PROTECT

imi efpia

Pharmacoepidemiological Research on Outcomes of Therapeutics by a European Consortium

Statistical signal detection

PROTECT Symposium tutorial

Andreas Brückner, Gianmario Candore, Jim Slattery, Niklas Norén

European Medicines Agency, London, United Kingdom

Feb 18, 2015

Agenda

14.00 – 14.45	Introduction + 3 perspectives on statistical signal detection in practice	All
14.45 – 15.30	Introduction to disproportionality analysis	Andreas Brückner
15.30 – 15.45	Break	
15.45 – 16.30	Pitfalls of disproportionality analysis	Niklas Norén
16.30 – 16.45	Break	
16.45 – 17.45	Introduction to empirical evaluation	Gianmario Candore Jim Slattery
17.45 – 18.00	Questions and closing	All

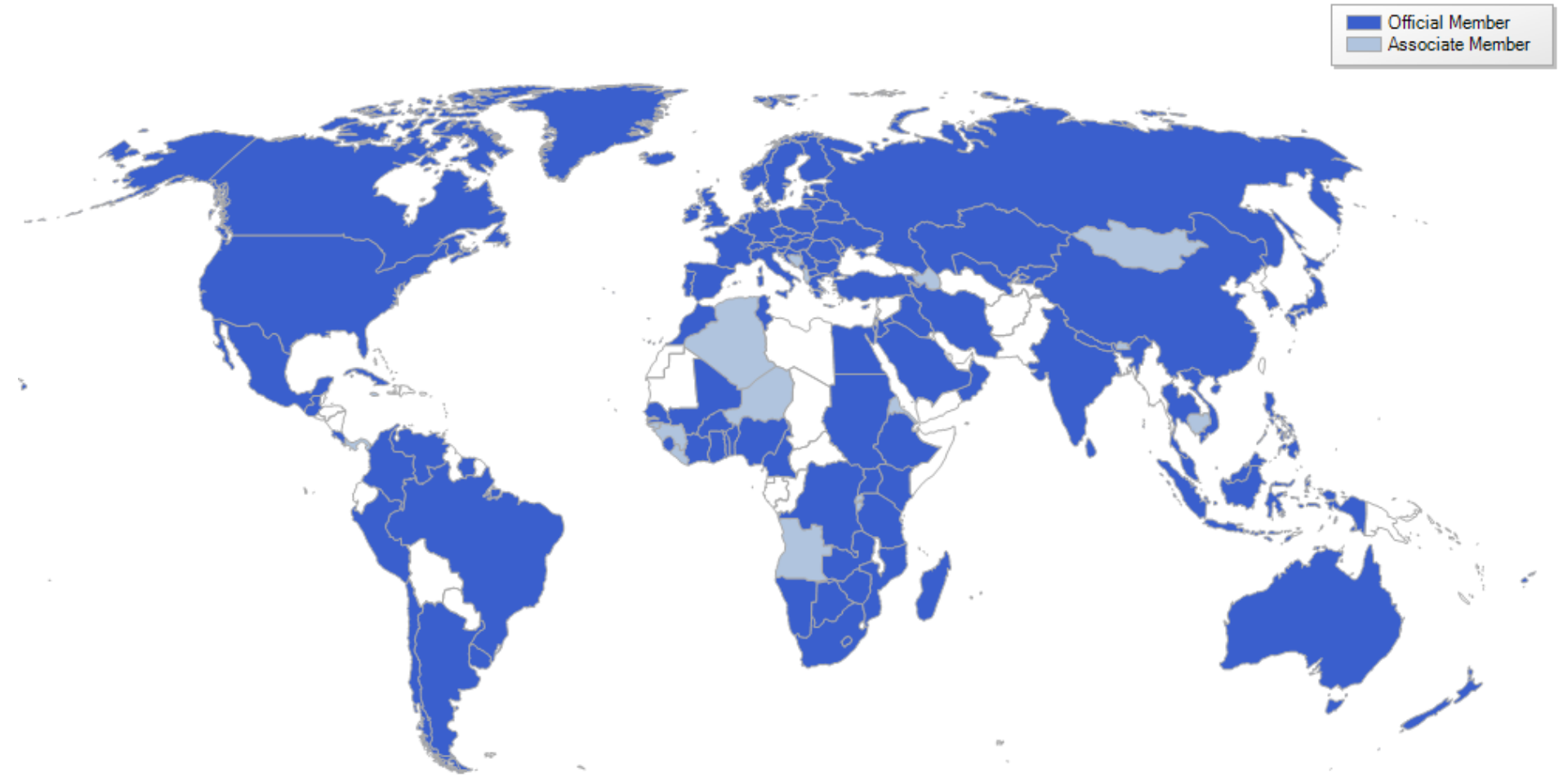
PROTECT

the UPPSALA MONITORING CENTRE

WHO Collaborating Centre for International Drug Monitoring

PROTECT

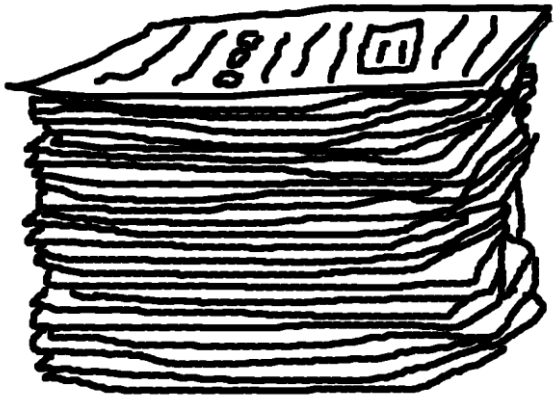
WHO Programme for International Drug Monitoring



PROTECT

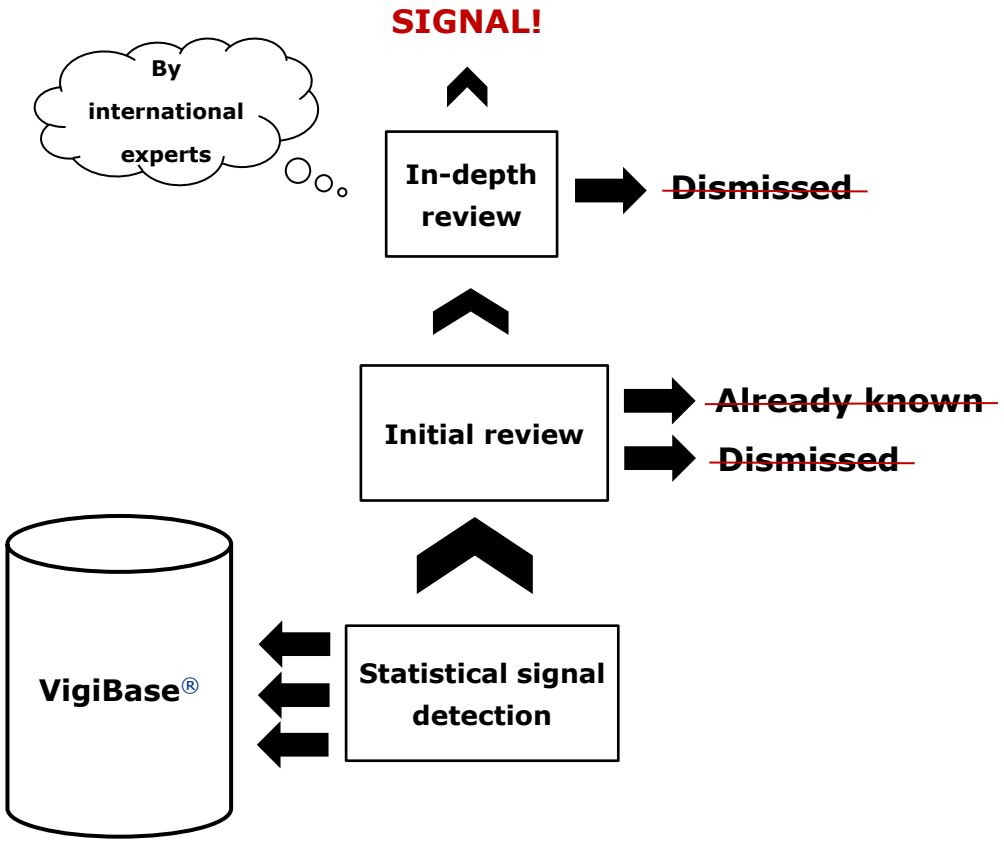
VigiBase®

120
countries



10
million
reports

Signal detection process



RESTRICTED

WHO Collaborating Centre for International Drug Monitoring

SIGNAL

Analyses of Adverse Reaction Reports in the WHO Database · April 2004

WHO Collaborating Centre
for International Drug Monitoring
Stora Torget 3, SE753 20 Uppsala, Sweden.
Tel +46 18 65 60 60. Fax +46 18 65 60 80
E-mail: info@who-umc.org

