Common Drug-Drug Interactions in the Community Setting

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Objectives

- Review impact of drug interactions on overall healthcare costs
- Discuss pharmacokinetic mechanisms of drug interactions in regards to absorption, distribution, metabolism, and elimination
- Describe pharmacodynamic drug interactions resulting in additive and antagonistic effects between drugs
- Apply knowledge of drug interactions to modify patient drug therapy and optimize outcomes
- Identify methods to prevent potential interactions and dispose of unused and expired medications

Background

- Drug-drug interaction (DDI) - one agent affecting the activity of another when administered together
- 2000 – Overall annual cost of drug-related morbidity and mortality exceeded $177 billion
- DDIs represents 3-5% of preventable in-hospital ADRs

Pharmacokinetic Drug Interactions

- Inhibits absorption
- Affects distribution
- Inhibits enzyme metabolism
- Induces enzyme metabolism
- Alters elimination

Drug Absorption

- Affect bioavailability of other drugs
- Binding agents
  - Bile acid sequestrants
- Chelation
  - Supplements and antacids
- pH dependent
  - PPIs, H2 blockers, antacids
- Altered gastric emptying/GI motility
  - Anticholinergics
  - Prokinetic agents

Drug Distribution

- Competition for plasma protein transport
- Temporary increases in free drug concentrations may be clinically significant
  - Warfarin, phenytoin, digoxin

Drug Metabolism

- Primarily cytochrome P450
- Inhibition or induction of enzyme can result in:
  - Increased risk of toxicity
  - Decreased drug effect
- Drug can be substrate for multiple CYP pathways
- Drug can inhibit/induce its own metabolism
- New interactions constantly being identified

Drug Metabolism

- Patient factors
  - Genetics – poor vs. extensive
  - Age, nutrition, stress, liver disease
- Drug factors
  - Dosing (timing, sequence, route, duration)
  - Narrow therapeutic index
  - Multiple metabolic pathways

Drug Metabolism – CYP1A2

- CYP1A2 Substrate
- CYP1A2 Inhibitors
- CYP1A2 Inducers

<table>
<thead>
<tr>
<th>Substrate</th>
<th>Inhibitors</th>
<th>Inducers</th>
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<tbody>
<tr>
<td>Alosetron</td>
<td>Haloperidol</td>
<td>Propranolol</td>
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<tr>
<td>Clomipramine</td>
<td>Imipramine</td>
<td>Ramelteon</td>
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<td>Clopidogrel</td>
<td>Melatonin</td>
<td>Rasagiline</td>
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<tr>
<td>Clozapine</td>
<td>Methadone</td>
<td>Roflumilast</td>
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<tr>
<td>Cyonbenzprine</td>
<td>Mexiletine</td>
<td>Theophylline</td>
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<tr>
<td>Desipramine</td>
<td>Mirtazapine</td>
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<td>Diazepam</td>
<td>Naproxen</td>
<td>Tizanidine</td>
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<td>Duloxetine</td>
<td>Norotopryline</td>
<td>Verapamil</td>
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<tr>
<td>Estradiol</td>
<td>Oxazepam</td>
<td>Warfarin</td>
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<tr>
<td>Frovatriptan</td>
<td>Ondansetron</td>
<td>Zolmitriptan</td>
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</tbody>
</table>

Drug Metabolism – CYP1A2

- CYP2C8 Substrate
- CYP2C8 Inhibitors
- CYP2C8 Inducers

<table>
<thead>
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<tbody>
<tr>
<td>Amiodarone</td>
<td>Avanafil</td>
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<td>Phenobarbital</td>
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<td>Gemfibrozil</td>
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<td>Pioglitazone</td>
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<td>Verapamil</td>
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<tr>
<td>Warfarin</td>
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</tbody>
</table>
### Drug Metabolism – CYP2C9

#### Substrate
- Amitriptyline
- Carbamazepine
- Citalopram
- Cinacalcet
- Clomipramine
- Clozapine
- Codeine
- Desipramine
- Dexmethylphenidate

