Discussion: Methodological Needs for Signal Refinement

Brookings Institution Expert Workshop

William DuMouchel, Phase Forward

September 21, 2010

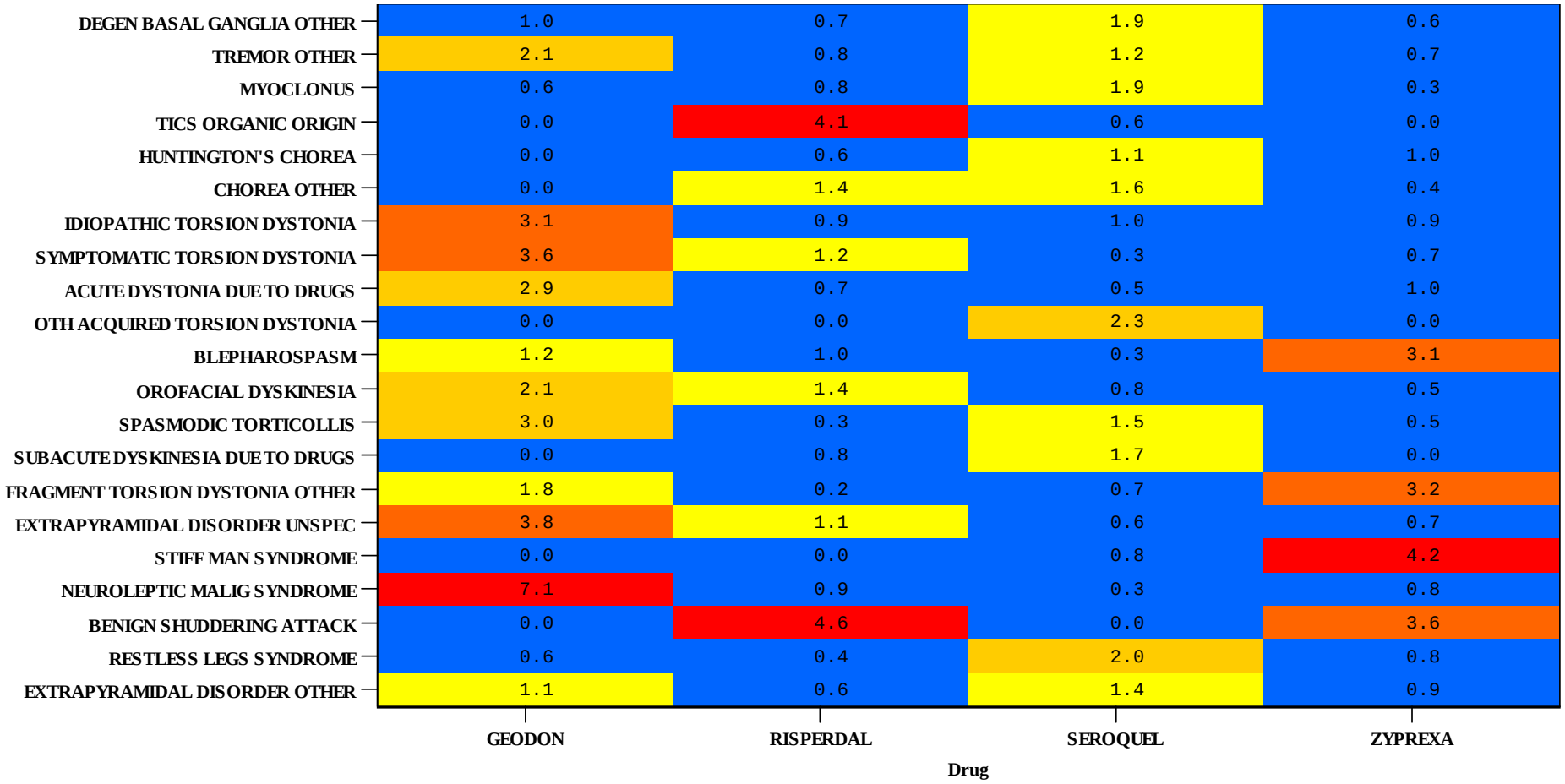
Broader View of Methodology Needs

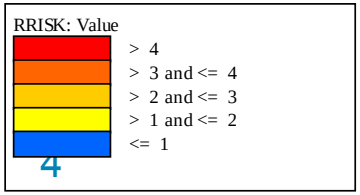
- Combining Analyses Across a Class of Drugs and a Class of Events, within the Longitudinal Health Data Framework
- Combining Results from Longitudinal Health Data Analyses with other Types of Data

Bayesian Two-Way Analysis Example

- Fine Granularity of ICD9 Coding Leads to Small Counts
- Perform Joint Analysis of Chemically Similar Drugs vs Medically Similar Events
- Example Using DoD Tricare Database
- Atypical Antipsychotics vs Movement Disorders
- Goal: Sharpen Estimates without Imposing Too Much Structure

