Objectives

- Describe basic drug interaction mechanisms
- Identify issues in determining which drug interactions are clinically important
- Discuss initiatives to identify clinically important drug interactions for clinical decision support

Terminology

- Drug-drug interaction (DDI): Clinically meaningful alteration in the effect of one drug (object) as a result of co-administration of another (precipitant)
- Potential drug-drug interaction (PDDI): Co-prescription or co-administration of drugs known to interact, regardless of whether harm ensues

Disclosures

- Daniel C. Malone, RPh, PhD
  - No relationships pertinent to this activity
- Lisa E Hines, PharmD
  - No relationships pertinent to this activity
- Karl F. Gumpper, BS, BCPS, CPHIMS, FASHP (staff)
  - No relationships pertinent to this activity
- ASHP Staff
  - No relationships pertinent to this activity

Do No Harm?

Clinical decision support for drug–drug interactions: Improvement needed

John R. Horn, Karl F. Gumpper, J. Chad Hardy, Patrick J. McDonald, Shobha Phansalkar, and Cynthia Reilly

Am J Health-Syst Pharm. 2013;70:905-9

The Problems

- Alert fatigue – too many alerts
  - =>80% overridden
- Severity classification accuracy
  - Variation across and within systems
- Severity definition differences
  - VA – Critical and Significant
  - Micromedex – minor, moderate, major

Horn JR et al. AJHP 2013; 70:905-9
The Problems

- Quality of the evidence for DDIs
  - Evidence for DDIs limited
- User-Interface Design
  - “Smart” alerting – based on “at-risk”
  - Known interactions – based on specialty

Horn JR et al. AJHP 2013; 70:905-9

Theoretically Possible Number of Drug-Drug Interactions

Number of drugs patient taking concurrently

- Possible Interactions

Possible

Interactions

Theoretically Possible Number of Drug-Drug Interactions

Object | Precipitant | Risk Hospitalization
---|---|---
ACE inhibitors, ARBs | K-sparing diuretics, trimethoprim | Hyperkalemia
Benzodiazipines | Interacting drugs | Hip fracture
CCBs | Clarithromycin, erythromycin | Hypotension or shock
Digoxin | Clarithromycin | Digoxin toxicity
Glipizide, glyburide | Sulfamethoxazole | Hypoglycemia
Theophylline | Ciprofloxacin | Theophylline toxicity
Warfarin | NSAIDs, fluconazole sulfamethoxazole | GI bleeding

ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; CCB = calcium-channel blockers; GI = gastrointestinal; NSAIDs = nonsteroidal anti-inflammatory drugs.


Drug Interaction Mechanisms

- **Pharmacodynamic**
  - Additive /synergistic
  - Antagonistic
- **Pharmacokinetic**
  - GI absorption
  - Renal excretion
  - CYP enzymes
  - Transporter proteins
Pharmacodynamic
i.e., response of object drug is modified by precipitant drug

Additive /synergistic
Oxycodone + hydrocodone + diazepam + temazepam + alprazolam + doxylamine
Amiodarone + levofloxacin
Warfarin + NSAIDs
Nitrates + sildenafil

Antagonistic
ACE inhibitors + NSAIDs
Albuterol + propranolol

Pharmacokinetic
i.e., delivery of object drug to its site of action is altered by precipitant drug

GI absorption
Drug binding, GI motility, GI pH

Renal excretion
Glomerular filtration, passive tubular secretion

CYP enzymes
1A2, 2C9, 2C19, 2D6, 3A4, 2B6, 2C8

Transporter proteins
OAT, OATP, OCT, PGP

CYP Inhibition or Induction

Transporter Protein Inhibition or Induction

- Actively pump drug molecules either out of cells (efflux) or into cells (influx)
- PGP transports substances
  - into gut
  - out of brain
  - into urine
  - into bile
  - out of other organs

Others:
OAT=organic anion transporter
OATP=organic anion transporting polypeptide
OCT=organic cation transporter

Polling Question:
When reviewing Drug-Drug Interaction (DDI) alerts, what interaction mechanisms do you consider?
A. Just pharmacodynamic interactions
B. Just pharmacokinetic interactions
C. Both pharmacodynamics and pharmacokinetic interactions
D. None of the above

“Clinically Significant” DDIs
Study Designs Relevant to DDIs

- Experimental Designs
  - Pharmacokinetic studies
  - Randomized controlled trials
  - Non-randomized controlled trials
- Non-Experimental Designs
  - Case Control
  - Case report / series

Concordance Among Compendia

- What is the agreement among commonly used compendia for “major” drug-drug interactions?
- OR
- “How do I implement meaningful use for drug-drug interactions?”

