Use of Real-World Data in Pharmacovigilance Signal Detection

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Use of Real-World Data in Pharmacovigilance Signal Detection

Gebruik van real-world data bij detectie van farmacovigilantiesignalen

Thesis

to obtain the degree of Doctor from the

Erasmus University Rotterdam

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In loving memory of my father

To my mother, with love and eternal appreciation

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Chapter 1

Introduction

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Regulatory agencies worldwide demand rigorous evaluation of safety data before approval of new medications [1-4]. These safety data are collected during the four major phases of development process of new medication. Phases I, II and III are conducted as a part of the clinical trial program prior to approval and Phase IV, also known as post-approval phase is where real-life utilization of medications occurs. Typically, clinical trials in Phases I-III are conducted in a controlled environment and a small population for a limited duration. Thus, rare adverse events and events with long latency are usually difficult to identify in the pre-marketing phase. Also, the inclusion and exclusion criteria in clinical trials limit true understanding of the safety if medications are used in the real-world. Due to these limitations, the full safety profile of a medication is not completely known at the time of market launch. A longer-term use in a large number of patients in a day-to-day setting provides additional understanding of safety profile in a real-world setting [5, 6].

The benefit-risk assessment of medication and medical devices hence continues in the post-marketing phase. This phase entails pharmacovigilance activities which include collection, assessment, and prevention of Adverse Drug Reactions (ADRs) as well as Adverse Events Following Immunization (AEFI). ADRs are the fifth common cause of death in Europe with an estimated 197,000 deaths per year and costing the society about 79 billion euros per year [7]. It is estimated that approximately $3.5 billion is spent on extra medical costs of ADRs annually in the United States (US) [7]. Pharmacovigilance activities involve patients, healthcare professionals, caregivers, regulatory authorities, Marketing Authorization Holders (MAHs) on data collection, signal detection, risk management, risk communication and minimization, reporting and auditing. This thesis is focused on comparison of signal detection results in post-marketing phase using traditional data sources (i.e. spontaneous reporting system data) vs. non-traditional data sources (real-world data).

The US Food and Drug Administration (FDA) and European Medicines Agency (EMA) are regulatory agencies that are responsible for monitoring the safety of medicines in the US and European Union (EU) member states, respectively. Their guidelines and regulations mandate MAHs to continuously review safety, efficacy, and effectiveness data and evaluate the benefit-risk profiles of medical products in their entire life cycle. There are also some local guidelines for countries outside of the US and EU.

In the post-marketing phase, the ADR data are observed and reported to MAH or regulatory agency by either a health care providers or patients. These reports are termed spontaneous as they take place voluntarily during the healthcare professional's routine diagnostic examination of a

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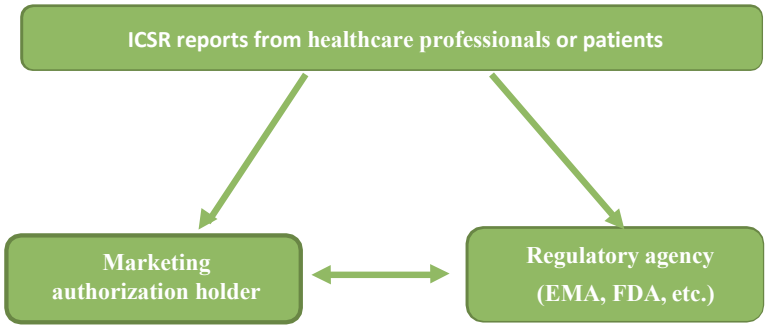
patient when the healthcare professional is drawing the conclusion that the observed clinical problems may be caused by a particular medication Therefore, the quality of the system relies on patients and healthcare professionals who not only generate a suspicion of an ADR but also report it. All MAHs are subsequently required to collect, process, and submit individual case safety reports (ICSRs) to worldwide regulatory agencies (such as FDA and EMA) on medical products that are reported directly to them by healthcare professionals or patient. These emerging safety issues may consequently alter the known safety profile. (Figure 1) MAHs and regulatory agencies consistently monitor these data to identify new safety signals and evaluate any change in the benefit-risk profile of the product.

