PERSPECTIVES ON AUTOMATED METHODS FOR PHARMACOVIGILANCE SIGNAL DETECTION

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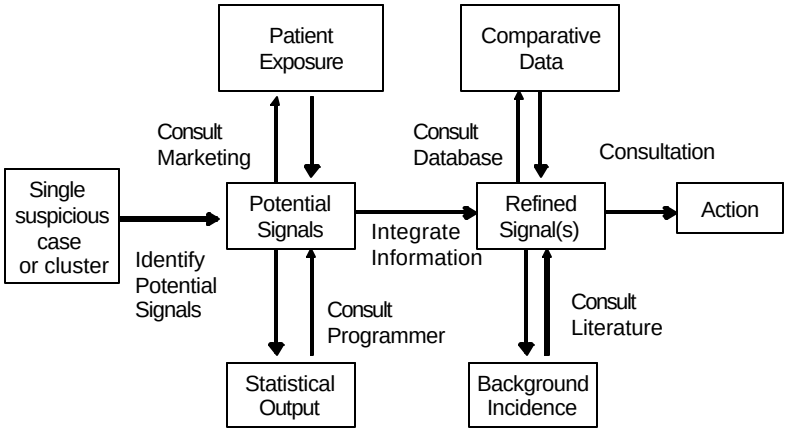
Spontaneous AE Reports

- Safety information from clinical trials is incomplete
  - Few patients -- rare events likely to be missed
  - Not necessarily 'real world'
- Need info from post-marketing surveillance & spontaneous reports
- Pharmacovigilance by reg. agencies & mfrs carried out by skilled clinicians & medical epidemiologists
- Long history of research on issue
  - Finney (MIMed1974, SM1982)
  - Inman (BMedBull1970)
  - Royall (Bcs1971)
  - Napke (CanPhJ1970)
  - and many more

Issues

- Incomplete reports of events, not necessarily reactions
- How to compute effect magnitude
- Many events reported, many drugs reported
- Bias & noise in system
- Difficult to estimate incidence because no. of pats at risk, pat-yrs of exposure seldom reliable
- Appropriate use of computerized methods, e.g., supplementing standard pharmacovigilance to identify possible signals sooner -- early warning signal
- No Gold Standard for comparison

Signal Generation: The Manual Method



Proportional Reporting Rate

- Usual basis for quantification

Drug	Target AE	All Other	Total
Target Drug	a	b	a + b
All Other	c	d	c + d
Total	a + c	b + d	N

PRR = a / (a + b) ÷ (a + c) / N

AE report ⊥ drug report ⇒ E(a) = (a + b)(a + c) / N

PRR = a / E(a)

Quite variable if E(a) is small

How to reduce imprecision & make interpretable?

Bayesian Approaches

- Two current approaches: DuMouchel & WHO
- 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'

$$IC_{ij} = \log_2 n_{ij} / E_{ij} = PRR_{ij}$$

- E_{ij} usually computed assuming drug i & event j are mentioned independently
- Ratio > 1 (IC > 0) ⇒ combination mentioned more often than expected if independent

WHO (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)

WHO, cont'd

- 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}
- WHO measure of importance = E(ICij) - 2 SD(ICij)
- Test of signal detection predictive value by analysis of signals 1993-2000: Drug Safety 2000; 23:533-542
- "Gold standard": appearance in reference texts (Matindale, PDR, etc.)
- 84% Negative Pred Val, 44% Positive Pred Val
- Good filtering strategy for clinical assessment

DuMouchel (AmStat1999)

- E_{ij} known, computed using stratification of database --
  $n_i^{(k)}$ = no. reports of drug i in stratum k
  $n_j^{(k)}$ = no. reports of event j in stratum k
  $N^{(k)}$ = total reports in stratum k
  $E_{ij} = \Sigma_k n_i^{(k)} n_j^{(k)} / N^{(k)}$ ($E(n_{ij})$ under independence)
- $n_{ij} \sim$ Poisson(μ_{ij}) -- interested in $\lambda_{ij} = \mu_{ij}/E_{ij}$
- Prior dist'n for λ = mixture of gamma dist'ns:
  $f(\lambda; a_1, b_1, a_2, b_2, \pi) = \pi\, g(\lambda; a_1, b_1) + (1-\pi)\, g(\lambda; a_2, b_2)$
  where $g(\lambda; a, b) = b\,(b\lambda)^{a-1} e^{-b\lambda} / \Gamma(a)$

