Drug Interactions
What Every Health Care Provider Needs to know

Ali J. Olyaei, PharmD, BCPS
Professor of Medicine & Pharmacotherapy
Nephrology & Hypertension
Oregon State University and Oregon Health & Science University
Objectives

- Evaluate the impact of alerting on a large number of potential interactions.
- Formulate a list of medications that have a high potential to interact.
- Evaluate the consequences of drug interactions.
- Provide suggestions for improving the alerting system.
OVER PRESCRIBED AMERICA

Are Americans taking too Many Prescription Drugs?

4.2 BILLION
prescriptions written in the U.S. in 2011

Rx in Oregon:
52 million Rxs

Cost: ~3 Billion

Oregon Population:
3.97 million

Americans have been led to believe – by their doctors, by advertisers, and by the pharmaceutical industry – that there is a pill to cure just about anything that ails them.
The FDA:
Watchdog Without a Bite
(and With No Incentive to Bark)
We Must Remember That the Absence of Evidence Is Not the Evidence of Absence
# Drugs Removed from the Market

<table>
<thead>
<tr>
<th>DRUG</th>
<th>CATEGORY</th>
<th>REASON</th>
</tr>
</thead>
<tbody>
<tr>
<td>Astemizole</td>
<td>antihistamine</td>
<td>serious metabolic drug intxns</td>
</tr>
<tr>
<td>Bromfenac</td>
<td>analgesic</td>
<td>hepatotoxicity</td>
</tr>
<tr>
<td>Dexfenfluramine</td>
<td>anorectic</td>
<td>cardiovascular tox</td>
</tr>
<tr>
<td>Felbamate</td>
<td>anticonvulsant</td>
<td>aplastic anemia</td>
</tr>
<tr>
<td>Flosequinan</td>
<td>vasodilator</td>
<td>increased mortality</td>
</tr>
<tr>
<td>Grepafloxacin</td>
<td>antibiotic</td>
<td>drug Intx/proarrhythmic</td>
</tr>
<tr>
<td>Mibefradil</td>
<td>Ca channel blocker</td>
<td>serious drug intxns</td>
</tr>
<tr>
<td>Temafloxacin</td>
<td>antibiotic</td>
<td>drug Intx/severe ADR</td>
</tr>
<tr>
<td>Terfenadine</td>
<td>antihistamine</td>
<td>serious drug intxn</td>
</tr>
<tr>
<td>Travafloxacin</td>
<td>antibiotic</td>
<td>hepatotoxicity</td>
</tr>
<tr>
<td>Cisapride</td>
<td>antihistamine</td>
<td>serious metabolic drug intxns</td>
</tr>
<tr>
<td>Baychol</td>
<td>Cholesterol</td>
<td>serious drug intx/renal failure</td>
</tr>
<tr>
<td>Vioxx</td>
<td>pain/NSAIDs</td>
<td>MI/CVD</td>
</tr>
<tr>
<td>Baxetra</td>
<td>pain/NSAIDs</td>
<td>skin Rx &amp; CVD</td>
</tr>
</tbody>
</table>
Background

- Drug Interactions can be a significant cause of medication errors, adverse medication reactions, and patient morbidity and mortality.
- HOWEVER not all drug interactions are “bad”.
- It is also equally important that they do not over react.
- Alarm fatigue or alert fatigue.
- Patients are heterogeneous and their responses to each drug therapy may be variable.
- Although most patients can take drugs with potential drug-drug interactions concurrently, polypharmacy may complicate the drug therapy.
- Legal ramifications possible.
Who’s at highest risk for a drug interaction?