#### Inhibitors
- Amiodarone
- Bupropion
- Chlorpromazine
- Clomipramine
- Desipramine

#### Inducers
- Carbamazepine
- Cimetidine
- Dextromethorphan
- Dexamethasone

### Drug Metabolism – CYP2C9

#### Substrate
- Imipramine
- Lansoprazole
- Lithium
- Lomepiramide
- Mirtazapine
- Nefazodone
- Oxcarbazepine
- Paroxetine

#### Inhibitors
- Amiodarone
- Bupropion
- Cinacalcet
- Clomipramine
- Desipramine

#### Inducers
- Carbamazepine
- Cimetidine
- Dextromethorphan
- Dexamethasone

### Drug Metabolism – CYP2C19

#### Substrate
- Imipramine
- Lansoprazole
- Lithium
- Lomepiramide
- Mirtazapine
- Nefazodone
- Oxcarbazepine
- Paroxetine

#### Inhibitors
- Amiodarone
- Bupropion
- Cinacalcet
- Clomipramine
- Desipramine

#### Inducers
- Carbamazepine
- Cimetidine
- Dextromethorphan
- Dexamethasone

### Drug Metabolism – CYP2D6

#### Substrate
- Donepezil
- Dextromethorphan
- Dexamethasone
- Dextromethorphan
- Dibenzepine

#### Not inducible
- Amiodarone
- Bupropion
- Chlorpromazine
- Cinacalcet
- Clomipramine
- Clozapine
- Codeine
- Desipramine
- Dextromethorphan

#### Inhibitors
- Amiodarone
- Bupropion
- Chlorpromazine
- Cinacalcet
- Clomipramine
- Clozapine
- Codeine
- Desipramine
- Dextromethorphan

#### Inducers
- Carbamazepine
- Cimetidine
- Dextromethorphan
- Dexamethasone
Drug Metabolism – CYP3A4

Substrate
- Alprazolam (D/M/T)
- Cisapride
- Es-/omeprazole
- Amitriptyline (N)
- Citalopram
- Estrogens
- Amiodarone
- Clarithromycin
- Ezopiclone
- Amlodipine (F/N)
- Clomipramine
- Exemestane
- Apixaban
- Colchicine
- Fentanyl
- Aripiprazole
- Cyclosporine
- Fexofenadine
- Atorvastatin (L/S)
- Diltiazem
- Guanfacine
- Avanafil (S/T/V)
- Dipyridamole
- Hydrocodone
- Carbamazepine
- Serythromycin
- Ipomepine

Drug Metabolism – CYP3A4

Substrate
- Imipramine
- Paroxetine
- Solfenacine
- Itraconazole
- Quetiapine
- Tacrolimus
- Ketoconazole
- Quinidine
- Tamoxifen
- Linagliptin
- Risperidone
- Tolerodine
- Loratadine
- Ritonavir
- Trazodone
- Lurasidone
- Rufumilast
- Verapamil
- Methadone
- Saxagliptin
- Vilaizone
- Ospefime
- Setraline
- Voriconazole
- Oxycodone
- Sirolimus
- Warfarin

Drug Metabolism – CYP3A4

Inhibitors
- Amiodarone
- Serythromycin*
- Nelfildpine
- Amlodipine
- Fluconazole*
- Ranolazine
- Cimetidine
- Ethnyl estradil
- Nitonavir**
- Ciprofloxacin*
- Fluoxetine
- Tamoxifen
- Clarithromycin**
- Fluvoxamine
- Ticagrelor
- Cyclosporine
- Isoniazid
- Verapamil*
- Diltiazem*
- Itraconazole**
- Voriconazole**
- Dronedarone*
- Ketoconazole**

Drug Metabolism – CYP3A4

Inducers
- Carbamazepine
- Etravirine
- Phenobarbital
- Clobazam
- Griseofulvin
- Phenytoin
- Dexamethasone
- Modafinil
- Primidone
- Elavirenz
- Oxcarbazepine
- Rifampin

Drug Metabolism

- Increased risk for upper GI bleeding
  - (ns)NSAIDs, LD-ASA, corticosteroids, aldosterone antagonists, anticoagulants, COX-2 inhibitors, SSRI
  - 2-4 fold increase in risk with drug alone
  - SSRI (fluo/fluvox) inhibit CYP3A4 – corticosteroids
  - SSRI inhibit CYP2C9 – warfarin and NSAIDs
- SSRI associated with higher major hemorrhage risk in patients taking warfarin

