PHARMACOEPIDEMIOLOGY AND DRUG SAFETY 2009; **18**: 1176–1184
Published online 15 September 2009 in Wiley InterScience (www.interscience.wiley.com) **DOI**: 10.1002/pds.1836

ORIGINAL REPORT

Data mining on electronic health record databases for signal detection in pharmacovigilance: which events to monitor?

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SUMMARY

Purpose Data mining on electronic health records (EHRs) has emerged as a promising complementary method for post-marketing drug safety surveillance. The EU-ADR project, funded by the European Commission, is developing techniques that allow mining of EHRs for adverse drug events across different countries in Europe. Since mining on all possible events was considered to unduly increase the number of spurious signals, we wanted to create a ranked list of high-priority events.

Methods Scientific literature, medical textbooks, and websites of regulatory agencies were reviewed to create a preliminary list of events that are deemed important in pharmacovigilance. Two teams of pharmacovigilance experts independently rated each event on five criteria: 'trigger for drug withdrawal', 'trigger for black box warning', 'leading to emergency department visit or hospital admission', 'probability of event to be drug-related', and 'likelihood of death'. In case of disagreement, a consensus score was obtained. Ordinal scales between 0 and 3 were used for rating the criteria, and an overall score was computed to rank the events.

Results An initial list comprising 23 adverse events was identified. After rating all the events and calculation of overall scores, a ranked list was established. The top-ranking events were: cutaneous bullous eruptions, acute renal failure, anaphylactic shock, acute myocardial infarction, and rhabdomyolysis.

Conclusions A ranked list of 23 adverse drug events judged as important in pharmacovigilance was created to permit focused data mining. The list will need to be updated periodically as knowledge on drug safety evolves and new issues in drug safety arise.

KEY WORDS — adverse event; data mining; drug safety; database; signal detection

Received 27 February 2009; Revised 8 July 2009; Accepted 14 July 2009

INTRODUCTION

In pharmacovigilance, a signal is defined by the World Health Organization as information on a possible causal relationship between an adverse event and a drug, which is unknown or incompletely documented.[1,2] Spontaneous reporting systems for adverse drug reactions (ADRs) have been the cornerstone of signal detection in pharmacovigilance for the last four decades.[3,4] In recent years, however, there has been a clamor for improved drug safety monitoring as a result of several high-impact safety issues.[5,6] It has become evident that some adverse effects of drugs may be detected too late,

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when millions of persons have already been exposed. The need for earlier detection and for a more pro-active approach to drug safety surveillance is receiving much attention both in Europe and in North America.[7–9]

The increasing availability of electronic health records (EHRs) presents opportunities to investigate a wide spectrum of adverse drug effects and to detect signals closer to real time.[10,11] Compared to clinical trial data, population-based EHR databases contain data from clinical practice about larger populations and longer follow-up periods.[12–15] Additionally, in contrast to spontaneous reporting systems, EHR databases do not suffer from underreporting and reporting biases thus potentially facilitating a more timely identification of signals.[11,16] It took 5 years for rofecoxib to be withdrawn from the market.[17] Using actual penetration of rofecoxib in the market, it has been calculated that if the medical records of 100 million patients would have been available for safety monitoring, the adverse cardiovascular effect would have been discovered in just 3 months.[18,19] A number of data mining techniques have been specifically developed for automatic detection of drug safety signals.[3,20–24]

It is within this context that the EU-ADR project (http://www.euadr-project.org) was funded by the European Commission with the aim to design, develop, and validate a computerized integrative system that exploits data from EHRs and biomedical databases for the early detection of ADRs. Beyond the current state-of-the-art, EU-ADR will lead to the federation of different population-based EHR databases, creating a resource of unprecedented size for drug safety monitoring in Europe (over 30 million patients from eight different databases). The initial stage of signal generation will be followed by signal substantiation and validation as described in Figure 1.

When using data mining to detect signals in EHR databases, a decision needs to be made about the type of approach, which can be drug- or event-based. In a drug-based approach, a set of specific drugs are monitored for their association with all possible events.[25] In an event-based approach, a set of specific events are inspected for their association with all possible drugs. The EU-ADR project is currently following the event-based approach. The definition of drugs across databases in various countries can more easily be harmonized compared to the definition of events. In addition, the event-based approach allows us to focuses on those events that are considered important from a public-health perspective irrespective of the drug causing the event.

One of the challenges in the event-based approach to signal detection through mining on EHR databases is the identification of events that are most important in pharmacovigilance and thus warrant priority for monitoring. Indeed, unconstrained data mining is likely to raise excessive numbers of spurious signals. Generating a long list of potential drug-event associations, especially in an automated fashion, may lead to so-called 'phantom ships',[26,27] which can have significant negative implications for public health, as demonstrated in the case of the atypical antipsychotic sertindole.[28] There is, however, no list available in the literature to date describing which are the primary events of interest for intensive monitoring in pharmacovigilance when applying data mining techniques. The aim of the current study was therefore to create such a list of events ranked by importance. This list of events shall be the starting point for signal detection in the EU-ADR project.