- Elderly
- Polypharmacy
  - 40% for patients taking 5 medications
  - 80% for patients taking 7 or more
- 60% of statin rhabdomyolysis cases are caused by a drug interaction
- Coadministration of drugs that prolong QT interval + additional risk factors
- Multiple providers & pharmacies
Overview

- 5-26% of adverse drug reactions (ADR) are attributed to drug interactions.
- 60-90% of alerts are overridden

- **Alarm fatigue or alert fatigue**
  - ~330 drug alerts have to be reviewed to prevent a single ADR of any severity.
  - 2700 to prevent death or disability
How do physicians respond?
Arch Intern Med 2013;163:2625-31

• 24,034 prescriptions over 3 month period
• Physician reviews judged 36.5% of alerts as inappropriate
• 3129 (13%) DDI alerts (moderate severity/strong evidence & high severity with moderate or strong evidence)
• **89.4% of high-severity DDI alerts were overridden**
• Resulting in 31 ADEs
How do physicians respond?

• 22% of 220 prescribers with alert systems in office admitted to frequent overrides without proper check.

• Perception that alerts are often irrelevant.

• 90% thought it should be more difficult to override potentially lethal interactions.
What do pharmacists do?

• 74% override with no further action
• 19% override & discuss with the patient
• 4% prescriber contacted & no change in therapy
• 3% prescriber contacted & medication changed
Drug interactions by level of severity and evidence

Pharm Pharmaceut Sci 12(3) 266 - 272, 2009
n=\sim3500 \text{ Rx}

**Table 1.**

**Severity; Level Frequency \% (n)**
- **Major** 22\% (278)
- **Moderate** 78\% (1004)

**Evidence; Level Frequency \% (n)**
- **Established** 16\% (206)
- **Probable** 37\% (479)
- **Suspected** 47 (597)
Length of hospital stay, in days, for patients with and without drug-drug interaction
Drug Interactions:
“When the Holes Line Up”

Hansten PD, Horn JR. Modified from: James Reason, Human Error, 1990
Drug Interactions: A Practical Approach

• Be alert for **patient groups most vulnerable** to drug interactions.

• **In general,**
  • Be alert for patients with a new med, dosage change, or recent health change that could change a tolerated interaction to a clinically significant interaction
  • **Older age and polypharmacy** are risk factors for clinically significant drug interactions.
  • Over 80% of patients taking seven or more drugs are at risk of a drug interaction
Be alert for drugs involved in clinically significant interactions.
Top Drug Interactions; 2016

- Warfarin & NOACs and NSAIDs
- Warfarin and Amiodarone
- Warfarin and TMP/SMZ
- ACE inhibitors — Potassium supplements
- ACE inhibitors and spironolactone
- ACE-inhibitors/Diuretics/NSAIDS
- Clonidine and Metoprolol
- Digoxin and Amiodarone
- Digoxin and Verapamil
- ACE-I and TMP/SMZ
- Warfarin and Quinolones (Cipro)
- Quinolones/thyroid and Iron/Ca/Mg
- SSRI plus tramadol
- HMG-CoA reductase inhibitor, gemfibrozil and Amiodarone
- HMG-CoA reductase inhibitor and Macrolide Abx
- HMG-CoA reductase inhibitor and Azole
A drug-drug interaction (DDI) is a pharmacokinetic or pharmacodynamic influence of one medication on another that differs from the known or anticipated effects of each agent alone. A DDI may result in a change in either drug efficacy or drug toxicity for 1 or both of the interacting medications. Pharmacokinetic DDIs result in altered absorption, distribution, metabolism, or excretion of a medication. A pharmacodynamic DDI occurs when 1 medication modifies the pharmacological effect of another in an additive, a synergistic, or an antagonistic fashion.

