the last 6 months of 2001
    • The single largest increase in any category
      – 133 cases were overdoses
        • 110 involved the use of another drug as well as meprobamate (Soma)

Methadone

• Urban myth - “I have to have a special license to prescribe methadone”. Not True
• Special license for heroin “maintenance” or “addiction”
• No special license for pain treatment
• Prescription must read “for pain”
Alterations in Metabolism

• Example: phenytoin
  – Increased metabolism (levels decreased) by:
    • Clonazepam, theophylline, carbamazepine
  – Decreased protein binding (levels increased):
    • Salicylates, diazepam, valproic acid, and phenylbutazone
  – Decreased metabolism (levels increased):
    • Dicumarol, disulfiram, and cimetidine

Alterations in Metabolism

• Example: methadone
  – Primarily metabolized by CYP3A4 (with 2D6 secondarily)
  – Increased metabolism (decreased blood levels):
    • Ethenyl, barbiturates, phenytoin, carbamazine, isoniazid, ritonavir
  – Decreased metabolism (increased blood levels):
    • Cimetidine, erythromycin, ciprofloxin, ketoconazole, fluoxamine
Alterations in Metabolism

- Example: anticonvulsants
- Most are metabolized by CYP2C9, CYP2C19, and CYP3A4
- Also metabolized by uridine diphosphate glucuronosyltransferase (UDGPT)
  - Phenytoin, phenobarbital, primidone, and carbamazepine induce CYP and UDPGT
  - Valproic acid inhibits them

Inter-Patient Variability

- Inter-patient variability in response to a drug is the rule rather than the exception
- Drug levels can vary more than 1000 fold between two individuals with the same weight and the same dose.
- Phenotypic variation accounts for 20-40% of the inter-individual response

## Phenotype by Ethnicity

<table>
<thead>
<tr>
<th>CYP Enzyme</th>
<th>Phenotype</th>
<th>Ethnic Group</th>
<th>Frequency</th>
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</thead>
<tbody>
<tr>
<td>1A2</td>
<td>PM</td>
<td>Caucasian</td>
<td>12%</td>
</tr>
<tr>
<td>2C9</td>
<td>PM</td>
<td>Caucasian</td>
<td>2-6%</td>
</tr>
<tr>
<td>2C19</td>
<td>PM</td>
<td>Caucasian</td>
<td>2-6%</td>
</tr>
<tr>
<td></td>
<td>PM</td>
<td>Chinese</td>
<td>15-17%</td>
</tr>
<tr>
<td></td>
<td>PM</td>
<td>Japanese</td>
<td>18-23%</td>
</tr>
<tr>
<td>2D6</td>
<td>PM</td>
<td>Caucasian</td>
<td>3-15%</td>
</tr>
<tr>
<td></td>
<td>PM</td>
<td>Oriental/African</td>
<td>&lt;&lt;2%</td>
</tr>
<tr>
<td></td>
<td>UR</td>
<td>Ethiopian</td>
<td>20%</td>
</tr>
<tr>
<td></td>
<td>UR</td>
<td>Hispanic</td>
<td>7%</td>
</tr>
</tbody>
</table>

## Pro-drugs

- Parent compound is inactive or less active than metabolite
  - Nabumetone (Relafen®) is inactive until it is absorbed and liver metabolized to 6-methoxy-2-naphthylacetic acid
Codeine Metabolism

- Pro-drug
- 50% is metabolized by CYP2D6 to morphine
- The rest is inactivated by glucuronidation and CYP 3A4
- CYP2D6 inhibitors or CYP2D6 deficiency decrease analgesia
- CYP3A4 inhibitors increase morphine levels

Active Metabolite

- Tramadol
  - M1 metabolite of tramadol has more activity than parent compound
  - CYP2D6 dependant
    - CYP2D6 deficient or inhibited patients will have decreased effect of tramadol
  - Unfortunately, the excretion of tramadol is also CYP2D6 dependant, so that an ineffective enzyme leads to increased blood levels and toxicity
Other Metabolism Issues

