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Applied Bayesian Approaches in Safety and Pharmacovigilance

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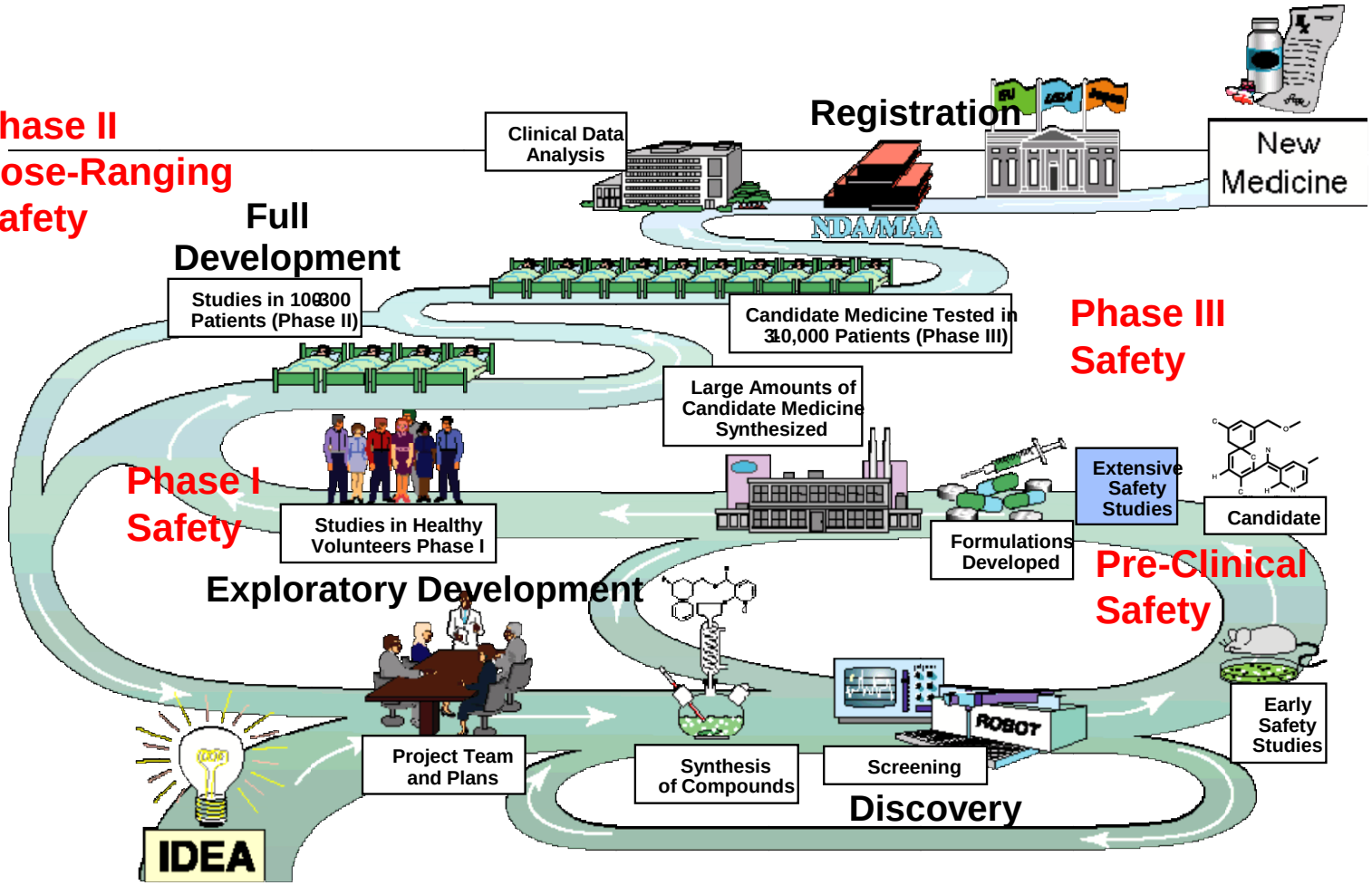
Outline

- Safety is an issue in all phases
- We (statisticians) have concentrated on efficacy
- There are numerous applications of statistical thinking to safety
  - Safety in a single clinical trial
  - Pharmacovigilance

The Long Road to a New Medicine
Constant Thread - Safety



"It is estimated that adverse drug reactions (ADRs) caused 100,000 deaths among hospitalized patients in the USA in 1994 (* 4th leading cause of death)" (Lazarou et al. JAMA 1998; 279:1200-1205)

Guidance for Industry Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment

TABLE OF CONTENTS

Post-Marketing Sources of Safety Information

- Sources of information include:
  - Controlled clinical trials
  - Cohort (observational) studies
  - “Sentinel” sites
  - Spontaneous Reporting Systems (SRS) Post-marketing registries

Safety Analysis of Data from Controlled Clinical Trials

General Issues

- Historically analysis of Safety data largely limited to tabular display of descriptive statistics
- Inadequate
  - both as an inferential tool
  - and as a non-inferential tool
- For the latter Graphical methods are better
  - Amit et al (2007) propose 10 methods

PHARMACEUTICAL STATISTICS
Pharmaceut. Statist. (in press)
Published online in Wiley InterScience
(www.interscience.wiley.com) DOI: 10.1002/pst.254

Graphical Approaches to the Analysis of Safety Data from Clinical Trials

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Graphical Display of QT data
Most Frequent On-Therapy AEs sorted by Relative Risk

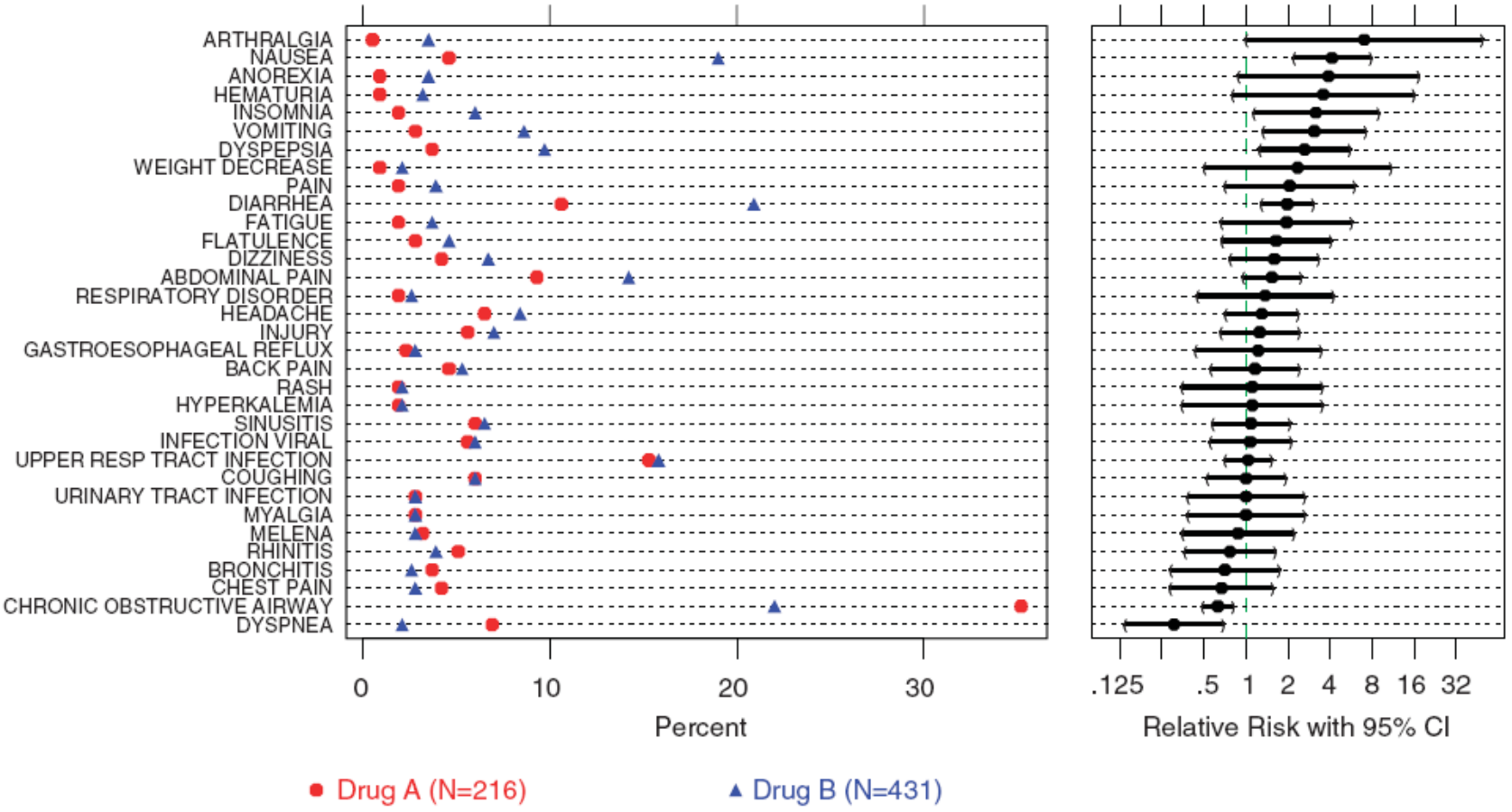


Figure 9. Most frequent on-therapy adverse events sorted by relative risk.

