

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
 - Under contract: FDA HHSF223200910006I
- No relationships to disclose



What is

- A signal detection / data-mining method
- Scans electronic health data that are grouped into hierarchical tree

structures

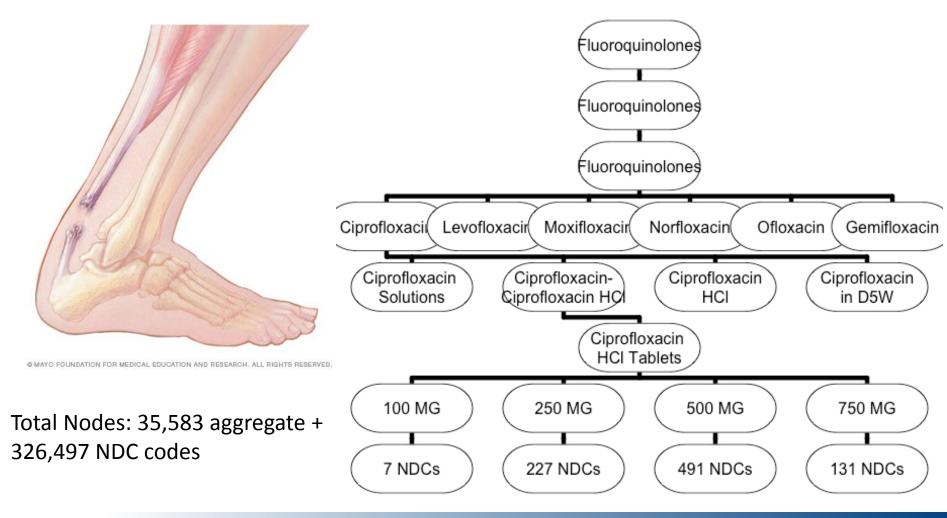
 Automatically adjusts for multiple hypothesis testing



http://www.treescan.org



What is an Outcome-Oriented Scan / DrugScan (1 Outcome: M Exposures)?





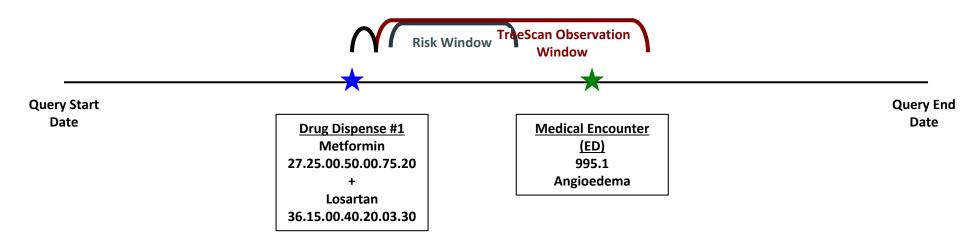
Surveillance Population

- 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

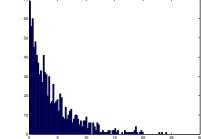


DrugScan Analytic Design and Statistics

- 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







Conditional Tree-Based Scan Statistic Hypotheses for Outcome-Oriented Scan

H₀: 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.

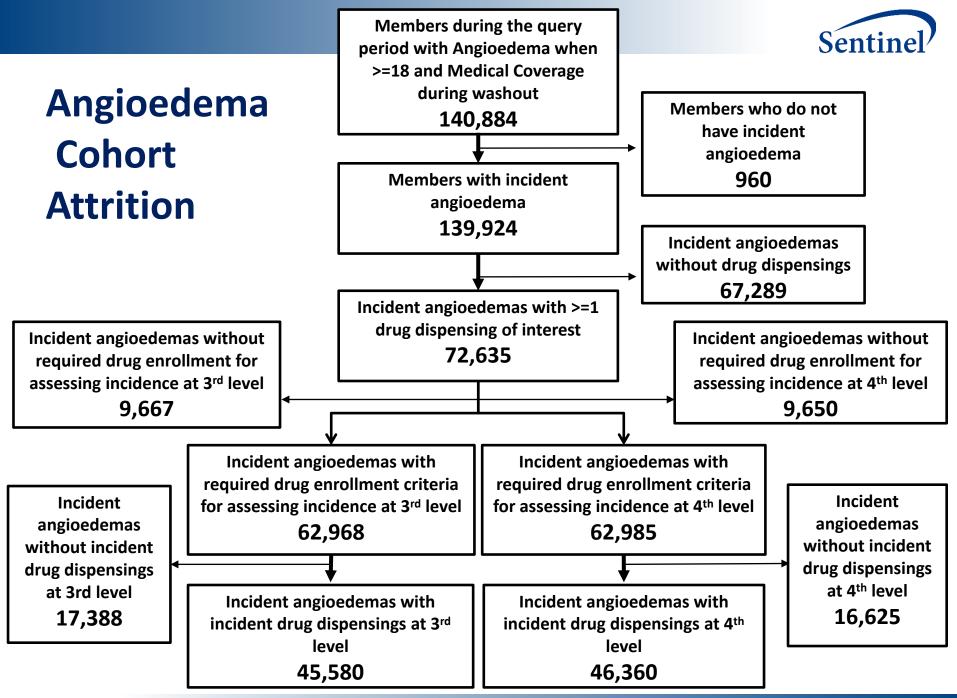
H_A: There are at least some time periods in the observation window when the probability of an outcome is higher
 . . . after various adjustments