Signals in this issue

- Lansoprazole and severe cutaneous reactions
- Ectopic pregnancy and use of etonogestrel implants
- Reports of leukaemia and lymphoma during the use of clozapine and other atypical neuroleptics
- Leflunomide and ulcerative colitis
  Response from Aventis
- Infliximab and intestinal obstruction
- Rosiglitazone and liver toxicity

Follow-up

- Nelfinavir and hepatotoxicity
  Response from Pfizer and Roche
- SSRIs and gum hyperplasia
  Response from Eli Lilly and Company
- SSRIs and gum hyperplasia
  Response from Lundbeck
- Thiazolidinediones and cardiac disease
  Response from Takeda

the UPPSALA MONITORING CENTRE

All correspondence regarding signals presented in this document should go through the Uppsala Monitoring Centre

WHO PHARMACEUTICALS NEWSLETTER

World Health Organization

prepared in collaboration with the
WHO Collaborating Centre for
International Drug Monitoring,
Uppsala, Sweden

The aim of the Newsletter is to disseminate information on the safety and efficacy of pharmaceutical products, based on communications received from our network of "drug information officers" and other sources such as specialized bulletins and journals, as well as partners in WHO. The information is produced in the form of résumés in English, full texts of which may be obtained on request from:

Quality Assurance and Safety: Medicines, EMP-HSS, World Health Organization, 1211 Geneva 27, Switzerland, E-mail address: pals@who.int

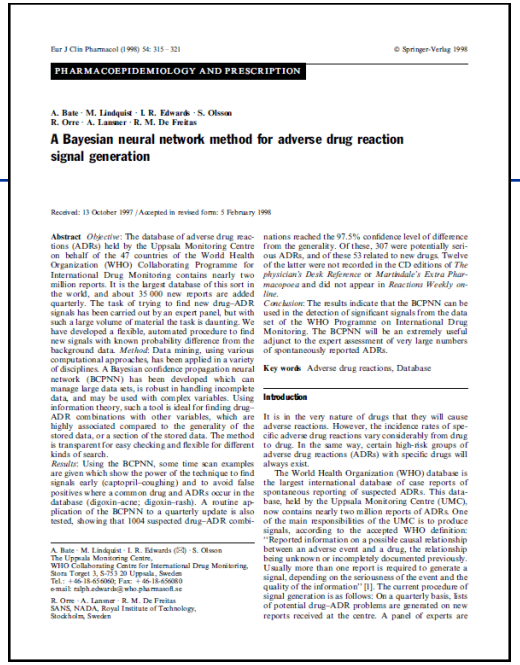
This Newsletter is also available on our Internet website: http://www.who.int/medicines

Further information on adverse reactions may be obtained from the WHO Collaborating Centre for International Drug Monitoring Box 1051 751 40 Uppsala Tel: +46-18-65.60.60 Fax: +46-18-65.60.80 E-mail: info@who-umc.org Internet: http://www.who-umc.org

No. 6, 2012

The WHO Pharmaceuticals Newsletter provides you with the latest information on the safety of medicines and legal actions taken by regulatory authorities across the world. It also provides signals from the Uppsala Monitoring Centre's SIGNAL document. We thank you for your interest in this publication and wish you a healthy and fulfilling year in 2013.