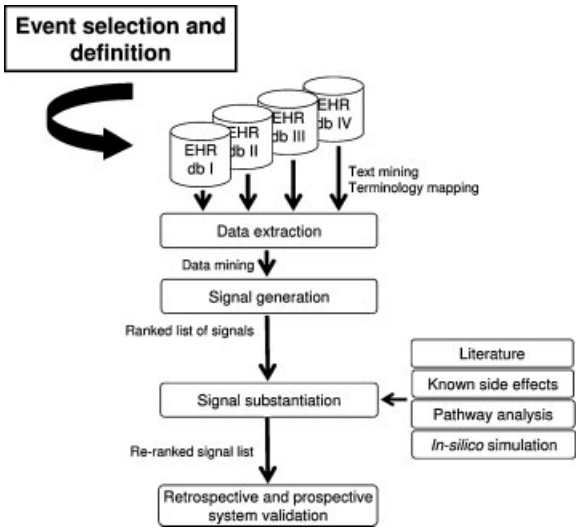

Figure 1. Framework of the EU-ADR project

METHODS

For the priority event selection and ranking, a four-step procedure was outlined by two teams of four pharmacovigilance experts each, from two institutions (Department of Pharmacology and Regional Pharmacovigilance Centre at the Université Victor-Segalen in Bordeaux, France, and the IRCCS Centro Neurolesi 'Bonino Pulejo', Messina, Italy).

Step 1: Identification of important events

A list of important adverse drug events was compiled, considering different system/organ classes. These

DOI: 10.1002/pds

events were identified from pharmacovigilance reference books and publications reviewing reasons for drug withdrawal (see Appendix), and from information on websites of drug regulatory agencies (Food and Drug Administration, European Medicines Agency, French Agency for the Safety of Health Products, and Italian Drug Agency).

Step 2: Creation of a criteria set for event rating

In order to rank the events according to public health importance, five criteria were considered (Table 1): (1) frequency of the event as trigger for drug withdrawal; (2) frequency of the event as trigger for black box warning; (3) leading to emergency department visit or hospital admission; (4) probability of event to be drug-related; and (5) likelihood of death. For each criterion, ordinal scales were defined ranging from 0 (irrelevant) to 3 (highly relevant).

Step 3: Score assignment

The two pharmacovigilance teams independently assigned scores for each of the events. Scores were based on a comprehensive review of the scientific literature over the past 10 years (see Appendix) and the evaluation of other sources of information (e.g., websites of regulatory agencies, medical textbooks). If literature review of the past 10 years was deemed insufficient, literature review was extended to the last 20 years. When review of the literature and other sources provided insufficient data, scoring of the criteria was based on expert opinion. In case of disagreement about a score, consensus was obtained after discussion among all members of the two teams.

Step 4: Ranking of events

For each event, an overall score was computed by summing up the five criteria scores. Based on the overall scores, a ranked event list was made. The top-ranked events were considered as having the highest priority for drug safety monitoring.

RESULTS

Twenty-three events were identified in the first step of the event selection process (Table 2). These were classified by organ/body system into: hematologic, cutaneous, liver and gastrointestinal, cardiac and vascular, neurologic, psychiatric, renal, and multi-systemic. Table 3 shows the scores on the five criteria for the 23 events. On the basis of the overall scores, the top-ranked events were: cutaneous bullous eruptions, acute renal failure, anaphylactic shock, acute myocardial infarction, and rhabdomyolysis.

As an example, cutaneous bullous eruption (Stevens-Johnson syndrome or Lyell's syndrome) emerged as one of the most important events, garnering a score of 15 points: at least five drugs have been withdrawn from the market due to this adverse reaction, viz., valdecoxib, chlormezanone, sulfamethoxypyridazine, sulfadimethoxine, and isoxicam, and multiingredients preparations containing phenobarbital[29–32] (criterion 'trigger for drug withdrawal', 3 points); a black box warning for risk of cutaneous bullous reactions has been imposed on more than 10 drugs ('trigger for black box warning', 3 points); more than five papers have reported this adverse event as being responsible for emergency department visit or hospitalization[33] ('leading to emergency department visit or hospital admission', 3 points); at least 70% of cutaneous bullous

Table 1. Description and score definition of five criteria for the rating of events