• Effect of metabolites
  – Prilocaine metabolism causes release of orthotoluidine
    • Causes methemoglobinemia
    • Seen when doses of prilocaine exceeds 8mg/kg or 500 to 600mg in adults
    • Reversed with methylene blue

Drug Excretion

• Liver
  – Hepatic clearance
  – Disease
• Renal
  – Active excretion
  – Passive excretion
  – Disease
• Competition for excretion
Hepatic Clearance

Classification of Some Common Pain Medications According to Hepatic Clearance

<table>
<thead>
<tr>
<th>Low</th>
<th>Intermediate</th>
<th>High</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chlordiazepoxide</td>
<td>Acetaminophen</td>
<td>Etoracaine</td>
</tr>
<tr>
<td>Ibuprofen</td>
<td>Alfentanil</td>
<td>Imipramine</td>
</tr>
<tr>
<td>Indomethacin</td>
<td>Bupivacaine</td>
<td>Lidocaine</td>
</tr>
<tr>
<td>Methadone</td>
<td>Codeine</td>
<td>Morphine</td>
</tr>
<tr>
<td>Phenobarbital</td>
<td>Meperidine</td>
<td>Pentazocine</td>
</tr>
<tr>
<td>Phenytoin</td>
<td>Sufentanil (?)</td>
<td>Phenacetin</td>
</tr>
<tr>
<td>Salicylic acid</td>
<td></td>
<td>Propoxyphene</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Salicylamide</td>
</tr>
</tbody>
</table>

Excretion

- pH issues
  - Changes in urine pH potentially increase or decrease excretion
    - Vitamin C will acidify the urine
      - Decrease excretion of acidic compounds such as aspirin
      - Increase excretion of basic compounds such as pseudoephedrine
  - Receptor interaction
Receptor Interactions

- **Receptors**
  - Drug activity receptors
  - Drug transport receptor
- **Synergy vs Antagonism**
  - **Synergy**
    - Increased activity at receptor
    - Decreased excretion leading to increased effect
  - **Antagonism**
    - Decreased activity at receptor
    - Increased excretion leading to decreased effect

Drug Activity Receptors

- **Opioid receptors**
  - Agonists
  - Antagonists
  - Agonist/antagonists
Drug Transport Receptors

- Human ATP-binding cassette (ABC) transporters
  - Active transport of drugs, peptides, and endogenous hormones
  - Widely distributed throughout the body
- P-glycoprotein (p-GP)
  - Cationic pump in liver, intestines, kidney and brain
  - Pumps toxins out of the cell
  - Works in tandem with CYP3A4 in the intestinal wall

P-GP Interactions

<table>
<thead>
<tr>
<th>Substrates</th>
<th>Increase in activity</th>
<th>Decrease in activity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cortisol</td>
<td></td>
<td>Rifampin (rifampin)</td>
</tr>
<tr>
<td>Digoxin</td>
<td></td>
<td>Valspodar (PSC-833)</td>
</tr>
<tr>
<td>Doxorubicin</td>
<td></td>
<td>Phenobarbital</td>
</tr>
<tr>
<td>Etoposide</td>
<td></td>
<td>Quinidine</td>
</tr>
<tr>
<td>Fexofenadine</td>
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<td>Cloftimazole</td>
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<tr>
<td>Indinavir</td>
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<td>Verapamil</td>
</tr>
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<td>Loperamide</td>
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<td>Reserpine</td>
</tr>
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<td>Mitomycin</td>
<td></td>
<td>Cyclosporin</td>
</tr>
<tr>
<td>Paclitaxel</td>
<td></td>
<td>Isosafrole</td>
</tr>
<tr>
<td>Saquinavir</td>
<td></td>
<td>Spironolactone</td>
</tr>
<tr>
<td>Tamoxifen</td>
<td></td>
<td>Midazolam</td>
</tr>
<tr>
<td>Vinblastine</td>
<td></td>
<td>Ketoconazole</td>
</tr>
<tr>
<td>Vinorelbine</td>
<td></td>
<td>Nifedipine</td>
</tr>
<tr>
<td>Quercetin</td>
<td></td>
<td>Erythromycin</td>
</tr>
<tr>
<td>Kaempferol</td>
<td></td>
<td>Amodarone</td>
</tr>
<tr>
<td>Galanin</td>
<td></td>
<td>Diacetazem</td>
</tr>
<tr>
<td>St John’s wort</td>
<td></td>
<td>Itraconazole</td>
</tr>
</tbody>
</table>