It is estimated that >2.8% of hospital admissions occur as a direct result of DDIs. However, the actual incidence of hospitalization secondary to clinically significant DDIs is likely to be highly underestimated because medication-related issues are more commonly reported as adverse drug reactions. Complex underlying disease states also may make recognizing a DDI more challenging, further contributing to a lower reported incidence. The overall clinical impact of a DDI can range from mild to life-threatening. Therefore, not all DDIs require a modification in therapy. The variability in the clinical significance of a DDI depends on both medication-specific and patient-specific factors. Medication-specific factors include the individual pharmacokinetic characteristics of each medication involved in the DDI (e.g., binding affinity, half-life, dose). Patient-specific factors include age, sex, lifestyle, genetic polymorphisms causing differences in enzyme expression or activity, and other disease states. The diagnosis of drug metabolism (e.g., hepatic or renal impairment, cardiac failure) or predisposition to changes in efficacy or safety (e.g., statin intolerance in patients with a history of myositis). Clinically significant DDIs are usually preventable. To optimize patient safety, healthcare providers must have an understanding of the mechanisms, magnitude, and potential consequences of any given DDI. Interpreting this information will assist clinicians in the safe prescribing of medications and permits careful consideration of the benefits and risks of concomitant medications.

Statins reduce morbidity and mortality in patients with known atherosclerotic cardiovascular disease (ASCVD) and in many primary prevention patients. Current guidelines recommend high-intensity statin therapy in all patients with ASCVD and age ≥75 years and moderate to high-intensity statin therapy in patients with ASCVD and age >75 years, diabetes mellitus, and familial hypercholesterolemia and in primary prevention patients with 10-year ASCVD risk ≥7.5%. Given the important role of statins in patients with ASCVD and those at high ASCVD risk, combination therapy with statins and other cardiovascular medications is highly likely, and potentially significant DDIs must be considered in patients treated with statins.

Another important aspect of prescribing medications in combination is evaluating the risks versus benefits. Given the continuing increase in healthcare costs, trying to minimize costs to the health system through minimization of adverse effects and optimizing efficacy is of paramount importance. Prescription drug coverage and

Barbara S. Wiggins, PharmD, FAHA, Chair
Joseph J. Saseen, PharmD, FAHA, Co-Chair
Robert L. Page II, PharmD, MSPh, FAHA
Brent N. Reed, PharmD, FAHA
Karin Sneed, PharmD
John R. Costis, MD, FAHA
David Lanier, MD, FAHA
Salim Virani, MD
Pamela E. Morris, MD, FAHA
On behalf of the American Heart Association Clinical Pharmacology Committee of the Council on Clinical Cardiology, Council on Hypertension; Council on Quality of Care and Outcomes Research; and Council on Functional Genomics and Translational Biology

Key Words: AHA Scientific Statements; anti-arrhythmic agents; anticoagulants; calcium channel blockers; cardiovascular drug-drug interactions; drug-related side effects and adverse reactions; fenofibrate; fenofibric acid derivatives; immunosuppressive agents; hydroxymethylglutaryl-CoA reducetase inhibitors; lovastatin; niacin; pravastatin; rosuvastatin; simvastatin; statins; statin-drug interactions; telmisartan; valsartan; warfarin
Clinically Significant Drug Interactions

- Antidepressants
- Anticonvulsants
- Antifungals (azoles, caspofungin)
- Protease Inhibitors
- Statins
- Anti-hypertensive medications
- Non-prescription medications
- Oral contraceptives
Drug-Induced Torsades de Pointes

- Low frequency event
- Potentially life threatening
- Not highly predictable despite known risk factors
QT prolongation

• When evaluating the significance of an interaction involving QT prolongation, keep in mind the risk factors for torsades de pointes:
  • QTc >480 ms (2- to 3-fold risk)
  • Female gender (2-fold risk),
  • Long QT interval syndrome
  • Use of more than one QT-prolonging drug
  • Hypokalemia, hypomagnesemia, hypocalcemia,
  • Others: diuretic use, bradycardia, Hospitalization, advanced age, and renal or hepatic insufficiency
Total deaths were nearly twice as high in the azithromycin group with an odds ratio of 1.85 (95% CI 1.25-2.75).

- These new study indicates only a small absolute risk of mortality of 0.01% with the use of azithromycin when compared with a risk of 0.006% in patients not using antibiotics.
  - Azithromycin was associated with 3.5 times more deaths than ciprofloxacin.
  - Azithromycin use was not associated with an increased risk of death from cardiovascular causes in a general population of young and middle-aged adults.