Criterion	Description
Trigger for drug withdrawal	Question: How many times (if any) did the event lead to drug withdrawal? Score: 0 = never; 1 = 1–3; 2 = 4–5; 3 = >5 Note: The event causing the drug withdrawal should specifically be indicated (e.g., 'cardiotoxicity' is not the same as 'acute myocardial infarction')
Trigger for black box warning	Question: How many times (if any) was the event a trigger for a black box warning? Score: 0 = never; 1 = 1–5; 2 = 6–10; 3 = >10 Note: The event causing the black box warning should specifically be indicated
Leading to emergency department visit or hospital admission	Question: How many published studies reported the event as an adverse drug reaction leading to an emergency department visit or to hospitalization? Score: 0 = none; 1 = 1–3; 2 = 4–5; 3 = >5 Note: Papers confined to emergency department visits and hospitalizations in Europe
Probability of event to be drug-related	Question: What is the probability that the event is caused by drugs? Score: 0 = not at all; 1 = <20%; 2 = 20–50%; 3 = >50% Note: In case of lack of information or equivocal findings, expert opinion is used to assign the score
Likelihood of death	Question: What is the likelihood that a certain event leads to death? Score: 0 = unlikely; 1 = <10%; 2 = 10–30%; 3 = >30% Note: This evaluation is independent of the etiology of the event and potential association with the drug

DOI: 10.1002/pds

Table 2. List of important events in pharmacovigilance, grouped according to system/organ involved

System/organ	Event
Hematologic	Hemolytic anemia
	Aplastic anemia/pancytopenia
	Neutropenia
	Thrombocytopenia
Cutaneous	Maculo-papular erythematous eruptions
	Bullous eruptions (Stevens Johnson Syndrome, Lyell's Syndrome)
Liver and gastrointestinal	Acute liver injury
	Acute pancreatitis
	Upper gastrointestinal bleeding
Cardiac and vascular	Acute myocardial infarction
	QT prolongation
	Cardiac valve fibrosis
	Venous thrombosis
Neurologic	Convulsions
	Peripheral neuropathy
	Extrapyramidal disorders
	Rhabdomyolysis
Psychiatric	Confusional state
	Mood changes: depression and mania
	Amnesias
	Suicidal behavior/attempt
Renal	Acute renal failure
Multi-systemic	Anaphylactic shock

reactions have been attributed to drug exposure[34,35] ('probability of event to be drug-related', 3 points); more than 30% of Stevens-Johnson/Lyell's syndrome cases are fatal, mainly because of progression to sepsis or pulmonary involvement ('likelihood of death', 3 points).[36]

DISCUSSION

This is the first study aimed at systematically creating a prioritized list of events to monitor when applying data mining techniques on large EHR databases for safety signal detection. This list comprises 23 events with high attributable risks of drugs based on seven system/organ classes that are most commonly involved in ADRs.[37–41] Most of the events identified in this study constitute potentially clinically serious outcomes resulting in hospitalization, life-threatening situations, or death. While many adverse drug events do not require hospital admission or emergency department visit, the prioritized events do strain healthcare resources and thus have stronger implications for public health. Most studies report that ADRs cause 3–6% of all hospital admissions and are responsible for about 5–10% of inpatient costs[38,42–47] Six of the 23 events identified in this study were associated with prolonged hospitalization in the UK, based on hospital episode statistics from 1996 to 2000 (hemolytic anemia, liver injury, extrapyramidal effects, renal failure, rhabdomyolysis, anaphylaxis, and aplastic anemia).[48]

While there are lists of most frequently reported adverse drug events available from various regulatory agencies and repositories of spontaneous reporting systems, frequency of reporting does not necessarily translate to clinical significance. In a review of adverse drug event surveillance and drug withdrawals in the US, the top 20 events reported from 1969 to 2002 were also very different from the events cited as reasons for removing drugs from the market, which were far more serious.[32] This is partly due to the fact that some ADRs are more easily recognized than others, because of the known pharmacology of the drug (type A ADRs, which account for over 80% of all reactions), patient experience or, probably most important, physician awareness.[47] On the other hand, more serious events that are unpredictable (idiosyncratic or type B ADRs) are less easily identified and may not be reported as often, but are frequently responsible for removal of drugs from the market.[49–51] In a French study that looked into drug withdrawal for pharmacovigilance reasons, type B reactions were responsible for the withdrawal of 11 out of 21 drugs.[52] Of the 23 events in our priority list, 18 have been implicated as reason for removal of drugs from the market (e.g., cutaneous bullous eruption for valdecoxib; liver injury for pemoline, benoxaprofen, and troglitazone; cardiac valve fibrosis for pergolide, fenfluramine, and dexfenfluramine; rhabdomyolysis for cerivastatin).[31–32,46,49]

The adverse events identified in this study can be further characterized in terms of pathogenesis (i.e., predictable or unpredictable from the drug's pharmacology, role of immune or allergic mechanisms), clinical course (acute, delayed, chronic) and susceptibility of special populations (e.g., children or elderly) to experience the event. From the 23 events, four (17.4%) are known to be idiosyncratic, or immunologically mediated (thrombocytopenia, cutaneous bullous eruptions, anaphylactic shock, and maculopapular erythematous eruption). While the precise hazard function of adverse drug events is most of the time unknown, some events are acute by definition (e.g., acute myocardial infarction, acute renal failure, acute liver injury, and acute pancreatitis), while cardiac valve fibrosis and peripheral neuropathy are considered chronic and delayed, respectively. Some events, such as convulsions, upper gastrointestinal bleeding and acute renal failure, may be more critical to monitor in the extremes of age.