Major DDIs at Class Level

<table>
<thead>
<tr>
<th>Compendium</th>
<th>No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>MicroMedex DRUG-REAX®</td>
<td>275</td>
</tr>
<tr>
<td>Evaluation of Drug Interactions</td>
<td>64</td>
</tr>
<tr>
<td>Drug Interactions: Analysis and Management</td>
<td>94</td>
</tr>
<tr>
<td>Drug Interaction Facts</td>
<td>141</td>
</tr>
<tr>
<td>Total</td>
<td>406</td>
</tr>
</tbody>
</table>

Which DDIs are Clinically Important?

- DDIs in 4 of 4: 2.2% (9/406)
- DDIs in 3 of 4: 8.6% (35/406)
- DDIs in 2 of 4: 17.4% (71/406)
- DDIs in 1 of 4: 71.7% (291/406)

| Intra-class Correlation Coefficient: -0.092 |
Concordance with VA

13.6% “critical interactions” listed in both compendia as level 1 or 2

Olvey et al, Clinical Pharmacology and Therapeutics 2011: 87:48-51

Reasons for Differences

- Different classification systems
- Few or no high-quality studies
  - Mostly case reports or case series
  - Determining harm is subjective
  - Different editors/contributors

Different editors/contributors

- FDA Labeling – Not always accurate

  - Ticagrelor boxed warning
    - Avoid aspirin > 100 mg/day (maintenance)
    - Hypothesis:
      - Decreased ticagrelor benefit from clinical trial subgroup analysis
      - Lacks biological plausibility
      - Inappropriate study interpretation


“Clinically Important” DDIs

<table>
<thead>
<tr>
<th>Interaction*</th>
<th>Leapfrog†</th>
<th>PharsaIker‡</th>
<th>POA†</th>
<th>Malone§</th>
<th>G-Standard∥</th>
</tr>
</thead>
<tbody>
<tr>
<td>Digoxin-macrolides</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Phenelzine – Fluoxetine</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Phentolamine – sumatriptan</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Simvastatin – Amiodarone</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Warfarin – clarithromycin</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Warfarin – ticlopride, TIAM/SAZ, Iloprost, NSAIDs</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Warfarin-thyroid</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
</tbody>
</table>

Selected examples

Drug Interaction Knowledge

- Prescriber knowledge is lacking¹,²
  - 42.7% of drug pairs correctly identified¹
- Information sources use by prescribers³
  - Pharmacists 68.4% also lacking knowledge⁴
  - PDA 15.8% similar to online resources
  - Alerts 10.8% known to be problematic
  - Other sources 5.1% e.g., compendia, labeling

Stage 2 Criteria

- “…enabled and implemented the functionality for drug-drug and drug-allergy interaction checks for the entire EHR reporting period.”

Meaningful Use Criteria

How Well Does Pharmacy DDI Software Perform?

- In-store (facility) analysis conducted at 64 pharmacies throughout AZ
- Fictitious patient profile
  - 18 medications
    - 19 drug pairs evaluation
      - 13 drug pairs interact
      - 6 drug pairs were non-interacting

Saverno et al. JAMIA 2011:18:32-37

Results – Test of Pharmacy CDS

<table>
<thead>
<tr>
<th>Geographical Location</th>
<th>N (%)</th>
<th>Pharmacy Type</th>
<th>N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urban</td>
<td>18.7%</td>
<td>Community</td>
<td>62.5%</td>
</tr>
<tr>
<td>Rural</td>
<td>81.3%</td>
<td>Hospital</td>
<td>15.6%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Other</td>
<td>11.3%</td>
</tr>
</tbody>
</table>


Pharmacy DDI Performance

<table>
<thead>
<tr>
<th></th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>PPV</th>
<th>NPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median</td>
<td>0.85</td>
<td>1.00</td>
<td>1.00</td>
<td>0.75</td>
</tr>
<tr>
<td>Maximum</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>Minimum</td>
<td>0.23</td>
<td>0.83</td>
<td>0.88</td>
<td>0.38</td>
</tr>
</tbody>
</table>