DuMouchel, cont'd

- Estimate π, a_1, b_1, a_2, b_2 using Empirical Bayes -- marginal dist'n of n_{ij} is mixture of negative binomials
- Posterior density of λ_{ij} also is mixture of gammas
- $\ln_2 \lambda_{ij} = IC_{ij}$
- Easy to get 5% lower bound or $E(IC_{ij})$ - 2 $SD(IC_{ij})$ (like WHO)

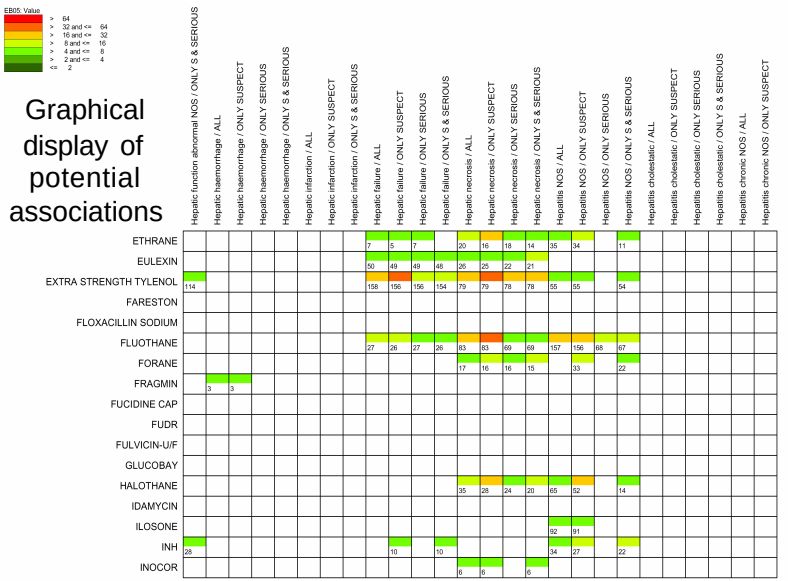
Example

- From DuMouchel (Table 3) N = 4,864,480, n_i = 85,304

$a_1 = 0.204$
$b_1 = 0.058$
$a_2 = 1.415$
$b_2 = 1.838$
$\pi = 0.097$

	Headache			Polyneuritis		
	n_j	n_{ij}	E_{ij}	n_j	n_{ij}	E_{ij}
	71,209	1,614	1,309	262	3	1.06
	RR	1.23 (0.30)			2.83 (1.25)	
	WHO	DuMouchel		WHO	DuMouchel	
$E(IC_{ij})$	0.37	0.301		-0.39	0.508	
$V(IC_{ij})$	0.00134	0.00129		0.599	0.676	
$SD(IC_{ij})$	0.037	0.036		0.774	0.822	
E - 2 SD	0.3	0.23		-1.94	-1.14	
5% Quantile	--	0.233 [1.18]		--	-0.79 [0.58]	
Excess n	300	225		0	0	

Graphical display of potential associations



Why Stratify (1)

- Report frequencies by stratum; target drug & target AE reported independently in each stratum

	Stratum A			Stratum B		
	Target AE	All Others	Total	Target AE	All Others	Total
Target Drug	80	320	400	810	90	900
All Others	120	480	600	90	10	100
Total	200	800	1000	900	100	1000

Why Stratify (2)

- Expected total Drug/AE reports under independence is sum of expected frequencies per stratum:

  $400 \times 200/1000 + 900 \times 900/1000 = 890$

- Same as obs'd no. of events, so PRR = 1
- Ignoring stratification gives expected total reports as

  $(400 + 900) \times (200 + 900)/2000 = 715$

  $\Rightarrow$ PRR = 890/715 = 1.24 Spurious association!
- Could be real associations $\Rightarrow$ separate evaluations per stratum may be useful & insightful

Result From 6 Years of Reports

Events w/EBGM$_{05}$ > 2 (Bold $\Rightarrow$ N $\geq$ 100)

