Concordance of Severity Ratings Among Drug Interaction Compendia

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WellPoint NextRx
• Discuss the drug-drug interaction (DDI) severity rating system used by compendia
• Discuss agreement between compendia on DDI severity ratings
Concordance Among Compendia

US Pharmacopeia Drug Utilization Review Advisory Panel

Research Question:
What is the level of agreement on “listing and clinical significance rating of drug-drug interactions” among 5 drug-drug interaction (DDI) compendia?

• Focused on:
  – Angiotensin-converting enzyme (ACE) inhibitors
  – Beta-blockers
  – Benzodiazepines
  – Calcium channel blockers
  – Nonsteroidal anti-inflammatory drugs (NSAID)

Tertiary References for Drug-Drug Interactions

- Drug Information Compendia:
  - US Pharmacopeia Drug Information
  - American Hospital Formulary Service Drug Information
  - Drug Interactions: Analysis and Management
  - Drug Interaction Facts (Facts and Comparisons)
  - Micromedex DRUG-REAX® system

Agreement on Listing

<table>
<thead>
<tr>
<th></th>
<th>Number of References</th>
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<tbody>
<tr>
<td></td>
<td>n</td>
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<tr>
<td>ACE Inhibitor</td>
<td>288</td>
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<tr>
<td>Benzodiazepines</td>
<td>1,061</td>
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<tr>
<td>Beta-blockers</td>
<td>1,267</td>
</tr>
<tr>
<td>Calcium Channel Blockers</td>
<td>485</td>
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<tr>
<td>NSAIDs</td>
<td>1,004</td>
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## Agreement on Significance Rating

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<th>2</th>
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<th>4</th>
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<tbody>
<tr>
<td>ACE Inhibitor</td>
<td>46.6%</td>
<td>38.0%</td>
<td>30.0%</td>
<td>66.7%</td>
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<tr>
<td>Benzodiazepines</td>
<td>49.5%</td>
<td>28.3%</td>
<td>34.7%</td>
<td>0%</td>
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<tr>
<td>Beta-blockers</td>
<td>43.3%</td>
<td>16.5%</td>
<td>2.2%</td>
<td>0%</td>
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<tr>
<td>Calcium Channel Blockers</td>
<td>46.7%</td>
<td>25.0%</td>
<td>7.7%</td>
<td>0%</td>
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<tr>
<td>NSAIDs</td>
<td>56.4%</td>
<td>8.8%</td>
<td>2.9%</td>
<td>0%</td>
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</table>

Concordance Among Compendia

University of Arizona CERT

Research Question:
What is the level of agreement among commonly used drug-drug interaction (DDI) compendia with regard to the severity ratings of ‘major’ drug-drug interactions?

Tertiary References for Drug-Drug Interactions

DRUG-REAX® System
from MICROMEDEX
Methods

• Study performed in Fall 2001
• Review compendia for “major” interactions
  – DDI listed in at least 3 compendia
  – Additional criteria:
    • Available in US for human use
    • Medications likely to be dispensed in community pharmacy
    • Medications likely captured in electronic database
    • Interacting medications not used for therapeutic benefit
• What’s a ‘major’ drug-drug interaction?

• No consistent definition across references
• Evaluation of Drug Interactions
  – Uses 4-item summary measure based on:
    • Potential harm to the patient
    • Frequency and predictability of occurrence
    • Degree and quality of documentation
  – Code 1: highly clinically significant
  – Code 2: moderately clinically significant
  – Code 3: minimally clinically significant
  – Code 4: not clinically significant
• Selected ‘Code 1’ interactions
• Drug Interaction Facts
  – Uses 5-item summary measure based on:
    • Severity (i.e., major, moderate, minor)
    • Documentation (i.e., established, probable, suspected, possible, unlikely)
    – 1: major/established, probable, suspected
    – 2: moderate/established, probable, suspected
    – 3: minor/established, probable, suspected
    – 4: major, moderate/possible
    – 5: minor/possible or any/unlikely
• Selected ‘major’ interactions
• Drug Interactions: Analysis and Management
  – Used 5-item summary measure based on:
    • Severity
    • Corresponding documentation
    • Availability of alternatives are considered
  – 1: Avoid combination
  – 2: Usually avoid combination
  – 3: Minimize risk
  – 4: No action needed
  – 5: No interaction
• Selected ‘1’ and ‘2’ interactions
• Drug-REAX (MicroMedex)
  – Used 5-item severity scale
    • Major
    • Moderate
    • Minor
    • None
    • Not specified
  – No summary measure
• Selected ‘major’ interactions
Results

- DDI listed in at least 3 compendia
  - 62 ‘major’ DDIs identified
- Additional criteria:
  - 18 ‘major’ DDIs excluded:
    - 8 DDIs - not available in U.S. (e.g., terfenadine, mibefradil)
    - 4 DDIs – not dispensed from a community pharmacy
    - 4 DDIs – not likely to be captured in electronic database (e.g., ethanol, tyramine-containing foods)
    - 1 DDI – occurs upon discontinuation (clonidine-β blockers)
    - 1 DDI – used for therapeutic benefit (phenothiazine-SSRI)
Problems with Identifying Drug-Drug Interactions

“Major” Drug Interactions (at *Medication Class Level*) by Compendium

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

- 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)

Agreement on Severity Ratings for Major Drug-Drug Interactions Among Compendia

- Intraclass Correlation Coefficient: -0.092
Limitations

- Medications available for use in Fall 2001
- Focus on ambulatory care prescriptions processed through community pharmacies
- Prescription products (no over-the-counter, herbal, food, ethanol)
Why Does This Happen?

- Different Rating Systems
- Limited evidence for many DDIs
- Different mechanisms of DDIs
- No standard criteria for determining a ‘major’ DDI
- Limited data on appropriate management of DDIs
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