Figure 1: Reporting of Individual Case Safety Reports (ICSRs)



A safety signal is any "information that arises from one or multiple sources, including observations and experiments which suggest a new potentially causal relationship, or a new aspect of a known association, between an intervention and an event or set of events, either adverse or beneficial, that is judged to be of sufficient likelihood to justify verificatory action." [8] Signal detection is a process of reviewing various data sources to identify a signal. Once a signal is identified, it is further evaluated to assess a causal relationship between the medication and the signal. The causality assessment is carried out by utilizing additional data sources such as literature information, indication of use, comorbidities related to the indication, existing safety profile of the product, etc.

All reports of ADRs are reviewed and analyzed by the MAHs to generate 'signals' or 'warnings' of serious, yet unrecognized. It also involves screening of publicly available large databases of spontaneous case reports for possible signals. [9] The most widely used spontaneous

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reporting system (SRS) databases are the World Health Organization's Vigibase database (WHO-Vigibase), [10, 11] the US FDA's Adverse Event Reporting System database (FAERS), [12-16] the US Vaccine Adverse Event Reporting System (VAERS), [17] the Eudravigilance system database, the Netherlands Pharmacovigilance Centre Lareb database, and the Medicines and Healthcare products Regulatory Agency's (MHRA) ADR database.

Spontaneous reporting is a cost-effective system to follow the safety of all medications during their entire life cycle. However, there are significant limitations related to the spontaneous reporting system. The system is highly dependent on reporter's ability to recognize such and their priority to report, especially for those adverse events that are not commonly thought to be drug-induced and have multiple risk factors. The spontaneous reporting system suffer from underreporting, where approximately <10% of serious ADRs are reported and also over-reporting due to publicity of ADRs. [18, 19] In addition, only a fraction of ADRs that are reported, are actually entered in the regulatory databases. Priority is given to serious and unexpected events for data entry.

To overcome limitations of SRS databases, in the last ten years there has been extensive research conducted to identify other data sources for carrying out signal detection. These data sources include longitudinal electronic health records (EHR) and social media feeds. In the US, in 2008, FDA has created the Sentinel System which is a national electronic system for medicinal product safety surveillance [20]. As of December 2018, the Sentinel Distributed Database contained 668 million person-years of data. Between 2008 and 2018, 11.7 billion records of pharmacy dispensing, and 15.0 billion unique medical encounters are captured. [20]. Also, in 2008, in the US, a public- private initiative called, formerly, Observational Medical Outcomes Partnership (OMOP), and currently Observational Health Data Sciences and Informatics (OHDSI) was established to research and educate stakeholders on the appropriate use of EHR for studying the effects of medicines. [21] In Europe, Exploring and Understanding Adverse Drug Reactions (EU-ADR) Project Focused on using clinical data from EHRs of over 30 million patients from several European countries (The Netherlands, Denmark, United Kingdom, and Italy) during 2008-2012 [22]. The Pharmacoepidemiological Research on Outcomes of Therapeutics by a European Consortium (PROTECT) project ran from 2009 – 2015. The project developed many innovative tools and methodological standards and contributed to helping enhance the monitoring of the safety of medicinal products, however, the tools are not widely utilized by the pharmacovigilance community and regulators. It also addressed limitations of current methods used in pharmacovigilance and pharmacoepidemiology. The focus was to significantly strengthen the monitoring of benefit-risk of medicines marketed in Europe, including improved evaluation and communication of their benefit-risk profile throughout their life cycle. [23]

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This thesis utilizes data from the EU-ADR Project and SRS databases to examine the utilization of real-world data for signal detection. Table 1 provides the overview of topics. Chapter 2 provides background information on how signal detection using EHR fits into post-marketing safety surveillance. Signal detection research was conducted using EU-ADR and compared to SRS data to study and evaluate the limitations of SRS as described above, preliminary results of which are described in Chapter 3. Chapter 4 shows how signal detection using EHR could complement spontaneous reports. Following that, Chapter 5 details a prospective study of EHR in the EU-ADR project which demonstrated the value of using EHR data in signal detection and strengthening. Chapter 6 focuses on the importance of early detection of a signal. In this chapter, we have aimed to explore time to detection of a signal. We used rofecoxib and acute myocardial infarction (AMI) to determine if the signal could have been identified in the EU-ADR earlier than the SRS and contribution of EU-ADR data in signal strengthening and possibly earlier rofecoxib withdrawal. When evaluating methods for signal detection using EHR databases, it is important to define reference standard the research. This is shown in Chapter 7. You will find the general discussion and summary in Chapter 8.