DOI: 10.1002/pds

Table 3. Ranked list of events

	Trigger for drug withdrawal	Trigger for black box warning	Requiring ED visit or hospital admission	Probability of event to be drug-related	Likelihood of death	Total score
Bullous eruptions (Stevens Johnson Syndrome, Lyell's Syndrome)	3	3	3	3	3	15
Acute renal failure	3	3	3	2	3	14
Anaphylactic shock	2	3	3	2	3	13
Acute myocardial infarction	2	3	3	1	3	12
Rhabdomyolysis	1	3	3	2	3	12
Aplastic anemia/pancytopenia	2	3	3	2	2	12
Neutropenia	2	3	3	2	2	12
Cardiac valve fibrosis	3	1	2	2	3	11
Acute liver injury	3	3	2	1	1	10
Extrapyramidal disorders	0	1	3	3	2	9
QT prolongation	3	2	2	1	1	9
Suicidal behavior/attempt	1	3	1	1	3	9
Confusional state	0	3	3	2	1	9
Thrombocytopenia	1	3	1	2	1	8
Upper gastrointestinal bleeding	0	3	2	2	1	8
Convulsions	1	2	2	1	2	8
Peripheral neuropathy	1	1	1	3	1	7
Maculo-papular erythematous eruptions	1	1	1	3	1	7
Venous thrombosis	1	2	2	1	1	7
Mood changes: depression and mania	0	3	2	1	1	7
Amnesias	1	3	2	1	0	7
Hemolytic anemia	1	1	1	1	2	6
Acute pancreatitis	0	1	2	1	2	6

CONCLUSION

Prioritization of adverse events judged as important in pharmacovigilance was undertaken to optimize data mining and to contain the number of spurious signals that data mining on EHR databases may generate. The first five of the 23 events in this list will be the initial focus of signal detection in the EU-ADR project.

Although the prioritization of adverse events for drug safety monitoring that was done in this study was based on thorough evaluation of evidence from various sources of information by pharmacovigilance experts, the list of events and their ranking is by no means definitive and is intended to be dynamic. As our knowledge on drug safety evolves and new issues in drug safety arise, the list will need to be updated.

CONFLICT OF INTEREST

Julia Hippisley-Cox is director of the Qresearch database which was used for this study. Qresearch is a not-for-profit partnership between the University of Nottingham and EMIS (main commercial supplier of clinical computer systems for GPs in the UK).

Mariam Molokhia has received grants from Pfizer and from the Serious Adverse Events Consortium (collaboration of industry and academia).

As an employee of Erasmus MC and project leader of the IPCI database Miriam Sturkenboom has been involved in studies that were contracted by various pharmaceutical companies. Unconditional research grants have been received from Pfizer, Merck, Johnson&Johnson, Amgen, Roche, GSK, Boehringer, Yamanouchi, and Altana. None of these research grants

KEY POINTS

- New methods are being developed to complement the traditional spontaneous reporting of adverse events; these methods include direct mining on health databases. For mining on health records it is necessary to define which events would require such monitoring.
- Criteria that can be used to make a list of events that are important for monitoring of drug safety are 'trigger for drug withdrawal', 'trigger for black box warning', 'leading to emergency department visit or hospital admission', 'probability of event to be drug-related', and 'likelihood of death'.
- Events that were judged as most important for monitoring in pharmacovigilance were cutaneous bullous eruptions, acute renal failure, anaphylactic shock, acute myocardial infarction, and rhabdomyolysis.

DOI: 10.1002/pds

was related to the subject of this study. Miriam Sturkenboom has been consultant to Pfizer, Servier, Celgene, Novartis, and Lundbeck on issues not related to this paper.

ACKNOWLEDGEMENTS

This research has been funded by the European Commission Seventh Framework Programme (FP7/2007-2013) under grant no. 215847—The EU-ADR Project.

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APPENDIX

The following pharmacovigilance reference books and articles were used for the score assignment.

General

1. Black box warnings (from FDA, by product): http://www.formularyproductions.com/master/showpage.php?dir=blackbox&whichpage=9 (Accessed 20 September, 2008).
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