- This translates into a number needed to harm (NNH) of 1 in 21400 where one death would be expected for approximately every 21400 courses of treatment. However This high-cardiovascular risk group a death rate is of about 1 in 2,000.

  - ~2570 death annually related to the use of azithromycin

- The benefits of this medication may still outweigh the risks for most patients.

statin induced myopathy

• Polypharmacy
• Multiple disease states (e.g., renal or hepatic insufficiency)
• Hypothyroidism/hypokalemia
• History of musculoskeletal symptoms or CK elevation
• Others neuromuscular disease, personal or family history of statin or other myopathy, use of medications or foods (e.g., grapefruit) that increase statin levels, age over 75 years, Asian ancestry, female gender, low BMI or small frame, frailty, physical activity, and alcohol or drug abuse
Mechanisms of drug interactions

Pharmacokinetics and Pharmacodynamics

Pharmacokinetics involve the effect of a drug on another drug kinetic that includes absorption, distribution, metabolism, and excretion.

Pharmacodynamics are related to the pharmacological activity of the interacting drugs. E.g., synergism, antagonism, altered cellular, transport effect on the receptor site.
Antiacids
H2 antagonists
PPI

Decrease the tablet dissolution of Ketoconazole and Mycophenolate (acidic)

Mycophenolate
Ketoconazole
Iron

Therefore, these drugs must be avoided
Altered intestinal bacterial flora;

40% or more of the administered digoxin dose is metabolized by the intestinal flora.

Antibiotics kill a large number of the normal flora of the intestine

Increase digoxin conc. and increase its toxicity
Complexation or chelation

Antibiotics [Quinolones, TCN] interacts with iron preparations

\[
\begin{align*}
&\text{Ca}^{2+} \\
&\text{Mg}^{+2} \\
&\text{Iron} \\
\rightarrow\quad \text{Unabsorbable complex}
\end{align*}
\]

Antacid (aluminum or magnesium) hydroxide Decrease absorption of ciprofloxacin by 85% due to chelation
Drug-induced mucosal damage.

**Antineoplastic agents**
- e.g., cyclophosphamide
- vincristine
- procarbazine

Inhibit absorption of several drugs, e.g., digoxin

**Altered motility**

Metoclopramide (antiemetic)

Increase absorption of cyclosporine due to the increase of stomach emptying time

Increase the toxicity of cyclosporine
Drug-Food interactions

- Grapefruit juice and Terfenadine
- Grapefruit juice and cyclosporin
- Grapefruit juice and felodipine
- Grapefruit contains furanocoumarin compounds that can selectively inhibit CYP3A4
Drug Metabolism Interactions

Eliminated Unchanged

P450-Phase I

Phase II

Phase II
PHARMACOKINETICS

METABOLISM

1. Cytochrome P-450 isoenzymes

2. P-glycoprotein transport

3. Genetic polymorphism
   - rapid acetylators
   - extensive metabolizers (EM), poor metabolizers (PM)
CYTOCHROME P-450
Nomenclature

• 3-tier Classification (e.g. CYP 3A4)
  • family, subfamily, specific gene

• Lipid bilayer of ER -- hepatocytes, enterocytes
  • kidney, lung, and brain

• Oxidative Metabolism -- drugs, steroid hormones, prostaglandins

• Over 1000 identified; CYP 3A4 metabolizes 35% of all prescribed drugs
• Many drugs induce or inhibit certain hepatic enzymes
• Many drugs are substrates of the CP 450 system

