Data-driven Prediction of Drug Effects and Interactions

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Columbia University

April 26th, 2013
Sources: Drug Topics Magazine and Wikipedia
Sources: Drug Topics Magazine and Wikipedia
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

Hundreds of people taking Avandia, a controversial diabetes medicine, needlessly suffer heart attacks and heart failure each month, according to confidential government reports that recommend the drug be removed from the market.

withdrawn in Europe...
Research Ties Diabetes Drug to Heart Woes

By GARDINER HARRIS
Published: February 19, 2010

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withdrawn in Europe...

F.D.A. Issues New Alerts About Cholesterol Drugs

By GARDINER 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.

Statins are considered some of the safest drugs
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.
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.
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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<thead>
<tr>
<th>Drugs</th>
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### Drugs
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### Adverse Events
- ACUTE RESP. DISTRESS
- ANEMIA
- DECR. BLOOD PRESSURE
- CARDIAC FAILURE
- DEHYDRATION

most of these red lines are false - which are true?
Spontaneous reporting systems are biased
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• These biases introduce “synthetic associations”
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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

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

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

• Example: Reporting of hyperglycemia with diabetes drugs

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

- Example: Reporting of hyperglycemia with diabetes drugs
- **Observed** reporting frequency: 17.7%
- **Expected** Estimates:
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 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
Drugs are biased toward side effects caused by their indication

![Graph showing reporting correlation between Drug and Indication]
Drugs are biased toward side effects caused by their indication

![Graph showing the relationship between reporting correlation and probability of false association.](graph.png)
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

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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

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Original PRR
Corrected PRR

Method corrects for indication biases.
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Original
Method corrects for indication biases

Original

After Correction
Implicit correction for prescription biases

Original
Implicit correction for prescription biases

Original

After Correction
Implicit correction of age differences in exposed vs non-exposed

(Average Age of Cases) - (Average Age of Controls)
Implicit correction for prescription biases

Original
Implicit correction for prescription biases

Original

After Correction
Method addresses one of the two primary concerns of SRS
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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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✓ 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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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
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- 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
### 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>
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</thead>
<tbody>
<tr>
<td>38</td>
<td>PAROXETINE HCL</td>
<td>PRAVASTATIN SODIUM</td>
<td>11.351896015</td>
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<tr>
<td>72</td>
<td>DIOVAN HCT</td>
<td>HYDROCHLOROTHIAZIDE</td>
<td>7.1786599539</td>
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<tr>
<td>94</td>
<td>CRESTOR</td>
<td>PREVACID</td>
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<tr>
<td>107</td>
<td>DESFERAL</td>
<td>EXJADE</td>
<td>3.97220625</td>
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<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>DEXAMETHASONE</td>
<td>VETHALIDOMIDE</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>
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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)

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

Baseline vs. After Treatment

+18 mg/dl incr.  
p < 0.001
no diabetics

Baseline vs. After Treatment

Blood Glucose Concentration (mg/dl)

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- Combination (N = 135)

Blood Glucose Concentration (mmol/L)

EMR shows evidence of interaction between paroxetine and pravastatin
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- other combinations of SSRIs and Statins
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  - time of day the glucose values were taken
  - 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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- 10 control mice on normal diet (Ctl Ctl)
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Simulating Pre-Diabetics
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  • 10 mice on paroxetine + HFD
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- Insulin Resistant Mouse Model
  - 10 control mice on normal diet (Ctl Ctl)
  - 10 control mice on high fat diet (HFD)
  - 10 mice on pravastatin + HFD
  - 10 mice on paroxetin + HFD
  - 10 mice on combination + HFD
Summary of fasting glucose levels

Average ITT Fasting Glucose (mg/dl)

- Ctl Ctl
- Pravastatin
- Paroxetine
- Control
- Combination
Summary of fasting glucose levels

Average ITT Fasting Glucose (mg/dl)

+60mg/dl same as for diabetics
Summary

• 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
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- Patrick Yue
- Roxana Daneshjou
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- Josh Denny (V)
- Dan Roden (V)
- Shawn Murphy (H)
- Zac Kohane (H)
- Gomathi Krishnan
- Victor Castro