Data-driven Prediction of Drug Effects and Interactions

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April 26th, 2013
Sources: Drug Topics Magazine and Wikipedia
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Sources: Drug Topics Magazine and Wikipedia
Merck Pulls Arthritis Drug Vioxx from Market

by RICHARD KNOX
The New York Times

Research Ties Diabetes Drug to Heart Woes

By GARDINER HARRIS
Published: February 15, 2010

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F.D.A. Issues New Alerts About Cholesterol Drugs
By GARDNER HARRIS
Published: February 29, 2012

CORRECTION APPENDED
Federal health officials on Tuesday added new safety alerts to the prescribing information for statins, the cholesterol-reducing medications that are among the most widely prescribed drugs in the world, citing rare risks of memory loss, diabetes and muscle pain.

 withdrawn in Europe...

Statins are considered some of the safest drugs
Public Database Is Urged to Monitor Drug Safety

By NATASHA SINGER
Published: November 23, 2009

What could be done to prevent another Vioxx? This pain medication for arthritis became a blockbuster after its introduction in 1999, only to be taken off the market in 2004 when a study linked the drug to an increased risk of heart attack and strokes.
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source: fda.gov
The Food and Drug Administration Collects Data

- Over 3 Million reports collected so far:
  - patient: age, sex, weight, country
  - drugs they are taking
  - diseases they were being treated for
  - the *adverse events* that occurred to that patient
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Just interpreting these reports is hard

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<td>METFORMIN</td>
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Most of these red lines are false - which are true?
Spontaneous reporting systems are biased
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- These biases introduce “synthetic associations”
Spontaneous reporting systems are biased

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- (e.g.) from concomitant drug use (co-Rx effect)
  - drugs co-prescribed with Vioxx more likely to be associated with heart attacks
Spontaneous reporting systems are biased

- These biases introduce “synthetic associations”
- (e.g.) from concomitant drug use (co-Rx effect)
  - drugs co-prescribed with Vioxx more likely to be associated with heart attacks
- (e.g.) from indications (indication-effect)
  - drugs given to diabetics more likely to be associated with hyperglycemia
Propensity score matching corrects for bias of measured covariates

• Identify matched controls for the studied cases

• Model the likelihood of a patient being selected into the cases based on the covariates
  • \(1\{\text{pt is exposed}\} \sim \text{age} + \text{sex} + \text{weight} + \ldots\)

• Match each case with a control with the same likelihood

• Requires measured covariates
Adapted form of propensity score matching

• IPSM, Implicit Propensity Score Matching

• Assumes combination of drugs and indications describes the patient covariates
IPSM produces better estimates of expected values
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Reports for query drug
IPSM produces better estimates of expected values

Reports for query drug

All Other Reports
IPSM produces better estimates of expected values

Reports for query drug
IPSM produces better estimates of expected values

- First, reduce to only those reports that have co-prescribed prescriptions listed
IPSM produces better estimates of expected values

• First, reduce to only those reports that have co-prescribed prescriptions listed
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- First, reduce to only those reports that have co-prescribed prescriptions listed
- Second, reduce to only those reports that have correlated indications listed
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Takes advantage of variables likely to co-vary with unmeasured covariates
IPSM produces better estimates of expected values

Reports for query drug

All Reports

Propensity-matched Background
IPSM produces better estimates of expected values

- Example: Reporting of hyperglycemia with diabetes drugs
IPSM produces better estimates of expected values

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- Observed reporting frequency: 17.7%
IPSM produces better estimates of expected values

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- Example: Reporting of hyperglycemia with diabetes drugs
  - **Observed** reporting frequency: 17.7%
  - **Expected** Estimates:
    - Entire database expected frequency: 1.5%
IPSM produces better estimates of expected values

- Example: Reporting of hyperglycemia with diabetes drugs
- **Observed** reporting frequency: 17.7%
- **Expected** Estimates:
  - Entire database expected frequency: 1.5%
  - IPSM-derived expected frequency: 17.6%
Drugs are biased toward side effects caused by their indication
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Drugs are biased toward side effects caused by their indication.
Method corrects for indication biases

