Drug-Drug Interactions and Their Clinical Relevance

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Myths & Facts: Drug Interactions

• Always compromise clinical outcomes
• Most adverse drug reactions are due to drug sensitivity.
• Not frequent enough to deserve our attention.
• Can only occur with pharmaceutical products.
• Most interactions are pharmacokinetically-mediated.
Defining a Drug Interaction

- “A measurable modification (in magnitude or duration) of the action of one drug by prior or concomitant administration of another substance.”
  - Drug-drug (Prescription, OTC)
  - Drug-herbal
  - Drug-food
  - Drug-disease
  - Drug-alcohol
  - Drug-gene (pharmacogenetic & pharmacogenomics)
Relationship of PD and PK in Determining Result of Drug Treatment

Magnitude = PD x PK

Clinical = Affinity x Conc.
response for *SOA at *SOA

*SOA=Site Of Action
Relationship of PD and PK and Biological Variance in Determining Overall Result of Drug Treatment

Magnitude of Effect = PD x PK x Biological Variance

Clinical response for *SOA at *SOA = Affinity x Conc. x Underlying biology of the patient

- Age
- Race
- Organ dysfunction
- Diagnosis/Disease
- Pregnancy/Lactation
- Gender
- Genetics
**Relationship of PD and PK and Biological Variance in Determining Overall Result of Drug Treatment**

| Magnitude = PD x PK x Biological Variance x Environment |
| Clinical response = Affinity for *SOA x Conc. at *SOA |
| Underlying biology of the patient |
| Extrinsic Factors |
| - Age |
| - Race |
| - Organ dysfunction |
| - Diagnosis/Disease |
| - Pregnancy/Lactation |
| - Gender |
| - Genetics |
| - Drug Interactions |
| - Smoking/Food/Herbs |
| - Alcohol use |
| - Medical Practice |
| - Regulatory |
| - Others |

- **It is critical to evaluate how these factors affect drug response and exposure**
- **Ultimate goal is optimal dosing for patients with these individual factors**
Different Types of Drug-Interactions

• Those interactions that result in alteration of mechanism of action of one drug by concomitant use of another drug are called **Pharmacodynamic Drug Interactions**.

• Those interactions that result in alteration of concentration of one drug at the SOA by concomitant use of another drug are called **Pharmacokinetic Drug Interactions**.

• These interactions are not mutually exclusive and can occur together with the same agent.
Pharmacodynamic (PD) Drug Interactions

- These drug interactions can be:
  - Additive (two or more analgesics)
  - Synergistic (Sinemet and selegiline)
  - Antagonistic (antipsychotic drugs and stimulants)
Pharmacodynamic Drug Interactions in Palliative Care

- **Anticholinergic effects** (low potency antipsychotic drugs and tertiary amine TCAs)
- **Constipation** (same as above)
- **Lowered seizure threshold** (same as above)
- **Serotonin syndrome** (MAO-I and SSRIs)
- **CNS depression** (benzodiazepines and narcotic analgesics)
- **QTc prolongation** (antipsychotic drugs and TCAs)
Pharmacokinetic (PK) Interactions

Since PK of a drug depends on its:

- Absorption
- Distribution
- Metabolism
- Elimination

- There are 4 types of PK drug interactions.
- The most clinically relevant are the METABOLIC DRUG INTERACTIONS.

How Knowledge of P-450 Enzymes Will Simplify Understanding of Metabolic Drug Interactions?

Alters

-Drug A  Enzyme X

Metabolizes

-Enzyme X  Drugs B, C, D, E, & F

Therefore, Alters

-Drug A  Drugs B, C, D, E, & F
A Case Report with Clinically Significant Impact

• In 1995, 64-year-old depressed female was on imipramine (IMI) since 8 years at doses of 150 or 200mg/d.

• Over this period, 10 levels at Css were drawn on IMI alone, and four were drawn when the patient was coprescribed bupropion (BUP) at 225 mg/day.

• The metabolism of IMI involves DM to desipramine (DMI) by CYP 3A3/4 & 1A2 and HO by CYP2D6.

• DMI levels were increased twofold more than the IMI levels suggests that BUP inhibited CYP2D6.

• A decrease in DMI levels would have suggested an inhibition of CYP1A2 & 3A3/4.

Drug Interaction in Reverse

• 35 year old WM taking fluoxetine 60mg/day for his depression and phenytoin for a seizure disorder.
• Fluoxetine was discontinued to see if patient still needs it.
• Few days later, patient started having seizures again.
Interaction with Meperidine in an ER Setting

- 59-year old female was being treated for major depressive disorder
- Meperidine was prescribed to treat acute pain
- Patient developed hyperreflexia, diaphoresis, diarrhea, disorientation, confusion and hallucinations
Interaction with Meperidine in an ER Setting

• Meperidine was discontinued but symptoms did not resolve even after IV lorazepam
• Poison Control suggested “Serotonin Syndrome” after learning patient was on sertraline
• Cyproheptadine was recommended at 4-8mg every 4 hours
• Symptoms dramatically resolved within hours
Case of 28 Year-Old Smoker with Depression

• After a suicide attempt a 28 year old 2 pack a day smoker is admitted to the hospital. He is started on fluvoxamine 200mg/d, but no response.