Graphical Display of QT data
Hazard Function Plot (inc SEs)

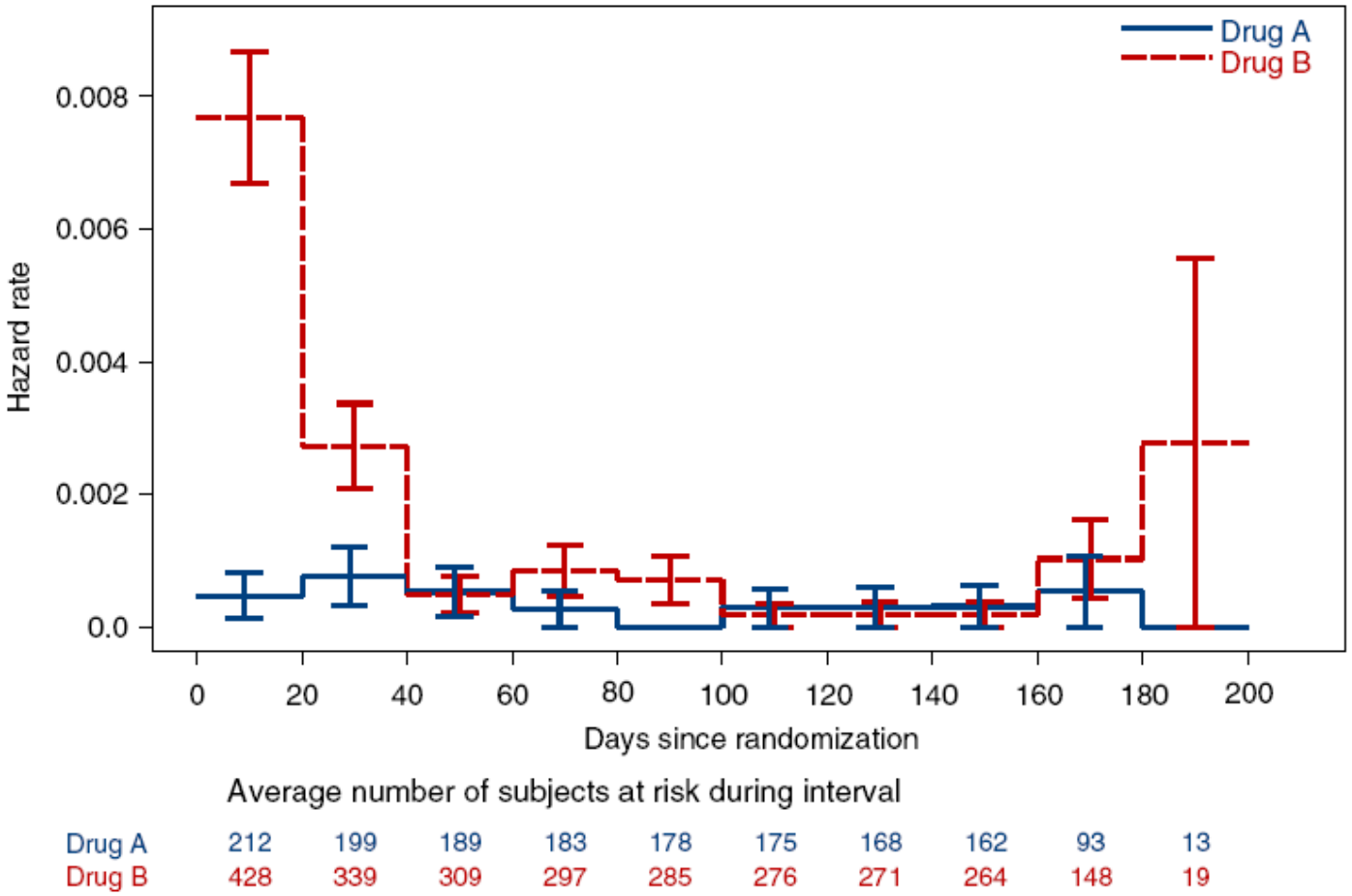


Figure 11. Hazard function for AEs of special interest (with SEs).

Types of Adverse Events

Statistical Methods in Medical Research 2004; **13**: 227–238

Use of the false discovery rate for evaluating clinical safety data

Devan V Mehrotra and **Joseph F Heyse** Merck Research Laboratories, Blue Bell, PA, USA

- Tier 1
  - Thought to be caused by drug
  - Specific hypothesis to be tested in the trial
- Tier 2
  - Routinely collected in RCT
  - No specific hypotheses
  - Routine estimates (CI, p-values) compared to control
  - Many types of Tier 2 AEs
- Tier 3
  - Rare spontaneous reports of serious events

George Chi, H.M. James Hung,Bob O'Neill (FDA CDER)

"Safety assessment is one area where frequentist strategies have been less applicable. Perhaps Bayesian approaches in this area have more promise." (Pharmaceutical Report, 2002)

Bayesian Analysis of Safety Data from Clinical Studies

Scott Berry and Don Berry (2004)
Accounting for Uncertainties in Assessing Drug Safety:
A Three-Level Hierarchical Model
Biometrics, 60, 418-426.

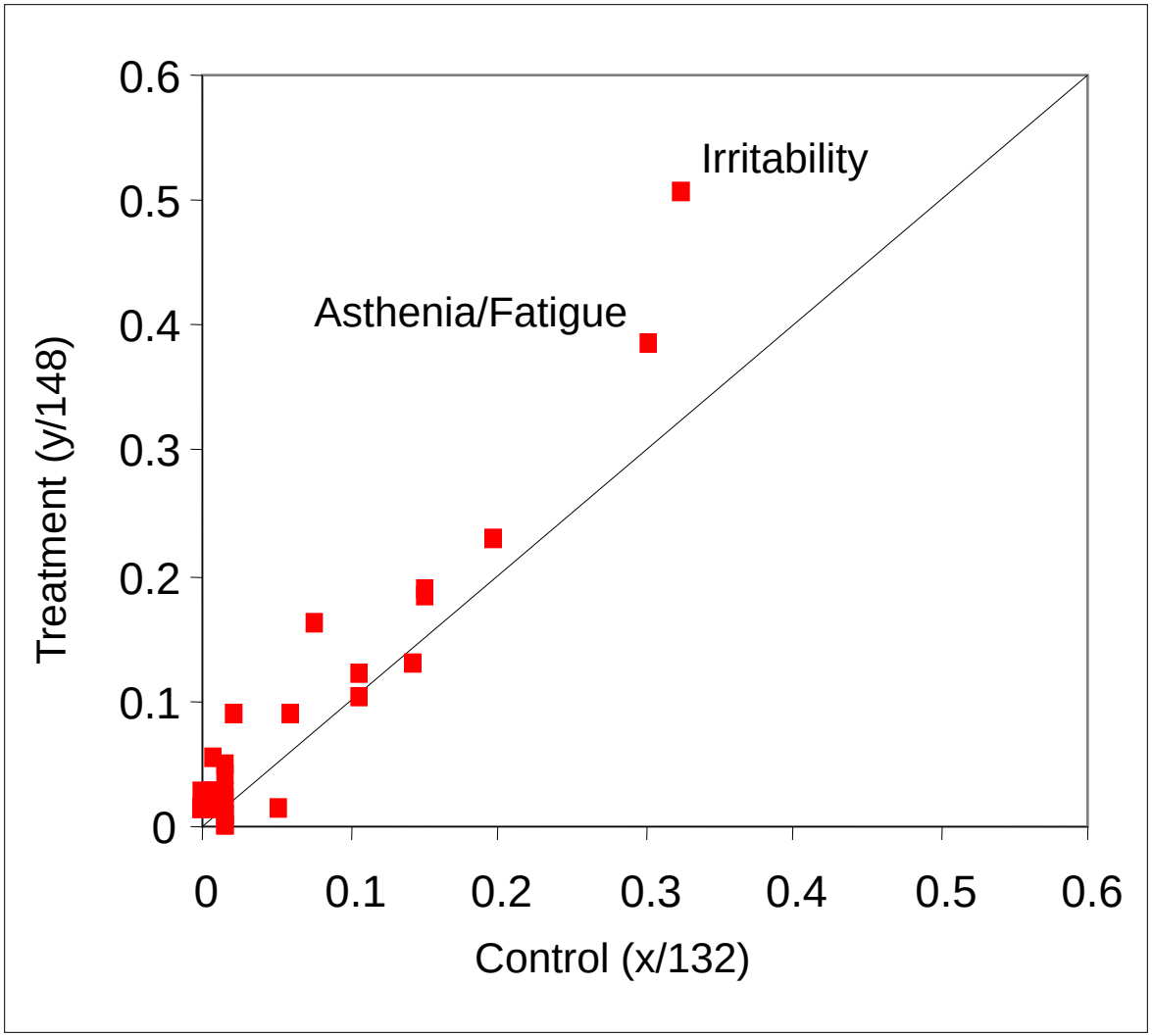
“Tier 2” safety data
Example (Mehrotra & Heyse)

