Towards Large-Scale Drug Safety Surveillance: A Big Data Perspective

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Can Big Data Tell Us What Clinical Trials Don’t?

Type 2 Diabetes, while male, age < 60

Type 2 Diabetes, Hypertension, Obesity, Depression, American African female, age > 70
Purpose of Post-marketing Safety Monitoring

- To learn about new risks
- To learn more about known risks
- To learn about medication errors
- To learn about how patterns of use may contribute to unsafe use
Historical Perspectives

• 1961 – 1962: Thalidomide tragedy
  • If adequate post-market monitoring had been in place in Europe in the 1950’s, it is believed that teratogenicity due to thalidomide would have been detected much earlier

• Post-marketing Adverse Event Reporting in USA
  – Begin in late 1950’s after registration of cases of aplastic anemia due to chloramphenicol
  – Expanded in 1962 when industry was required to report adverse drug reactions to FDA
  – Since 1969 reports have been computerized
  – 1993 “MedWatch” expanded and facilitated reportings
What is an adverse drug reaction?

- Adverse drug reaction (ADR) is a noxious and unintended response to a drug at normal doses during normal use (WHO)
  - Teratogenicity <- Thalidomide
  - Side effect == Adverse drug reaction == adverse event

- Public Health
  - 4th - 6th leading cause of death
  - > 10% of hospitalization

- Financial Burden
  - $5.6 billion annually

Classen DC 1997, Cullen DJ 1995, 1997;
Drug safety (pharmacovigilance) happens from the time a drug is discovered throughout it’s approval and release to the market

- Side effects are collected during animal studies conducted during the “preclinical phase.” Adverse events reported during clinical trials before FDA / EMA review help form the drug’s label or approved claims. Side effects reported after approval are collected in a process called “post marketing surveillance”
Late discovery of safety signals during post marketing is a real challenge

Approved August, **2004**: Brain cancer, Colorectal cancer, Lung Cancer, etc., Warning added **2011**: Ovarian Failure

Approved August, **2002**: Depression Warning added **2016**: Binge eating, shopping

Approved August, **2009**: Type II Diabetes Warning added April **2016**: Heart Failure

Approved August, **2001**: heart burn Warning added **2016**: Kidney failure

Approved **1996**: Pneumonia Warning added May **2016**: Central Nervous system damage

Approved **2006**: smoking cessation Warning added March, **2015**: alcohol interaction, Mood alterations, rare seizures

Abilify gets potential for binge eating; Astra and Merck Diabetes Drugs Get Warnings; PPIs get new warnings; Doctors didn’t Know this common antibiotic was deadly; FDA issues warnings for Chantix
Data sources of drug safety information in post market stage

- Phase IV Clinical Trials
- Spontaneous Adverse Event Reports
- Observational healthcare data
- Scientific Literature
- Search Engine Log
- Social Media

2007 FDA Amendments act FDAAA
Outline

Data Source

Strengths & Limitations

Methods

Performance & case studies

Spontaneous Adverse Event Reports

Observational healthcare data

Scientific Literature

Social Media

Search Engineer

Evidence Integration
Reference Standard – benchmark

- What ADR to monitor?
  - Acute myocardial infarction
  - Acute renal failure
  - Acute liver failure
  - Upper gastrointestinal bleeding

SPL: Structured Product Label
Tisdale: Tisdale’s literature review.
Positive literature indicates the set of cases with at least one article confirming the existence of a causal relationship.
Negative literature indicates the set of cases with at least one published study that was sufficiently powered but found no relationship between the drug and outcome.

OMOP Reference Standard

<table>
<thead>
<tr>
<th>Event</th>
<th>Positive Cases</th>
<th>Negative Case</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastrointestinal Bleeding</td>
<td>24</td>
<td>67</td>
<td>91</td>
</tr>
<tr>
<td>Acute Liver Injury</td>
<td>80</td>
<td>37</td>
<td>117</td>
</tr>
<tr>
<td>Acute Myocardial Infarction</td>
<td>36</td>
<td>66</td>
<td>102</td>
</tr>
<tr>
<td>Acute Renal Failure</td>
<td>24</td>
<td>64</td>
<td>88</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>164</strong></td>
<td><strong>234</strong></td>
<td><strong>398</strong></td>
</tr>
</tbody>
</table>
Other reference standards

• SIDER : Side Effect Resource
  – Automatic extraction from FDA structured product label (SPL)
• Time-index reference standard (2013)

<table>
<thead>
<tr>
<th>EVENT</th>
<th>DRUG</th>
<th>MONTH</th>
<th>APPROVED</th>
<th>BW</th>
<th>W</th>
<th>AR</th>
<th>AR_POSTMARKETING</th>
</tr>
</thead>
<tbody>
<tr>
<td>Taste disorders</td>
<td>Pantoprazole</td>
<td>12</td>
<td>2000</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hematopoietic disorders</td>
<td>Pantoprazole</td>
<td>12</td>
<td>2000</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anaphylaxis</td>
<td>Dalfampridine</td>
<td>1</td>
<td>2010</td>
<td>1</td>
<td></td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Anaphylaxis</td>
<td>Mesalamine</td>
<td>12</td>
<td>1993/2007</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anaphylaxis</td>
<td>Ketoconazole</td>
<td>7</td>
<td>1981</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Angioedema</td>
<td>Fidaxomicin</td>
<td>4</td>
<td>2011</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>Solifenacin</td>
<td>10</td>
<td>2004</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bradycardia</td>
<td>Lacosamide</td>
<td>2</td>
<td>2008</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Biliary tract disorders</td>
<td>Sunitinib</td>
<td>8</td>
<td>2006</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Coronary Heart Disease</td>
<td>Niacin</td>
<td>2</td>
<td>1997/2008</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Drug reaction with eosinophil</td>
<td>Terbinafine</td>
<td>6</td>
<td>1996</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Drug reaction with eosinophil</td>
<td>Mesalamine</td>
<td>12</td>
<td>1993/2007</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Drug reaction with eosinophil</td>
<td>Clopidogrel</td>
<td>9</td>
<td>1997</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dysphonia</td>
<td>Levalbuterol</td>
<td>9</td>
<td>1999</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Outline

Data Source

Strengths & Limitations

Methods

Performance & case studies

Spontaneous Adverse Event Reports
Spontaneous reporting systems

**Strengths**
- Detect rare adverse events
  - Acute liver failures
  - Stevens Johnson syndrome
  - Torsade de pointes

**Limitations**
- Under and bias reporting
- Lack of accurate “denominators”
- Difficulty detecting events with long latency and with high background rate
**Examples of SRSs**

<table>
<thead>
<tr>
<th>SRS</th>
<th>Organization</th>
<th>Number of reports</th>
<th>Availability</th>
<th>Update frequency</th>
</tr>
</thead>
</table>
| Vigibase                           | WHO Programme for International Drug Monitoring    | >13 million (1968-present)      | Health professionals can request access
Public may use VigiAccess for summary statistics | Continuous as received (countries report at least quarterly) |
## Method - Disproportionality Analysis

- A 2 × 2 Table for Disproportionality Calculation

<table>
<thead>
<tr>
<th></th>
<th>Reports with AE</th>
<th>Reports Without AE</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reports with drug</td>
<td>a</td>
<td>b</td>
<td>a+b</td>
</tr>
<tr>
<td>Reports without drug</td>
<td>c</td>
<td>d</td>
<td>c+d</td>
</tr>
<tr>
<td>Total</td>
<td>a+c</td>
<td>b+d</td>
<td>a+b+c+d</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Measure of association</th>
<th>Formula</th>
<th>Probabilistic interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Relative reporting (RR)</td>
<td>( \frac{a(a+b+c+d)}{(a+c)(a+b)} )</td>
<td>( \frac{\Pr(\text{ae} \mid \text{drug})}{\Pr(\text{ae})} )</td>
</tr>
<tr>
<td>Proportional reporting rate ratio (PRR)</td>
<td>( \frac{a(c+d)}{c(a+b)} )</td>
<td>( \frac{\Pr(\text{ae} \mid \text{drug})}{\Pr(\text{ae} \mid \sim \text{drug})} )</td>
</tr>
<tr>
<td>Reporting odds ratio (ROR)</td>
<td>( \frac{ad}{cb} )</td>
<td>( \frac{\Pr(\text{ae} \mid \text{drug}) \Pr(\sim \text{ae} \mid \sim \text{drug})}{\Pr(\sim \text{ae} \mid \text{drug}) \Pr(\text{ae} \mid \sim \text{drug})} )</td>
</tr>
<tr>
<td>Information component (IC)</td>
<td>( \log_2 \frac{a(a+b+c+d)}{(a+c)(a+d)} )</td>
<td>( \log_2 \frac{\Pr(\text{ae} \mid \text{drug})}{\Pr(\text{ae})} )</td>
</tr>
</tbody>
</table>
Evolution of disproportionality signal detection methods

- **Outdated techniques**
  - $\chi^2$
  - ROR

- **Current techniques**
  - GPS
  - MGPS
  - GPS + Regression based technology

- **Emerging techniques**
  - PRR
  - PRR-TA

- **Frequentist**
  - GPS (Gamma Poisson Shrinker) is the simpler precursor to MGPS
  - PRR-TA (PRR by therapeutic area) restricts background to therapeutic area of interest, so far seems superior to simple PRR
  - GPS + Regression based technology

- **Bayesian**
  - BCPNN

**Outdated techniques**

**Current techniques**

**Emerging techniques**
Interpreting FAERS reports is hard

- Many drugs, many adverse events
  - What causes what?
  - Most of these red lines are false - which are true?
- Is primary suspected information always right?