Contents



Eur J Clin Pharmacol (1998) 54: 315–321 © Springer-Verlag 1998

PHARMACOEPIDEMIOLOGY AND PRESCRIPTION

A. Bate · M. Lindquist · I. R. Edwards · S. Olsson
R. Orre · A. Lansner · R. M. De Freitas

A Bayesian neural network method for adverse drug reaction signal generation

Received: 13 October 1997 / Accepted in revised form: 5 February 1998

Abstract *Objective:* The database of adverse drug reactions (ADRs) held by the Uppsala Monitoring Centre on behalf of the 47 countries of the World Health Organization (WHO) Collaborating Programme for International Drug Monitoring contains nearly two million reports. It is the largest database of this sort in the world, and about 35 000 new reports are added quarterly. The task of trying to find new drug–ADR signals has been carried out by an expert panel, but with such a large volume of material the task is daunting. We have developed a flexible, automated procedure to find new signals with known probability difference from the background data. *Method:* Data mining, using various computational approaches, has been applied in a variety of disciplines. A Bayesian confidence propagation neural network (BCPNN) has been developed which can manage large data sets, is robust in handling incomplete data, and may be used with complex variables. Using information theory, such a tool is ideal for finding drug–ADR combinations with other variables, which are highly associated compared to the generality of the stored data, or a section of the stored data. The method is transparent for easy checking and flexible for different kinds of search. *Results:* Using the BCPNN, some time scan examples are given which show the power of the technique to find signals early (captopril–coughing) and to avoid false positives where a common drug and ADRs occur in the database (digoxin–acne; digoxin–rash). A routine application of the BCPNN to a quarterly update is also tested, showing that 1004 suspected drug–ADR combinations reached the 97.5% confidence level of difference from the generality. Of these, 307 were potentially serious ADRs, and of these 53 related to new drugs. Twelve of the latter were not recorded in the CD editions of *The physician's Desk Reference* or *Martindale's Extra Pharmacopoea* and did not appear in *Reactions Weekly online*. *Conclusion:* The results indicate that the BCPNN can be used in the detection of significant signals from the data set of the WHO Programme on International Drug Monitoring. The BCPNN will be an extremely useful adjunct to the expert assessment of very large numbers of spontaneously reported ADRs.

Key words Adverse drug reactions, Database

Introduction

It is in the very nature of drugs that they will cause adverse reactions. However, the incidence rates of specific adverse drug reactions vary considerably from drug to drug. In the same way, certain high-risk groups of adverse drug reactions (ADRs) with specific drugs will always exist.

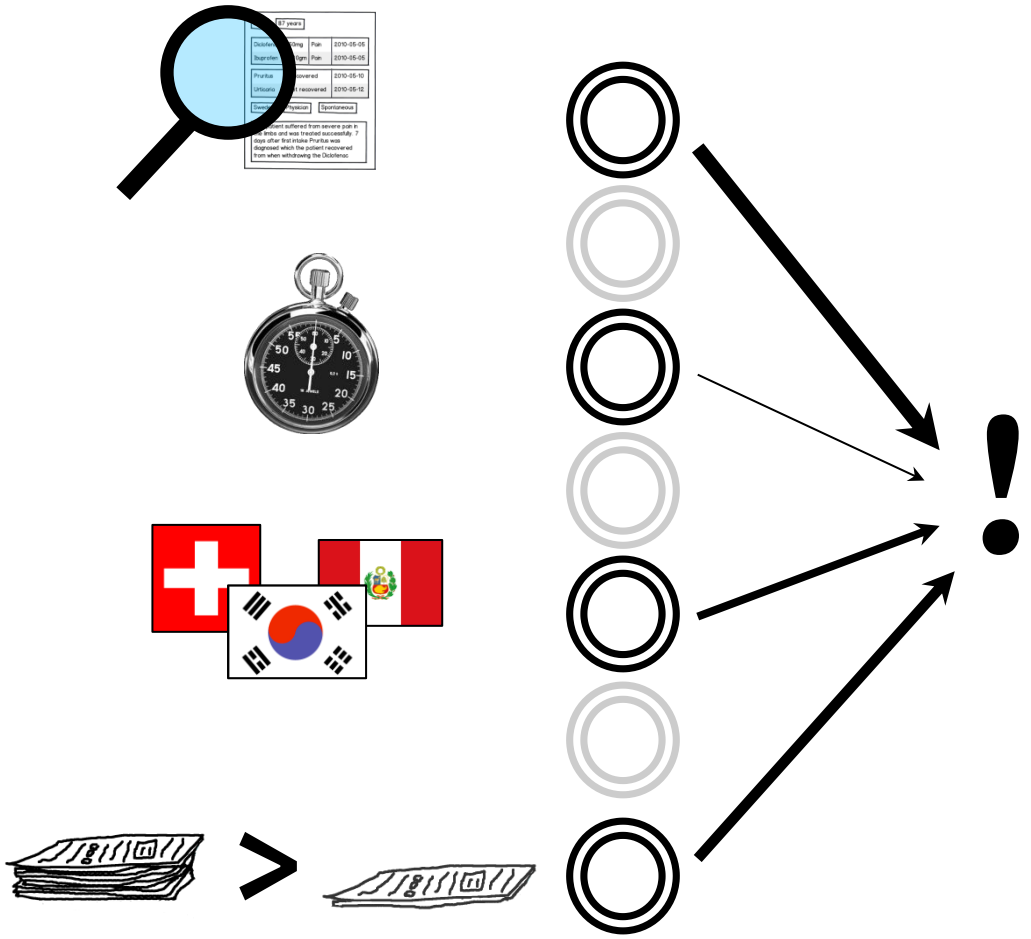
The World Health Organization (WHO) database is the largest international database of case reports of spontaneous reporting of suspected ADRs. This database, held by the Uppsala Monitoring Centre (UMC), now contains nearly two million reports of ADRs. One of the main responsibilities of the UMC is to produce signals, according to the accepted WHO definition: "Reported information on a possible causal relationship between an adverse event and a drug, the relationship being unknown or incompletely documented previously. Usually more than one report is required to generate a signal, depending on the seriousness of the event and the quality of the information" [1]. The current procedure of signal generation is as follows: On a quarterly basis, lists of potential drug–ADR problems are generated on new reports received at the centre. A panel of experts are

