Evaluation of Drug-Drug Interaction Consumer Applications

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Overview

• Background on drug-drug interaction (DDI)
• Availability and quality of DDI resources
• Embedded results of an accepted paper which will be presented at this fall’s AMIA meeting (Co-authored with Joe Vang in the undergraduate McNair Scholar program and current year one pharmacy student)
• Methods to evaluate DDI on websites
  – DDI site identification
  – Content Assessment
• Study Results
• Future Work
Adverse Drug Events

- Historical challenges of identifying and managing adverse drug events
- National data estimates of adverse drug events of over 1 million events per year\(^1\)
- Associated with increased costs ($2500-5500) and to length of inpatient stay (2-4 days)\(^2,3\).
- Mix of preventable and non-preventable events to identify and manage
- Number of factors which affect risk: complex regimens, high-risk medications, drug-drug interactions, other factors

Drug-Drug Interactions

• Definition of drug-drug interaction:
• Operational definition: Drug interaction occurs when one medication affects the activities of another drug
• Differentiation between “potential” and actual drug-drug interaction
• Many “potential” DDI are identified without confirmation of actual clinical effect
• Modeling DDI events in the real world can be complicated
Modeling DDI Risk: Basic Approach

Drug A \(\rightarrow\) Drug B

- **Adherent**
  - Genetic Factors
  - Dosage Timing
  - Dietary Factors

- **Non-Adherent**
  - No DDI Event

New Medicine
If an adverse drug event occurs, was it due to a new drug?
Which medication caused the interaction with the new drug?
Is a multiple drug interaction present?
DDI Mediated Adverse Drug Events

• Major clinical concern for patient safety due to POTENTIAL TO PREVENT the events

• High degrees of variance in estimates on the risk of adverse drug events associated with DDI exposures

• Range of 2.2% to 70% of drug-drug interactions lead to adverse events\(^1,2\)

• DDI are the most frequently reported drug related problem (DRP) in ambulatory settings\(^3\)

• Limited understanding beyond binary exposures though multiple drug interactions are pharmacologically plausible

Type of Interactions

• Drug-drug—occurs when a pair of drugs effect each other
  • One drug can increase the effect of another drug (drug toxicity)
  • One drug can decrease the effect of another drug (therapeutic failure)
• Drug-food interactions (think grapefruit)
• Alcohol and drug interactions
• Cigarettes
• Food supplements (DSHEA)$^1$—certain food supplements affect medication metabolic and therapeutic effects via changes to absorption, distribution, metabolism and excretion.

1. Dietary Supplement Health and Education Act of 1994
Use of DDI Alerts for Patient Safety

- Long history of alert availability especially on the pharmacy dispensing component of care
- Unlike medicine, pharmacy has had real-time online submission and adjudication of prescription claims for 20 years
- This capacity has allowed for the use of decision support in pharmacy dispensing as well as the prescription writing process
- Substantial potential for alert fatigue as well as data fragmentation problems due to differences in medication lists at the prescribing, pharmacy and payor ends if patient has multiple providers among other issues.
Why drug-drug interactions are problematic

- Frequent occurrences with limited supporting data (in many cases)
- Rating systems vary but smaller numbers are usually more severe
- Qualitative assessment: Contraindicated, major/high risk, moderate risk, minor/low risk
- Usually communication is some version of an alert when operationalized
- Envision a 200 patient encounters per day and easy to see that a lot of alerts may be generated.
- Each occurrence is a potential adverse event or potential safety concern for patients
Problems with DDI Data Quality

- Historically the alert systems for drug-drug interactions were among the earliest clinical decision support systems.
- Easy to implement with drug dispensing in pharmacies where expert review by pharmacists would review and update drug information.
- Most drug data was structured which made it possible to do prospective assessment.
- Early assessments showed problems among clinical DDI databases in early compendia studies.
Drug-Drug Interactions

• Challenge of identifying what interactions are truly important and need an intervention
• Use of information systems to identify “potential” drug-drug interactions is highly prevalent
• Underlying data in many cases is not always consistent
• Evaluation of severity of 4 key compendia completed (Abarca paper)
  • Evaluations of Drug Interactions
  • Drug Interaction Facts
  • Drug Interactions: Analysis and Management
  • Micromedex

DDI in Four Compendia

• Only 9/408 (2.2%) are major interactions in all 4 compendia
• 35/408 (8.6%) are listed in 3 compendia
• 71/408 (17.4%) listed in 2 compendia
• 291/408 (71.7%) listed in only 1 compendia
• Summary: Little overall agreement on major DDI
• If the experts don’t agree then how is the non-expert clinician supposed to make decisions?
Publications on Alerts

