SAS® BI and JMP® Signal Detection of Adverse Drug Events in the FDA/AERS Database

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Introduction

- Need for proactive monitoring of drugs for suspected ADRs and serious AEs after marketing approval
- Challenge is how to detect safety signals from routinely collected spontaneous reports in FDA/AERS that lack drug exposure data and subject to reporting biases
- Employ adhoc-disproportionality analysis and signal detection methods to look for unexpected drug reaction and events in the AERS database
- Technologies to help the safety investigators triage and interpret safety signals generated using the disproportionality methods

Objectives

- Evaluate the performance characteristics of two disproportionality analysis (DA) methods for predicting drug safety signals in FDA/AERS
- Employ **SAS© BI/JMP** software to produce interactive graphical plots and tables to aid interpretation of the signal detection and data mining results

Study Design and Methods

- Reports database: FDA/AERS with coverage period from 1989Q1 to 2008Q4
- Drugs of interest: All drugs coded as suspect, possible or secondary suspects and having a minimum frequency of 50 reports
- Event-based sampling method to create analytic file for the drug-event pairs stratified by levels of gender, age, and reporting period
  - Considered AERS reports with MedDRA PT field coded as ‘torsades de pointes’ (TdP)
- Disproportionality methods for generating drug safety signals
  - Multi-Gamma Poisson Shrinker MGPS/EBGM (DuMouchel 1999)
  - Proportional Reporting Ratio (Evans et al. 2001)
- Employed a reference drug-TdP association database derived from the published list of drugs with TdP/QT-risk ratings from www.qtdrugs.org (administered by the University of Arizona CERT)
- Construction of ‘truth table’ for each DA method to obtain performance measures

Results

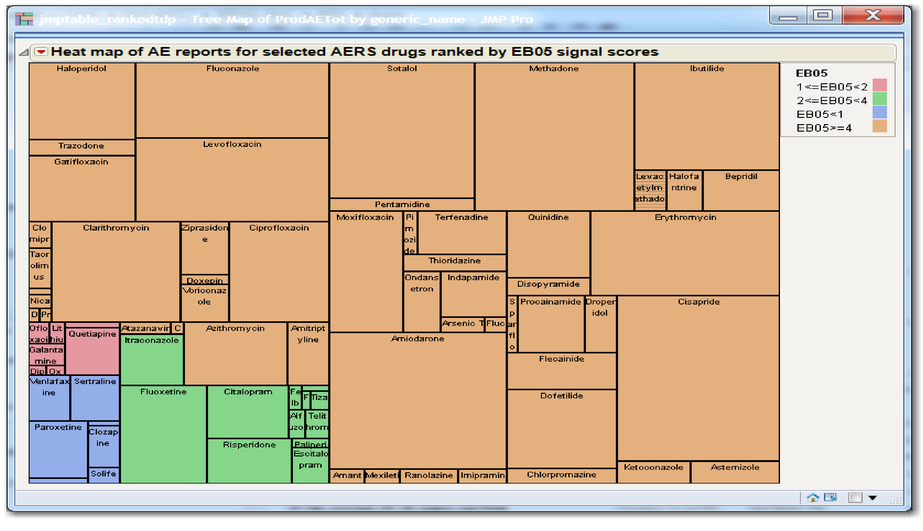

Figure 1. Heat map of AE reports for selected FDA/AERS drugs ranked by EB05 signal scores

Results

Target Event: Torsade de pointes (Total Drug-TdP Pairs, N=404)

Test method (Signal criterion)	Measure (%, N)	TdP risk classification based on AzCERT risk ratings: Definite Torsades	Definite or Possible Torsades	Definite/Possible/ Conditional Torsades
MGPS (EB05>=2)	Sensitivity	100.0 (27)	86.4 (51)	82.1 (64)
	Specificity	41.6 (157)	43.2 (149)	43.9 (143)
	PPV	10.9	20.6	25.9
	AUC	95.0 (92.0-98.0)	78.5 (71.7-85.3)	76.1 (69.7-82.4)
PRR ($PRR_c \geq 2$, $\chi^2 \geq 4$, N≥3)	Sensitivity	88.9 (24)	61.0 (36)	61.5 (48)
	Specificity	68.7 (259)	69.3 (239)	71.2 (232)
	PPV	16.9	25.4	33.8
	AUC	84.8 (77.4-92.2)	67.8 (60.4-75.1)	68.4 (62.1-74.8)

Table 1: ROC analysis results for MGPS and PRR disproportionality methods for predicting torsades de pointes AE

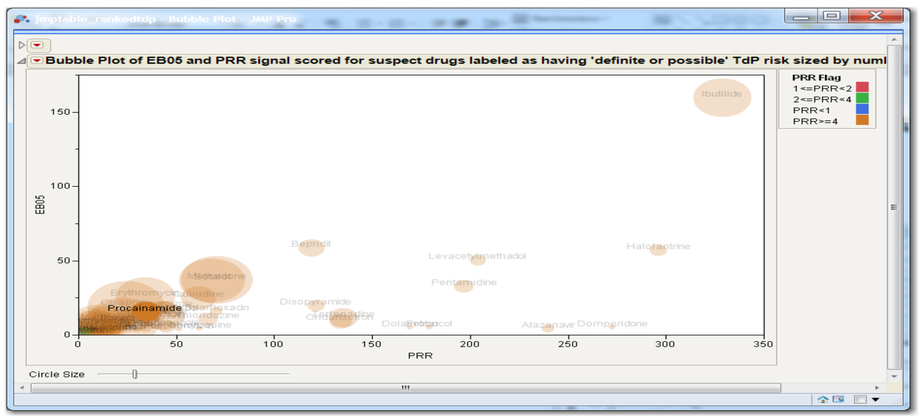

Figure 2: Bubble plot of EB05 and PRR signal scores for suspect drugs labeled as having ‘definite or possible' TdP risk sized by number of reports.

Discussion and concluding remarks

- For drugs categorized as ‘Definite Torsades’ in the reference database, the MGPS method predicted all the 27 drugs (sensitivity=100%) whereas PRR method predicted 24 of the 27 (sensitivity=88.9%). Both DA methods demonstrated high AUC scores.
- The predictive ability to detect true drug-TdP associations (PPV) for the PRR method was about 17% compared to 11% for MGPS
- Strength and limitations of study
  - SDAs are good screening tools for detecting meaningful drug-event associations and generating hypothesis in passive surveillance databases such as FDA/AERS
  - Not appropriate for computing AE risk ratios and rate incidence
  - Detected drug-event associations may require confirmatory follow-up studies
  - Potential for signal misclassification is high given that the reports used to generate signal scores for drug-AE pairs are not independent

Reference

- Evans, S.J. et al. Use of proportional reporting ratios (PRRs) for signal generation from spontaneous adverse drug reaction reports. Pharmacoepidemiol. Drug Saf 2001; 10: 483–486
- DuMouchel W. Bayesian data mining in large frequency tables, with an application to the FDA spontaneous reporting system. Am. Stat 1999; 53:177–190

Acknowledgement

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