Table 1: Overview of topics described in this thesis

Chapter	Research topic	Data sources
2	Overview of signal detection using electronic healthcare records and how it fits in with traditional signal detection approach	N/A, Literature review
3	Preliminary comparison of EU-ADR healthcare database network vs. spontaneous reporting system databases	EU-ADR, FAERS, and WHO-Vigibase
4	Retrospective evaluating of performance of electronic healthcare record database and the spontaneous reporting system database	EU-ADR and FAERS
5	Prospective evaluation of utilizing electronic healthcare record database for pharmacovigilance signal detection and comparing it with results from the spontaneous reporting system databases	EU-ADR, FAERS, and WHO-Vigibase
6	Exploration of time to signal and signal strengthening effect using electronic healthcare data	EU-ADR, and WHO-Vigibase
7	Development of a reference standard for evaluation of methods for drug safety signal detection using electronic healthcare record databases	EU-ADR

N/A: Not applicable; EU-ADR; FAERS: the US Food and Drug Administration's (FDA) Adverse Event Reporting System database; WHO-Vigibase: The World Health Organization's Vigibase database

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Chapter 2

Postmarketing safety surveillance Where does signal detection using electronic healthcare records fit into the big picture?

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Vaishali Patadia
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Drug Safety, 2013 Mar;36(3):183-97

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Abstract

The safety profile of a drug evolves over its lifetime on the market; there are bound to be changes in the circumstances of a drug's clinical use which may give rise to previously unobserved adverse effects, hence necessitating surveillance post-marketing. Post-marketing surveillance has traditionally been carried out by systematic manual review of spontaneous reports of adverse drug reactions. Vast improvements in computing capabilities have provided opportunities to automate signal detection, and several worldwide initiatives are exploring new approaches to facilitate earlier detection, primarily through mining of routinely collected data from electronic healthcare records (EHR). This paper provides an overview of ongoing initiatives exploring data from EHR for signal detection vis-a`-vis established spontaneous reporting systems (SRS). We describe the role SRS has played in regulatory decision making with respect to safety issues and evaluate the potential added value of EHR-based signal detection systems to the current practice of drug surveillance. Safety signal detection is both an iterative and dynamic process. It is in the best interest of public health to integrate and understand evidence from all possibly relevant information sources on drug safety. Proper evaluation and communication of potential signals identified remains an imperative and should accompany any signal detection activity.

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1 Introduction

A drug's efficacy and safety must be demonstrated in a series of clinical trials conducted prior to approval. Phase III studies, consisting of randomized controlled trials, are considered to be the most rigorous approach to determining cause-and-effect relationship between an intervention and an outcome. The controlled nature of such trials, however, calls for a limited number of patients who may not always be representative of the population of all potential users of the drug and a relatively short observation period, making it difficult to detect adverse drug reactions (ADRs) that are rare or with a long latency [1–4]. Hence, to protect public health, it is imperative to continue monitoring and evaluating the safety of a drug once it is on the market. The safety profile of a drug evolves over its lifetime on the market; after years, or even decades, of experience there are bound to be changes in the circumstances of a drug's clinical use (in the population for whom it is recommended, including off-label use, concomitant use with other drugs and dosing regimen changes) which may give rise to previously unobserved adverse effects. Even over-the-counter products that have been available for a long time, such as phenylpropanolamine and NSAIDs, have been found to be associated with adverse effects necessitating labelling changes several years after drug approval or even market withdrawal [5–8].

Post-marketing drug safety surveillance has traditionally been carried out by systematic manual review of reports of suspected ADRs sent by healthcare professionals, consumers, and pharmaceutical manufacturers, and registered in national pharmacovigilance database systems. Qualitative review of all reports has become progressively more difficult and impractical because of the exponential increase in the number of cases over the years as well as the continuous influx of new drugs. In addition, vast improvements in computing capabilities in the last few decades have provided an opportunity to automate signal detection. For this reason, quantitative and automatic methods have been developed to supplement qualitative clinical evaluation, with quantitative signal detection being performed mostly, although not exclusively, on databases of spontaneous ADR reports [9–13]. Systems employing active ascertainment of adverse events related to specific drugs of interest have likewise been used for signal detection; these include the Prescription Event Monitoring (PEM) systems in the UK and its counterpart in New Zealand [14, 15]. Recent high-profile safety issues such as those involving rofecoxib and rosiglitazone have stimulated initiatives in North America and Europe to explore new approaches to facilitate earlier signal detection, primarily through mining of routinely-collected, longitudinal data from electronic healthcare records (EHR), including medical records and claims for healthcare services [16, 17].