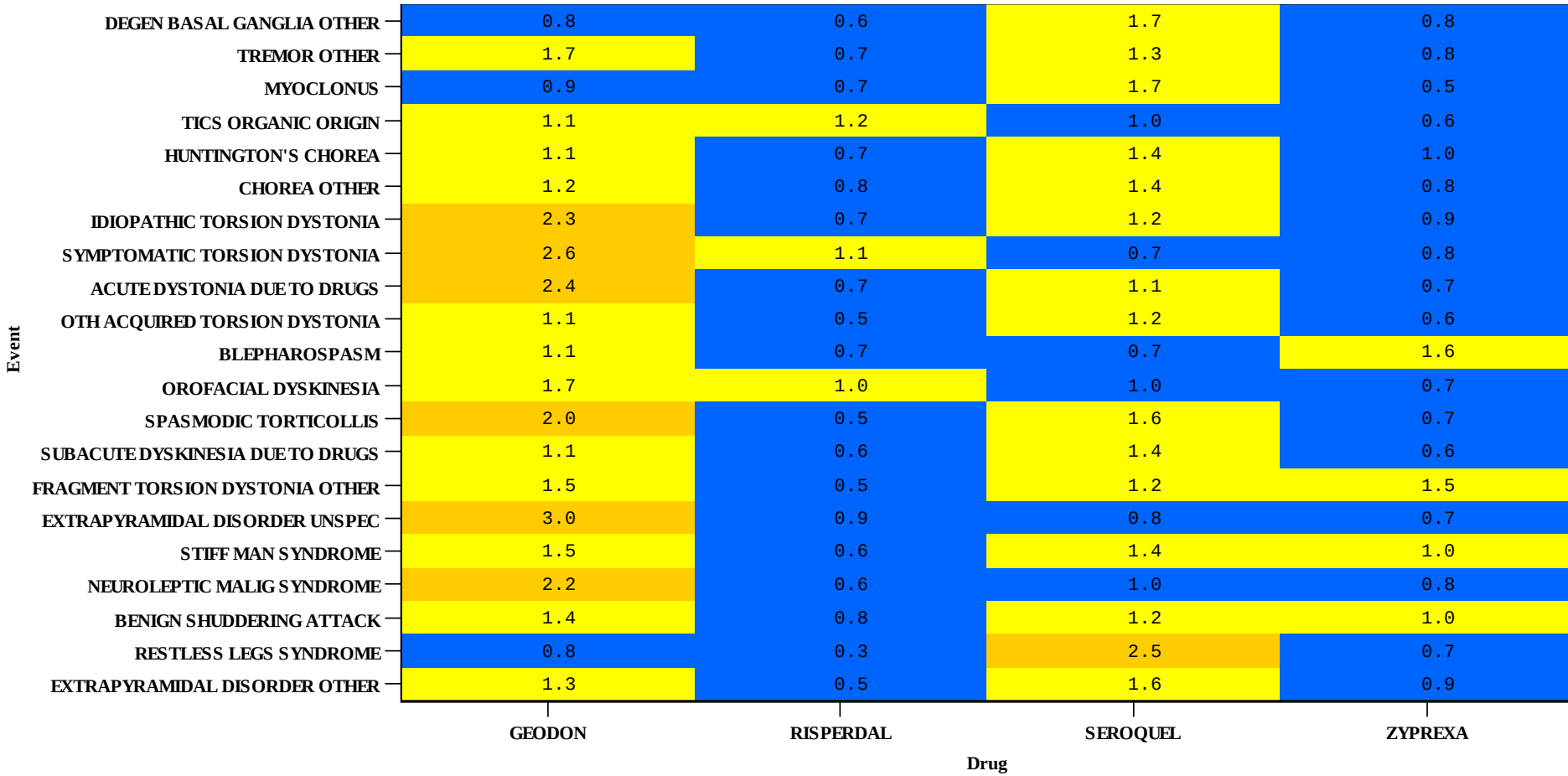
Separately Computed Risk Ratios

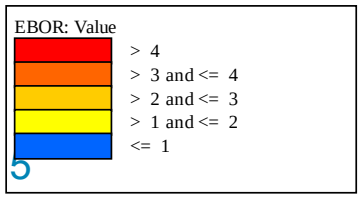




- **Each of the four drugs is compared to the other three**
  - **RR = (Event rate this drug)/(Event rate other drugs)**
  - **Small counts make the risk ratios unstable**

Empirical Bayes Model Estimates





- **Drug effect x Event effect x Interaction effect**
  - **All effects shrunk towards 1 using Bayesian model**
  - **“Borrowing strength” paradigm**

Combine the Three Data Types?

- Spontaneous Reports, Clinical Trials ADRs, and Longitudinal Medical and Billing Records
- Similar concept of counting drug-event occurrences
- Can a Bayesian model use pre-marketing data to better analyze post-marketing data?
  - Complementary hypothesis generation/confirmation
  - Formal synthesis of estimates?
- Clinical trials and spontaneous reports use MedDRA, while E-Health data is mostly ICD-9
- Other differences in terminology between and within the different data types

MedDRA and ICD-9 Inconsistencies

STATISTICS IN MEDICINE, VOL. 10, 565–576 (1991)

USING A CLAIMS DATABASE TO INVESTIGATE DRUG-INDUCED STEVENS–JOHNSON SYNDROME

BRIAN L. STROM, JEFFREY L. CARSON*, ALLAN C. HALPERN†, RITA SCHINNAR, ELLEN SIM SNYDER AND PAUL D. STOLLEY
[and eight more authors]

Table I. ICD-9-CM Code 695.1: Erythema multiforme

Erythema iris
Herpes iris
Lyell's syndrome
Staphylococcal scalded skin syndrome
Stevens–Johnson syndrome
Toxic epidermal necrolysis

Medicaid data alone cannot identify SJS because ICD-9 695.1 is too general
Recent revision of ICD-9 may help in future studies:

- New code 695.10 Erythema multiforme, unspecified
  - Erythema iris
  - Herpes iris
- New code 695.11 Erythema multiforme minor
- New code 695.12 Erythema multiforme major
- New code 695.13 Stevens-Johnson syndrome
- New code 695.14 Stevens-Johnson syndrome-toxic epidermal necrolysis overlap syndrome

Valdecoxib and SJS, Erythema mult.