Drugs given to Diabetics

- lisinopril
- acarbose
- chlorpropamide
- rosiglitazone
- metformin
- pioglitazone
- glibenclamide
- repaglinide
- glimepiride
- nateglinide
- glipizide

Proportional Reporting Ratio
Method corrects for indication biases

Drugs given to Diabetics

Proportional Reporting Ratio

lisinopril
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Significance Threshold
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Proportional Reporting Ratio

Original PRR
Corrected PRR

Significance Threshold
Method corrects for indication biases

Anti-arrhythmics and Arrhythmia

- hydroxyzine
- tirofiban
- lidocaine
- quinidine
- verapamil
- mexiletine
- diltiazem
- amiodarone
- propafenone
- flecainide
- sotalol
- dofetilide
- disopyramide

Proportional Reporting Ratio
Method corrects for indication biases

Anti-arrhythmics and Arrhythmia

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Proportional Reporting Ratio

Original PRR
Corrected PRR
Method corrects for indication biases
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Original

After Correction

<table>
<thead>
<tr>
<th>Reporting correlation to causative indication</th>
<th>Probability of synthetic association</th>
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</thead>
<tbody>
<tr>
<td>0.01</td>
<td>0.2</td>
</tr>
<tr>
<td>0.1</td>
<td>0.4</td>
</tr>
<tr>
<td>1</td>
<td>1</td>
</tr>
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</table>

Implicit correction for prescription biases

Original

Average MI PRR Score

Average Age

Implicit correction for prescription biases

Implicit correction of age differences in exposed vs non-exposed
Implicit correction for prescription biases
Implicit correction for prescription biases

Original

After Correction
Method addresses one of the two primary concerns of SRS
Method addresses one of the two primary concerns of SRS

1. Uncharacterized bias
Method addresses one of the two primary concerns of SRS

1. Uncharacterized bias
2. Under and non-reporting of adverse events
Method addresses one of the two primary concerns of SRS

1. Uncharacterized bias

2. Under and non-reporting of adverse events
   - if no reports, then current methods cannot find associations
Method addresses one of the two primary concerns of SRS

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   - if no reports, then current methods cannot find associations
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✓ 1. Uncharacterized bias

? 2. Under and non-reporting of adverse events

• if no reports, then current methods cannot find associations
Diseases can be identified by the side effects they elicit
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- physicians use observable side effects to form hypothesis about the underlying disease

Diabetes

- level of detection
- measured minor effects
- unmeasured severe effect
Diseases can be identified by the side effects they elicit

- physicians use observable side effects to form hypothesis about the underlying disease
- e.g. you can’t see diabetes, but you can measure blood glucose
Severe ADE’s can be identified by the presence of more minor (and more common) side effects.
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- First, identify the common side effects that are harbingers for the underlying severe AE.
Severe ADE’s can be identified by the presence of more minor (and more common) side effects

- First, identify the common side effects that are harbingers for the underlying severe AE
- Then, combine these side effects together to form an “effect profile” for an adverse event
Severe ADE’s can be identified by the presence of more minor (and more common) side effects.
How do we validate?
Electronic Health Records

• Clinical data on millions of patients
  • diagnoses
  • lab measurements
  • prescription orders
  • clinical notes
DDI prediction validation

Table S3 Novel drug-drug interaction predictions for diabetes related adverse events.