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1.1 What Constitutes a 'Signal'?

The concept of a signal, from a drug surveillance point of view, has evolved from its definition by the WHO in 2002 [18] to a more synthesized and comprehensive definition proposed by Hauben and Aronson, which has subsequently been adapted by the CIOMS: [19, 20] (i) it is based on information from one or more sources (including observations and experiments), suggesting an association (either adverse or beneficial) between a drug or intervention and an event or set of related events (e.g. a syndrome); (ii) it represents an association that is new and important, or a new aspect of a known association, and has not been previously investigated and refuted; and (iii) it demands investigation, being judged to be of sufficient likelihood to justify verificatory and, when necessary, remedial actions. It is thus evident that a signal in pharmacovigilance may, and will, arise from various data sources.

In this review we provide an overview of ongoing initiatives exploring data from EHR for signal detection vis-à-vis established spontaneous reporting systems (SRS). We describe the role SRS has played in regulatory decision making with respect to safety issues. We further evaluate the potential added-value of EHR-based signal detection systems to the current practice of drug safety surveillance.

2 Traditional Data Sources for Safety Surveillance: Spontaneous Reports

In the aftermath of the thalidomide tragedy in the late 1960s, the US FDA, the WHO and the UK's Medicines and Healthcare products Regulatory Agency (MHRA) independently set up voluntary reporting systems that collect, and subsequently analyses, post-marketing safety information. Establishment of other country-wide spontaneous reporting databases soon followed. More than 70 countries, including a number of developing countries, have their own reporting systems, which attempt to ensure that signals of possible ADRs are detected as soon as possible after licensing. Some of the largest SRS databases available worldwide, including the FDA's Adverse Event Reporting System (AERS) [21] and Vaccine Adverse Event Reporting System (VAERS) [22], as well as EudraVigilance [23, 24] and the WHO's VigiBase™ [25, 26], are described in Table 1. Although the geographical catchment area of each database is different, there is some degree of overlap or duplication among the databases in the reports submitted, particularly with respect to serious and severe ADRs, which are usually reported to multiple authorities. Reports made to the AERS or EudraVigilance, for example, are also often submitted to VigiBase™, which is a global repository [27, 28].

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Table 1 Description of main spontaneous reporting system data sources

Database	Geographical origin of reports	Current number of reports available	Average number of reports received	Catchment period	Source of reports	Content of reports
US FDA AERS [21]	Mostly US (≈66 %)	>4 million (as of 31 December 2010)	300,000 per year (from 2000 to 2010)	1969–present	Healthcare professionals, pharmaceutical companies, patients/consumers	Obligatory postmarketing reports of serious and unexpected ADEs from drug manufacturers Voluntary reports (via MedWatch) from healthcare professionals and the public about serious reactions and other problems regarding drugs and medical devices
US FDA VAERS [22]	US	>200,000	30,000 per year	1990–present	Healthcare professionals, pharmaceutical companies, patients/consumers	Reports of adverse events occurring after administration of vaccines licensed for use in the US
EudraVigilance [23, 24]	EU	>600,000 (within the period 1 January–31 December 2009)	48,000 per month (within the period 1 January–31 December 2009)	2001–present	National competent authorities and marketing authorization holders (soon to include direct reports from patients/consumers and healthcare professionals)	Individual case safety reports of suspected ADRs associated with medicinal products authorized for use in the EEA Suspected unexpected serious ADR reports from pre-authorization drug trials

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Database	Geographical origin of reports	Current number of reports available	Average number of reports received	Catchment period	Source of reports	Content of reports
WHO VigiBase™ [25, 26]	Worldwide (107 official member countries and 33 associate members), but majority of reports come from Europe and the US	>7 million (as of January 2012)	200,000	1968–present	National pharmacovigilance centres (which may receive reports directly from patients/consumers, healthcare professionals, or pharmaceutical companies)	Individual case safety reports of suspected ADRs Case reports from studies or special monitoring