• Smoking
Proportion of Drugs Metabolized by CYP450 Isozymes

- CYP3A4: 36%
- CYP2D6: 19%
- CYP2C19
- CYP2C9
- CYP2E1
- CYP1A2
- CYP2B6
- CYP2A6

OHSU
## Human Liver Drug CYPs

<table>
<thead>
<tr>
<th>CYP enzyme</th>
<th>Level (%total)</th>
<th>Extent of variability</th>
</tr>
</thead>
<tbody>
<tr>
<td>1A2</td>
<td>~13</td>
<td>~40-fold</td>
</tr>
<tr>
<td>1B1</td>
<td>&lt;1</td>
<td></td>
</tr>
<tr>
<td>2A6</td>
<td>~4</td>
<td>~30 - 100-fold</td>
</tr>
<tr>
<td>2B6</td>
<td>&lt;1</td>
<td>~50-fold</td>
</tr>
<tr>
<td>2C</td>
<td>~18</td>
<td>25-100-fold</td>
</tr>
<tr>
<td>2D6</td>
<td>Up to 2.5</td>
<td>&gt;1000-fold</td>
</tr>
<tr>
<td>2E1</td>
<td>Up to 7</td>
<td>~20-fold</td>
</tr>
<tr>
<td>2F1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2J2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3A4</td>
<td>Up to 28</td>
<td>~20-fold</td>
</tr>
<tr>
<td>4A, 4B</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

S. Rendic & F.J. DiCarlo, Drug Metab Rev 29:413-80, 1997
Cytochrome P450

CYP P450

P450 I

P450 II

C9

C19

D6

A2

A4

A5

ERY

Tacrolimus
## CYP3A4

<table>
<thead>
<tr>
<th>Substrate</th>
<th>Inhibitors</th>
<th>Inducers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cyclosporine, FK506 Corticosteroids</td>
<td>Erythromycin</td>
<td>Carbamazepine</td>
</tr>
<tr>
<td>Erythromycin</td>
<td>Clarithromycin</td>
<td>Phenobarbital</td>
</tr>
<tr>
<td>Felodipine, isradipine</td>
<td>Diltiazem</td>
<td>Rifampin</td>
</tr>
<tr>
<td>Nifedipine</td>
<td>Ketoconazole</td>
<td>Rifabutin</td>
</tr>
<tr>
<td>Nisoldipine</td>
<td>Fluconazole</td>
<td>Phenytoin</td>
</tr>
<tr>
<td>Nitrendipine</td>
<td>Itraconazole</td>
<td>Corticosteroids</td>
</tr>
<tr>
<td>Digoxin, quinidine</td>
<td>Quinidine</td>
<td>INH</td>
</tr>
<tr>
<td>Verapamil</td>
<td>Grapefruit juice</td>
<td>St. John’s wort</td>
</tr>
<tr>
<td>Warfarin</td>
<td>Cimetidine</td>
<td></td>
</tr>
<tr>
<td>Sildenafil</td>
<td>Indinavir</td>
<td></td>
</tr>
<tr>
<td>Astemizole</td>
<td>Fluoxetine</td>
<td></td>
</tr>
<tr>
<td>Terfenadine</td>
<td>Zileuton, Zafirlukast</td>
<td></td>
</tr>
<tr>
<td>Pioglitazone</td>
<td>Verapamil</td>
<td></td>
</tr>
<tr>
<td>R-Warfarin</td>
<td>Amiodarone</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Corticosteroids</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Fluvoxamine</td>
<td></td>
</tr>
</tbody>
</table>
## CYP 2D6

<table>
<thead>
<tr>
<th>Substrate</th>
<th>Inhibitors</th>
<th>Inducers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Codeine</td>
<td>Amiodarone</td>
<td>Carbamazepine</td>
</tr>
<tr>
<td>Dextromethorphan</td>
<td>Fluoxetine</td>
<td>Phenytoin</td>
</tr>
<tr>
<td>Metoprolol</td>
<td>Labetalol</td>
<td>Phenobarbital</td>
</tr>
<tr>
<td>Paroxetine</td>
<td>Paroxetine</td>
<td>Rifampin</td>
</tr>
<tr>
<td>Haloperidol</td>
<td>Propafenone</td>
<td></td>
</tr>
<tr>
<td>Propranolol</td>
<td>Quinidine</td>
<td></td>
</tr>
<tr>
<td>Risperidone</td>
<td>Sertraline</td>
<td></td>
</tr>
<tr>
<td>Timolol</td>
<td>Cimetidine</td>
<td></td>
</tr>
<tr>
<td>Amitriptyline</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nortriptyline</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clozapine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Morphine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Methadone</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
# CYP 2C (9 and 19)