p-GP protects the patient from digoxin toxicity
  - ↓ GI absorpsion
  - ↑ biliary excretion
  - ↑ renal tubular excretion
  - Nifedipine ↑ absorpsion
  - Rifampin ↓ digoxin levels
  - ↓ p-GP after small bowel resection
Grapefruit Interactions

• First reported in 1989 when, during a study looking at ethanol-drug interactions used grapefruit juice as the vehicle for the ethanol

• The clinical significance of the interaction depends on
  – The magnitude of the change in drug profile
  – Drug concentration response relationships
  – Individual patient response

Grapefruit Interactions

• The main enzyme implicated is CYP3A4
  – Furanocoumarins irreversibly inhibit intestinal wall CYP3A4 leading to:
    • Decreased pre-systemic metabolism
    • Increased amount of drug entering systemic circulation
    • Increased drug levels
    • Increased therapeutic effect
  – Inhibition may last 72 hours
Grapefruit Interactions

• Also weakly inhibits intestinal wall p-glycoprotein (p-GP) which actively secretes some drugs back into the lumen
  – Not all CYP3A4 drugs are p-GP substrates
  – Most pronounced for drugs with large amounts of pre-systemic metabolism (low bioavailability)
• Organic anion transporting polypeptide (OATP) is also affected by grapefruit causing decreased absorption

Medications to Avoid with Grapefruit

- amiodarone (Cordarone)
- astemizole (Hismanal)
- atorvastatin (Lipitor)
- budesonide (Entocort)
- buspirone (BuSpar)
- cerivastatin (Baycol)
- clofazizol (Pletal)
- colchicine
- eletriptan (Relpax)
- etoperide (Veslrid)
- halofantrine (Halpan)
- lovastatin (Mevacor)
- mifepristone (Mifepr)
- pimozide (Clop)
- quinidine (Quinaglute, Quinidex)
- sildenafil (Viagra)
- simvastatin (Zocor)
- sirolimus (Rapamune)
- terfenadine (Seldane)
- ziprasidone (Geodon)
Medications to to Use Cautiously with Grapefruit

albendazole (Albenza)  
almitrin (Altenta)  
alfuzosin (Uroxatral)  
almotripitant (Axert)  
alopizole (Abilify)  
attropine (Wellbutrin, Zyban)  
carbomazepine (Tegretol)  
demeclocycline (Serpasil)  
demipramine (Anafranil)  
cyclosporine (Neoral)  
daniolacine (Enablex)  
delavirdine (Fuluspiv)  
doxorubicin (Pallorphan)  
diazepam (Valium)  
dolafide (Tikosyn)  
emetin (Sustiva)  
extenib (Tarceva)  
eyethromycin (Eryc, E-mycin, Erythem, Ebyrd)  
exzampione (Lunesta)  
felecepin (Pendil, Pendil)  
exotenzoline (Allegra)  
fluoxamine (Luvan)  
gatifinhib (Iressa)  
instatin mesylate (Gleevec/Gleeve)  
ibronazol (Sporanox)  
losartan (Cozart)  
methadone (Dolophine)  
methylprednisolone (Medrol)  
midazolam (Versed)  
montelukast (Singular)  
nicardipine (Cardene)  
nitrofurine (Procain)  
nisodipine (Nimotop)  
nisoldipine (Sular)  
ocybutryacin (Ditropan)  
opipatone (Fyrimol)  
quetafine fumarate (Seroquel)  
quinine  
rantodone (Rizaterm)  
safiquafine (Invise)  
sertaline (Zolof)  
solifomacin (Vesicare)  
tacrolimus (Prograf)  
tamoxifen (Novaco)  
tamoxifen (Framax)  
fludorodone (Dolor)  
triazolam (Halcion)  
tracodon (Desyrel)

