Monitoring all Drugs for a Specific Outcome in the Sentinel System

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ICPE Disclosure Slide

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  - Mini-Sentinel Operations Center Response to Evaluation of Exposure/Outcome Associations, HHSF22301007T
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- No relationships to disclose
What is

- A signal detection / data-mining method
- Scans electronic health data that are grouped into hierarchical tree structures
- Automatically adjusts for multiple hypothesis testing

http://www.treescan.org
What is an Outcome-Oriented Scan / DrugScan (1 Outcome: M Exposures)?

Total Nodes: 35,583 aggregate + 326,497 NDC codes
Surveillance Population

- Claims Data from 3 Data Partner Sites (2000-2014)
  - Not all sites had data back to 2000
- Males and Females >=18 years with medical and drug coverage and incident outcome of interest
- Outcome of Interest
  - Angioedema
DrugScan Analytic Design and Statistics

- Case-Crossover Design (Self-Controlled)
- Incident Exposures or New “Starts” of Therapeutic
- Duration of Treatment Ignored
  - not “As Treated”
- Fixed and Variable Risk Window Scan Statistics
H$_0$: The probability of an outcome after the dispensing of a drug is modified (conditioned) by the total number of events in the dataset across the observation window on that given day.

H$_A$: There are at least some time periods in the observation window when the probability of an outcome is higher . . . after various adjustments.
Angioedema Takeaways

1) Manageable Total Number of Alerts
2) More Potential Misclassification of Disease Onset than Anticipated

Results
Angioedema Cohort Attrition

Members during the query period with Angioedema when >=18 and Medical Coverage during washout

- 140,884

Members with incident angioedema

- 139,924

Members who do not have incident angioedema

- 960

Incident angioedemas without drug dispensings

- 67,289

Incident angioedemas without required drug enrollment for assessing incidence at 3rd level

- 9,667

Incident angioedemas with >=1 drug dispensing of interest

- 72,635

Incident angioedemas with required drug enrollment criteria for assessing incidence at 3rd level

- 62,968

Incident angioedemas with required drug enrollment criteria for assessing incidence at 4th level

- 62,985

Incident angioedemas with incident drug dispensings at 3rd level

- 45,580

Incident angioedemas with incident drug dispensings at 4th level

- 46,360

Incident angioedemas with required drug enrollment criteria for assessing incidence at 3rd level

- 62,985

Incident angioedemas without required drug enrollment for assessing incidence at 4th level

- 9,650

Incident angioedemas without incident drug dispensings at 3rd level

- 17,388

Incident angioedemas without incident drug dispensings at 4th level

- 16,625
- 110,785 pairs; 45,580 events at 3\text{rd} level
- On average, 2.4 incident dispensings per incident angioedema
- Day of the Week Effects
Angioedema Results

- 28 unique alerts at 0.05 level, 20 meaningfully different
  - 9 were angioedema treatments
    - e.g., Glucocorticosteroids, Hydroxyzine, Diphenhydramine
  - Rest were known positives or likely positives
    - ACE inhibitors, Bupropion, Simvastatin, Antibiotics
Angioedema Sensitivity Analyses

1. Pruned out all anti-histamines and other angioedema treatments (e.g., hydroxyzine, glucocorticosteroids)
   - Strong known positives remain with slight adjustment of time-to-event
   - Lose some known positives (adjusted conditional analysis)
   - Some new alerts
Tree-Temporal Alerts after Pruning

- 13 unique at 3rd level, 9 meaningfully different
- Some new antibiotics, ACEI Combos are statistically significant.
- Some alerts become not statistically significant at 0.05 level (e.g., simvastatin)
Angioedema Summary

1. Misclassification of Disease Onset is present
   - DESIGN: Prune out anti-histamines from the tree *a priori*
   - DESIGN: Refine outcome definitions with MORE exclusions
   - ANALYSIS: Prune based at analysis phase

2. Detects known positives without too many false positives
Acknowledgments

- DrugScan Team
  - Jeff Brown
  - Gerald Dal Pan
  - Inna Dashevsky
  - Martin Kulldorff
  - Andrew Petrone
  - Carolyn Balsbaugh

- DrugScan Protocol Reviewers
  - Mark Levenson
  - Rita Ouellet-Hellstrom
  - Simone Pinheiro
Q&A

You Are

(Not) Small
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