DoD Tricare vs Unexposed

Generic Name	ICD9 code plus text (5 digit)	PAT1	PAT2	RRISK_C	RRISK_B	RRISK_B05	RRISK_B95
Valdecoxib	6951: ERYTHEMA MULTIFORME	15	151	3.33	2.61	1.66	3.92

DoD Tricare vs Other Coxibs

Generic Name	ICD9 code plus text (5 digit)	COMPARATOR	PAT1	PAT2	RRISK_C	RRISK_B	RRISK_B05	RRISK_B95
Valdecoxib	6951: ERYTHEMA MULTIFORME	Celecoxib, Rofecoxib	10	25	2.69	2.10	1.21	3.40

AERS Spontaneous Reports through 2003

	Generic_Name	PT	SUBSET	N	E	RR	EBGM	EB05	EB95	PRR
	Valdecoxib	Erythema multiforme	[1968-85]-[2003]	29	2.40	12.1	11.2	7.62	15.6	6.83
	Rofecoxib	Erythema multiforme	[1968-85]-[2003]	24	26.1	0.919	0.898	0.637	1.24	0.567
	Celecoxib	Erythema multiforme	[1968-85]-[2003]	18	17.0	1.06	1.02	0.686	1.47	0.607
	Valdecoxib	Stevens-Johnson syndrome	[1968-85]-[2003]	61	5.54	11.0	10.7	8.41	13.2	12.5
	Rofecoxib	Stevens-Johnson syndrome	[1968-85]-[2003]	27	51.9	0.520	0.519	0.375	0.702	0.554
	Celecoxib	Stevens-Johnson syndrome	[1968-85]-[2003]	48	35.5	1.35	1.32	1.04	1.66	1.42

Integrating More Types of Knowledge

- Chemical Structure, Physical Properties
- Bioassay, Toxicology, Genomics
- Pharmokinetics, Metabolic Pathways
- Human Safety Experience
- Data Warehouse May Help Us Cross Boundaries
- FDA-IOM Emerging Safety Science Workshop
  - Chapter 9 of Proceedings
    - <http://www.nap.edu/catalog/11975.html>

Patrick Ryan Presentation

- Focus on huge number of potential signal estimation methods (including their many tuning constants)
  - Each has its champions in the data mining community
- Attributes that could influence method performance
  - Related to the Drug, the Event, the Database, etc.
- Proposal for Method Evaluation
  - Define a set of test cases
  - Sensitivity analyses from varying parameters, databases, etc.
- Understanding overall error rates will influence (undermine?) our confidence in any particular result
  - Intimidating amount of research remains to be done
  - OMOP is making impressive progress!

Sebastian Schneeweiss Presentation

- Focus on a family of methods consistent with the epidemiology literature
- Lays out the various options within the class of cohort comparisons with adjustment for propensity scores
- Useful flow charts for what to do depending on data characteristics
- More of a focus on “let’s get started and get answers” rather than considering too many alternate methods
  - Importance of rapid protocol development and implementation
- But sensitivity analyses are also emphasized here too
  - More as a practical tool than as a theoretical evaluation

Bruce Fireman Presentation

- Most specific of the 3 presentations—proposal for active surveillance of anti-diabetes drug users
  - New-user cohort design, similar to Schneeweiss proposal
  - Multiple active comparator drugs
  - Multiple pair-wise comparisons but no adjustment for multiplicity
- Censor observation time of switchers and non-adherent
  - But may re-analyze using other strategies (more multiplicities?)
- Subgroup analyses galore: comparator drug, partner site, medical history, follow-up period
  - Could Bayesian models help with post-hoc comparisons?
- Upper bounds of CI are important (Reassurance)
- Comparing the comparators—bound to be interesting

Summary

- Cohort study with propensity score matching
  - Everyone likes some variation of this design
  - Uncertainty about when to use within-subject variation
- Sensitivity analysis is necessary because there are so many reasonable design variations
  - Perhaps a large set of example analyses where the answer is thought to be known can show the advantages of some variations over others
  - Some question as to whether adjustment for multiplicity is proper in a safety analysis
  - Noticing general trends of results, as parameters vary, is useful
- Embedding individual drug-event risk estimates within a more global analysis helps to get the big picture