<table>
<thead>
<tr>
<th>Rank</th>
<th>Drug A</th>
<th>Drug B</th>
<th>Score</th>
<th>Minimum Randomization Rank</th>
<th>Known DDI exists</th>
</tr>
</thead>
<tbody>
<tr>
<td>38</td>
<td>PAROXETINE HCL</td>
<td>PRAVASTATIN SODIUM</td>
<td>11.351896015</td>
<td>62</td>
<td></td>
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<tr>
<td>72</td>
<td>DIOVAN HCT</td>
<td>HYDROCHLOROTHIAZIDE</td>
<td>7.1786599539</td>
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<td></td>
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<tr>
<td>94</td>
<td>CRESTOR</td>
<td>PREVACID</td>
<td>4.7923771645</td>
<td>148</td>
<td></td>
</tr>
<tr>
<td>107</td>
<td>DESFERAL</td>
<td>EXJADE</td>
<td>3.97220625</td>
<td>129</td>
<td></td>
</tr>
<tr>
<td>159</td>
<td>COUMADIN</td>
<td>VESICARE</td>
<td>0.8928376683</td>
<td>169</td>
<td></td>
</tr>
<tr>
<td>160</td>
<td>DEXAMETHASONETHALIDOMIDE</td>
<td></td>
<td>0.8928376683</td>
<td>168</td>
<td>CRITICAL</td>
</tr>
<tr>
<td>170</td>
<td>FOSAMAX</td>
<td>VOLTAREN</td>
<td>0.5033125</td>
<td>1138</td>
<td></td>
</tr>
<tr>
<td>175</td>
<td>ALIMTA</td>
<td>DEXAMETHASONE</td>
<td>0.2442375</td>
<td>197</td>
<td></td>
</tr>
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- Focus on top hit from diabetes classifier
- paroxetine = depression drug, pravastatin = cholesterol drug
- Popular drugs, est. ~1,000,000 patients on this combination!
Analyzed **blood glucose values** for patients on either or both of these drugs
Blood Glucose Concentration (mg/dl)

Blood Glucose Concentration (mmol/L)

Baseline

After Treatment

Pravastatin (N = 2,063)

Blood Glucose Concentration (mg/dl)

Pravastatin (N = 2063)
Paroxetine (N = 1603)

Baseline
After Treatment

Blood Glucose Concentration (mg/dl)

- Pravastatin (N = 2,063)
- Paroxetine (N = 1,603)
- Combination (N = 135)

Baseline vs. After Treatment

+18 mg/dl incr.  p < 0.001

no diabetics

Blood Glucose Concentration (mg/dl)

- Pravastatin (N = 2,063)
- Paroxetine (N = 1,603)
- Combination (N = 135)

Baseline
After Treatment

Blood Glucose Concentration (mg/dl) for no diabetics:
- Pravastatin (N = 2,063)
- Paroxetine (N = 1,603)
- Combination (N = 135)

Blood Glucose Concentration (mg/dl) for including diabetics:
- Pravastatin
- Paroxetine
- Combination (N=177)

Baseline vs. After Treatment:
- Increase of +60 mg/dl with combination treatment.
EMR shows evidence of interaction between paroxetine and pravastatin
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- Observational study could be biased by confounders, we checked
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- other combinations of SSRIs and Statins
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• Observational study could be biased by confounders, we checked
  • other combinations of SSRIs and Statins
  • time of day the glucose values were taken
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  • concomitant medications
EMR shows evidence of interaction between paroxetine and pravastatin

- Observational study could be biased by confounders, we checked
  - other combinations of SSRIs and Statins
  - time of day the glucose values were taken
  - concomitant medications
- None of these were significant
Informatics methods have taken us far, skeptics remain
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• Insulin Resistant Mouse Model
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- Insulin Resistant Mouse Model
- 10 control mice on normal diet (Ctl Ctl)
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Simulating Pre-Diabetics
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  - 10 mice on pravastatin + HFD
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  - 10 mice on paroxetine + HFD
Informatics methods have taken us far, skeptics remain

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  - 10 control mice on normal diet (Ctl Ctl)
  - 10 control mice on high fat diet (HFD)
  - 10 mice on pravastatin + HFD
  - 10 mice on paroxetine + HFD
  - 10 mice on combination + HFD
Summary of fasting glucose levels
Summary of fasting glucose levels

Average ITT Fasting Glucose (mg/dl)

- Ctl Ctl
- Pravastatin
- Paroxetine
- Control
- Combination

+60mg/dl same as for diabetics
• Correct for biases introduced by hidden covariates
• Infer presence of latent adverse drug events when primary evidence is unavailable
• Validated interaction between paroxetine and pravastatin retrospectively (EHR) and prospectively (mouse model)
Thank you

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- Patrick P. Ye
- Roxana Daneshjou
- Russ Altman


- Russ Biagio Altman
- Phil Tsao
- Guy Haskin Fernald
- Patrick Yue
- Roxana Daneshjou
- Rohan Mahajan
- Josh Denny (V)
- Dan Roden (V)
- Shawn Murphy (H)
- Zac Kohane (H)
- Gomathi Krishnan
- Victor Castro