- Vaccine trial
  - Quadrivalent vaccine containing measles, mumps, rubellA and varicella (MMRV)
  - 296 healthy young children (12-18 months)
  - Treatment : MMRV Day 0
  - Control : MMR Day 0 , V Day 42
  - Comparison : between AE’s Days 0-42 Control
  - AE’s Days 42-84 Treatment
- 40 AEs within 8 body systems
- Which to flag?

Example from Mehrota and Heyse

#	BS	AE	y/148	x/132	p-value
1	1	Asthenia/Fatigue	57	40	0.17
2	1	Fever	34	26	0.56
3	1	Infection/fungal	2	0	0.5
4	1	Infection/viral	3	1	0.62
5	1	Malaise	27	20	0.52
6	3	Anorexia	7	2	0.18
7	3	Candidiasis/oral	2	0	0.5
8	3	Constipation	2	0	0.5
9	3	Diarrhea	24	10	0.029*
10	3	Gastroenteritis/infectious	3	1	0.62
11	3	Nausea	2	7	0.09
12	3	Vomiting	19	19	0.73
13	5	Lymphadenopathy	3	2	1
14	6	Dehydration	0	2	0.22
15	8	Crying	2	0	0.5
16	8	Insomnia	2	2	1
17	8	Irritability	75	43	0.0025**
18	9	Bronchitis	4	1	0.37
19	9	Congestion/nasal	4	1	0.37
20	9	Congestion/respiratory	1	2	0.6
21	9	Cough	13	8	0.5
22	9	Infection,respiratory,upper	28	20	0.43
23	9	Laryngotracheobronchitis	2	1	1
24	9	Pharyngitis	13	8	0.5
25	9	Rhinorrhea	15	14	1
26	9	Sinusitis	3	1	0.62
27	9	Tonsillitis	2	1	1
28	9	Wheezing	3	1	0.62
29	10	Bite/sting/non-venomous	4	0	0.12
30	10	Eczema	2	0	0.5
31	10	Pruritus	2	1	1
32	10	Rash	13	3	0.021*
33	10	Rash/diaper	6	2	0.29
34	10	Rash/measles/rubella-like	8	1	0.039*
35	10	Rash/varicella-like	4	2	0.69
36	10	Urticaria	0	2	0.22
37	10	Viral/exanthema	1	2	0.5
38	11	Conjunctivitis	0	2	0.22
39	11	Otitis/Media	18	14	0.71
40	11	Otorrhea	2	1	1

Example from Mehrota and Heyse
Raw Rates



Bayesian Shrinkage Models

- Statistical validity of searching for extreme differences
  - Most significant adverse event or patient subgroup
- Classical approach to post-hoc interval estimates
  - Maintain centers of CI at observed differences
  - Expand widths of every CI
  - Expansion is greater the more differences you look at
  - If you look at too many, the CI's are too wide to be useful
- Bayesian approach
  - Requires a prior distribution for differences
    - Can estimate it from the multiple observed differences available
  - Centers of CI's are "shrunk" toward average or null difference
    - High-variance differences shrink the most
    - Widths of CI's usually shrink a little too
    - The more you look at, the better you can model the prior distribution

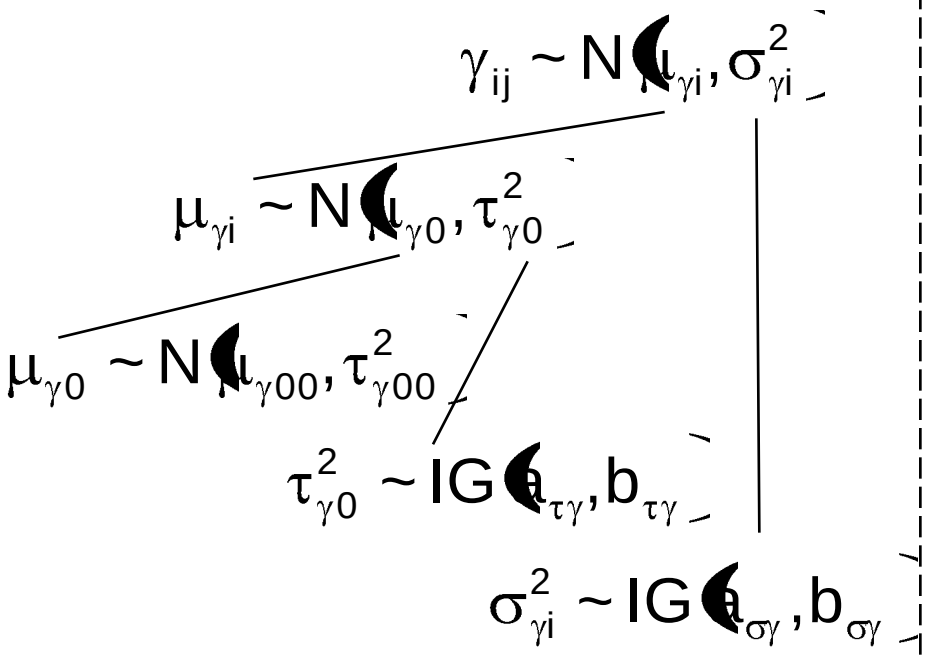
Levels of Experimental Units

- Body systems
- Adverse effects within body system
- Patient (depending on treatment)
- 3-way hierarchical model

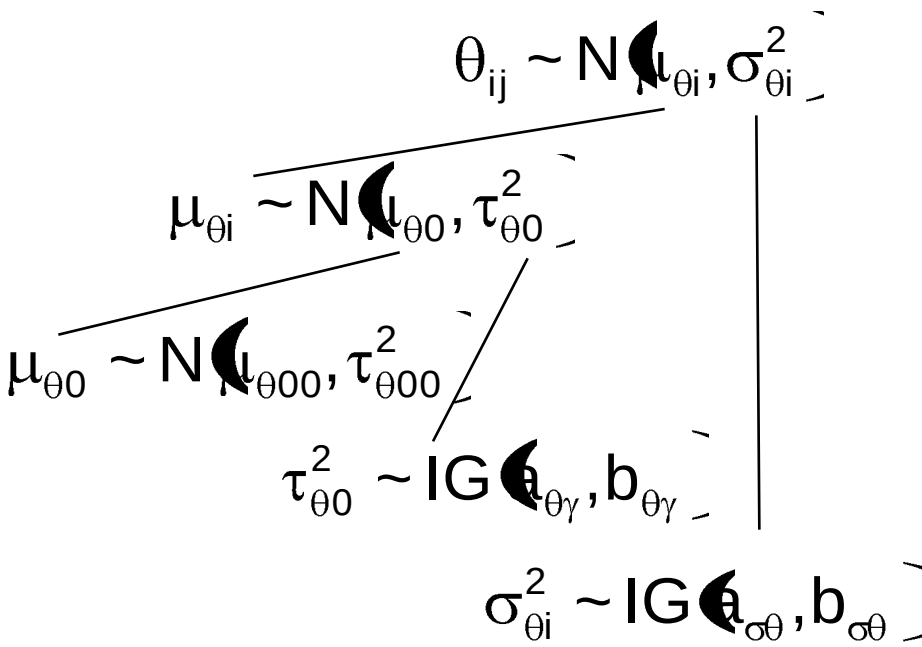
Model
Patient Level

- B body systems
- k_i adverse effects within body system i (i=1,..,B)
- Data: For AE ij, i = 1, . . ., B; j=1, . . .,k_i
  - Control : x_{ij} events in n_C patients
  - Treatment : y_{ij} events in n_T patients
- H_0: $c_{ij} = t_{ij}$, where c_{ij} & t_{ij} are event rates
- $\text{logit}(c_{ij}) = \gamma_{ij}$
- $\text{logit}(t_{ij}) = \gamma_{ij} + \theta_{ij}$