<table>
<thead>
<tr>
<th>Drugs</th>
<th>Adverse Events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metformin</td>
<td>Acute respiratory distress</td>
</tr>
<tr>
<td>Rosiglitazone</td>
<td>Anemia</td>
</tr>
<tr>
<td>Pravastatin</td>
<td>Decrease Blood Pressure</td>
</tr>
<tr>
<td>Tacrolimus</td>
<td>Heart failure</td>
</tr>
<tr>
<td>Prednisolone</td>
<td>Dehydration</td>
</tr>
</tbody>
</table>
The Confounding Effect poses many challenges for ADR detection of real world events.

**Co-Prescription Confounders**

Mary has hypertension and arthritis. She has been taking both Aspirin and Vioxx. Which drug caused her heart attack?

**Drug Indicator Confounders**

Joe is an alcoholic who develops Pancreatitis. He has been drinking daily and taking Naltrexone. What caused the Pancreatitis?
Implicit Propensity Score Matching (IPSM)

\[
\logit(P(\text{Drug} = 1)) = \alpha + \sum_{i=1}^{200} \delta_i R x_i + \sum_{j=1}^{200} \gamma_j D x_j
\]
IPSM corrects for indication and co-Rx biases

Drugs given to Diabetics
- lisinopril
- acarbose
- chlorpropamide
- rosiglitazone
- metformin
- pioglitazone
- glibenclamide
- repaglinide
- glimepiride
- nateglinide
- glipizide

Association Score with Hyperglycemia (PRR)

Anti-arrhythmics and Arrhythmia
- quinidine
- verapamil
- mexiletine
- diltiazem
- amiodarone
- propafenone
- flecainide
- sotalol
- dofetilide
- disopyramide

Association Score with Arrhythmia (PRR)

Drugs co-reported with rofecoxib (Vioxx)
- terazosin
- dicyclomine
- monamine
- quinapril
- nabumetone
- benazepril
- amitriptyline
- clopidogrel
- methiocarbamol
- oxaprozin
- tramadol
- nitroglycerin
- trazodone
- celecoxib
- valdecoxib
- cerivastatin

Association Score with Myocardial Infarction (PRR)

Drugs co-reported with pergolide
- orphenadrine
- entacapone
- selegiline
- tolcapone
- trihexyphenidyl
- amantadine
- cabergoline

Association Score with Heart Valve Damage (PRR)
IPSM implicit correction for other biases

Drugs preferentially associated with males are more likely to be associated with 33 sex-related (male) effects

Drugs preferentially associated with young/old patients are more likely to be associated with 48 age-related effects
Evolution of regression based signal detection

- LR (logistic regression) computes odds ratios to measure strength of association between a drug and event while controlling for confounding effect
- ELR (extended logistic regression) is a modification of LR for rare events

Outdated techniques

Current techniques

Emerging techniques
Performance of Pharmacovigilance Signal-Detection Algorithms for the FDA Adverse Event Reporting System

- Data: FAERS data covered the period from 1968 through 2011 Q3, totaling 4,784,337 reports.

<table>
<thead>
<tr>
<th>Method name</th>
<th>Signal score computed</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Disproportionality Analysis</strong></td>
<td></td>
</tr>
<tr>
<td>Multi-item Gamma Poisson Shrinker (MGPS)</td>
<td>EBGM (empirical Bayes geometric mean): a centrality measure of the posterior distribution of the true observed-to-expected in the population</td>
</tr>
<tr>
<td></td>
<td>EB05: lower 5th percentile of the posterior observed-to-expected distribution</td>
</tr>
<tr>
<td>Proportional Reporting Ratio (PRR)</td>
<td>PRR: point estimate (mean) of the relative risk reporting ratio distribution</td>
</tr>
<tr>
<td></td>
<td>PRR05: lower 5th percentile of the relative risk reporting ratio distribution</td>
</tr>
<tr>
<td>Reporting Odds Ratio (ROR)</td>
<td>ROR: point estimate (mean) of the reporting odds ratio distribution</td>
</tr>
<tr>
<td></td>
<td>ROR05: lower 5th percentile of the reporting odds ratio distribution</td>
</tr>
<tr>
<td><strong>Multivariate Modeling</strong></td>
<td></td>
</tr>
<tr>
<td>Logistic Regression (LR)</td>
<td>LR: point estimate of the odds ratio distribution obtained from logistic regression</td>
</tr>
<tr>
<td></td>
<td>LR05: lower 5th percentile of the odds ratio distribution obtained from logistic regression</td>
</tr>
<tr>
<td>Extended Logistic Regression (ELR)</td>
<td>ELR: point estimate of the odds ratio distribution obtained from extended logistic regression</td>
</tr>
<tr>
<td></td>
<td>ELR05: lower 5th percentile of the odds ratio obtained from extended logistic regression</td>
</tr>
</tbody>
</table>

Performance of Pharmacovigilance Signal-Detection Algorithms for the FDA Adverse Event Reporting System

Reference Standard

<table>
<thead>
<tr>
<th>Event</th>
<th>Positive Cases</th>
<th>Negative Case</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastrointestinal Bleeding</td>
<td>24</td>
<td>67</td>
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<td>24</td>
<td>64</td>
<td>88</td>
</tr>
<tr>
<td>Total</td>
<td>164</td>
<td>234</td>
<td>398</td>
</tr>
</tbody>
</table>

Harpaz, Rave, et al. 2013, CPT; Ryan, Patrick B., et al., 2013, Drug Safety
Summary - strengths and weaknesses of notable signal detection methods

<table>
<thead>
<tr>
<th>Feature</th>
<th>PRR</th>
<th>ROR</th>
<th>MGPS</th>
<th>BCPNN</th>
<th>LR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Simple to use</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
</tr>
<tr>
<td>Applicable to low event counts</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
</tr>
<tr>
<td>Easy to interpret</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
</tr>
<tr>
<td>Usable with SRS data</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
</tr>
<tr>
<td>Accounts for confounding factors</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
</tr>
<tr>
<td>Sensitivity</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
</tr>
<tr>
<td>Specificity</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
</tr>
</tbody>
</table>

Notes: The ROR can be incorporated into a logistic regression analysis. A kind of de-confounding can be done with PRR and ROR by splitting the data inputs into separate contingency tables, but is not inherent to the algorithm.
Triaging to select signals and follow up

**QUANTITATIVE “RULES”**

- Apply fixed thresholds
  - \( \text{EB05} \geq 2; \text{EBGM} \geq 2; \text{EBGM} \geq 4; \)
  - \( \text{PRR} \geq 2; \) a number of reports \( (N) \geq 3; \) a Chi-square \( \geq 4 \)
  - Lower 95% CI of PRR \( \geq 1 \)
  - Lower 95% CI of ROR \( \geq 1 \)
  - \( \text{IC025} > 0 \)
- Apply flexible thresholds
  - Estimate the false discovery rate (FDR) to decide threshold on a signal-by-signal basis

**QUALITATIVE “RULES”**

- Novel
  - Not currently known and on drug label
  - New adverse event or new drug (“early warning”)
- High potential relevance
  - Public health issue – e.g. important drug (serious indication, widely used), serious reaction, many cases
  - Change in merit/harm
- Strong evidence
  - Exposure-response relationship (site, time-to-onset, dose, reversibility in dechallenge/rechallenge)
  - Reasonable from a biological mechanism perspective
- Time trend
  - Surge in recent reporting, notable increase in reporting over time

Unsupervised method - Biclustering

Table 1. Contingency table specifying the number of reports mentioning a specific drug and a specific adverse effect (AE)

<table>
<thead>
<tr>
<th>Target AE</th>
<th>All other AEs</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Target drug</td>
<td>a</td>
<td>b</td>
</tr>
<tr>
<td>All other drugs</td>
<td>c</td>
<td>d</td>
</tr>
<tr>
<td>Total</td>
<td>m=a+c</td>
<td>b+d</td>
</tr>
</tbody>
</table>

\[ b_{ij} = \begin{cases} 
1 & \text{if } a_{ij} \geq T \\
0 & \text{if } a_{ij} < T 
\end{cases} \]

\( a_{ij} \) contains GPS' EBGM association strength value computed for the \( i \)-th drug and the \( j \)-th AE pair.