Alcohol Interactions

• Alcohol is a drug that interacts with almost every medication  
  – Especially antidepressants, opioids, and other CNS active drugs
• Antioxidants and beta-carotene intensify alcohol’s effect on the liver, as does acetaminophen
• Ethnic differences in metabolism by alcohol dehydrogenase  
  – Chinese have ↓ alcohol tolerance with flushing
Tobacco Interactions

• Smoking may
  – increase the metabolism of some drugs
    • Propoxyphene => decreased analgesia
    • Induces 1A2 enzyme metabolism, leading to decreased levels of:
      – Amitriptyline
      – Estradiol
      – Haloperidol
      – Tizanidine

Other Food/Drug Interactions

• Black licorice
  – When used with diuretics can cause dangerously low potassium
  – When used with digoxin can cause arrhythmias and cardiac arrest
  – Can interact with calcium channel blockers
Other Food/Drug Interactions

– Orange juice
  • Will increase the absorption of aluminum in aluminum antacids
  • Will decrease the effectiveness of antibiotics

– Caffeinated Beverages
  • Cimetidine, quinolone antibiotics (Cipro), and BCP will slow down the metabolism of caffeine, leading to an increased “Java jolt”

Other Food/Drug Interactions

• Grilled meat
  – Can decrease the absorption of theophylline

• High dietary fat
  – When taken with NSAIDs can cause kidney damage and leave the patient feeling drowsy and sedated
  – ↓ GI motility

• Turnips
  – Contain two goiterogenic compounds

• Strawberries, raspberries, spinach, and rhubarb
  – Contain oxalic acid which can aggravate kidney stones
  – Can reduce the absorption of iron and calcium
## Food/Drug Interactions

<table>
<thead>
<tr>
<th>Drugs</th>
<th>Effects and Precautions</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Antibiotics</strong></td>
<td></td>
</tr>
<tr>
<td>Cephalosporins, penicillin</td>
<td>Take on an empty stomach to speed absorption of the drugs.</td>
</tr>
<tr>
<td>Erythromycin</td>
<td>Don’t take with fruit juice or wine, which decrease the drug’s effectiveness.</td>
</tr>
<tr>
<td>Sulfas drugs</td>
<td>Increase the risk of Vitamin B-12 deficiency</td>
</tr>
<tr>
<td>Tetracycline</td>
<td>Dairy products reduce the drug’s effectiveness. Lowers Vitamin C absorption</td>
</tr>
<tr>
<td><strong>Anticonvulsants</strong></td>
<td></td>
</tr>
<tr>
<td>Dilantin, phenobarbital</td>
<td>Increase the risk of anemia and nerve problems due to deficiency of folic acid and other B vitamins.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Drugs</th>
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</tr>
</thead>
<tbody>
<tr>
<td><strong>Antidepressants</strong></td>
<td></td>
</tr>
<tr>
<td>Fluoxetine</td>
<td>Reduce appetite and can lead to excessive weight loss</td>
</tr>
<tr>
<td>Lithium</td>
<td>A low-salt diet increases the risk of lithium toxicity; excessive salt reduces the drug’s efficacy</td>
</tr>
<tr>
<td>MAO Inhibitors</td>
<td>Foods high in tyramine (aged cheeses, processed meats, legumes, wine, beer, among others) can bring on a hypertensive crisis.</td>
</tr>
<tr>
<td>Tricyclics</td>
<td>Many foods, especially legumes, meat, fish, and foods high in Vitamin C, reduce absorption of the drugs.</td>
</tr>
</tbody>
</table>
Food/Drug Interactions