1. *ADE* adverse drug event, *ADRs* adverse drug reactions, *AERS* Adverse Event Reporting System, *EEA* European Economic Area, *VAERS* Vaccine Adverse Event Reporting System

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3 Signal Detection in Spontaneous Reporting Systems: Methodology and Examples

Many signal detection methods have been developed for data mining in SRS. These methods, comprising primarily of disproportionality analyses, are based on statistical algorithms that detect drug-adverse event combinations occurring at higher than expected frequencies [29, 30]. Techniques such as proportional reporting ratios (PRR, used in EudraVigilance) compare the proportion of events reported for a particular drug within a database with the background proportion for that same event for all drugs in the database [31]. Another method is the Reporting Odds Ratio, which is a reformulation of the PRR as an odds ratio [32]. The Multi-Item Gamma Poisson Shrinker (MGPS, used in the FDA AERS) [9, 33] and the Bayesian Confidence Propagation Neural Network (BCPNN, used in VigiBaseTM) [34] also examine disproportionality of reports for a specific drug compared with all other exposures, but draw on Bayesian models to shrink estimates of risk. In addition, these methodologies have been employed to assess time trends and drug-drug interactions [10]. The PRR and MGPS have been further explored to determine their utility in identification of so-called 'surprise' ADRs (i.e. reactions with a low drug-attributable risk) [35]. More recently, chemical information from analysis of molecular fingerprints have been combined with several data mining algorithms to enhance potential signals from the FDA AERS and to provide a decision support mechanism to facilitate the identification of novel adverse events [36].

3.1 Examples of Signals Identified in SRS

SRS gather real-life data on marketed drugs and, when review of individual case reports or case-series analysis is possible, may permit the identification of potential safety concerns. Examples of signals that have been generated or reinforced through SRS include haemolytic anaemia associated with temafloxacin, ventricular arrhythmias with terfenadine and cisapride, and cardiac valvulopathy with fenfluramine [37–40]. In addition, such reports have been useful in defining the nature of some ADRs. An under- standing of factors involved in flucloxacillin-induced hepatitis, such as delayed time to onset, predominant cholestatic pattern and delayed recovery, were brought to light by ADR reports [41]. The delayed onset and typically cholestatic pattern of amoxicillin/clavulanic acid-induced hepatitis has likewise been recognized through such reports [42, 43]. Higher than expected reports of intussusception following administration of the RotaShield rotavirus vaccine were initially identified in the VAERS in 1999 [44, 45]. The vaccine was voluntarily removed from the market by the manufacturer following the finding of an increased risk in epidemiological studies [46, 47]. The potential risk for development of Guillain–Barre syndrome (GBS) after administration of a meningococcal conjugate vaccine was first observed in the VAERS [48]

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3.2 Limitations

Despite their proven usefulness, there are several limitations in the use of SRS, primarily because SRS are mostly voluntary and studies have shown that only about 10 % of serious adverse events are reported [49]. Underreporting can lead to protracted delays between marketing and discovery of, and subsequent regulatory action regarding, an ADR. Close to 7 million patients were exposed to fenfluramine before the association with valvular heart disease led to its withdrawal from the market [50]. More than 80 million people worldwide (nearly 107 million prescriptions dispensed in the US alone) have been exposed to rofecoxib before it was voluntarily withdrawn by the manufacturer [51, 52]. Case reports in SRS may not always be consistent or complete with respect to medical history or comorbidities and data quality varies by region, country and reporting individual (i.e. consumer vs. healthcare professional). SRS databases generally do not have exposure information and are therefore deficient in providing a true incidence rate of an event [53, 54]. Furthermore, the phenomenon of masking has been shown to potentially cause signals of disproportionate reporting to be missed [55].

4 Electronic Healthcare Records (EHR) as Data Source for Safety Surveillance

The greatest limitation in the current approach to safety surveillance is that most hitherto existing systems are passive and reactive. The imperative to shift the paradigm towards a more proactive approach has resulted in the exploration of accessible data resources, whether or not the data are collected for the primary purpose of drug safety monitoring [56, 57]. These potential resources include electronic medical records with detailed clinical information such as patients' symptoms, physical examination findings, diagnostic test results and prescribed medications or other interventions. Automated electronic recording of filled prescriptions, laboratory and ancillary tests, as well as hospitalizations, are increasingly collected routinely for the payment and administration of health services. These EHR databases (medical records databases and administrative/claims databases) have been employed to characterize healthcare utilization patterns, monitor patient outcomes and carry out formal pharmacoepidemiological studies [58–60]. With regard to drug safety surveillance, such databases have been commonly used to confirm or refute potential signals detected initially by SRS, including vaccine-related signals [61]. EHR databases reflect practical clinical data culled from real-world settings. Being routine byproducts of the healthcare delivery system, the use of these databases offers the advantage of efficiency in terms of time necessary to conduct a study, manpower, as well as financial costs.