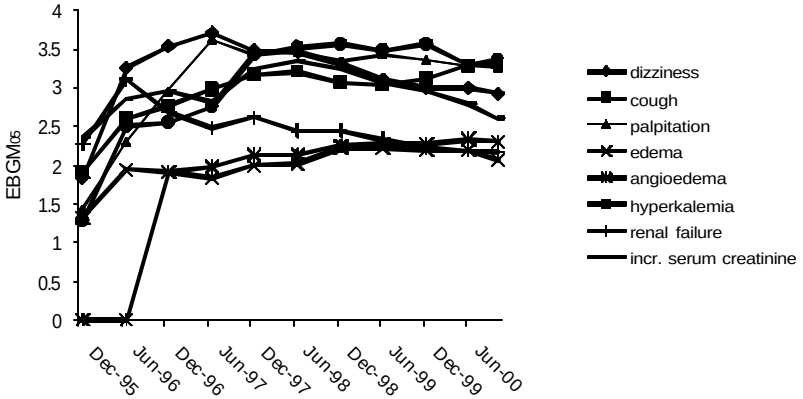
N	E	AE (preferred term)	EBGM	5% Lwr Bnd	Excess N
6	0.55	toxicerythema	8.19	2.73	0.9
8	0.82	obstipation	7.97	3.30	1.9
9	1.15	labile hypertension	6.15	2.79	2.1
51	8.39	erythrocytes decreased	5.85	4.53	29.6
53	9.37	peripheral vascular disorder	5.41	4.21	30.1
50	11.5	anginapectoris	4.08	3.18	25.0
124	**30.9**	**hyperkalemia**	**3.91**	**3.36**	**72.7**
225	**60.5**	**palpitation**	**3.66**	**3.28**	**137.7**
696	**195.9**	**cough**	**3.54**	**3.32**	**454.5**
904	**290.6**	**dizziness**	**3.10**	**2.93**	**562.0**
99	**31.0**	**serum creatinine increased**	**3.09**	**2.61**	**49.9**
214	**81.6**	**angioedema**	**2.59**	**2.31**	**107.0**
102	**38.6**	**renal failure**	**2.57**	**2.18**	**45.5**
216	**91.9**	**edema**	**2.32**	**2.08**	**98.8**

Persistence (& Reliability) of Early Signals

Adverse Event	As of Dec 1996 N	Mean EBGM	Lower 5% Bnd	As of Oct 2000 N	Mean EBGM	Lower 5% Bnd
renal artery stenosis	6	6.96	2.41	7	4.78	2.03
exanthema	23	4.74	3.23	48	2.73	2.14
peripheral vascular disorder	**23**	**4.74**	**3.23**	**53**	**5.41**	**4.23**
angina pectoris	**15**	**4.36**	**2.68**	**50**	**4.08**	**3.18**
serum creatinine increased	**36**	**3.94**	**2.95**	**99**	**3.09**	**2.60**
dizziness	**349**	**3.86**	**3.53**	**904**	**3.1**	**2.93**
myocardial infarction	26	3.67	2.62	--	--	--
palpitation	**73**	**3.59**	**2.95**	**225**	**3.66**	**3.27**
hyperkalemia	**32**	**3.46**	**2.55**	**124**	**3.91**	**3.36**
renal failure	**53**	**3.39**	**2.69**	**102**	**2.57**	**2.17**
pulmonary edema	10	3.16	1.82	--	--	--
cough	**209**	**3.11**	**2.77**	**696**	**3.54**	**3.32**
migraine	19	2.87	1.95	--	--	--
vertigo	22	2.51	1.75	84	2.36	1.97
angioedema	**62**	**2.35**	**1.91**	**214**	**2.59**	**2.31**
edema	**72**	**2.32**	**1.91**	**216**	**2.32**	**2.07**
headache	255	2.21	2.00	--	--	--

Accumulating Information over Time

- 5% Lower EBGM values stabilized fairly soon



Time-Sliced Evolution of Risk Ratios

- Value may lie in seeing how values of criteria change over time within time intervals of fixed length