### Antihypertensives, Heart Medications

<table>
<thead>
<tr>
<th>Medication</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACE inhibitors</td>
<td>Take on an empty stomach to improve the absorption of the drugs.</td>
</tr>
<tr>
<td>Alpha blockers</td>
<td>Take with liquid or food to avoid excessive drop in blood pressure.</td>
</tr>
<tr>
<td>Antiarrhythmic drugs</td>
<td>Avoid caffeine, which increases the risk of irregular heartbeat.</td>
</tr>
<tr>
<td>Beta blockers</td>
<td>Take on an empty stomach; food, especially meat, increases the drug's effects and can cause dizziness and low blood pressure.</td>
</tr>
<tr>
<td>Digitalis</td>
<td>Avoid taking with milk and high fiber foods, which reduce absorption, increases potassium loss.</td>
</tr>
<tr>
<td>Diuretics</td>
<td>Increase the risk of potassium deficiency.</td>
</tr>
<tr>
<td>Potassium sparing diuretics</td>
<td>Unless a doctor advises otherwise, don't take diuretics with potassium supplements or salt substitutes, which can cause potassium overload.</td>
</tr>
<tr>
<td>Thiazide diuretics</td>
<td>Increase the reaction to MSG.</td>
</tr>
</tbody>
</table>

### Asthma Drugs

<table>
<thead>
<tr>
<th>Medication</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pseudoephedrine</td>
<td>Avoid caffeine, which increase feelings of anxiety and nervousness.</td>
</tr>
<tr>
<td>Theophylline</td>
<td>Charbroiled foods and high protein diet reduce absorption. Caffeine increases the risk of drug toxicity.</td>
</tr>
</tbody>
</table>

### Cholesterol Lowering Drugs

<table>
<thead>
<tr>
<th>Medication</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cholestyramine</td>
<td>Increases the excretion of folate and vitamins A, D, E, and K.</td>
</tr>
<tr>
<td>Gemfibrozil</td>
<td>Avoid fatty foods, which decrease the drug's efficacy in lowering cholesterol.</td>
</tr>
</tbody>
</table>

### Heartburn and Ulcer Medications

<table>
<thead>
<tr>
<th>Medication</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antacids</td>
<td>Interfere with the absorption of many minerals; for maximum benefit, take medication 1 hour after eating.</td>
</tr>
<tr>
<td>Cimetidine, Famotidine, Sucralfate</td>
<td>Avoid high protein foods, caffeine, and other items that increase stomach acidity.</td>
</tr>
</tbody>
</table>
Porphyria

- Inherited defect of hemoglobin metabolism
- One or more of 8 enzymes are involved
- Symptoms are triggered by light and/or “porphyrogenic” drugs

<table>
<thead>
<tr>
<th>Type of Acute Porphyria</th>
<th>Synonyms</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALAD</td>
<td>ALAD deficiency</td>
</tr>
<tr>
<td></td>
<td>ALA-uria</td>
</tr>
<tr>
<td>AIP</td>
<td>Hydroxymethylbilane synthase deficiency</td>
</tr>
<tr>
<td></td>
<td>Waldenstrom porphyria</td>
</tr>
<tr>
<td>HCP</td>
<td>Coproporphyria</td>
</tr>
<tr>
<td>VP</td>
<td>Protoporphyrinogen oxidase deficiency</td>
</tr>
<tr>
<td></td>
<td>Porphyria variegata</td>
</tr>
</tbody>
</table>