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Table 2 International initiatives using Electronic Healthcare Records databases for drug safety signal detection

	Data sources	Catchment area	Source population (available lives)	Adverse events currently being evaluated[a]	Drugs being investigated
EU-ADR [69, 70] (started 2008)	Medical records (primary care/general practitioner)	Denmark, Italy, the Netherlands, UK	30 million	Haemolytic anaemia	All drugs in the database network
				Aplastic anaemia/pancytopenia	
				Neutropenia	
				Thombocytopenia	
				Maculo-papular erythematous eruptions	
				Bullous eruptions (Stevens-Johnson Syndrome, Lyell's Syndrome)	
				Anaphylactic shock	
				Acute liver injury	
				Acute pancreatitis	
				Upper gastrointestinal bleeding	
				Acute myocardial infarction	
				QT prolongation	
				Cardiac valve fibrosis	
				Venous thrombosis	
	Administrative claims			Rhabdomyolysis	
				Hip Fracture	
				Convulsions	

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	Data sources	Catchment area	Source population (available lives)	Adverse events currently being evaluated[a]	Drugs being investigated
				Peripheral neuropathy	
				Extrapyramidal disorders	
				Confusional state	
				Mood changes (*depression, mania*)	
				Amnesias	
				Suicidal behaviour/attempt	
				Progressive multifocal leukoencephalopathy	
				Acute renal failure	
MINI-SENTINEL [63, 64, 71] (started 2009)	Administrative claims[b]	US	126 million	A, B, O incompatibility	Drugs, biologics and devices regulated by the FDA
				Erythema multiforme	
				Hypersensitivity reactions	
				Anaphylaxis	
				Pancreatitis	
				Cardiac arrhythmias	
				Atrial fibrillation	
				Congestive heart failure	
				Venous thromboembolism	
				Seizures	
				Stroke/transient ischaemic attack	

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	Data sources	Catchment area	Source population (available lives)	Adverse events currently being evaluated[a]	Drugs being investigated
				Depression	
				Suicide	
				Respiratory failure	
				Pulmonary fibrosis	
				Lymphomas	
				Transfusion sepsis	
				Transfusion/graft infections	
				Orthopaedic device removal	
				Implantable device revision	
OMOP [65, 66] (started 2009)	Medical records	US	325 million	*Aplastic anaemia*	ACE inhibitors
				Bleeding	Amphotericin B
				Angioedema	Antibiotics
					Antiepileptics
				Acute liver injury	
					Benzodiazepines

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	Data sources	Catchment area	Source population (available lives)	Adverse events currently being evaluated[a]	Drugs being investigated
				Gastrointestinal ulcer hospitalization	
					β-blockers
					Tricyclic antidepressants
	Administrative claims			*Myocardial infarction*	
					Typical antipsychotics
				Mortality after myocardial infarction	
					Warfarin
				Hip fracture	
				Renal failure	
				Hospitalization	
				All other outcomes recorded in the databases	

1. *OMOP* Observational Medical Outcomes Partnership;
2. [a]Outcomes that are common to more than one of the initiatives are shown in italics
3. [b]Data from outpatient and inpatient electronic health records and registries will be added subsequently

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5 International Collaborations

Within the last 5 years international collaborations have been forged to venture beyond using EHR databases for signal validation to developing EHR data-based drug safety signal detection systems. Some of these collaborations are briefly described below and their major features summarized in Table 2.