- VA based evaluation-ambulatory study
- About nearly 300,000 overrides of DDI alerts
- 72% for critical DDI
- Response by providers needed for override
  - 53% No answer provided for critical alerts (though required)
  - 47% provided answer but only 20% of answers considered “useful”
- Conclusion—lots of overrides occur and providers are unwilling to provide rationale or good feedback
- Indicates likely alert fatigue concerns and potential workflow issues as well

U of A Study (JAMIA)

- Work done at U of Arizona
- Focus on drug-drug interactions in the clinical setting
- Unique characteristic is multiple onsite review methodology
- Travel throughout state to get local implementation information at 64 pharmacies
- 24 different software vendors
- Identified a list of relevant interactions from expert review and literature evaluation
Only 28% correctly got all elements correct
Median correct DDI was 89%
Dosage form created some problems with non-interactions
Shows there is still variability even among well documented cases

Maintenance of Certification Question

• The expert consensus on the level of evidence for the clinical risk for most drug-drug interactions is?

• 1) High quality with randomized control trial data to estimate clinical risk
• 2) Has a high degree of consistency no matter which clinical decision support database is used
• 3) Is often based on clinical case report data and drug class effects with limited information on estimated actual risk of adverse events
• 4) None of the above
Background Summary

• The fundamental data on DDI risk varies by source on the estimates of importance and potential presence of interactions
• When alerts are provided to providers they are frequently overridden
• More recent review of pharmacies show the systems are pretty good but not perfect
• Given these challenges, patient facing systems need an assessment on their capacity to provide information to patients in case the prescribing and dispensing sides have systematic failures
Methods

• Website Identification and study eligibility:
  • Identified available DDI websites available to consumers with no fees but could require a valid submitted email address for access
  • Utilized internet searches via Google as well as any known websites used by clinical users with verification of each current site address. The Google search terms included: drug-drug interaction, drug-drug interaction checker and drug-drug interaction assessment
  • Required drug level data for DDI assessment
  • Excluded any sites which were available at one time and unavailable for validation of the address at end of study and excluded any non-English websites or those with only therapeutic class level data
  • Study period was from July to September 2014.
  • No IRB approval needed since only public access sites were utilized and contained no protected health information
Methods: Information Assessment

• Identified clinically important DDI combinations with high clinical significance based on literature review and expert evaluation

• Drug Pairs Evaluated:
  • Simvastatin & Itraconazole
  • Warfarin & Gemfibrozil
  • Warfarin & Levothyroxine
  • Fluoxetine (SSRI) & Selegiline (MAO-I)
  • Selegiline & Phenelzine (MAO-I)

• Included dual MAO-I combination to nest in therapeutic duplication evaluation. Fluoxetine-Selegiline in place for primary assessment of serotoninergic DDI events
Methods: DDI Information Capacity

- Created a metric for the information provided to the end user

<table>
<thead>
<tr>
<th>DDI Identified</th>
<th>Severity Rating listed</th>
<th>Drug-Food Reaction</th>
<th>Drug-Alcohol Reaction</th>
<th>Therapeutic Duplication</th>
<th>Max Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-5</td>
<td>0-5</td>
<td>0-5</td>
<td>0-4</td>
<td>0-2</td>
<td>21</td>
</tr>
</tbody>
</table>

- No expected alcohol reaction for simvastatin and itraconazole
- Therapeutic duplication assessed presence of a therapeutic and drug class duplication
Methods: Patient Usability

- Focused on the consumer approach to DDI assessment website and evaluates if the content is patient friendly and contained clinically useful features
- One point was received in categories for alert icons, color coding, and severity rating scale presence, medication pick list, and login/profile management for a total of 5 possible points

<table>
<thead>
<tr>
<th>Alert Icons</th>
<th>Color Coding</th>
<th>Severity Rating Scale</th>
<th>Medication Pick List</th>
<th>Login/Profile Save for Multiple Drugs</th>
<th>Total Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-1</td>
<td>0-1</td>
<td>0-1</td>
<td>0-1</td>
<td>0-1</td>
<td>0-5</td>
</tr>
</tbody>
</table>
Methods: Patient Readability

- Patient readability was determined through the Flesch-Kincaid grading model.
- The content of information for the simvastatin and itraconazole interaction for each website was the only information content which was graded for readability.
- Assessed using the Microsoft 2010 Flesch Kincaid scoring assessment.
- Due to the potential for the commercial or generic drug names to affect this grading model, each of the drug names were replaced with the generic word “drug” instead of simvastatin and itraconazole.
- The Flesch Reading Ease score was also assessed for each of the sites to provide additional measures on readability.
Results
Results: Drug-drug interaction Severity