Case Study

Binary inclusion-maximal biclustering

Harpaz, Rave, et al., Clinical Pharmacology & Therapeutics 89.2 (2011): 243-250.
Beyond ADR detection

Common drug combo increases diabetes risk

Hypothesis generation based on FAERS → Signal validation based on EHR databases → Mice model validation

Tatonetti, Nicholas P., et al. Clinical pharmacology and therapeutics 90.1 2011
Beyond ADR detection

Common drug combo decreases adverse drug reactions

Data-Driven Prediction of Beneficial Drug Combinations in Spontaneous Reporting Systems

Our novel regularized logistic regression is able to reveal two different mechanism of drug combinations

\( (\beta_3 + \beta_5) \): the degree that a patient who is on Drug A could benefit or suffer from taking Drug B for the ADR of interest

\( \beta_5 \): the degree that the interaction effect between Drug B and Drug A on the ADR

\[
\text{logit}(P(ADR = 1)) = \beta_0 + \beta_1 \text{DrugA} + \beta_2 P_1 + \beta_3 \text{DrugB} + \beta_4 P_2 + \beta_5 \text{DrugA} \times \text{DrugB} + \lambda |\beta|_1
\]
Clinical validation

List of 15 predicted beneficial drug combinations and their ADR reduction

<table>
<thead>
<tr>
<th>Drug A name</th>
<th>ADRs associated with drug A</th>
<th>Drug B name</th>
<th>Predicted beneficial score</th>
<th>Common ATC code</th>
<th>Evidence for combined use</th>
</tr>
</thead>
<tbody>
<tr>
<td>benazepril</td>
<td>DIZZINESS</td>
<td>amlodipine besylate</td>
<td>-0.57</td>
<td>yes</td>
<td>F</td>
</tr>
<tr>
<td>atovaquone</td>
<td>PYREXIA</td>
<td>proguanil</td>
<td>-0.36</td>
<td>yes</td>
<td>F</td>
</tr>
<tr>
<td>rofecoxib</td>
<td>MYOCARDIAL</td>
<td>pamidronate</td>
<td>-0.33</td>
<td>yes</td>
<td></td>
</tr>
<tr>
<td>rosiglitazone</td>
<td>INFACTION</td>
<td>exenatide</td>
<td>-0.32</td>
<td>yes</td>
<td></td>
</tr>
<tr>
<td>progesterone</td>
<td>BREAST CANCER</td>
<td>adalimumab</td>
<td>-0.27</td>
<td>no</td>
<td></td>
</tr>
<tr>
<td>trimethoprim</td>
<td>PYREXIA</td>
<td>sulfamethoxazole</td>
<td>-0.17</td>
<td>yes</td>
<td>F</td>
</tr>
<tr>
<td>exemestane</td>
<td>ARTHRITIS</td>
<td>everolimus</td>
<td>-0.16</td>
<td>yes</td>
<td>III</td>
</tr>
<tr>
<td>amoxicillin</td>
<td>DIARRHOEA</td>
<td>clavulanic acid</td>
<td>-0.15</td>
<td>yes</td>
<td>IV</td>
</tr>
<tr>
<td>ampicillin</td>
<td>PYREXIA</td>
<td>sulbactam</td>
<td>-0.15</td>
<td>yes</td>
<td>F</td>
</tr>
<tr>
<td>desmopressin</td>
<td>HYPONATRAEMIA</td>
<td>somatropin</td>
<td>-0.15</td>
<td>yes</td>
<td></td>
</tr>
<tr>
<td>sertraline</td>
<td>ANXIETY</td>
<td>nicotinic acids</td>
<td>-0.14</td>
<td>no</td>
<td></td>
</tr>
<tr>
<td>sumatriptan</td>
<td>MIGRAINE</td>
<td>naproxen</td>
<td>-0.14</td>
<td>no</td>
<td>F</td>
</tr>
<tr>
<td>olanzapine</td>
<td>MELLITUS</td>
<td>biperiden</td>
<td>-0.13</td>
<td>yes</td>
<td></td>
</tr>
<tr>
<td>clindamycin</td>
<td>DIARRHOEA</td>
<td>benzoyl</td>
<td>-0.13</td>
<td>yes</td>
<td>F</td>
</tr>
<tr>
<td>fluticasone</td>
<td>DYSPNOEA</td>
<td>salmeterol</td>
<td>-0.13</td>
<td>yes</td>
<td>F</td>
</tr>
</tbody>
</table>

F: FDA approved drug combination; III: phase III clinical trial; IV: phase IV clinical trial

a NSAID. On September 30, 2004, Merck withdrew rofecoxib from the market because of concerns about increased risk of heart attack and stroke associated with long-term, high-dosage use.
From Passive to Active Surveillance

Regulatory Agencies

[Logos of various regulatory agencies]

Academic and Nonprofit Organizations

[Logos of academic and nonprofit organizations]

http://www.mini-sentinel.org/
Outline

Data Source

Spontaneous Adverse Event Reports

Strengths & Limitations

Observational healthcare data

Methods

Performance & case studies
Observational healthcare databases (OHD)

**Subtype**
- EHR
- Claims

**Strength**
- No reporting biases
- Events with high background rate
- Information with exposed patients
- Comprehensive and longitudinal patient information

**Limitations**
- Biases due to secondary use
- Confounding
- False positive discovery
- Missing and irregular data
- Not publicly available

---

**Patient Demographics**
- Age
- Race
- Ethnicity
- Gender
- Zip 3
- Payer
- Status
- Tenure

**Provider Demographics**
- Specialty
- Role

**Clinical**
- EMR and Billing Diagnoses
- Problem list
  - w/Start & end dates
- Allergies
- Immunizations
- Procedures
  - CPT, HCPCS, ICD-9/10
- Medical & Social History
- Surgical history

**Utilization**
- Site of care & service dates
- Encounters, admissions, and discharges
  - Inpatient, ambulatory, ED, SNF, etc.
- IDN and Community (CINs)
- Length of Stay and Discharge Disposition
- Appointments
  - Missed, Cancelled, Scheduled, Left w/o seen

**Therapeutics**
- Ambulatory & Inpatient
- Drug - Brand and Class
  - SNOMED, NDC, RxNorm
- Medication start & end dates
- Select Reasons for Stopping
- Dosage, refills, & quantity

**Vitals & Biometrics**
- BP
- BMI
- Body temp
- Heart rate
- Respiratory rate
- BSA

**Laboratory (representative only)**
- CBC
- Fibrinogen
- Hemoglobin A1C
- BMP & CMP
- DHEA
- PSA
- Homocysteine
- C-reactive protein
- TSH & T4
- Testosterone
- Estradiol
- Amylase
- PT (Prottime)
- Electrolytes
- ESR
- Glucose
- hCG
- Lipid profile
- Liver panel
- Microalbumin
- Sodium
- BNP

**Device**
- Implant site & type
- Date of implant
- Manufacturer
- Model no.

**Financial**
- Billing
  - 837/835
- Claims

**PROs**
- HOOS
- KOOS
- PHQ2/9
Summary statistics for OHD


CCA : MarketScan Commercial Claims and Encounters
MDCD : MarketScan Multi-State Medicaid
MDCR : MarketScan Medicare Supplemental Beneficiaries
MSLR : MarketScan Lab Supplemental
Common Data Model

Mini-sential Common Data Model; I2B2 common data model; PCORnet Common Data Model (CDM) - PCORnet

Overview of methods based on OHD

• Disproportionality methods
• Longitudinal Gamma Poisson Shrinker
• Observational screen
• Multiple self-controlled case series
• High-dimensional Propensity Score
Disproportionality methods – How to count

Prevalence based

<table>
<thead>
<tr>
<th>Event X</th>
<th>Not X</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>1 (patient 1)</td>
</tr>
<tr>
<td>Not A</td>
<td>1 (patient 3)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Event X</th>
<th>Event X</th>
<th>Non X</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>3 (A+X1, A+X2, A+X3)</td>
<td>0</td>
</tr>
<tr>
<td>Not A</td>
<td>1 (B+X5)</td>
<td>2 (B+O1, C+O1)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>X</th>
<th>Non X + not X</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>3 (A+X1, A+X2, A+X3)</td>
</tr>
<tr>
<td>Not A</td>
<td>3 (X4, B+X5, X6)</td>
</tr>
</tbody>
</table>

Disproportionality methods – How to count (cont’)

Incidence based

<table>
<thead>
<tr>
<th>Event X</th>
<th>Not X</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>1 (patient 1)</td>
</tr>
<tr>
<td>Not A</td>
<td>1 (patient 3)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Event X</th>
<th>Non X</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>1 (patient 1)</td>
</tr>
<tr>
<td>Not A</td>
<td>0</td>
</tr>
</tbody>
</table>

Disproportionality methods - Results

MAP Scores for DP Methods (simulated data).