Model 1
Basic Hierarchical Model



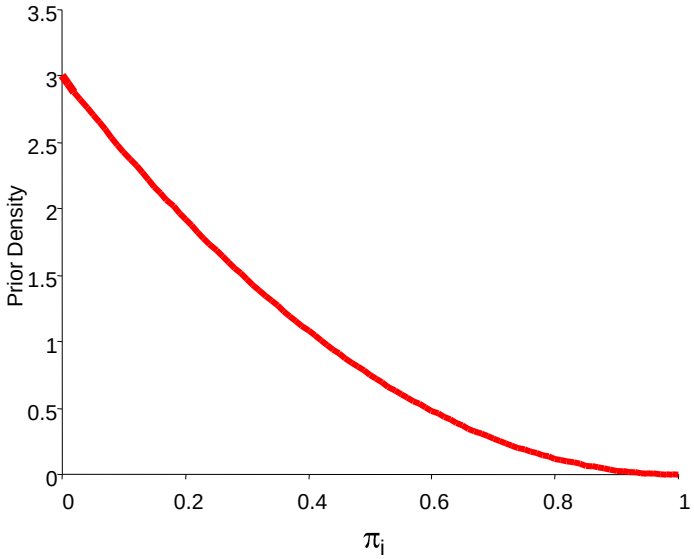
Control



Treatment

Model 2
Mixture Model

- Associated with body system i is a probability π_i that drug has no effect on AEs in that system
- In previous model each $\pi_i \equiv 0$
- Assumption $\pi_i \sim$ Beta(a, b)
- Eg. a=1, b=3

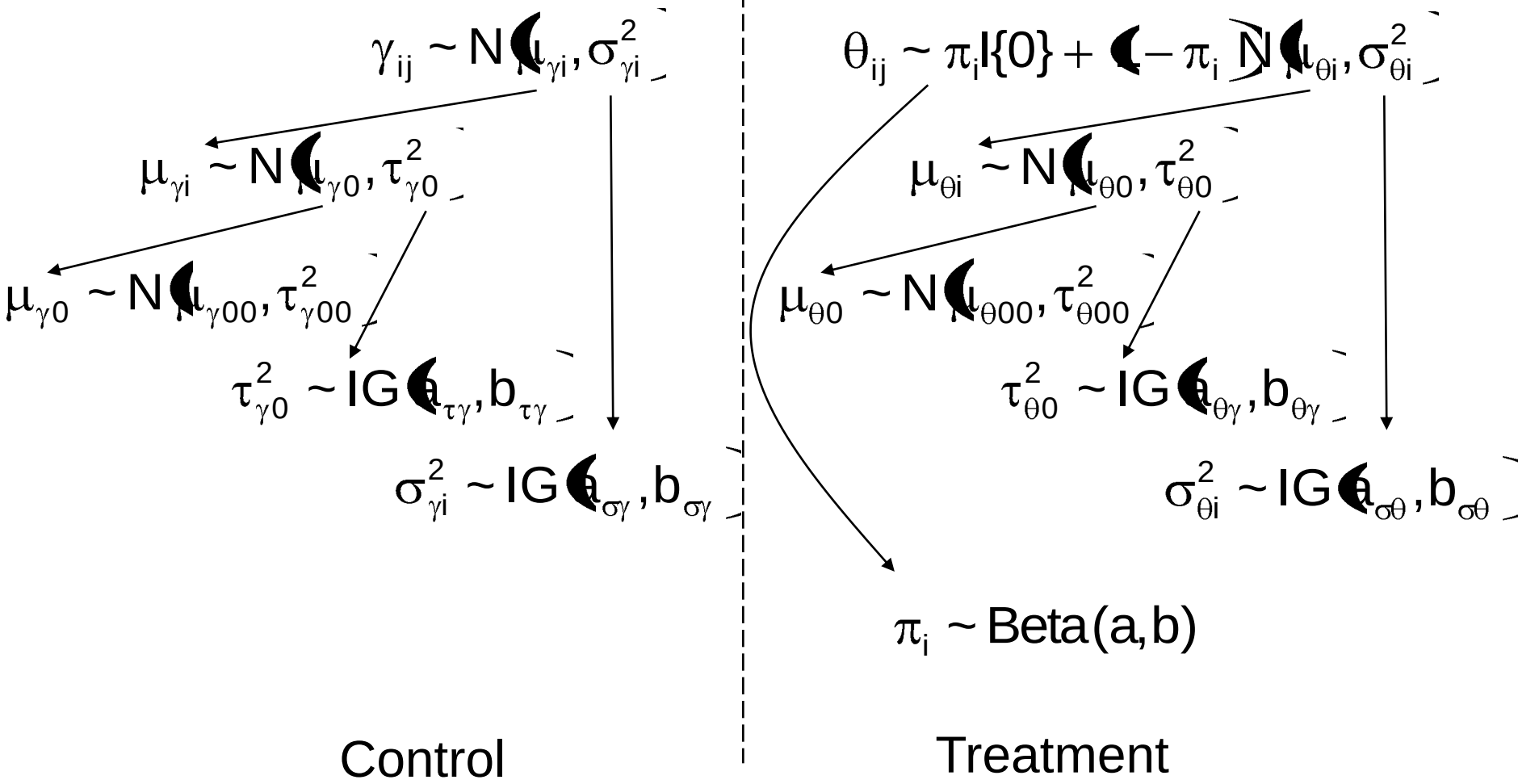


Berry & Berry :

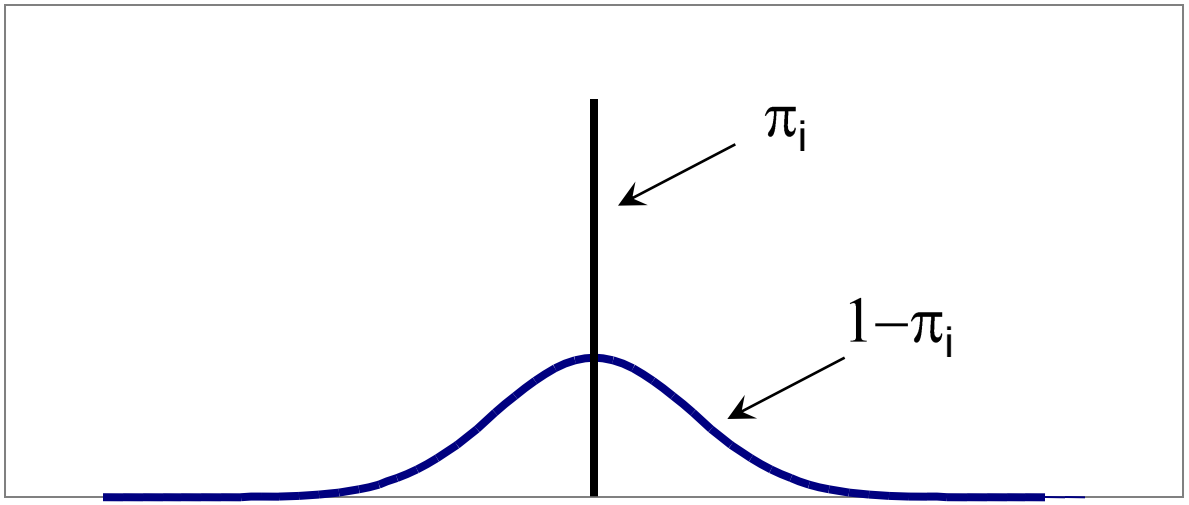
$$\pi_i \sim \text{Beta}(a,b)$$

$$a \sim \frac{\lambda_a \exp(-a\lambda_a)}{\exp(-\lambda_a)} I\{a > 1\} \quad , \quad b \sim \frac{\lambda_b \exp(-b\lambda_b)}{\exp(-\lambda_b)} I\{b > 1\}$$