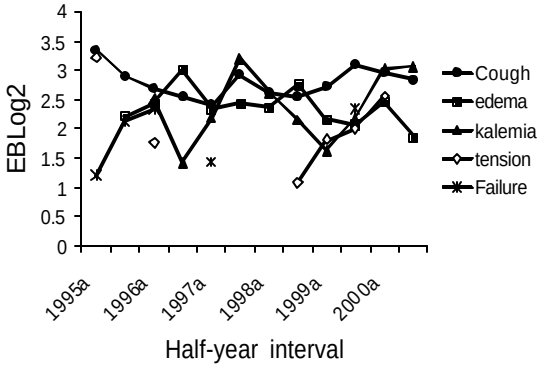
Change in IC_{ij} for reports of selected events on A2A from 1995 to 2000

tension = hypotension

failure = heart failure

kalemia = hyperkalemia

edema = angioedema



Cloaking of AE-Drug Relationships (1)

- Company databases smaller than regulatory db, more loaded with 'similar' drugs
- eg, Drug A is 2nd generation version of Drug B, similar mechanism of action, many reports with B
- Effect of B could mask effect of A
- May be useful to provide results when reports mentioning Drug B are omitted

Cloaking of AE-Drug Relationships (2)

	Drug A	Drug B	Others	Total
Event	n_{AE}	n_{BE}	n_{OE}	n_E
Total	n_A	n_B	n_O	N

- $PRR_{inc\,B} = n_{AE} \times N / n_A \times n_E$
- $PRR_{exc\,B} = n_{AE} \times (N - n_B) / n_A \times (n_E - n_{BE})$
- Ratio of these measures effect of Drug B experience on risk of event using Drug A
- $$PRR_{exc\,B}/PRR_{inc\,B} = 1 + \frac{n_B}{n_E - n_{BE}}\left(\frac{n_{BE}}{n_B} - \frac{n_E}{N}\right)$$
- Elevated risk on B decreases apparent risk on A

Cloaking of AE-Drug Relationships (3)

	Drug B Included		Omitted	
Preferred Term	EBGM05	Excess	EBGM05	Excess
atopic dermatitis	1.96	9.8	2.11	10.9
hypotension	1.87	29.5	2.44	38.2
left cardiac failure	1.99	3.0	2.20	3.7
lichen planus	1.79	4.1	2.04	5.1
pharyngeal edema	1.47	5.8	2.32	10.8
psoriasis vulgaris	1.92	8.4	2.37	10.4
pulmonary congestion	1.65	3.8	2.23	5.4
pulmonary edema			2.12	6.1
renal insufficiency			2.10	12.2
sudden death	1.96	3.0	2.58	4.0
tachycardia	1.86	40.9	2.21	49.0
tongue edema			2.73	10.7
vertigo	1.97	33.4	2.51	41.7

Effect of Combinations of Drugs or Vaccines

- GPS gives effect of individual drugs ignoring what else patient was taking
- But combinations of drugs may increase risk more than just effects of individual drugs
- FDA recognizes problem; multi-item version of GPS will be available soon (can purchase now)

Discussion

- Bayesian approaches useful for detecting possible emerging signals, espcially with few events, especially with precision is considered
- MCA (UK) currently uses PRR for monitoring emergence of drug-event associations
- Signal detection = a combination of numerical data screening and clinical judgement

Discussion

- Most apparent associations represent known problems
- Some reflect disease or patient population
- ~ 25% may represent signals about previously unknown associations
- Statistical involvement in implementation & interpretation is important
- The actual false positive rate is unknown as are the legal and resource implications

Future Work

- Apply methods to larger databases

  Small databases → risk of swamping signal (eg, lots of ACE info masks potential A2A associations)

- Develop effective ways to use methods -- eg, time slicing
- Big problems remain -- need effective dictionaries: many synonyms → difficult signal detection
  - Event names: MedDRA may help
  - Drug names: Essential to have a commonly accepted dictionary of drug names to minimize dilution effect of synonyms

Summary and Conclusions

- Automated signal detection tools have promise
  - spontaneous reports
  - clinical trials
  - multiple event terms: syndrome recognition
  - multiple drug terms: drug interaction identification
- Still need clinical/epidemiological interpretation -- how to integrate methods into detection process effectively