5.1 The SENTINEL Network

The SENTINEL Initiative was established in 2008 after the US FDA Amendments Act mandated the creation of a new post-marketing surveillance system that will utilize electronic health data to prospectively monitor the safety of marketed medical products [16, 62]. Two pilot initiatives have been launched to help develop the eventual SENTINEL system: the Mini-Sentinel and the Federal Partners' Collaboration. Mini-Sentinel, launched at the end of 2009, will enable the FDA to query privately-held electronic healthcare data representing over 100 million individuals [63]. Data sources currently available include administrative claims with pharmacy dispensing data, but data from outpatient and inpatient medical records and registries will be added later. The administrative claims data contain details regarding patient enrollment, demographics, healthcare counters, diagnoses and procedures, some lab- oratory results, as well as death and causes of death. The Federal Partners' Collaboration, which includes the Centres for Medicare & Medicaid Services, the Veterans Health Administration at the Department of Veterans Affairs, and the Department of Defense, will enable the FDA to query federally-held electronic healthcare data. The Mini-Sentinel pilot focuses on drugs, vaccines, other biologics and medical devices regulated by the FDA. The vaccine safety activities together constitute the Post- Licensure Rapid Immunisation Safety Measurement (PRISM) Program. From an original list of 140 health outcomes of interest (HOI), Mini-Sentinel is currently evaluating 20 HOIs, including two outcomes that pertain specifically to medical devices (i.e. removal of implanted orthopaedic device and surgical revision of implantable orthopaedic device) [see Table 2]. The Mini Sentinel website provides further information on the tools currently being developed and the conduct of validation of HOI [63, 64].

5.2 Observational Medical Outcomes Partnership

The Observational Medical Outcomes Partnership (OMOP) is a public-private partnership among the FDA, academia, data owners and the pharmaceutical industry, and is administered by the Foundation for the National Institutes of Health. It was initiated to identify the needs of an active drug safety surveillance system and to develop the necessary technology and methods to refine the secondary use of observational data for maximizing the benefit and minimizing the risk of pharmaceuticals.

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OMOP's database network consists of both commercially licensed databases, university- or practice-based healthcare databases and federal (i.e. US Veterans Affairs) databases, and representing both administrative claims and medical records [65]. OMOP is initially investigating ten HOIs, which is a subset of all conditions considered important due to their historical associations with drug toxicities, their medical significance and/or public health implications (Table 2) [66]. In 2009, OMOP organized a methods competition to facilitate development and evaluation of novel approaches for identifying drug safety issues in EHR [67] and have gone on to further investigate how these methods can be optimized for active surveillance both using simulated data and real healthcare data. Updates are continually posted in the OMOP website, with methods and simulated data, as well as other resources, publicly available for download and testing [68].

5.3 EU-ADR

The EU-ADR Project (Exploring and Understanding Adverse Drug Reactions by Integrative Mining of Clinical Records and Biomedical Knowledge), launched in 2008, is funded by the European Commission under its Seventh Framework Programme [69]. EU-ADR is a collaboration of 18 public and private institutions representing academic research, general practice, health services administration, and the pharmaceutical industry. EU-ADR currently has access to eight population-based administrative claims databases and general practitioner databases in four European countries (Denmark, Italy, the Netherlands and the UK), and has set up a computerized integrated framework for the detection of drug safety signals [17]. The databases contain demographic information, details of registration and utilization of services within the healthcare system, clinical data (including diagnoses, symptoms, procedures, some laboratory results), as well as drug prescription and/or dispensing information. Potential signals identified in the network are further substantiated by semantic mining of the literature and computational analysis of pharmacological and biological information on drugs, molecular targets and pathways.

The EU-ADR takes an event-based approach to signal detection (i.e. all drugs are evaluated for their association with a set of specific events), using as a guide a ranked list of 23 adverse events judged as important in pharmacovigilance based on predefined criteria (see Table 2) [70]. Three additional events are being looked into (progressive multifocal leukoencephalopathy, acute pancreatitis and hip fracture) subsequent to a request made by regulatory authorities and after consultation with other stakeholders. The rationale behind pursuing the event-based approach is to avoid unconstrained data mining, which is likely to raise excessive numbers of false positive signals. While the aim in the long- run is for the system to be able to detect a much broader range of events, this set of 'high-priority' events was deemed a good starting point. (Note: The EU-ADR Project was officially finished last year, but the EU-ADR Alliance has been created as a stable collaboration frame- work for running drug safety studies

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in a federated manner, especially when the participation of several EHR databases is required.)