Model 2
Hierarchical Mixed Model



Mixture Prior



Parameters at Highest Level

$$\mu_{\gamma 0} \sim N(0, 10^2)$$

$$\tau^2_{\gamma 0} \sim IG(3, 1)$$

$$\sigma^2_{\gamma i} \sim IG(3, 1)$$

$$\mu_{\theta 0} \sim N(0, 10^2)$$

$$\tau^2_{\theta 0} \sim IG(3, 1)$$

$$\sigma^2_{\theta i} \sim IG(3, 1)$$

3 Level Hierarchical Models
Prob (θ>0) - Model 1
Prob (θ>0) and Prob(θ=0) - Model 2

#	BS	AE	y/148	x/132	P1(θ>0)	P2(θ=0)	P2(θ>0)
1	1	Asthenia/Fatigue	57	40	0.956	0.56	0.44
2	1	Fever	34	26	0.89	0.77	0.21
3	1	Infection/fungal	2	0	0.83	0.84	0.14
4	1	Infection/viral	3	1	0.84	0.83	0.15
5	1	Malaise	27	20	0.89	0.75	0.23
6	3	Anorexia	7	2	0.9	0.88	0.11
7	3	Candidiasis/oral	2	0	0.79	0.95	0.04
8	3	Constipation	2	0	0.78	0.96	0.03
9	3	Diarrhea	24	10	0.987	0.48	0.52
10	3	Gastroenteritis/infectiou	3	1	0.79	0.94	0.04
11	3	Nausea	2	7	0.46	0.94	0.01
12	3	Vomiting	19	19	0.7	0.94	0.04
13	5	Lymphadenopathy	3	2	0.77	0.59	0.24
14	6	Dehydration	0	2	0.51	0.56	0.11
15	8	Crying	2	0	0.86	0.58	0.34
16	8	Insomnia	2	2	0.8	0.63	0.24
17	8	Irritability	75	43	0.999	0.02	0.981
18	9	Bronchitis	4	1	0.86	0.99	0.01
19	9	Congestion/nasal	4	2	0.86	0.99	0
20	9	Congestion/respiratory	1	2	0.73	0.99	0
21	9	Cough	13	8	0.92	0.97	0.03
22	9	Infection,respiratory,upper	28	20	0.943	0.97	0.03
23	9	Laryngotracheobronchitis	2	1	0.8	0.99	0
24	9	Pharyngitis	13	8	0.91	0.98	0.02
25	9	Rhinorrhea	15	14	0.83	0.99	0.01
26	9	Sinusitis	3	1	0.84	0.99	0
27	9	Tonsillitis	2	1	0.81	0.99	0
28	9	Wheezing	3	1	0.84	0.99	0
29	10	Bite/sting/non-venomous	4	0	0.93	0.9	0.1
30	10	Eczema	2	0	0.84	0.96	0.04
31	10	Pruritus	2	1	0.82	0.97	0.03
32	10	Rash	13	3	0.997	0.42	0.58
33	10	Rash/diaper	6	2	0.946	0.88	0.12
34	10	Rash/measles/rubella-like	8	1	0.976	0.67	0.33
35	10	Rash/varicella-like	4	2	0.87	0.93	0.07
36	10	Urticaria	0	2	0.62	0.97	0.01
37	10	Viral/exanthema	1	2	0.71	0.97	0.02
38	11	Conjunctivitis	0	2	0.5	0.78	0.05
39	11	Otitis/Media	18	14	0.82	0.73	0.23
40	11	Otorrhea	2	1	0.71	0.8	0.1

- Irritability
  - smallest p-value
  - Largest Prob (θ>0)
- Rash
  - 2nd smallest p-value
  - Considerable shrinkage
- Rash belongs to largest body system with inconsistent evidence
- Irritability is the only AE with strong evidence of being associated with treatment

WinBUGS Code
Berry and Berry Analysis

```
model   {

for(i in  1 : Num ) {

                    xbj[i] ~ dbin(pc[i], nc)                    # binomial likelihood for control (xbj) group
                    ybj[i] ~ dbin(pt[i], nt)                    # binomial likelihood for control (xbj) treatment group

                    logit(pc[i]) <- gamma[i]                    # logit transformation for control rates
                    logit(pt[i])  <- gamma[i] + theta[i]        # logit transformation for treatment rates
                    gamma[i]~dnorm(mu_gb[b[i]],pre_g)           # 1st  stage prior for the control effects

                    y1b[i]~dbern(pib[b[i]])                     # mixture prior for the treatment differences
                    y2b[i]<-1-y1b[i]
                    y3b[i]~dnorm(mu_tb[b[i]],pre_tb[b[i]])
                    theta[i]<-y2b[i]*y3b[i]

                    prob0[i]<-step(theta[i])+step(-theta[i])-1  #probability of +ve treatment differences
                    probu[i]<-step(theta[i])-prob0[i]
                    probl[i]<-1-prob0[i]-probu[i]
                    }

for(k in 1:nb)      {
                    mu_gb[k]~dnorm(mu_g_0,pre_g_0)              # 2nd stage prior for the control effects
                    mu_tb[k]~dnorm(mu_t_0,pre_t_0)              # 2nd stage prior for the treatment differences

                    pre_tb[k]~dgamma(3, 1)

                    pib[k]~dbeta(alp_pi,bet_pi)
                    }

mu_g_0~dnorm(3,0.1)                                             # 3rd stage prior for the control effects
pre_g_0~dgamma(3, 1)
pre_g~dgamma(3, 1)

mu_t_0~dnorm(0,0.1)                                             # 3rd stage prior for the teatment differences
pre_t_0~dgamma(3, 1)

alp_pi~dexp(1)I(1,)                                             # prior for the beta parameters
bet_pi~dexp(1)I(1,)
```

Adverse Event Reporting System (AERS)

- Strengths
  - Power: can identify rare events not seen in clinical trials or cohort studies
  - Can identify toxicity in special populations
  - AERS is already available.

- Limits
  - Ambiguity about rules governing entries into AERS
  - Under reporting
  - No concurrent control; no case-control studies
  - Limited information may limit causality assessment
  - Cannot provide reliable rates since it is “numerator” data
  - Different populations, Co-morbidities, Co-prescribing, Off-label use, Rare events
  - Report volume for a drug is affected by, volume of use, publicity, type and severity of the event and other factors =>reporting rate is not a true measure of the rate or the risk

Fundamental Principles for Safety Data Mining

- Safety data mining is an exploratory analysis of large databases in order to find previously unsuspected relationships which are of interest or value to the sponsors, regulatory agencies, and the user community.
- The goal is to detect "higher than expected by chance alone" drug-event frequencies based on post-marketing spontaneous reports.
  - AERS (VAERS) has been the primary database for this in the US. Some sponsors also use their in-house PV database.
- Safety data mining cannot replace sound clinical assessment.

Turning Cases into Evidence

- If an AE is rare then a signal can be generated by small series (3-5 reports)
- In general no answer to the question “How many reports constitute a signal?”
- Subjective judgement
  - Number and quality of case reports
  - Nature of the AE
  - Type of drug and level of use

Turning Cases into Evidence

- To judge whether the number of cases reported spontaneously exceeds what might be expected by chance or by “background noise” 2 approaches
- Approach 1
  - Denominator data related to drug use (prescriptions,sales) and determine *reporting rates : #reports / #prescriptions*
  - Comparisons between drugs based on reporting rates may be biased – increased reporting of new drugs, calendar time and publicity
- Approach 2
  - Use the total number of reports for the drug as a denominator and calculate the proportion of all reactions of the type of interest
  - The proportion can be compared to the proportion for other drugs
  - Advantages – no external data needed, may overcome some of the biases eg new drug

Disproportionality Measures
An Example

	Specific Event	All Other Events
Drug of Interest	A (=n_{ij})	B
All Other Drugs	C	D

- An example: determine proportions of specified reactions (groups of reactions) for drugs of interest and all other drugs in database
- Calculate the ratio ie : $$\frac{A/(A+B)}{C/(C+D)}$$
- This is the *proportional reporting ratio*

Disproportionality Measures
An Example

	Uveitis	All Other AEs
Rifabutin	41	14
All Other Drugs	754	591,958

- PRR = $\dfrac{41/55}{754/591958} = 586$
- Null Value = 1 , similar to a relative risk , significance can be assessed by a χ^2-test (1df with continuity correction)
- Judgement about strength of signal
  - MHRA : PRR >2, $\chi^2(1) > 4$, and at least 3 cases
- Example :
  - PRR = 586 >2 ; $\chi^2(1) = 22{,}740 > 4$; #cases=41 > 3
  - Real signal

Disproportionality Analysis

- Although the idea of computing disproportionality measures (DM) for all or some drug-event combinations is simple, its widespread use is relatively recent
  - Computer and database advances enabled ease of use and evaluation
- Biostatisticians were uncomfortable with performing formal analyses on tabulations of spontaneous reports
  - Unknown reporting mechanism can lead to reporting biases
  - Frequent noncausal associations with indications and comorbidities
  - All large values of *DM* require follow-up for medical validity
- Bayesian statistical methods produce “shrinkage” values of *DM*
  - Help avoid the “multiple comparisons” fallacy
  - US FDA, UK MHRA and WHO UMC have each adopted Bayesian disproportionality methods

Bayesian Approaches

- Two current approaches: MGPS & BCPNN
- Both use ratio n_{ij} / E_{ij} where
  - n_{ij} = no. of reports mentioning both drug i & event j
  - E_{ij} = expected no. of reports of drug i & event j
- Both report features of posterior dist'n of 'information criterion'
- E_{ij} usually computed assuming drug i & event j are mentioned independently

Basic Data

- TRT (Drug) i and Adverse Event j
- n_{ij} = no. of reports mentioning both drug i & event

Treatment	Adverse Event				
	AE 1	AE 2	AE 3	….	AE j
TRT 1	n_{11}	n_{12}	n_{13}	…	n_{1j}
TRT 2	n_{21}	n_{22}	n_{23}	…	n_{2j}
TRT 3	n_{31}	n_{32}	n_{33}	…	n_{3j}
…	…	…	…	…	…
TRT i	n_{i1}	n_{i2}	n_{i3}	…	n_{ij}

Expected Cell Count

- If there is no association between treatment and AE, then expected values of the cell are

$$E_{ij} = E(n_{ij}) = \frac{\left(\sum_i n_{ij}\right)\left(\sum_j n_{ij}\right)}{\sum_i \sum_j n_{ij}}$$

$$Relative\,Risk\ R_{ij} = \frac{n_{ij}}{E_{ij}}$$

Finding “Interestingly Large” Counts

- Relative Risk
  - Is appealing and easy to interpret.
  - Requires no probabilistic calculation.