A. Bate · M. Lindquist · I. R. Edwards (✉) · S. Olsson
The Uppsala Monitoring Centre,
WHO Collaborating Centre for International Drug Monitoring,
Stora Torget 3, S-753 20 Uppsala, Sweden
Tel.: +46-18-656060; Fax: +46-18-656080
e-mail: ralph.edwards@who.pharmasoft.se

R. Orre · A. Lansner · R. M. De Freitas
SANS, NADA, Royal Institute of Technology,
Stockholm, Sweden

Disproportionality analysis

Anno 1998



DOI 10.1007/s40264-014-0204-5

ORIGINAL RESEARCH ARTICLE

Improved Statistical Signal Detection in Pharmacovigilance by Combining Multiple Strength-of-Evidence Aspects in vigiRank

Retrospective Evaluation against Emerging Safety Signals

Ola Caster · Kristina Juhlin · Sarah Watson · G. Niklas Norén

Abstract

Background Detection of unknown risks with marketed medicines is key to securing the optimal care of individual patients and to reducing the societal burden from adverse drug reactions. Large collections of individual case reports remain the primary source of information and require effective analytics to guide clinical assessors towards likely drug safety signals. Disproportionality analysis is based solely on aggregate numbers of reports and naively disregards report quality and content. However, these latter features are the very fundament of the ensuing clinical assessment.

Objective Our objective was to develop and evaluate a data-driven screening algorithm for emerging drug safety signals that accounts for report quality and content.

Methods vigiRank is a predictive model for emerging safety signals, here implemented with shrinkage logistic regression to identify predictive variables and estimate their respective contributions. The variables considered for inclusion capture different aspects of strength of evidence, including quality and clinical content of individual reports, as well as trends in time and geographic spread. A reference set of 264 positive controls (historical safety signals from 2003 to 2007) and 5,280 negative controls (pairs of drugs and adverse events not listed in the Summary of Product Characteristics of that drug in 2012) was used for model fitting and evaluation; the latter used fivefold cross-validation to protect against over-fitting. All analyses were performed on a reconstructed version of VigiBase® as of 31 December 2004, at around which time most safety signals in our reference set were emerging.

Results The following aspects of strength of evidence were selected for inclusion into vigiRank: the numbers of informative and recent reports, respectively; disproportionality analysis alone

Key Points

Today, automated screening of large collections of individual case reports to identify possible drug safety issues often relies on disproportionality analysis, which is based solely on aggregate numbers of reports, disregarding report quality and content

This study identifies the following variables as strong predictors of emerging drug safety issues: the number of informative reports, recent reports, and reports with free-text descriptions; disproportional reporting; and geographic spread. Simultaneously accounting for these aspects of strength of evidence significantly improves the accuracy of automated screening of individual case reports compared with disproportionality analysis alone

Utilizing the identified predictive model can be expected to reduce the number of false alerts and uncover drug safety issues that would otherwise go undetected

O. Caster (✉) · K. Juhlin · S. Watson · G. N. Norén
Uppsala Monitoring Centre, Box 1051, SE-75140 Uppsala, Sweden
e-mail: ola.caster@who-umc.org

O. Caster
Department of Computer and Systems Sciences, Stockholm University, Forum 100, SE-164 40 Kista, Sweden

G. N. Norén
Department of Mathematics, Stockholm University, SE-106 91 Stockholm, Sweden

Published online: 23 July 2014

△ Adis

vigiRank

Anno 2014