<table>
<thead>
<tr>
<th>Substrate</th>
<th>Inhibitors</th>
<th>Inducers</th>
</tr>
</thead>
<tbody>
<tr>
<td>S-Warfarin</td>
<td>Amiodarone</td>
<td>Carbamazepine</td>
</tr>
<tr>
<td>Losartan</td>
<td>Cimetidine</td>
<td>Phenytoin</td>
</tr>
<tr>
<td>Diazepam</td>
<td>Chloramphenicol</td>
<td>Rifampin</td>
</tr>
<tr>
<td>Imipramine</td>
<td>Fluconazole</td>
<td></td>
</tr>
<tr>
<td>Amitriptyline</td>
<td>Isoniazid</td>
<td></td>
</tr>
<tr>
<td>Phenytoin</td>
<td>Ketoconazole</td>
<td></td>
</tr>
<tr>
<td>Rosiglitazone</td>
<td>Zafirlukast</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Fluoxetine</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Fluvoxamine</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Sertraline</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Rosiglitazone</td>
<td></td>
</tr>
</tbody>
</table>
Carbamazepine

- Diltiazem increases carbamazepine serum concentration and frequently results in toxicity

- Verapamil increases carbamazepine serum concentration

- Nifedipine has no effect on carbamazepine PK

- Felodipine is highly susceptible to enzyme induction; it may be difficult to achieve therapeutic felodipine blood concentration
Drug prices are rising at an unsustainable and seemingly irrational rate.


Insulin is lifesaving for Type 1 diabetics.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Percent Change</th>
<th>Base Price</th>
<th>Current Price</th>
</tr>
</thead>
<tbody>
<tr>
<td>Januvia6</td>
<td>93%</td>
<td>$572</td>
<td>$1,102</td>
</tr>
<tr>
<td>Humalog7</td>
<td>127%</td>
<td>$93</td>
<td>$210</td>
</tr>
<tr>
<td>Novolin8</td>
<td>167%</td>
<td>$41</td>
<td>$110 current</td>
</tr>
<tr>
<td>Levermir9</td>
<td>189%</td>
<td>$86</td>
<td>$249 current</td>
</tr>
<tr>
<td>Lantus10</td>
<td>189%</td>
<td>$86</td>
<td>$249 current</td>
</tr>
<tr>
<td>SymlinPen 6011</td>
<td>252%</td>
<td>$168</td>
<td>$590 current</td>
</tr>
<tr>
<td>Humulin12</td>
<td>325%</td>
<td>$258</td>
<td>$1,097 current</td>
</tr>
</tbody>
</table>

Source: Medi-Span® Price Rx®. Figures reflect wholesale acquisition cost.

High costs affect both brand-name and generic drugs and span therapeutic areas. This graphic focuses on brand-name diabetes drugs, with no generic options yet available for insulin in the U.S.
Thousands of generic drugs saw prices rise between 2008 to 2015

Of 21,006* generic drugs analyzed by Connecture, 9,613 saw price movement during the period. The remaining 11,393 drugs saw no price change.

*Individual drug/dosage/package combinations.

Source: Connecture
Average annual inflation
Therapies Always Cause a Combination of:

Good Effects  Bad Effects
Conclusions

• Most interactions are not clinically significant.
• Many, if not most, drug interactions can be avoided.
• We are responsible for making drug therapy safe for our patients.
• We need to work together to change the system so it works better.
• Reduce alert fatigue.
• Make important interactions difficult to override.
• Exposure to potential drug-drug interactions may result in unnecessary and unintended health care costs.
Take Home Message

• Drug interactions are common, increasing with the number of administered drugs.
• Serious life threatening side effects can occur.
• Interactions can be avoided