- But,
  - Has extreme sampling variability when expected frequencies are small.
  - n=1, E=0.01 is different from n=100, E=1.0, even though both lead to RR=100.

Multi-item gamma-Poisson Shrinker (MGPS). Empirical Bayes Model

- This approach shrinks the relative risk RR toward the prior mean in the presence of large sampling variation.
- Assume $n_{ij} \sim$ Poisson(μ_{ij})

$$\lambda_{ij} = \frac{\mu_{ij}}{E_{ij}}$$

- Prior for λ_{ij} ~ mixture of two Gamma distributions

$$= \theta\, G(\alpha_1,\beta_1) + (1-\theta)\, G(\alpha_2,\beta_2)$$

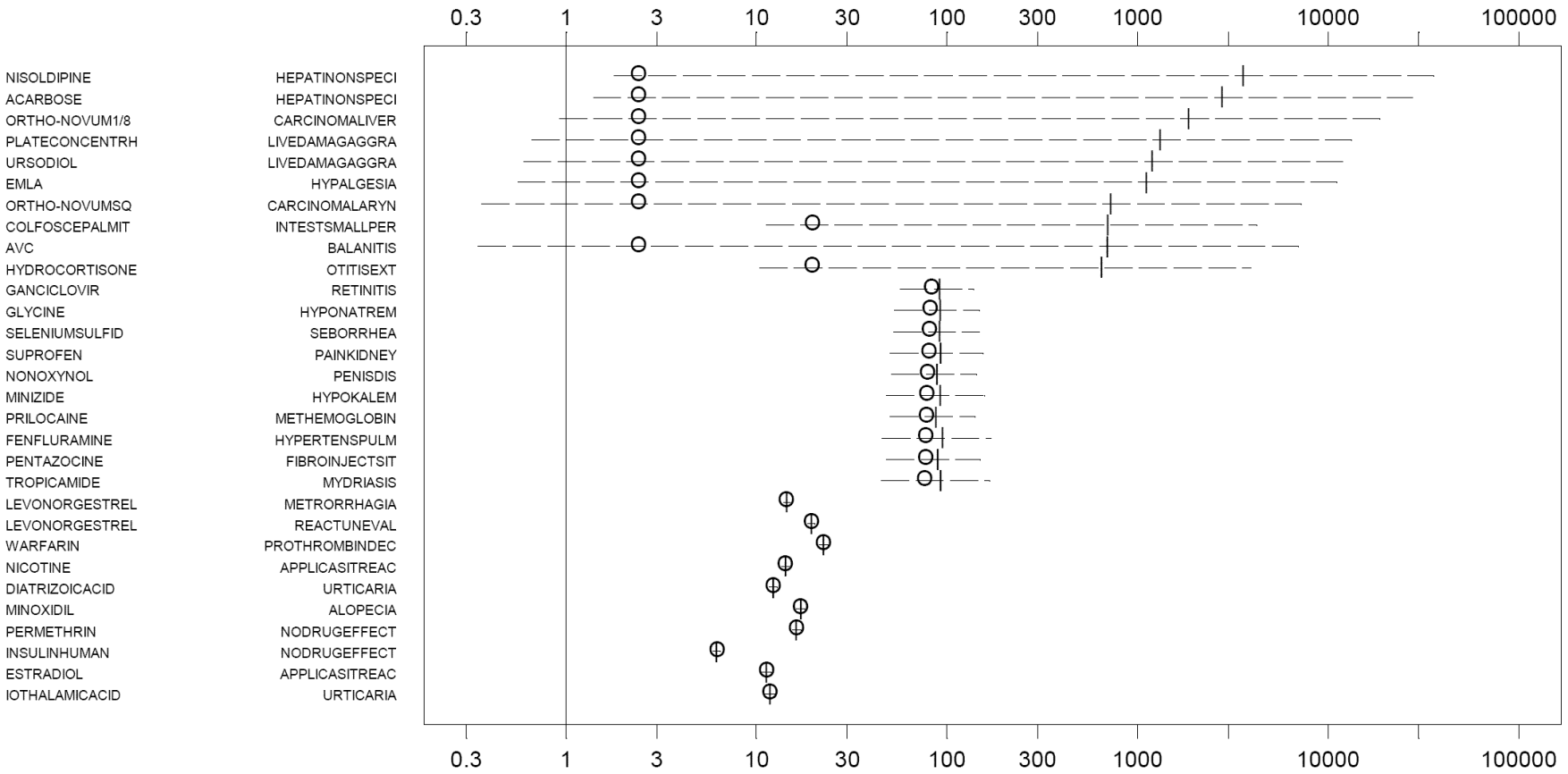
Multi-item gamma-Poisson Shrinker (MGPS). Empirical Bayes Estimation

- Estimate θ and the prior parameters $\{\alpha_i,\beta_i\}$ by maximizing the marginal distribution of $\{n_{ij}\}$ – which is a mixture of Negative Binomials
- Posterior density of λ_{ij} is also a mixture of gammas
- Calculate the posterior mean of $\{\lambda_{ij}\}$. The latter with $\{\alpha_i,\beta_i\}$ replaced by their estimates is the EB estimate for λ_{ij}.
- Order the (drug,event) pairs by the magnitude of the EB estimate for λ_{ij}. Large values suggest a signal.
- Usually, we look at the (treatment,event) pair that has the lower bound of the 95% CI for $\lambda_{ij} > 2$.

Multi-item gamma-Poisson Shrinker (MGPS). Empirical Bayes Estimation

- Order the (drug,event) pairs by the magnitude of the EB estimate for λ_{ij}. Large values suggest a signal.
- Usually, we look at the (treatment,event) pair that has the lower bound of the 95% CI for $\lambda_{ij} > 2$.
- The bound comes from $\ln_2(\lambda_{ij}) = IC_{ij} > 1$ (IC=Information Component – log(Relative Risk))
- Fairly easy to get 5% lower bound using $E(IC_{ij}) - 2\ SD(IC_{ij})$