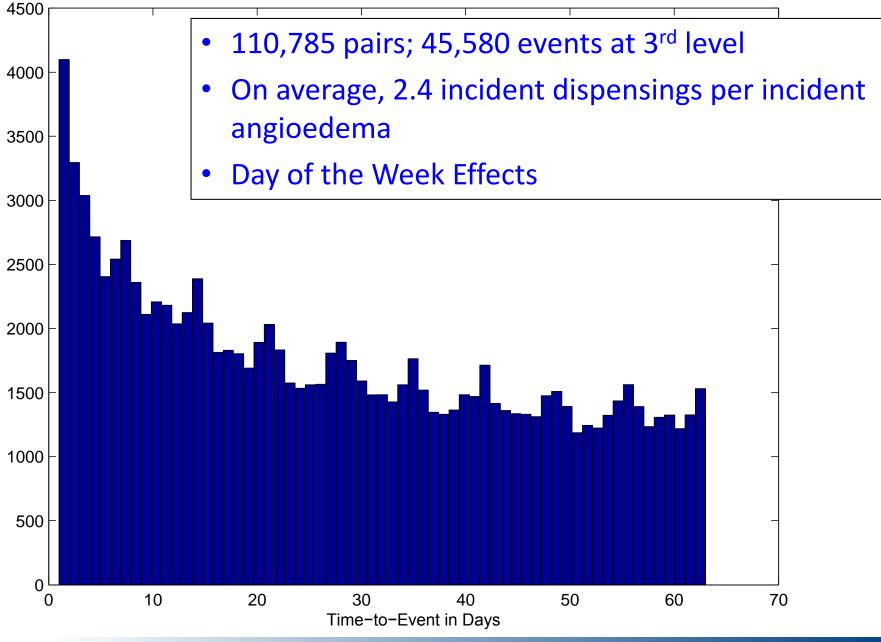
Angioedema Takeaways

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

Results







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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, Buproprion, Simvastatin, Antibiotics



Angioedema Sensitivity Analyses

- Pruned out all antihistamines and other angioedema treatments (e.g., hydroxyzine, glucocorticosteroids)
 - Strong known positives
 remain with slight
 adjustment of time-toevent
 - 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* OR
 - DESIGN: Refine outcome definitions with MORE exclusions
 OR
 - 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
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 - Carolyn Balsbaugh
- DrugScan Protocol Reviewers
 - Mark Levenson
 - Rita Ouellet-Hellstrom
 - Simone Pinheiro



Q&A

You Are (Not) Small



Angioedema, 3rd level, Nade Name D Events Start End Window Cases Expected Statistic P-value 3rd level, 3rd level, **Glucconticosteroids*** 2210004 500 11127 1 8 3526 2324.33 1.53 2279 1.00E-05 Tree-temporal, Conditional Methylprednisolone 221000300 3893 1 8 1140 812.8 1.44 559.1 1.00E-05 Epinephrine 3890004000 3640 1 15 1925 1256.27 1.53 154.87 1.00E-05 -28 unique mantidine 492000201 939 1 6 251 153.37 1.64 26.05 1.00E-05 -20 different *Antianxiety Agents - Misc.*** 572000402 2174 1 4 477 226.31 1.75 62.47 1.00E-05 Grey=Mis- Classification *Midrowyine Pamoate 572004010 1931 1 4 472 25.97 1.75 62.47 1.00E-05	· ·		Node	Node	Window	Window	Cases in	Expected	Observed/	Test	intinci
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False Positive Inhibitors*** 394000 2008 42 54 414 322.99 1.28 11.80 0.02207 Selective Serotonin Reuptake Inhibitors 581600 1044 32 59 469 372.2 1.26 11.66 0.02514	Pink=Likelv		3940007500	802	42	54	188	129	1.46	11.82	0.0217
*Selective Serotonin Reuptake Inhibitors (SSRIs)*** 581600 1044 32 59 469 372.2 1.26 11.66 0.02514											
Reuptake Inhibitors 581600 1044 32 59 469 372.2 1.26 11.66 0.02514	False Positive		394000	2008	42	54	414	322.99	1.28	11.80	0.02207
(SSRIs)*** 581600 1044 32 59 469 372.2 1.26 11.66 0.02514											
		•									
Triazolam 6020104000 35 51 52 8 0.77 10.41 11.51 0.02985											
		Triazolam	6020104000	35	51	52	8	0.77	10.41	11.51	0.02985

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Tree-Temporal Alerts after Pruning

			Window	Window	Cases in	Exp	ected	Observed/	Test	
Node Name	Node ID	Node Cases	Start	End	Window	Cas	es	Expected	Statistic	P-Value
Sulfamethoxazole-Trimethoprim	1699000230	1812	2	3	12	598	373.06	1.6	5 57.51	1.00E-05
Lisinopril	3610003000	2169)	1	8	590	402.72	1.4	7 38.23	1.00E-05
*ACE Inhibitors***	361000	2649)	2	8	594	407.13	1.40	5 37.71	1.00E-05
Levofloxacin	500003400	1115	5	1	6	249	158.23	1.5	7 22.18	1.00E-05
Levofloxacin	5000034	1116	5	1	6	249	158.39	1.57	7 22.08	1.00E-05
*Fluoroquinolones***	50000	3159)	1	6	588	447.95	1.3	L 20.02	1.00E-05
Minocycline HCl	400004010	199)	15	19	44	15.95	2.70	5 16.60	3.00E-05
Clindamycin	16220020	770)	1	7	189	127.28	1.48	3 13.02	0.0012
Clindamycin HCl	1622002010	769)	1	7	188	127.1	1.48	3 12.71	0.0018
Bupropion HCl	5830004010	390)	18	31	136	85.58	1.59) 12.59	0.00199
Lisinopril & Hydrochlorothiazide	3699180255	748	3	2	9	188	128.84	1.40	5 11.90	0.00465
ACE Inhibitors & Thiazide/Thiazide-Like	36991802	814	1	2	9	201	139.95	1.44	11.74	0.00571
Triazolam	6020104000	35	5	51	52	8	0.94	8.48	3 10.05	0.0463

- 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)