Take home messages

- Shrinkage measures, IC and EBGM performs best

- Derivative shrinkage measures, EB05 and IC05 and signed chi-square test, have the second best performance

- SRS and modified SRS are better representations than distinct patients

Longitudinal Gamma Poisson Shrinker (LGPS)

Observational screen

Specifically

\[ \text{Screening Rate (SR)} = \frac{\text{# of outcome}}{\text{Total time at risk}} \]

\[ \text{Screening Rate Ratio (SRR)} = \frac{\text{SR of exposed group}}{\text{SR of unexposed group}} \]

SR of exposed group = \( \frac{1+1+2}{2+3+5} \)

SR of unexposed group = \( \frac{1+1}{3+5} \)

SRR = \( \frac{4/10}{2/8} \) = 1.6

Multiple self-controlled case series

\[ p(y_i | x_i) = \prod_{d=1}^{t_i} p(y_{id} | x_{id}) = \prod_{d=1}^{t_i} \frac{e^{-\lambda_{id}} \lambda_{id}^{y_{id}}}{y_{id}!} \]

\[ = \exp(\phi_i n_i - \phi_{id} \sum_d e^{x_{id}^T \beta}) \prod_{d=1}^{t_i} \frac{(e^{x_{id}^T \beta})^{y_{id}}}{y_{id}!} \]

\[ x_{id} = (x_{id1}, ..., x_{idJ})' \]

\[ \mathcal{L}(\beta) = \sum_{i=1}^{N} \left[ \sum_{d=1}^{t_i} y_{id} x_{id}^T \beta - n_i \log \left( \sum_{d=1}^{t_i} e^{x_{id}^T \beta} \right) \right] - f(\beta) \]

\[ f(\beta) = \begin{cases} 
\lambda_1 \sum_{j=1}^{J} |\beta_j| & \text{under an } L_1 \text{ norm} \\
\lambda_2 \sum_{j=1}^{J} \beta_j^2 & \text{under an } L_2 \text{ norm} 
\end{cases} \]

\[ i = 1, 2, ..., n, \text{ index patients; } d \text{ index days; } t_i \text{ is the total number of days for a patient observed in a database; } (i,d) \text{ identifies their } d_{th} \text{ day of observation; } j = 1, 2, ..., J \text{ are } J \text{ drugs of interest; } \]

High-dimensional Propensity Score + New user cohort design

Parameters:

- **Washout period:** 180 d;
- **Surveillance window:** 30 d from exposure start; exposure+30d; all time from exposure start
- **Covariate eligibility window:** 30 d prior to exposure
- **# of confounders:** 100, 200, 500
- **Propensity strata:** 5, 20 strata
- **Analysis strategy:** Mantel-Haenszel stratification, propensity adjusted, propensity strata adjusted
- **Comparator cohort:** drugs with same indication, not in same class; most prevalent drug with same indication, not in same class

\[
\begin{align*}
\text{logit}(P(Drug_A = 1)) &= \alpha + \sum_{i=1}^{200} \delta_i R x_i + \sum_{j=1}^{200} \gamma_j D x_j \\
\text{logit}(P(Drug_B = 1)) &= \alpha + \sum_{i=1}^{200} \delta_i R x_i + \sum_{j=1}^{200} \gamma_j D x_j
\end{align*}
\]

A systematic statistical approach to evaluating evidence from observational studies


CC, case control; CM, cohort method-propensity score method; DP, disproportionality analysis; ICTPD, information component temporal pattern discovery; LGPS, longitudinal gamma Poisson shrinker; SCC, self-controlled cohort, observational screening; SCCS, self-controlled case series; MSLR, MarketScan Lab Supplemental; MDCD, MarketScan Multi-State Medicaid; MDCR, MarketScan Medicare Supplemental Beneficiaries; CCAE, MarketScan Commercial Claims and Encounters; GE, GE Centricity;

His past medical history is significant for asthma

<problem v = "asthma" code = "UMLS:C0004096_asthma">
  <certainty v = "high certainty"/>
  <parsemode v = "model1"/>
  <sectname v = "report past history item"/>
  <sid idref = "s2"/>
  <status v = "past history"/>
  <code v = "UMLS:C0004096_asthma"/>
</problem>
Natural Language Processing

- **Segmentation**: Splitting a document along sentence and section boundaries.
- **Tokenization**: Splitting sentences up into their parts, individual words and punctuation.
- **Part of speech (POS) tagging**: Assigning grammatical parts of speech to individual tokens.
- **Parsing**: Shallow parsing is used to identify the constituents (e.g. noun phrases).
- **Named entity recognition (NER)**: Identifying terms or phrases of interest (‘entities’) in the text.
- **Negation detection**: Determining whether a named entity is present or absent.
- **Word sense disambiguation (WSD)**: Words with identical spellings but different meanings.
- **Temporal inference**: Adverse event occurred after prescription of drug.
Active computerized pharmacovigilance using natural language processing, statistics, and electronic health records: a feasibility study

Recall = 75%
Precision = 31%

Outline

Data Source

Strengths & Limitations

Methods

Performance & case studies

Spontaneous Adverse Event Reports

Observational healthcare data

Scientific Literature
Biomedical Literature

Subtypes
- Research article
- Review
- Case study

Strengths
- Provide biological/physiological insights

Limitations
- Delay for drug surveillance

<table>
<thead>
<tr>
<th>Data source</th>
<th>Amount of data</th>
<th>ADR Specific articles</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medline</td>
<td>&gt;26 million articles, all time</td>
<td>340,000</td>
<td>13,000 new ADR-related articles each year</td>
</tr>
</tbody>
</table>
An example

NL indexers select the most appropriate MeSH descriptors and subheadings (or qualifiers) to resume the full content of an article after reading the full text.
Design and validation of an automated method to detect known adverse drug reactions in MEDLINE

- Using a threshold of three or more publications containing adverse event and drug co-occurrences
- Sensitivity of 90%
- Specificity of 100%
- Precision of up to 93%

Using information mining of the medical literature to improve drug safety

Social Media

Subtypes
- Patient web forums
- Twitter/facebook

Strengths
- Internet-based
- Patient-generated
- Unsolicited
- Up to date

Limitations
- Discrepancy in language (Non-medical, descriptive terms)
- Highly subjective, duplicates, hearsay information
Challenges

• No-medical, descriptive terms
  – Messed up my sleeping patterns -> sleep disturbance
  – Feeling need of deep breaths -> short of breath

• Complicated drug-condition relationship
  – Adverse effect: A reaction to the drug experienced by the patient, which the user considered negative
  – Beneficial effect: A reaction to the drug experienced by the patient, which the user considered positive
  – Indication: The condition for which the patient is taking the drug
  – Other: A disease or reaction related term not characterizable as one of the above
## Complicated drug-condition relationship

<table>
<thead>
<tr>
<th>Sample Comments</th>
<th>Annotations</th>
</tr>
</thead>
</table>
| This has helped take the edge off of my constant sorrow. It has also perked up my appetite. I had lost a lot of weight and my doctor was concerned. | “constant sorrow” - depression: indication;  
“perked up my appetite” - appetite increased: beneficial effect; “lost a lot of weight” - weight loss: other |
| Works to calm mania or depression but zonks me and scares me about the diabetes issues reported. | “mania” - mania: indication; “depression” - depression: indication; “zonks me” - somnolence: adverse effect; “diabetes” - diabetes: other (hearsay) |
| Twitter Example: #Schizophrenia #Seroquel did not suit me at all. Had severe tremors and weight gain | “schizophrenia” – schizophrenia: indication;  
“tremors” – tremors: adverse effect; “weight gain” – weight gain: adverse effect |