- Simvastatin-Itraconzole: 12 contraindicated, 6 major interaction and 26 with no severity
- Warfarin-Gemfibrozil: 2 contraindicated, 9 major interaction, 9 moderate interaction, 1 minor, 23 no severity, 1 non-interaction
- Warfarin-Levothyroxine: 2 contraindicated, 5 major interaction, 14 moderate interaction, 23 no severity, 1 non-interaction
- Fluoxetine-Selegilene: 12 contraindicated, 5 major interaction, 1 moderate interaction, 26 no severity
- Selegilene-Phenelzine: 9 contraindicated, 3 major interactions, 1 moderate interaction, 31 no severity (26 with no indicated DDI)
- About $\frac{1}{2}$ of the interaction data has no severity information
Results: Drug-Drug Interaction Severity

Drug-Drug Interaction Severity Frequency

<table>
<thead>
<tr>
<th>Drug Pairs</th>
<th>Percent of Websites</th>
</tr>
</thead>
<tbody>
<tr>
<td>Simvastatin &amp; Itraconazole</td>
<td><img src="image" alt="Simulation" /></td>
</tr>
<tr>
<td>Warfarin &amp; Gemfibrozil</td>
<td><img src="image" alt="Simulation" /></td>
</tr>
<tr>
<td>Warfarin &amp; Levothyroxine</td>
<td><img src="image" alt="Simulation" /></td>
</tr>
<tr>
<td>Fluoxetine &amp; Selegiline</td>
<td><img src="image" alt="Simulation" /></td>
</tr>
<tr>
<td>Selegiline &amp; Phenelzine</td>
<td><img src="image" alt="Simulation" /></td>
</tr>
</tbody>
</table>

Legend:
- Contraindicated
- Major
- Moderate
- Minor
- Severity N/A
Results: Information Capacity Score

- Average Information Capacity score was 13.36 with a standard deviation of 3.09
- Maximum score achieved was 21 with a low score of 4
- Most frequently missing feature was Therapeutic Duplication
- Nearly 21 of 44 had the same score (13)
- Somewhat normal looking distribution of scores (figure)
Information Capacity Score

Information Capacity Score Data Distribution

Number of Websites

Information Capacity Score

1  2  3  4  5  6  7  8  9  10  11  12  13  14  15  16  17  18  19  20  21
1  3  5  2  21  6  3  2  1

0  5  10  15  20  25
Results: Patient Usability

- Average Score of 2.9 points with a standard deviation of 1.06 points.
- 5 sites had perfect scores
- Half of the websites has a score of 2
- Alert icons and severity scales most frequently missing elements
- Profile capacity also missing for several sites
Results: Patient Readability

- Flesch-Kincaid grade level scored was 11.2. Highest grade level was 16.2, the lowest grade level was 6.7. Standard deviation of 2.29 (Bimodal distribution)
- Ideally would like to see results closer to 6th grade
Results: Patient Readability

- The Flesch Reading Ease score was 40.27 with the highest score being 70.9, the lowest score being zero and the standard deviation being 15.11
- Ideally would like scores above 60 if feasible
Results: Missed Interactions

- The two drug pairs, Simvastatin-Itraconazole and fluoxetine-selegiline, were correctly identified for a potential interaction by all of the DDI checkers.
- Three of the DDI combinations were not correctly identified by all of the DDI checkers.
  - All but one website correctly identified the Warfarin-Gemfibrozil drug interaction.
  - Another website failed to identify the Warfarin-Levothyroxine drug pair, but correctly identified all other drug interactions
  - 26 of 44 sites lacked interaction for selegiline-phenelzine.
Study Limitations

• Limited to free sites which may affect data quality since pay sites are presumably better quality and may maintain better databases

• Limited scope of medications were assessed. Newer medications not evaluated which would help assess timeliness of database updates

• Ratings scales not previously used or validated, but based on expert review as to relative importance

• Limited inter-rater reliability. Most reviews completed by a single reviewer with limited audits of results

• Readability was limited to the output of a single drug and did not incorporate front end readability which may be as much of a problem for patients
Future Work

• Consider further exploration of the front-end of the websites and a more detailed evaluation of the input and profile systems

• Expand the drug scope and include newer medications which may have been recently approved and have well established DDI risk to assess information timeliness

• Further exploration of site readability as this may be the biggest problem for most patients using such systems

• Consider comparisons with automated data extraction from the clinical literature to identify potential DDI combinations which are not present in existing DDI databases
Questions?

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