Drug Elimination

- Kidney
  - Glomerular filtration
  - Active tubular secretion
  - Tubular reabsorption
- Other routes
  - Liver/bile
  - Gut/feces
**Drug Elimination**

- Inhibit secretion via p-glycoprotein transport
  - Amiodarone, carvedilol, clarithromycin, cyclosporine, erythromycin, itraconazole, ketoconazole, propafenone, quinidine, ritonavir, tacrolimus, tamoxifen, verapamil
- Inhibit cationic secretion
  - Amiodarone, cimetidine, diltiazem, ketoconazole, levofloxacin, quinidine, trimethoprim, verapamil
- Inhibit anionic secretion
  - Cimetidine, ciprofloxacin, NSAIDs, probenecid

**Pharmacodynamic Drug Interactions**

- More prevalent (80%)
- Two drugs exhibit additive effects
  - May result in excessive response/toxicity
  - OR
- One drug antagonize effects of another drug
  - May result in reduced effect

**Pharmacodynamic Drug Interactions**

- Additive Examples
  - Pain/migraine
  - Nitrates and 5-PDE inhibitors
  - Synergistic effects on blood pressure
  - QTc prolongation
  - Antiarrhythmics
  - Azole Antifungals, Fluoroquinolones, Macrolides
  - SSRIs, TCAs, Venlafaxine, Antipsychotics
  - Cisapride, Methadone
  - Serotonin syndrome

**Antagonistic Examples**

- NSAIDs and ACE inhibitors
  - Inhibit BP lowering effects
  - Theophylline and benzodiazepines

**Which Mechanism?**

- Clopidogrel and Omeprazole?
  a. Inhibits absorption
  b. Inhibits enzyme metabolism
  c. Induces enzyme metabolism
  d. Alters elimination
  e. Antagonistic effect
- Result of interaction?
- Recommendation?

- Methotrexate and PPIs?
  a. Inhibits absorption
  b. Inhibits enzyme metabolism
  c. Induces enzyme metabolism
  d. Alters elimination
  e. Antagonistic effect
- Result of interaction?
- Recommendation?
Which Mechanism?

- Trimethoprim and K+ Supplement?
  - a. Inhibits absorption
  - b. Inhibits enzyme metabolism
  - c. Alters elimination
  - d. Additive effect
  - e. Antagonistic effect
- Result of interaction?
- Recommendation?

Common Drugs for Potential DDIs

- NSAIDs most commonly involved in hospital admission associated DDIs (36.4%)
- Warfarin frequently involved in DDIs detected at hospital visits as outpatients/emergencies

Common Drugs for Potential DDIs

- HMG-CoA reductase inhibitors
- Psychiatric/seizure medication
- Antibiotics/antifungals
- Drugs affecting potassium
- Narrow therapeutic index

Systematic Approach to Addressing DDIs

- Identify interaction
- Determine clinical significance
- Formulate patient-specific recommendations
  - Hold/change medication dose
  - Discontinue/switch to alternative therapy
  - Closely monitor for adverse effects
  - More frequent lab monitoring
- Communicate recommendations

How Patients Can Help Avoid Potential DDIs

- Report all medications to health care providers
- Encourage to ask questions
- Take medications as prescribed
- Dispose of unused or expired medications

Medication Disposal

- TakeAway Environmental Return Program
- Local law enforcement agencies
- Local free medical clinics
- FDA – If not available, mix medications with dirt/litter/used coffee grounds in sealed plastic bag and place in household trash
- FDA – list of flushable medications

**TakeAway Environmental Return Program**

- Bag/envelopes for purchase
- Drop-off locations/pharmacies
  - www.iarx.org (search “takeaway”)
- No controlled medications accepted
- No liquids >4 ounces

**Drug Interaction Tools**

- www.hanstenandhorn.com (drug interactions)
- www.credibledrugs.org (drug-induced arrhythmia)
- www.drug-interactions.com (CYP450-mediated)

**References**


**References**

- www.hanstenandhorn.com
- www.pharmacistletter.com