Challenges: Own experience or hearsay

<table>
<thead>
<tr>
<th>Category</th>
<th>Example</th>
</tr>
</thead>
<tbody>
<tr>
<td>Personal experience</td>
<td>I had memory problems with Simvastatin also to the point that I forgot where I was while driving.</td>
</tr>
<tr>
<td>An experience of a close family member or a friend</td>
<td>My step-dad was on Effexer, taking supplements for energy and drinking like a fish when he shot my daughter and me</td>
</tr>
<tr>
<td>Hearsay</td>
<td>There are more people out here having memory loss problems from statin drug that anyone can count.</td>
</tr>
</tbody>
</table>
A possible system architecture

Biomedical Terminology
Drug: RxNorm, DrugBank, ATC, UMLS
ADR: MedDRA, SIDER, UMLS, Consumer Health Vocabulary

SamPATHKumar, Hariprasad, Xue-wen Chen, and Bo Luo. BMC medical informatics and decision making 14.1 (2014): 1
ADR Relation Extraction

• Co-occurrence
  – Association rule mining
  – Disproportionality analysis

• Semi/supervised learning based approach
  – Hidden Markov Model
  – Conditional Random Field
    • POS, semantic type, word2vec, topic modeling
Case study: statins label change on 2012

Data (2003-2011)

<table>
<thead>
<tr>
<th>Forum</th>
<th>No. of unique messages</th>
<th>No. of sentences</th>
<th>No. of unique usernames</th>
</tr>
</thead>
<tbody>
<tr>
<td>medhelp.org</td>
<td>1,887</td>
<td>14,276</td>
<td>647</td>
</tr>
<tr>
<td>exchanges.webmd.com</td>
<td>5,492</td>
<td>32,693</td>
<td>854</td>
</tr>
<tr>
<td>healthboards.com</td>
<td>32,665</td>
<td>207,765</td>
<td>3,250</td>
</tr>
<tr>
<td>ehealthforum.com</td>
<td>1,042</td>
<td>7,150</td>
<td>562</td>
</tr>
</tbody>
</table>


Relation Extraction

Drug-ADR in the same sentence

I took Lipitor and (I) suffered muscle weakness and memory loss.

Figure 1: An example of a MPR candidate. (Curly brackets denote an implicit word in the sentence.)

Drug-ADR in the adjacent sentence

My husband took statins for 9 years, the last one was Lipitor. Side effects included severe neck and shoulder pain, muscle atrophe, loss of muscle strength and both short term and long term memory loss.

Figure 2: An example of a MPRE candidate.

Co-occurrence + filters
Case study: statins label change on 2012

Statistical Analysis

- **classic-induced lift:**
  \[
  \frac{\Pr(\text{message has } D \rightarrow S \text{ relation})}{\Pr(\text{message has } D \text{ entity}) \times \Pr(\text{message has } S \text{ entity})}
  \]

- **relation-driven lift:**
  \[
  \frac{\Pr(D_0 - S_0 \text{ relation})}{\sum_i \Pr(D_i - S_0 \text{ relations}) \times \sum_i \Pr(D_0 - S_i \text{ relations})}
  \]

* Chi-square test statistics

Results 1. Lifts and respective chi-square values preceded the relevant FDA label change

<table>
<thead>
<tr>
<th>Year</th>
<th>Relation-driven lift</th>
<th>Chi-square value</th>
<th>Classic-induced lift</th>
<th>Chi-square value</th>
</tr>
</thead>
<tbody>
<tr>
<td>2011</td>
<td>1.20</td>
<td>13.33</td>
<td>1.99</td>
<td>49.28</td>
</tr>
<tr>
<td>2010</td>
<td>1.21</td>
<td>13.24</td>
<td>1.94</td>
<td>42.21</td>
</tr>
<tr>
<td>2009</td>
<td>1.22</td>
<td>13.35</td>
<td>1.97</td>
<td>40.03</td>
</tr>
<tr>
<td>2008</td>
<td>1.21</td>
<td>10.70</td>
<td>1.89</td>
<td>31.42</td>
</tr>
<tr>
<td>2007</td>
<td>1.20</td>
<td>9.95</td>
<td>2.00</td>
<td>36.46</td>
</tr>
<tr>
<td>2006</td>
<td>1.21</td>
<td>10.30</td>
<td>1.89</td>
<td>28.20</td>
</tr>
<tr>
<td>2005</td>
<td>1.20</td>
<td>6.63</td>
<td>2.04</td>
<td>25.12</td>
</tr>
<tr>
<td>2004</td>
<td>1.25</td>
<td>3.46</td>
<td>2.18</td>
<td>12.93</td>
</tr>
<tr>
<td>2003</td>
<td>1.27</td>
<td>1.55</td>
<td>2.16</td>
<td>5.79</td>
</tr>
</tbody>
</table>

Results 2. Lifts and respective chi-square values

<table>
<thead>
<tr>
<th>Relation-Driven Lift</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
</tr>
</thead>
<tbody>
<tr>
<td>pain</td>
<td>1.13</td>
<td>0.09</td>
<td>0.07</td>
<td>0.02</td>
<td>0.12</td>
<td>0.01</td>
</tr>
<tr>
<td>muscle pain</td>
<td>0.09</td>
<td>0.11</td>
<td>0.15</td>
<td>0.02</td>
<td>0.11</td>
<td>0.00</td>
</tr>
<tr>
<td>flushing</td>
<td>0.05</td>
<td>0.00</td>
<td>0.00</td>
<td>0.23</td>
<td>0.15</td>
<td>0.00</td>
</tr>
<tr>
<td>heart attack</td>
<td>0.02</td>
<td>0.07</td>
<td>0.45</td>
<td>0.52</td>
<td>0.12</td>
<td>0.00</td>
</tr>
<tr>
<td>muscle damage</td>
<td>0.03</td>
<td>0.04</td>
<td>0.09</td>
<td>0.24</td>
<td>0.03</td>
<td>0.10</td>
</tr>
<tr>
<td>feeling weak</td>
<td>0.03</td>
<td>0.13</td>
<td>0.20</td>
<td>0.02</td>
<td>0.11</td>
<td>0.00</td>
</tr>
<tr>
<td>allergic reaction</td>
<td>0.10</td>
<td>0.24</td>
<td>0.05</td>
<td>0.11</td>
<td>0.12</td>
<td>0.10</td>
</tr>
<tr>
<td>liver failure</td>
<td>0.10</td>
<td>0.02</td>
<td>0.00</td>
<td>0.00</td>
<td>0.29</td>
<td>0.07</td>
</tr>
<tr>
<td>diabetes</td>
<td>0.25</td>
<td>0.30</td>
<td>0.06</td>
<td>0.08</td>
<td>0.13</td>
<td>0.09</td>
</tr>
<tr>
<td>cognitive impairment</td>
<td>0.04</td>
<td>0.00</td>
<td>0.13</td>
<td>0.03</td>
<td>0.02</td>
<td>0.12</td>
</tr>
<tr>
<td>leg pain</td>
<td>0.23</td>
<td>0.00</td>
<td>0.16</td>
<td>0.13</td>
<td>0.06</td>
<td>0.10</td>
</tr>
<tr>
<td>muscle problems</td>
<td>0.12</td>
<td>0.23</td>
<td>0.09</td>
<td>0.20</td>
<td>0.02</td>
<td>0.10</td>
</tr>
<tr>
<td>infection</td>
<td>0.06</td>
<td>0.00</td>
<td>0.00</td>
<td>0.03</td>
<td>0.10</td>
<td>0.11</td>
</tr>
<tr>
<td>leg cramps</td>
<td>0.20</td>
<td>0.28</td>
<td>0.10</td>
<td>0.13</td>
<td>0.02</td>
<td>0.11</td>
</tr>
<tr>
<td>muscle weakness</td>
<td>0.00</td>
<td>0.00</td>
<td>0.00</td>
<td>0.00</td>
<td>0.00</td>
<td>0.00</td>
</tr>
</tbody>
</table>
Outline

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Strengths & Limitations

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Spontaneous Adverse Event Reports