• Discharged after 4 days.

• Does not resume smoking.

• Gradually develops headache, sleepiness and nausea.
Recurrence of Breast CA

- A patient with estrogen receptor-responsive breast CA treated with tamoxifen
- Develops MDD, treated with paroxetine 40 mg day
- Two years later patient experienced recurrence of breast CA

What could be the reason?

Stearns et al. 2003; Kelly et al. 2010
Clozapine Toxicity at Usually Prescribed Doses

• 41 year-old WM with SAD was gradually cross titrated to 400mg/day of clozapine due to inadequate response on 6mg/day of risperidone.

• A week later the patient became gradually confused and disoriented and eventually lost consciousness and ended up in ER.

• The combined clozapine and norclozapine levels were elevated at 2500ng/mL.

• Patient’s symptoms resolved after clozapine was reduced to 75mg/day with a reduction in clozapine and norclozapine levels to 420ng/mL.

Clozapine Toxicity at Usually Prescribed Doses

- Clozapine (Clz) is primarily metabolized by CYP1A2 to norclozapine (Nclz).
- Though it is unlikely that CYP1A2 was responsible, as there was no increase in Clz/Nclz ratio.
- Genetic testing was requested for other CYP enzymes but without any findings.
- The routine labs including liver function tests were WNL.
- Some patients can develop unusually high levels of clozapine and/or its metabolites on routine clozapine dosages without any definitive explanation for it.

Why Is It Important To Know About Drug-Drug Interactions?

- Extent and prevalence of polypharmacy
- Cost of drug interactions

- National survey of 2005 community residing adults (>57 year old) in US
  - 80% take > 1 medical product (prescription, OTC, supplement).
  - 50% take at least 5 medical products
  - 30% take at least 5 prescription drugs
  - 4% at risk of major DDI

Qato et al. JAMA 2008
Why is There an Increased Risk for Drug Interactions?

Use of Medications by Sex and Age

Use, %

Any Use
> 5 drugs
> 10 drugs

Total 18-44y > 65 y
men men men

18-44y 45-64y > 65 y
women women women

< JAMA 2002;287:337-344 >
VA Medical Center (in- and outpatients) (n=1076)
Drugs prescribed to patients on at least one antidepressant

Number of drugs prescribed

Percentage of patients

1 drug: 7%
2 drugs: 12%
3 drugs: 13%
4 or more drugs: 68%
Use of Herbal Agents has Significantly Increased

• 18.4% Americans take prescription medications concurrently with at least one herbal agent, a high dose vitamin, or both.

• Thus, 15 millions are at risk for potential drug interactions and related adverse effects.

• 3 millions of these are 65 years of age or older.

Eisenberg et al. JAMA 1998
Complimentary and alternative medicines (CAM): Patients’ Report

N = 31,044 U.S. adults interviewed for 2002 National Health Interview Survey

Percent of respondents

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<th>Activity</th>
<th>Percent</th>
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<td>5.0</td>
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<td>Diets</td>
<td>3.5</td>
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</table>
Costs Associated with Drug Interactions Frequently Reported as Adverse Drug Reactions (ADRs)

- Drug interactions are 3-5% all ADRs (under-estimated)
- We spend 136 billion yearly on ADRs, which is greater than total cost of CV or diabetic care.
- Resulting in 1 out of 5 injuries or death per year to hospitalized patients.
- Mean inpatient costs for patients with ADRs are double the cost of those without ADRs

Drugs Removed in the US Market Because of Drug Interactions

• Terfenadine (Seldane®) February 1998
• Mibefradil (Posicor®) June 1998
• Astemizole (Hismanol®) July 1999
• Cisapride (Propulsid®) January 2000
Drugs that may cause Torsades

- Drugs commonly involved
  - Disopyramide, dofetilide, ibutilide
  - Procainamide, quinidine, sotalol, bepridil

- Other drugs
  - Amiodarone, arsenic trioxide, cisapride
  - Erythromycin, clarithromycin, halofantrine, pentamidine, sparfloxacin, chloroquine
  - Domperidone, droperidol
  - Chlorpromazine, haloperidol, thioridazine
  - Methadone

Methadone and Long QT Syndrome (LQTS) and TdP

- Increasingly prescribed for chronic pain
- Associated mortality rising disproportionately relative to other opioids
- Potent blocker of delayed rectifier potassium ion channel
- Results in QT-prolongation and torsades in susceptible individuals
Cytochrome P-450 (CYP) Enzyme System