Medicines to Avoid in Porphyria

- Barbiturates
- Butalbital
- Carbamazepine
- Carisoprodol
- Chloroquine
- Clonidine
- Diclofenac
- Ergot
- Erythromycin
- Erythropoietin
- Estrogens
- Fluoxene
- Griseofulvin
- Heavy metals
- Hydralazine
- Ketamine
- Meprobamate

- Methyldopa
- Metoclopramide
- Nortriptyline
- Pargyline
- Pentazocine
- Phenobarbital
- Phenoxybenzamine
- Phenytoin
- Plaquinil
- Progestins
- Ranitidine
- Rifampin
- Spironolactone
- Sulfonamides
- Theophylline
- Valproate
Herbal Medications

- **Kava Kava**
  - Used for insomnia, nervousness, and IBS
  - Inhibits CYP1A2, CYP2D6, and CYP3A4
  - Increases the sedative effects of other medicines
  - Interacts with benzodiazapams, barbiturates, haloperidol
- **Black Cohosh**
  - Used as a mild relaxant, antidepressant, and anti-rheumatic
  - Interferes with HRT, BCP, and estrogen promoters for osteoporosis
- **Feverfew**
  - Used for treatment and prevention of migraines
  - Also used for fevers, dizziness, minor arthritis
  - When used with sumatriptan or other migraine medications can cause increased heart rate and blood pressure
- **Ginkgo biloba**
  - Used to increase circulation leading to increased mental sharpness and decreased cold extremities/intermittent claudication as well as macular degeneration
- **Garlic**
  - Used to increase circulation by decreasing blood viscosity
  - May decrease blood sugar

All three can increase bleeding time. May cause increased bleeding with NSAIDs, coumadin, and antiplatelet meds
Herbal Medications

- St. Johns Wort
  - Mild sedative and antidepressant
  - Active ingredient is hypericin
  - Inhibits CYP2C9 and CYP1A2
  - Induces CYP3A4 and intestinal p-GP
    - May increase metabolism of estradiols (CYP3A4)
      - Women should be advised to use other means of birth control
    - Will decrease digoxin levels by 15-20% (p-GP)
      - 2 weeks of St. Johns Wort in normal volunteers increased p-GP 1.4 fold
  - Probably works as an MAOI; may cause MAOI interactions
  - May cause serotonin syndrome if used with SSRIs
  - May decrease blood levels of theophylline

Herbal Medications

- Goldenseal
  - Used for coughs, stomach upset, menstrual problems
  - May raise blood pressure,
  - May cause electrolyte imbalance

- Ginseng
  - Multiple uses including chronic fatigue, anemia, forgetfulness, and impotence
  - May cause hypertension and MAOI interaction
  - May cause bleeding

- Yohimbine
  - Used to treat impotence
  - Alpha 2 agonist, increasing flow to penis
  - May counteract clonidine antihypertensive effect and increase effect of TCAs
Other Interactions

• Vitamin E (>1000 units/day)
  – Enhance the anticoagulant effect of warfarin

• Melatonin
  – Fluoxetine
    • ↑ endogenous melatonin secretion
    • ↓ the metabolism of melatonin
      – CYP1A2 or CYP2C9 inhibition
    • Results in ↑ sedation, esp with haloperidol and diazepam (also metabolized by CYP1A2 or CYP2C9)
  – Reduced effect of slow-released nifedipine
    • Melatonin seems to play a role in CV regulation

So What Should You Do?

• Review carefully all medicines the patient is taking, including OTC and herbal supplements
• Understand the pharmacology of the medicines you prescribe
  – Route of excretion, metabolism, half-life, bioavailability
• Review previous effects from medications
  • “Darvocet works better than Lortab”
  • “Codeine doesn’t work”
• Minimize the number of prescriptions you write
• Look for clues in the UDT
  – +/- hydromorphone in a patient on hydrocodone
• Watch for changes in drug effect with introduction of new medicines
"If it were not for the great variability among individuals medicine might as well be a science and not an art”

William Osler (1892)