Multi-item gamma-Poisson Shrinker (MGPS). Bayesian Shrinkage Estimators



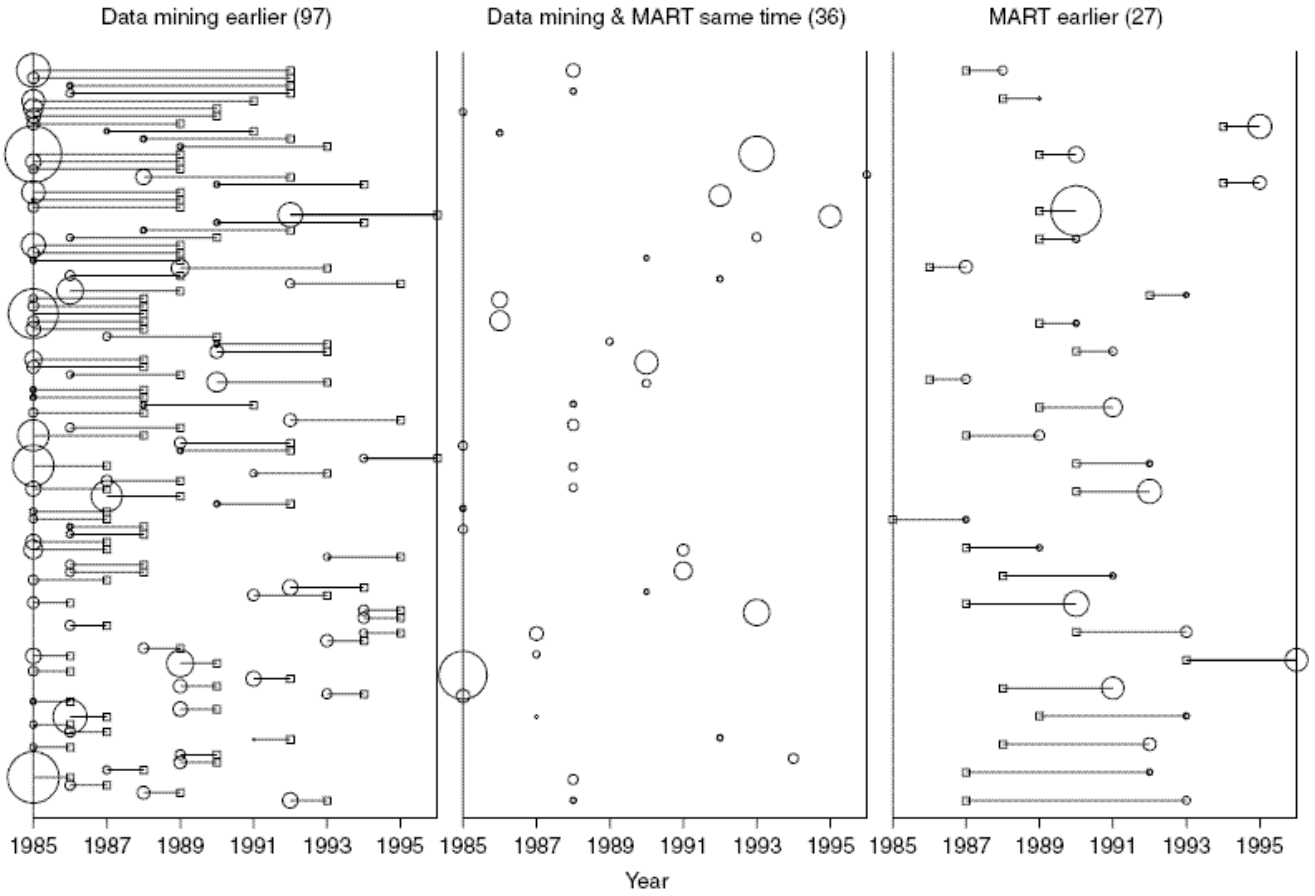
Bill DuMouchel, Emerging Safety Science Workshop, Silver Spring, MD, April 23-24, 2007

MGPS Used by Both Regulators and Companies

- The MGPS methodology has been commercialized by Lincoln Technologies.
- FDA is using MGPS to explore the AERS data.
- Several major PhRMA companies such as GSK, Merck, BMS, and Pfizer have either used this approach routinely or are experimenting with it.
- The operating characteristics of MGPS is not fully known. The agreement between MGPS and PRR is not always high. The effect of lumping or splitting of events under this approach needs to be further investigated.

Difference in detection Time MGPS vs Traditional Manual Approach 160 Drug-AE pairs

- Differences in time to detection of 160 different drug-event combinations coded as ‘signals’ (95 drugs) in the Monitoring Adverse Reports Tracking (MART) system by current and data mining method.
- The length of each line represents the difference in the time of detection between the two methods.
- The size of the circles is proportional to the number of reports when the first signal scores were detected.



Szarfman, Machado and O’Neill, Drug Safety, 2002

Bayesian Confidence Propagation Neural Network (BCPNN)

(Bate et al, EurJClPhrm1998)

- 'Bayesian Confidence Neural Network' (BCNN) Model:
  - n_{ij} = no. reports mentioning both drug i & event j
  - n_{i+} = no. reports mentioning drug i
  - n_{+j} = no. reports mentioning event j
- Usual Bayesian inferential setup:
- Binomial likelihoods for n_{ij}, n_{i+} , n_{+j}
- Beta priors for the rate parameters (r_{ij}, p_i, q_j)

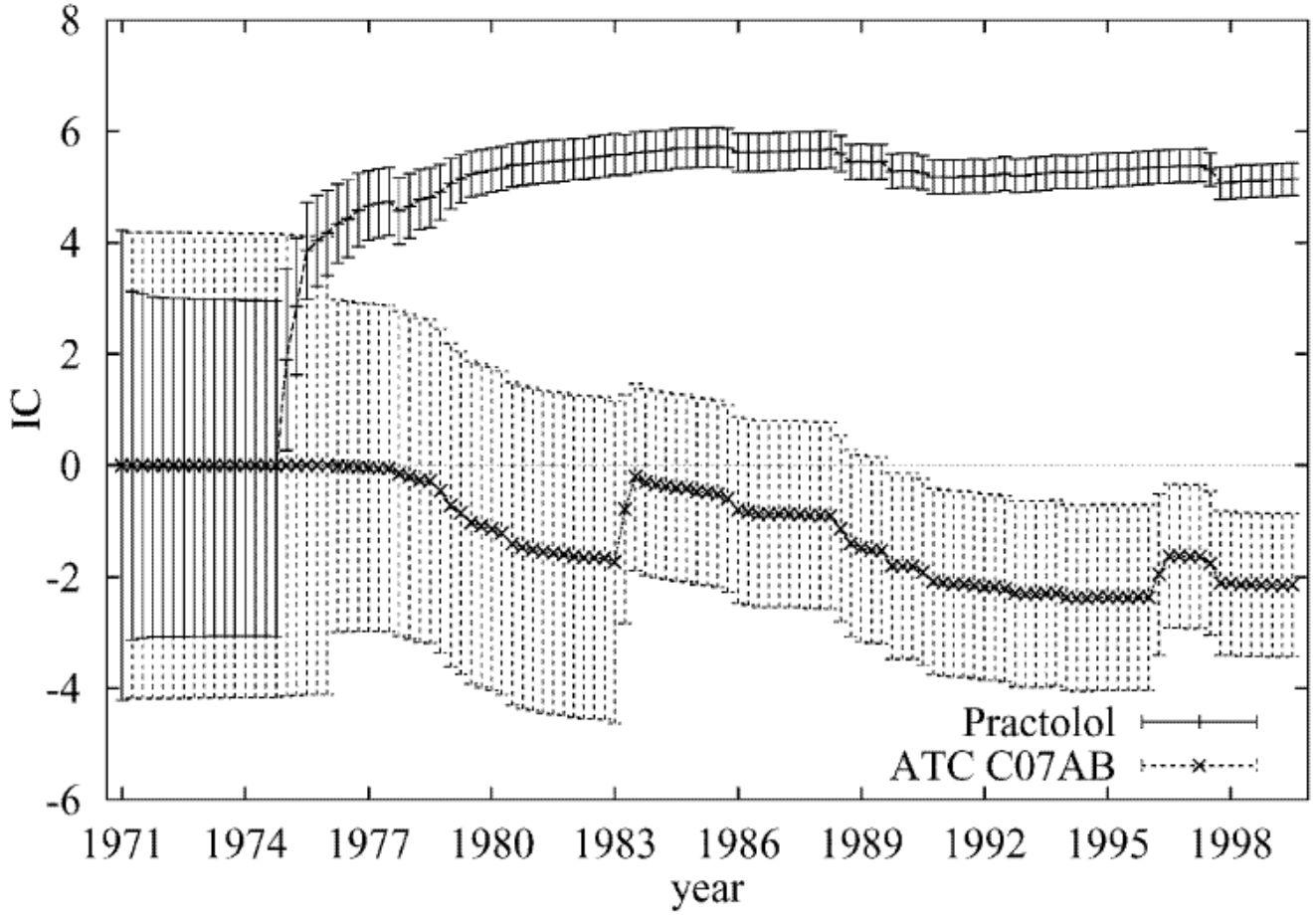
Bayesian Confidence Propagation Neural Network (BCPNN)

(Bate et al, EurJClPhrm1998)

- Uses ‘delta method’ to approximate variance of
- $Q_{ij} = \ln(r_{ij} / p_i q_j) = \ln 2 \times IC_{ij}$
- However, can calculate exact mean and variance of Q_{ij} (Noren et al (2006). Extending the methods used to screen the WHO drug safety database towards analysis of complex associations and improved accuracy for rare events. Stats in Medicine, 25:3740–3757)
- WHO measure of importance = $E(IC_{ij}) - 2\ SD(IC_{ij})$
- Test of signal detection predictive value by analysis of signals 1993-2000: Drug Safety 2000; 23:533-542
- 84% Negative Pred Val, 44% Positive Pred Val
- Good filtering strategy for clinical assessment

Beta-Blockers: Peritonitis BCPNN Methodology

A.Bate, M. Lindquist, R. Orre, IR Edwards, RHB Meyboom, Eur L Clin Pharmacol, 2002