Observational healthcare data

Scientific Literature

Social Media

Search Engineer
Search engine logs - Google Flu Trend

Side effect detection based on search engine logs

\[ N_i^+ = \# \left\{ q_i^{(c)} \mid q_i^{(c)} \in C \cup S, T_i^0 + (\alpha + \beta) < t \leq T_i^0 + \theta \right\} \]

\[ N_i^- = \# \left\{ q_i^{(c)} \mid q_i^{(c)} \in C \cup S, T_i^0 - \theta < t \leq T_i^0 - (\alpha + \beta) \right\} \]

\[ QRR = \frac{\sum_i N_i^+}{\sum_i N_i^-} \]

\[ 2N^-N^+ + Z_{\alpha/2}^2(N^- + N^+) \pm \sqrt{Z_{\alpha/2}^2(N^- + N^+)(4N^-N^+ + Z_{\alpha/2}^2(N^- + N^+))} \]

\[ 2(N^-)^2 \]

Comparison between FAERS and search log based signal detection

<table>
<thead>
<tr>
<th></th>
<th>AERS (EB05)</th>
<th>Search Logs (QRR05)</th>
<th>AUC difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute Renal Failure</td>
<td>0.88</td>
<td>0.88</td>
<td>-4%</td>
</tr>
<tr>
<td>Upper GI Bleed</td>
<td>0.89</td>
<td>0.92</td>
<td>29%</td>
</tr>
<tr>
<td>Acute Liver Injury</td>
<td>0.79</td>
<td>0.81</td>
<td>12%</td>
</tr>
<tr>
<td>Acute Myocardial Infarction</td>
<td>0.70</td>
<td>0.73</td>
<td>9%</td>
</tr>
<tr>
<td>Average</td>
<td>0.81</td>
<td>0.83</td>
<td>11%</td>
</tr>
</tbody>
</table>

**Partial AUC at 0.3 FPR**

<table>
<thead>
<tr>
<th></th>
<th>AERS (EB05)</th>
<th>Search Logs (QRR05)</th>
<th>AUC difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute Renal Failure</td>
<td>0.19</td>
<td>0.19</td>
<td>-2%</td>
</tr>
<tr>
<td>Upper GI Bleed</td>
<td>0.21</td>
<td>0.22</td>
<td>17%</td>
</tr>
<tr>
<td>Acute Liver Injury</td>
<td>0.14</td>
<td>0.16</td>
<td>10%</td>
</tr>
<tr>
<td>Acute Myocardial Infarction</td>
<td>0.10</td>
<td>0.14</td>
<td>19%</td>
</tr>
<tr>
<td>Average</td>
<td>0.16</td>
<td>0.18</td>
<td>12%</td>
</tr>
</tbody>
</table>
Evidence Integration

- Spontaneous Adverse Event Reports
- Observational healthcare data
- Scientific Literature
- Social Media
- Search Engineer

Evidence Integration
Literature review

• Combine SRS and search logs
• Combine SRS and literature
• Combine observational health data and literature
• Combine SRS and observational health data
ADR detection based on SRS and EHR/Claims

**Methods**

- Observational healthcare data
- EHR or Claims
- FAERS

**Data preprocessing**
- ADR cohort identification
- Two-step regression-based method (reduce false positive rates)

**Signal Integration Engine**
- Signals from an observational healthcare data
- Signals from FAERS
- Combined signals from the observational healthcare data and FAERS

**Results**

<table>
<thead>
<tr>
<th>ADR</th>
<th>FAERS</th>
<th>GE</th>
<th>Combined</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute renal failure</td>
<td>0.91</td>
<td>0.68</td>
<td>0.92</td>
</tr>
<tr>
<td>Acute liver injury</td>
<td>0.71</td>
<td>0.63</td>
<td>0.76</td>
</tr>
<tr>
<td>Acute myocardial infarction</td>
<td>0.72</td>
<td>0.80</td>
<td>0.82</td>
</tr>
<tr>
<td>Upper GI bleeding</td>
<td>0.80</td>
<td>0.77</td>
<td>0.87</td>
</tr>
<tr>
<td>Total</td>
<td>0.76</td>
<td>0.76</td>
<td>0.82</td>
</tr>
</tbody>
</table>

**Combining FAERS and MarketScan claims**

<table>
<thead>
<tr>
<th>ADR</th>
<th>FAERS</th>
<th>Claims</th>
<th>Combined</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute renal failure</td>
<td>0.91</td>
<td>0.83</td>
<td>0.93</td>
</tr>
<tr>
<td>Acute liver injury</td>
<td>0.72</td>
<td>0.69</td>
<td>0.79</td>
</tr>
<tr>
<td>Acute myocardial infarction</td>
<td>0.71</td>
<td>0.77</td>
<td>0.82</td>
</tr>
<tr>
<td>Upper GI bleeding</td>
<td>0.81</td>
<td>0.83</td>
<td>0.86</td>
</tr>
<tr>
<td>Total</td>
<td>0.76</td>
<td>0.78</td>
<td>0.82</td>
</tr>
</tbody>
</table>

* Evaluated based on known drugs which cause or do not cause the specific ADR
* Combined signals perform significantly better than signals acquired from each individual data source

*Significant improvement over signal detection from single data source*

Real world scenario

<table>
<thead>
<tr>
<th>FAERS</th>
<th>OHD</th>
<th>GE EHR</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>Positive</td>
<td>Negative</td>
</tr>
<tr>
<td>Exhibit in both sources</td>
<td>Appear in SRS but not in OHD</td>
<td></td>
</tr>
<tr>
<td>Negative</td>
<td>Appear in OHD but not in SRS</td>
<td>The lack of a signal in either source</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>FAERS</th>
<th>GE EHR</th>
<th>FAERS/GE/Combined AUCs (TP/TN)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive</td>
<td>Positive</td>
<td>Negative</td>
</tr>
<tr>
<td>NA (25/0)</td>
<td>0.73/0.78/0.89 (29/11)</td>
<td></td>
</tr>
<tr>
<td>Negative</td>
<td>0.60/0.68/0.68 (38/23)</td>
<td>0.71/0.69/0.75 (61/152)</td>
</tr>
</tbody>
</table>

Detecting Drugs that Could Possibly Cause Acute Myocardial Infarction (AMI)

EHR based evidence

<table>
<thead>
<tr>
<th>Drug</th>
<th>AMI Signal Score in EHR</th>
</tr>
</thead>
<tbody>
<tr>
<td>amoxapine</td>
<td>0.118</td>
</tr>
<tr>
<td>diflunisal</td>
<td>0.192</td>
</tr>
<tr>
<td>eletriptan</td>
<td>0.072</td>
</tr>
<tr>
<td>nabumetone</td>
<td>0.494</td>
</tr>
<tr>
<td>nelfinavir</td>
<td>0.263</td>
</tr>
<tr>
<td>zolmitriptan</td>
<td>0.381</td>
</tr>
</tbody>
</table>

FAERS based evidence

<table>
<thead>
<tr>
<th>Drug</th>
<th>AMI Signal Score in FAERS</th>
</tr>
</thead>
<tbody>
<tr>
<td>amoxapine</td>
<td>0.076</td>
</tr>
<tr>
<td>diflunisal</td>
<td>0.109</td>
</tr>
<tr>
<td>eletriptan</td>
<td>0.682</td>
</tr>
<tr>
<td>nabumetone</td>
<td>0.079</td>
</tr>
<tr>
<td>nelfinavir</td>
<td>0.292</td>
</tr>
<tr>
<td>zolmitriptan</td>
<td>0.224</td>
</tr>
</tbody>
</table>

Combined evidence

<table>
<thead>
<tr>
<th>Drug</th>
<th>Combined AMI Signal Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>amoxapine</td>
<td>0.007</td>
</tr>
<tr>
<td>diflunisal</td>
<td>0.007</td>
</tr>
<tr>
<td>eletriptan</td>
<td>0.034</td>
</tr>
<tr>
<td>nabumetone</td>
<td>0.035</td>
</tr>
<tr>
<td>nelfinavir</td>
<td>0.044</td>
</tr>
<tr>
<td>zolmitriptan</td>
<td>0.034</td>
</tr>
</tbody>
</table>

• Drugs in red are known to cause AMI
• Drugs in green are known to not cause AMI
• None of the six drugs passed the signal threshold of <0.05 based on either EHR or FAERS
• Combined evidence from EHR and FAERS strength the signals with signal score <0.05

Why drugs fail in clinical trial?

Safety (toxicology or clinical safety) and efficacy (failure to achieve sufficient efficacy) are two major reasons for which a drug fails clinical trials.