Results by Pharmacy Type

<table>
<thead>
<tr>
<th>Community Pharmacies (n=40)</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>PPV</th>
<th>NPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median</td>
<td>0.92</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>Maximum</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>Minimum</td>
<td>0.31</td>
<td>0.83</td>
<td>0.88</td>
<td>0.40</td>
</tr>
</tbody>
</table>

In-patient Hospital Pharmacies (n=14)

<table>
<thead>
<tr>
<th>Sensitivity</th>
<th>Specificity</th>
<th>PPV</th>
<th>NPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median</td>
<td>0.87</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>Maximum</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>Minimum</td>
<td>0.28</td>
<td>0.83</td>
<td>0.88</td>
</tr>
</tbody>
</table>

Other Pharmacies (n=10)

<table>
<thead>
<tr>
<th>Sensitivity</th>
<th>Specificity</th>
<th>PPV</th>
<th>NPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median</td>
<td>0.86</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>Maximum</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>Minimum</td>
<td>0.23</td>
<td>1.00</td>
<td>1.00</td>
</tr>
</tbody>
</table>


Potential Sources of Error

- Software settings
- Lack of updates (KB, drug file updates)
- Incorrect product identification
- No link to knowledge database
- Use of multiple pharmacies /OTC /herbals
- Relying on printouts

General Recommendations
- Test the software with high-priority DDIs and potential false positives
- Compare performance with benchmarks
- Have clear policies and procedures
- Pharmacists should review all DDI alerts
- Customize and filter to avoid alert fatigue
- Know software capabilities and limitations
- Know software settings


Assessment Tool for DDI Software
- Purpose
  - Assess performance of DDI software
  - Identify opportunities for improvement
- Steps to test DDI software
  1. Create a test patient profile
  2. Enter medication orders and complete data collection form
  3. Assess software responses
  4. Calculations
  5. Share findings with stakeholders


POLLING QUESTION:
When determining whether or not a DDI alert should fire in your CPOE/Pharmacy system, what criteria do you evaluate? (Choose the one answer you most frequently utilize)

A. Black Box Warnings
B. Published Compendia Resources
C. Knowledge Vendors Recommendations/On-Line Tools
D. We do not customize and utilize materials presented from knowledge vendors

Initiatives to Improve DDI CDS

DDI Conference Series Schematic

DDI Conference Series Site

Drug-Drug Interaction Clinical Decision Support Conference Series
Supported in part by a grant from IMS HEALTH FOR HEALTHCARE RESEARCH AND QUALITY
ID: 5105502000-97

Project at a Glance
- Project Period: 05/01/2012 – 04/30/2013
- Theme: Developing and implementing a DDI Clinical Decision Support System

Objectives
1. Develop an ongoing process for DDI evidence interpretation and clinical decision support (CDS) within the clinical environment
2. Establish an evidence-based classification for CDS systems
3. Implement evidence-based DDI CDS systems

Key Features of the Conference Series
- Three workshops, one each in 2012, 2013, and 2014
- DDI CDS Conference Series Schematic
**Agency for Healthcare Research and Quality**

**Grant #**1R13HS021826-01

**Additional Support**
- Cerner
- Epocrates
- First Databank
- Truven Health Analytics
- Wolters Kluwer Health

**Aim 1 - Evidence Workgroup**

**Aim**
- Develop guidelines for systematic appraisal of DDI evidence

**Long-Term Goals**
- Develop standards for rigorous, balanced, systematic, and transparent evaluation of DDI evidence
- Propose steps needed to validate instruments for appraising DDI evidence

**Aim 2 – Content Workgroup**

**Aim**
- Recommend principles for including DDIs in CDS

**Long-Term Goals**
- Coordinate with ONC initiatives on meaningful use criteria
- Determine what process should be used for ongoing assessment of a common set of DDIs

**Aim 3 – Usability Workgroup**

**Aim**
- Establish preferred strategies for presenting DDI CDS

**Long-Term Goals**
- Recommend the optimum approach to integrate DDI information into CDS to prevent harm without impeding efficiency
- Develop and promote a national standard for DDI information that should be presented to end users

**POLLING QUESTION:**

The University of Arizona’s AHRQ Grant is developing a structured process to improve the quality of DDI alerting systems used by health care providers, and thereby improve patient safety. Which of the specific aims of this project are the most important to you?

A. Develop an ongoing process for DDI evidence integration into clinical decision support (CDS)
B. Recommend standards for DDI classification for CDS
C. Establish basic standards for communicating DDI information within CDS
D. None are important to my current work and/or practice setting