Practolol

All Other Selective Beta-Blockers

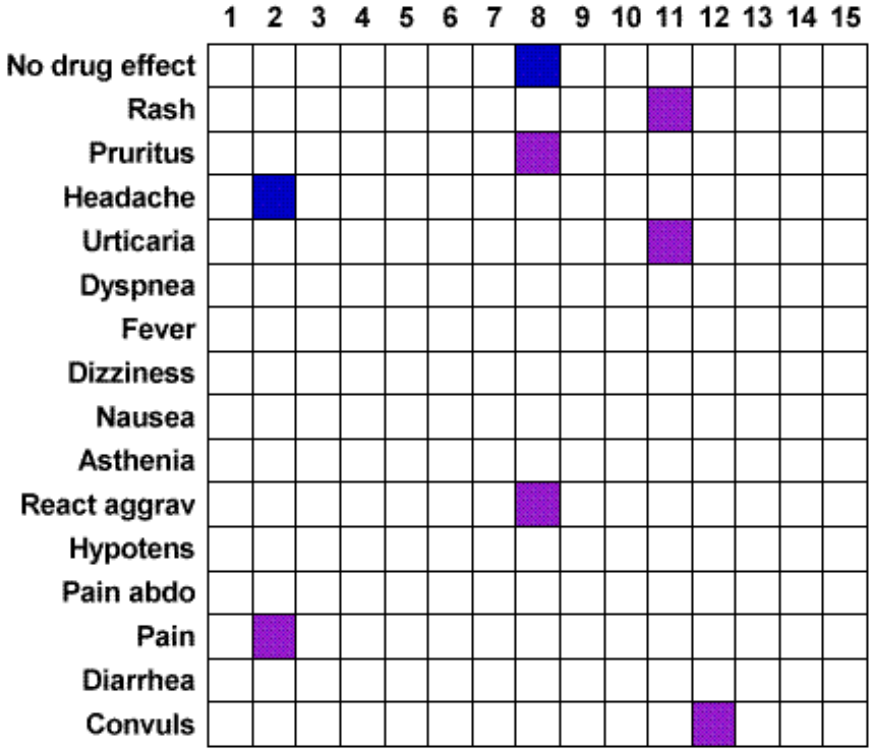
Practolol withdrawn from UK in 1976: occulo-mucocutaneous syn. (included sclerosing peritonitis) Never launched in US

Interpreting the Signal Through the Role of Visual Graphics

- Four examples of spatial maps that reduce the scores to patterns and user friendly graphs and help to interpret many signals collectively (O'Neill & Szarfman, *The American Statistician*, Vol. 53, 1999, pp. 190-196.)
- Graphical displays developed using the software *CrossGraphs*

Example 1

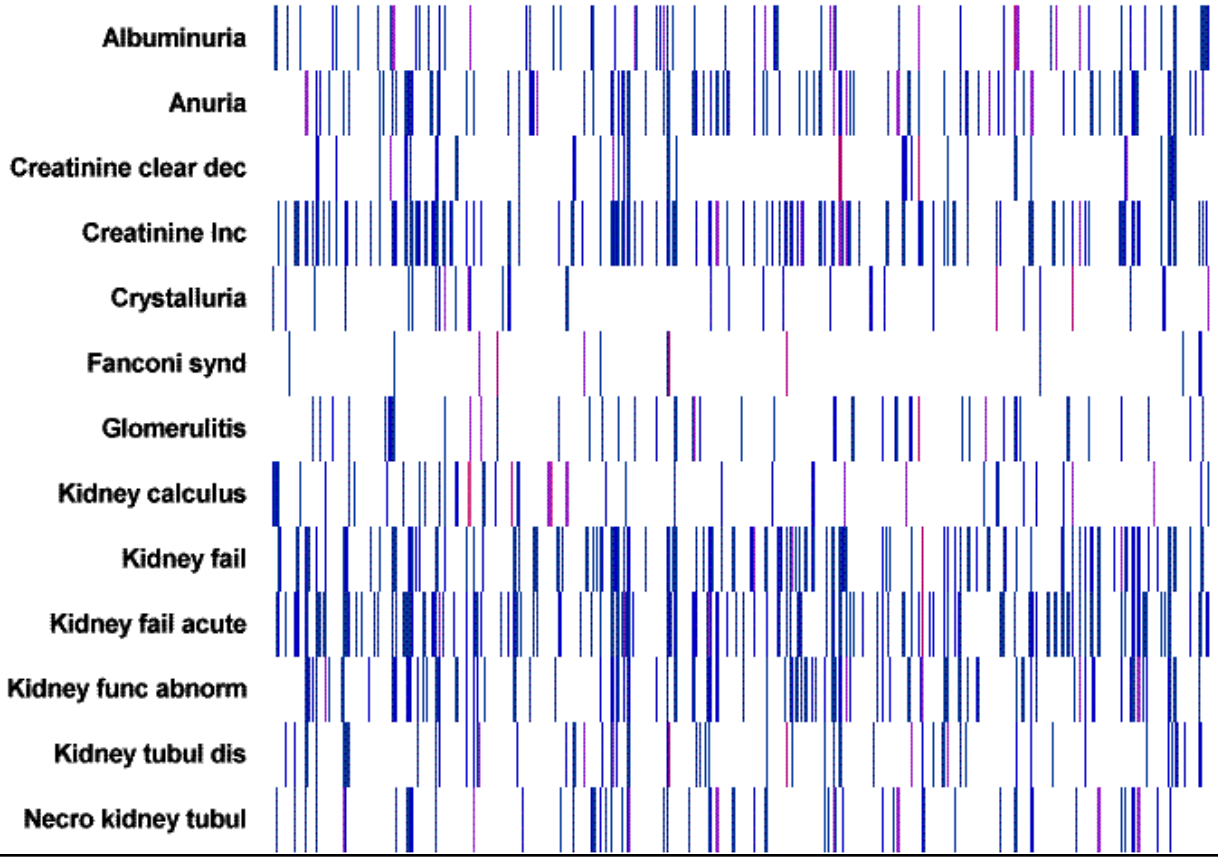
A spatial map showing the "signal scores" for the most frequently reported events (rows) and drugs (columns) in the database by the intensity of the empirical Bayes signal score (blue color is a stronger signal than purple)



O'Neill & Szarfman, *The American Statistician*, Vol. 53, 1999, pp. 190-196.

Example 2

Spatial map showing 'fingerprints' of signal scores allowing one to visually compare the complexity of patterns for different drugs and renal events and to identify positive or negative co-occurrences



O'Neill & Szarfman, *The American Statistician*, Vol. 53, 1999, pp. 190-196.

What Can Statisticians Contribute?

- Pre-marketing phase:
- Help identify biomarkers for faster and earlier detection of adverse drug reactions.
- Build the integrated safety database as the development program progresses; actively explore the integrated database in real time.
- Work closely with clinicians and possibly Risk Management / Global Safety
- Help apply what we learned in the pre-marketing phase to help design pharmacovigilance studies.

What Can Statisticians Contribute?

- Post-marketing phase:
- Help evaluate existing mining tools for their performance.
- Help develop methods for signal detection, risk assessment and risk/benefit evaluations.
- Help determine background risk from national databases for incremental risk assessment and risk/benefit evaluations.
- Most importantly, safety analysis should not be an afterthought

Back-up Slides.

Common Disproportionality Measures for 2x2 tables in SRS

	Specific Event	All Other Events
Drug of Interest	A	B
All Other Drugs	C	D

Measure of Association	Formula	Probabilistic Interpretation
Relative Risk	$\frac{A(A+B+C+D)}{(A+C)(A+B)}$	$\frac{\Pr(ae \mid drug)}{\Pr(ae)}$
Proportional Reporting Ratio	$\frac{A/(A+B)}{C/(C+D)}$	$\frac{\Pr(ae \mid drug)}{\Pr(\neg ae \mid drug)}$
Reporting Odds Ration	$\frac{A/C}{B/D}$	$\frac{\Pr(ae \mid drug)/\Pr(\neg ae \mid drug)}{\Pr(ae \mid \neg drug)/\Pr(\neg ae \mid \neg drug)}$
Information Component	$\log_2\left[\frac{A(A+B+C+D)}{(A+C)(A+B)}\right]$	$\log_2\left[\frac{\Pr(ae \mid drug)}{\Pr(ae)}\right]$

Uncertainty of Measures

	AE=yes	AE=no
D1=yes	A=1	B=100
D1=No	C=5	D=1080

	AE=yes	AE=no
D2=yes	A=2	B=100
D2=No	C=5	D=1080

Relative Risk	2.0	4.3
Proportional Reporting Ratio	2.1	4.3
Reporting Odds Ration	2.2	1.7
Information Component	1.0	3.3

M Hauben, D Madigan, Cm Gerrits, L Walsh, EP Van Puijenbroek, Expert Opinion Drug Safety, 2005