Can predictive modelling techniques help to generate hypothesis on efficacy and safety profiles of drugs?
Pharmacology 101: A Simplified Path from Drug to Effect

- Drug
- Action
- Reaction/Effect

2D/3D structure
Fingerprint

Drug

On/off-target binding
Binding assays
Computational simulation

(Metabolite)

Action

Gene expression change
Microarray
RNASEq

Physicochemical properties

Side effect (SE)
Surveillance database

Indication
Literature
EHR

Reaction/Effect
Free big data in the domain

Drug structures
2,198 approved drugs
5,022 experimental drugs (DrugBank)

Chemical structures
89,124,716 compounds
219,712,379 substances (PubChem)

Drug

On/off-target binding
1,154,431 BioAssays (PubChem)
118,748 crystal structures (RSCB PDB)
551,193 reviewed protein sequences
62,148,086 not reviewed (UniProt)

Action

Gene expression change
3,775 human genomes (1000 genome)
15,819 sequencing platforms (GEO)
68,503 gene expression series (GEO)
1,801,592 gene expression samples (GEO)

Effect

Indication
57,805 drug-indication pairs (NDF-RT)
215,433 clinical trials (ClinicalTrials.gov)
22,000,000+ articles (PubMed)

Side effect (SE)
5,868 side effects
139,756 drug-SE pairs (SIDER)
6,503,071 reports (FAERS)

By May 2016
From Surveillance to Prediction: A Few Case Studies

- Predicting drug-drug interactions through implementing the chemical-protein interactome
- Predicting drug-drug interactions through large-scale similarity-based link prediction
- Predicting drug repositioning opportunities through integrating multiple aspects of drug similarity and disease similarity
Statistics of Prescriptions in USA and Drug-Drug Interactions (DDIs)

- (a) Number of prescription drugs used in the past 30 days by percentage of the USA population
- (b) Average number of prescriptions filled in 2011 in the USA by age

• DDIs may happen unexpectedly when more than one drugs are co-prescribed, causing serious ADRs.
• DDIs are serious health threats that can result in significant morbidity and mortality - causing nearly 74,000 emergency room visits and 195,000 hospitalizations each year in the USA.
Pharmacokinetic (PK) and Pharmacodynamic (PD): Another Definition of DDIs

- PK and PD properties of one drug affect either the PK or PD of another drug

Antagonistic
Synergistic
Types of DDIs

• **Potentiation**: Drugs with similar actions cause an additive effect. e.g.,
  – Coumadin and aspirin taken together cause excessive bleeding
  – Sedatives and alcohol cause excessive sedation

• **Interference**: One drug accelerates or slows the metabolism or excretion of another drug. e.g., Erythromycin taken with
  – Digoxin = elevated blood levels of digoxin
  – Coumadin = enhanced action of Coumadin

• **Antagonism**: One drug decreases the effectiveness of another drug because of divergent actions
  – Oral ketoconazole (Nizoral) is absorbed in an acidic environment
  – H2-receptor antagonists or proton pump inhibitors decrease acidity in the stomach

• **Displacement**: Two drugs compete for protein binding sites
  – One drug “wins” (is bound to protein)
  – Displaced drug is active in greater quantities
  – Same effect as taking a higher dose of the displaced drug!

A major cause of DDIs
Molecular docking and chemical-protein interactome (CPI)

Use AutoDock Vina to simulate the binding between a small molecule and a protein target.

- Provide the theoretical binding conformation (i.e., free energy) of the drug's binding to protein
- A lower docking score means a higher binding strength

Simulation of a CPI
Biological rationale of DDI-CPI

• Biological rationale
  – Competition between protein resources (e.g., metabolizing enzyme, transporter, or unexpected off-targets) can cause DDIs.
  – MOAs are simple in explanation, such as which PK/PD proteins may be involved in this DDI; and are there any comparable strong CPI for this protein.

• Preparation of the library drugs and targets
  – 2515 library drug molecules (85% are FDA approved drugs)
  – 611 representative collection of PK/PD proteins (239 human PK proteins and 372 PD proteins)

PK proteins:
PDB with all available metabolite enzymes

PD proteins:
PDBBind database with binding pocket information

• all proteins have X-ray crystal structures
• all structures have better resolution than 3.4 Å
• binding pockets were identified around the embedded ligands in the crystal structure

239 PK proteins and 372 PD proteins
### Workflow of DDI-CPI server

**Model training**

(A) **12,656 drug pairs** (DrugBank)

<table>
<thead>
<tr>
<th>Drug pair</th>
<th>DDI?</th>
</tr>
</thead>
<tbody>
<tr>
<td>A and B</td>
<td>Yes</td>
</tr>
<tr>
<td>B and C</td>
<td>Yes</td>
</tr>
<tr>
<td>A and D</td>
<td>No</td>
</tr>
</tbody>
</table>

(B) **Docking scores** (2,515 drugs against 611 targets)

<table>
<thead>
<tr>
<th>Drug</th>
<th>T&lt;sub&gt;1&lt;/sub&gt;</th>
<th>T&lt;sub&gt;2&lt;/sub&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>-9.3</td>
<td>-9.8</td>
</tr>
<tr>
<td>B</td>
<td>-8.4</td>
<td>-10.1</td>
</tr>
<tr>
<td>C</td>
<td>-7.3</td>
<td>-9.1</td>
</tr>
</tbody>
</table>

(C) **Training set**

The sum and the absolute difference of the docking scores as features

<table>
<thead>
<tr>
<th>Drug pair</th>
<th>T&lt;sub&gt;1&lt;/sub&gt; Sum</th>
<th>T&lt;sub&gt;1&lt;/sub&gt; Dif.</th>
<th>T&lt;sub&gt;2&lt;/sub&gt; Sum</th>
<th>T&lt;sub&gt;2&lt;/sub&gt; Dif.</th>
<th>DDI?</th>
</tr>
</thead>
<tbody>
<tr>
<td>A and B</td>
<td>-17.7</td>
<td>0.9</td>
<td>-19.9</td>
<td>0.3</td>
<td>Yes</td>
</tr>
<tr>
<td>B and C</td>
<td>-15.5</td>
<td>0.9</td>
<td>-17.6</td>
<td>0.6</td>
<td>Yes</td>
</tr>
<tr>
<td>A and D</td>
<td>-19.7</td>
<td>1.1</td>
<td>-20.3</td>
<td>0.7</td>
<td>No</td>
</tr>
</tbody>
</table>

(D) **Logistic regression models**

(E) **Drug X**

(F) **Docking score** towards 611 targets

<table>
<thead>
<tr>
<th>Drug</th>
<th>T&lt;sub&gt;1&lt;/sub&gt;</th>
<th>T&lt;sub&gt;2&lt;/sub&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>X</td>
<td>-6.0</td>
<td>-8.2</td>
</tr>
</tbody>
</table>

(G) **DDI predictions**

<table>
<thead>
<tr>
<th>Drug pair</th>
<th>T&lt;sub&gt;1&lt;/sub&gt; Sum</th>
<th>T&lt;sub&gt;1&lt;/sub&gt; Dif.</th>
<th>T&lt;sub&gt;2&lt;/sub&gt; Sum</th>
<th>T&lt;sub&gt;2&lt;/sub&gt; Dif.</th>
<th>DDI?</th>
<th>Probability</th>
</tr>
</thead>
<tbody>
<tr>
<td>A and X</td>
<td>-15.3</td>
<td>3.3</td>
<td>-18.0</td>
<td>1.6</td>
<td>Yes</td>
<td>0.68</td>
</tr>
<tr>
<td>B and X</td>
<td>-14.4</td>
<td>2.4</td>
<td>-18.3</td>
<td>1.9</td>
<td>Yes</td>
<td>1.00</td>
</tr>
<tr>
<td>C and X</td>
<td>-13.3</td>
<td>1.3</td>
<td>-17.3</td>
<td>0.9</td>
<td>Yes</td>
<td>1.00</td>
</tr>
</tbody>
</table>

Demo: DDI-CPI

DDI-CPI, a server Predicting Drug-Drug Interaction via Chemical-Protein Interactome

Submit a molecule

In order to protect privacy, your submissions will not be shown to others.

You can upload a single-molecule file to be processed by our server.

Here is an example file, upload it and wait for about 15 mins to check the result.

Upload a molecular file: Browse... No file selected.

Or input SMILES string: Draw Molecular name:

E-mail Address: The access link will be sent in the email (optional)

Your remark:

Submit Reset

Disclaimer: The server is for research purposes only and the authors and their organizations are excluded from all liability for any costs, claims, expenses, charges, losses, damages or penalties of any kind incurred directly or indirectly arising from the use of this server.