- Evolved over one billion years ago
- Present in every cell in the body
- Highest concentration in hepatocytes
- Located in
  - Mitochondria: steroidogenic P-450s
  - Endoplasmic reticulum: xenobiotic
- Mediate primarily oxidations
- Unintended target of some drugs
Cytochrome P450 Nomenclature Using Example of CYP2D6

- CYP = Cytochrome P450
- 2 = genetic family
- D = genetic subfamily
- 6 = specific gene

- The nomenclature is genetically based: it has no functional implications
Gingko Biloba

Phenytoin
Warfarin
Tolbutamide
Losartan
NSAIDS

CYP2C9

Elimination
**Transport Systems: P-Glycoprotein (P-gp): Variation in Drug Response**

- P-gp is an ATP-Binding Cassette B1 (ABCB1) protein transporter or efflux pump.
- Extrudes toxins and xenobiotics.
- Limits cellular uptake of drugs into brain & GIT.
- Genetic polymorphism in P-gp may cause gene-drug interactions.
Transport Systems: P-gp: Variation in Drug Response

- Linked to development of multidrug resistance (MDR) in cancer cells.
- Plays a role in transport of β-amyloid out of the CNS.

Drug Concentrations in P-glycoprotein Knock-Out Mice vs Wild Type Animals

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<th>Molecule</th>
<th>Plasma</th>
<th>Brain</th>
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<td>55-fold</td>
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<td>Digoxin</td>
<td>1.9-fold</td>
<td>35-fold</td>
</tr>
<tr>
<td>Methadone</td>
<td>1.5-fold</td>
<td>15- to 23-fold</td>
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<tr>
<td>Risperidone</td>
<td>1.4-fold</td>
<td>13-fold</td>
</tr>
</tbody>
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Interactions may be underestimated with plasma levels.
**Alterations in Absorption: Drug Transport**

- **Efflux proteins**
  - P-glycoprotein, MRP1, MRP2, OAT3
  - Extrude drug from gut back into lumen limiting drug absorption
  - Transporter induction may result in ↓ absorption
  - Transporter inhibition may result in ↑ absorption
  - Effects often difficult to assess (vs. metabolism; vs. anatomic site)
  - Inhibition may be of clinical significance for drugs that are large molecules, have low bioavailability, dissolve slowly and/or incompletely (clinical significance may be overstated in medical literature)
St John’s wort (2)

• Cases of rejection of heart transplant patients on St John’s wort

• Up to 2001, FDA’s Adverse Event Reporting System (AERS) in CDER indicated up to 39 case reports

<Chen M, Drug-Herb Interactions, Eds. Lam, Huang, Hall, Taylor & Francis, in press>
St John’s wort (5) - Effect on OC -

• 8 weeks of St John’s Wort decreased norethindrone levels and ethinyl estradiol t1/2

• More breakthrough bleeding occurred in St John’s Wort phase

• Higher midazolam clearance for those with breakthrough bleeding (216+ 67 vs. 98 +37)

Other botanical products?

- Ginkgo Biloba extract induced CYP2C19

- AUC ratio (omeprazole/5-OH omeprazole) decreased by 68%; the extent of interactions appear to be CYP2C19 genotype-dependent

<Yin OQ et al, Pharmacogenetics, 2004 Dec;14(12):841-50>
Effect of various juices on fexofenadine (n=10)

Effect on OATP > P-gp?

(1.2 L over 3 hours) in a randomized 5-way crossover

Other interactions with citrus fruit

Calcium-fortified Orange juice

Chelation + transporter?

Evaluation of -floxacin derivatives from various studies (n=15-16)

Do Gene-Drug Interactions have Similar Consequences as Drug-Drug Interactions?

- Genetic variation (polymorphism) affecting drug response are also known as gene-drug interaction
- These interactions can also result in similar outcomes as any other drug interactions
- In other words, drugs can change the phenotype from extensive to poor metabolizer or visa versa.
Gene-Drug Vs. Drug-Drug Interactions: Atomoxetine

**CYP2D6 Poor Metabolizers**

A 10-fold higher AUC and a 5-fold higher Cmax to a given dose

Average HL increases from 5.2 to 21.6 hrs.

**CYP2D6 Inhibitors**

Atomoxetine concentration increases by 3-4 fold when given with paroxetine.