Recommended browsers: FireFox, Chrome or Internet Explorer 9 (HTML5 support), resolution: 1366*768 or higher
Model evaluation and comparison

The ROC and precision-recall curve comparison for different DDI prediction methods based on independent validation

**P-score:** uses side-effect similarities to predict target sharing (Campillos, et al. Science (2008), 321, 263-266.)

**S-score:** uses drug-target network to predict DDIs (Huang, et al. PLoS Comput Biol (2013), 9, e1002998)

**LR(S-score and P-score):** integrates P-score and S-score by a Bayesian probabilistic model

**DDI-CPI:** predicts DDI using machine learning models via CPI
Case study - MAO-A inhibitors

Table 3 (adapted from reference 6, 7)

<table>
<thead>
<tr>
<th>Drugs to Avoid When Taking MAOIs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amphetamines</td>
</tr>
<tr>
<td>Cyclobenzaprine</td>
</tr>
<tr>
<td>Linezolid</td>
</tr>
<tr>
<td>Methadone</td>
</tr>
<tr>
<td>SSRIs/SNRIs</td>
</tr>
<tr>
<td>Triptans</td>
</tr>
<tr>
<td>Vasoconstrictors (psuedoephedrine, phenylephrine, cocaine)</td>
</tr>
<tr>
<td>Chlorpheniramine, brompheniramine</td>
</tr>
<tr>
<td>St. John’s Wort</td>
</tr>
</tbody>
</table>

- SSRI with MAOI results in high extracellular serotonin (5-HT) concentration – serotonin syndrome.

Source: pharmacytimes.org, Terry Gotham, dancesafe.org
Case study - MAO-A inhibitors

- The server predicts that sertraline may interact with isocarboxazid, linezolid, and naratriptan.
- All of the predicted drugs can rank the monoamine oxidase A (MAO-A) targets to the top 20% – possible mechanism suggested.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Zyx 1</th>
<th>Zyx 2</th>
<th>Zyx 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isocarboxazid</td>
<td>-9.4</td>
<td>-9.3</td>
<td>-9.2</td>
</tr>
<tr>
<td>Linezolid</td>
<td>-9.4</td>
<td>-10.2</td>
<td>-9.6</td>
</tr>
<tr>
<td>Naratriptan</td>
<td>-9.3</td>
<td>-8.8</td>
<td>-8.9</td>
</tr>
<tr>
<td>Sertraline</td>
<td>-8.8</td>
<td>-9.7</td>
<td>-9.7</td>
</tr>
</tbody>
</table>
From Surveillance to Prediction: A Few Case Studies

• Predicting drug-drug interactions through implementing the chemical-protein interactome
• Predicting drug-drug interactions through large-scale similarity-based link prediction
• Predicting drug repositioning opportunities through integrating multiple aspects of drug similarity and disease similarity
Similarity-based Drug-Drug Interaction (DDI) Predictions

- Inspired from content-based recommender systems: Predict the existence of an DDI through comparisons with known DDIs

- Drug T might interact with drug X based on T’s similarity to drug A and X similarity to drug E:
  - A-E already known to interact

- Limitation of prior arts
  - Skewed distribution
  - Appropriate evaluation metrics
  - Incompleteness of similarity measures
Overview of DDI-SIM

Known DDIs

<table>
<thead>
<tr>
<th>Drug1</th>
<th>Drug2</th>
<th>Sim</th>
</tr>
</thead>
<tbody>
<tr>
<td>Salsalate</td>
<td>Aspirin</td>
<td>.9</td>
</tr>
<tr>
<td>Dicoumarol</td>
<td>Warfarin</td>
<td>.7</td>
</tr>
</tbody>
</table>

Candidate Features

<table>
<thead>
<tr>
<th>Drug1</th>
<th>Drug2</th>
<th>Feature Vector</th>
</tr>
</thead>
<tbody>
<tr>
<td>Salsalate</td>
<td>Gliclazide</td>
<td>[.9, .., .7]</td>
</tr>
<tr>
<td>Salsalate</td>
<td>Warfarin</td>
<td>[.7, .., .4]</td>
</tr>
</tbody>
</table>

DDI Predictions

<table>
<thead>
<tr>
<th>Drug1</th>
<th>Drug2</th>
<th>score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Salsalate</td>
<td>eltrombopag</td>
<td>0.98</td>
</tr>
<tr>
<td>Salsalate</td>
<td>colesevelam</td>
<td>0.94</td>
</tr>
</tbody>
</table>

Logistic Regression Model (λ, η)

Build adjusted logistic regression models

Select model & threshold

Fokoue, A., Sadoghi, M., Hassanzadeh, O., Zhang, P. Predicting Drug-Drug Interactions through Large-Scale Similarity-Based Link Prediction. ESWC, 2016.
13 Drug Similarity Measures

Chemical-Protein Interactome (CPI)  
Pathway  
Target  

Molecular Structure  
Therapeutic classification  

And others such as:  
• Mechanism of Action  
• Physiological Effect  
• Metabolizing Enzyme  
• MeSH term  
• ......
Feature Generation

Only feature used in previous work: eg., Gottlieb et al.
Limited view of all ($\text{Sim}_1$, $\text{Sim}_2$) scores

$(\text{Sim}_1, \text{Sim}_2)$
- max: 0.8
- mean: 0.6
- std: 0.16
- max z-score: 1.22
- max with tested drug?: 0
- mean over all drug pairs (even not known DDI pairs): 0.6

Total number of features:
$13^2 \times 6 = 1014$

$\Rightarrow$ Higher risk of over-fitting addressed by testing multiple regularization values at validation
Demo: DDI-SIM
Experimental Evaluation: 10-fold cross validation

1) Using calibration features and unbalanced training/validation data significantly outperforms the baseline.

2) For a fixed DDI prevalence at training/validation, using calibration features is always better.

3) No similarity measure by itself has good predictive power (ATC is the best with 0.58 F-Score and 0.56 AUPR), removing any given similarity measure has limited impact on the quality of the predictions (< 1% decrease).
Experimental Evaluation: Retrospective Analysis (Predicting new DDIs in DrugBank 4.0 based on DrugBank 3.0)

Predictions using only known DDIs as of 2011

Predict up to 68% of DDIs found after 2011
From Surveillance to Prediction: A Few Case Studies

• Predicting drug-drug interactions through implementing the chemical-protein interactome
• Predicting drug-drug interactions through large-scale similarity-based link prediction
• Predicting drug repositioning opportunities through integrating multiple aspects of drug similarity and disease similarity
Drug repositioning

- **Drug repositioning** (also known as Drug repurposing, Drug re-profiling, Therapeutic Switching and Drug re-tasking) is the application of known drugs and compounds to new indications (i.e., new diseases).

<table>
<thead>
<tr>
<th>Drug</th>
<th>Original indication</th>
<th>New indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Viagra</td>
<td>Hypertension</td>
<td>Erectile dysfunction</td>
</tr>
<tr>
<td>Wellbutrin</td>
<td>Depression</td>
<td>Smoking cessation</td>
</tr>
<tr>
<td>Thalidomide</td>
<td>Antiemetic</td>
<td>Multiple Myeloma</td>
</tr>
</tbody>
</table>

The repositioned drug has already passed a significant number of toxicity and other tests, its safety is known and the risk of failure for reasons of adverse toxicology are reduced.
Next: Multi-channel detailed computational hypothesis generation
And even beyond the hypothesis generation...

Validation methods are increasingly commoditized

Big data researchers will have a higher impact in biomedicine 😊
Challenges and opportunities: multiscale networks instead of a diagnosis

Dynamic network: timeline of individualized genomic medicine

During an individual’s lifespan: **from prewomb to tomb**

Personalized multiscale networks to model dynamics of complex disease

DNA
Cell-specific RNA
Cytokines
Clinical labs
Mobile devices
Microbiome
Physiometrics

Dudley J. Big data in biology and medicine. Retrieved at www.aaas.org
Healthcare is really a big data industry

60% Exogenous Factors
30% Genomics Factors
10% Clinical Factors

1,100 Terabytes
Generated per lifetime

6 Terabytes
Per lifetime

0.4 Terabytes
Per lifetime

Help people live longer and feel better
Our commitment to Health – IBM Moonshot

“I’m telling you, our moonshot will be the impact we will have on Healthcare. It has already started. We will change and do our part to change the face of Healthcare. I am absolutely positive about it. And that, to me, while we do many other things, that will be one of the most important.”

Ginni Rometty
IBM Chairman, President and CEO
April 16, 2015
Multiple positions are available!!!
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Questions?

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