ANTIDEPRESSANTS AND DRUG-DRUG INTERACTIONS
## Effects of Antidepressants on CYP-Enzymes at Minimum Effective Doses

<table>
<thead>
<tr>
<th></th>
<th>Mild (20-50%)</th>
<th>Moderate (50-100%)</th>
<th>Substantial (&gt; 150%)</th>
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<tr>
<td>Citalopram</td>
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<tr>
<td>Fluoxetine</td>
<td>3A3/4</td>
<td>2C19</td>
<td>2D6,2C9/10</td>
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<tr>
<td>Fluvoxamine</td>
<td>--</td>
<td>3A3/4</td>
<td>IA2,2C19</td>
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<tr>
<td>Nefazodone</td>
<td>--</td>
<td>--</td>
<td>3A4</td>
</tr>
<tr>
<td>Paroxetine</td>
<td>--</td>
<td>--</td>
<td>2D6</td>
</tr>
<tr>
<td>Sertraline</td>
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<tr>
<td>Venlafaxine</td>
<td>2D6</td>
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</table>

Preskorn S. Clinical Pharmacology of Selective Serotonin Reuptake Inhibitors. 1996.
## Common Substrates for Different CYP-Enzymes

<table>
<thead>
<tr>
<th>1A2</th>
<th>2C19</th>
<th>2C9</th>
<th>2D6</th>
<th>2E1</th>
<th>3A4</th>
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<tbody>
<tr>
<td>clozapine</td>
<td>omeprazole</td>
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<td>S-metoprolol</td>
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<td>olanzapine</td>
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<td>paroxetine</td>
<td>quinidine</td>
<td>clarithromycin</td>
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</table>

- 1A2: clozapine, olanzapine, imipramine, mexiletine, naproxen, riluzole, tacrine, theophylline, caffeine, cyclobenzaprine
- 2C19: omeprazole, lansoprazole, pantoprazole, clozapine, ibuprofen, diclofenac, piroxicam, timolol
- 2C9: clozapine, omeprazole, pantoprazole, ibuprofen, diclofenac, timolol, amitriptyline
- 2D6: S-metoprolol, propafenone, timolol, amitriptyline, desipramine
- 2E1: acetaminophen, chlorzoxazone, ethanol
- 3A4: clarithromycin, erythromycin, quinidine, alprazolam, diazepam, midazolam, triazolam, cyclosporine, FK 506, indinavir, ritonavir, saquinavir, astemizole, chlorpheniramine, cimapride, diltiazem
### Commonly Substrates for Different CYP-Enzymes (Contd.)

<table>
<thead>
<tr>
<th>1A2</th>
<th>2C19</th>
<th>2C9</th>
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ANTIPSYCHOTICS AND DRUG-DRUG INTERACTIONS
## Drug-Drug Interactions: Metabolic Pathways for Atypical APDs (Contd.)

<table>
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<tr>
<th>Drug</th>
<th>Renal Elimination</th>
<th>CYP 1A2</th>
<th>CYP 2C</th>
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<th>CYP 3A4</th>
<th>Other Pathways</th>
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<td>Clozapine</td>
<td>---</td>
<td>++</td>
<td>+/-</td>
<td>+/-</td>
<td>++</td>
<td>CYP 2E1</td>
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<td>Olanzapine</td>
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<td>+/-</td>
<td>+</td>
<td>---</td>
<td>FMO</td>
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<td>Risperidone</td>
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<td>---</td>
<td>---</td>
<td>++</td>
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<td>?</td>
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<td>++</td>
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# Common Inhibitors of Different CYP-Enzymes

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### Common Inducers of Different CYP-Enzymes

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<th>2C9</th>
<th>2D6</th>
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Which Factors Make a Metabolic Interaction Clinically Significant

• Therapeutic Index.
• Drugs with a therapeutic window.
• Metabolites (biologically active/MOA).
• Presence of enantiomers.
• Number of CYP enzymes mediating primary metabolic pathway(s).
Which Factors Make a Metabolic Interaction Clinically Significant (Cont’d)

- Extent and nature of polypharmacy.
- Metabolic Status (age, gender, medical illness).
- Unknown factors.
Role of TDM in Clinical Practice

• To ensure safety and tolerability of drugs especially those with narrow therapeutic index
• To check medication-adherence
• A change in dose of a drug known to alter metabolism of another drug
• To diagnose a drug-drug interaction (e.g., unusual response at usual doses or usual response at a usual dose)
Myths & Facts: Drug Interactions

• Always compromise clinical outcomes
• Most adverse drug reactions are due to drug sensitivity.
• Not frequent enough to deserve our attention.
• Can only occur with pharmaceutical products.
• Most interactions are pharmacokinetically-mediated.
References

FDA Drug Development and Drug Interactions Website:

Genomics at the FDA:
http://www.fda.gov/Drugs/ScienceResearch/ResearchAreas/Pharmacogenetics/default.htm

Drugs@FDA:
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Clinical Pharmacology Guidance for industry:
http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm064982.htm

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http://www.fda.gov/ForConsumers/ConsumerUpdates/ucm212747.htm