The EU-ADR, OMOP and Mini-Sentinel all employ a distributed network approach in which data holders retain ownership and physical control of their protected data. Each initiative has developed its own common data model, within this distributed system, that allows standardization of data from each individual data source and local execution of various analyses via pre-specified computer programs [17, 65, 71]. The common data model also allows for the consideration of the different disease and drug coding terminologies used by the databases within each network, ensuring that the shared information can be consistently applied and interpreted across the heterogeneous data sources.

5.4 Other Initiatives

The Canadian Government has likewise established the Drug Safety and Effectiveness Network (DSEN) to increase the available evidence on drug safety and effectiveness by leveraging existing public resources such as the National Prescription Drug Utilisation System [72]. Other recently launched initiatives partly focusing on improving methods for safety signal detection include Pharmacoepidemiological Research on Outcomes of Therapeutics by a European Consortium (PROTECT) [73] and Global Research Initiative in Paediatrics (GRIP) [74].

While Asia is still lagging behind in terms of utilizing electronic healthcare data for pharmacovigilance, there is great potential in national health insurance claims databases in Japan, Korea and Taiwan, where universal health insurance covers entire populations [75]. The Korean Health Insurance Review & Assessment Service database, for example, has been explored for detection of signals potentially associated with statins using data mining techniques [76]. In Africa, data from EHR are increasingly being used to monitor adherence to antiretroviral therapy [77], and it will not be long before these data will be used for safety surveillance [78]. In South America, electronic immunization registries that are often linked to electronic patient files, are already being used to evaluate vaccination coverage [79]; these same registries may be further explored to evaluate vaccine safety.

6 Signal Detection Using EHR: Methodology

There have been several efforts in recent years to evaluate the usefulness of EHR databases for drug safety signal detection, initially using methods derived from SRS. The WHO Uppsala Monitoring Centre adapted the BCPNN to the UK primary care database IMS Disease Analyser MediPlus to show how longitudinal data may facilitate early signal detection [80]. Another study assessed the feasibility of using the MGPS algorithm to Medicare claims data in order to evaluate adverse outcomes associated with cyclooxygenase-2 inhibitors (coxibs) [81]. Sub- sequent efforts focused on development of novel

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methods, or modification of existing methods, to be employed specifically within the context of EHR. Wang and colleagues demonstrated that applying natural language processing and association statistics on unstructured data from hospital records can make such data useful for pharmacovigilance [82]. A team of Danish investigators performed temporal data mining on EHR databases to evaluate adverse events potentially related to the measles mumps rubella (MMR) vaccine [83]. Employing traditional epidemiological methods (nested case-control analysis and self- controlled case series), the Meningococcal Vaccine Study demonstrated that a distributed network of administrative claims databases may facilitate large-scale surveillance of vaccine-related GBS [84]. The maximized sequential probability ratio testing (maxSPRT), a signal detection method that supports continuous or time-period analysis of data as they are collected, was developed as part of the real-time surveillance system that has been used, among others, for evaluating meningococcal conjugated vaccine vaccination among members of a US healthcare maintenance organization (HMO) network [85]. In addition, the Vaccine Safety Datalink has performed active surveillance of over a dozen vaccines using a variety of different statistical methods. Two new methods—Longitudinal GPS (LGPS) and Longitudinal Evaluation of Observational Profiles of Adverse Events Related to Drugs (LEOPARD)—have been evaluated using both simulated data and actual data from the Dutch Integrated Primary Care Information (IPCI) database. LGPS is a modification of GPS that uses person- time rather than case counts for estimation of the expected number of events, while LEOPARD is a method designed to automatically discard false drug- event associations caused by protopathic bias or misclassification of the date of adverse event by comparing rates of prescription starts in a fixed window prior to and after the occurrence of an event [86]. Temporal pattern discovery is another method that looks into the chronology of drug prescription and occurrence of an adverse event and has been evaluated in the IMS Disease Analyser MediPlus containing observational healthcare data from the UK [87]. There are many other methods currently being developed for use in signal detection using EHR data [64, 88]; describing them all is beyond the scope of this review. It is clear, however, that the applicability and usefulness of various methods for signal detection in EHR will depend on specific type of analyses of interest, e.g. whether signal detection is done for pre-specified outcomes or for all possible outcomes.

Safety surveillance using EHR data is an emerging science still in its infancy and to date there are no signals identified in EHR that have been published in the literature. However, several studies evaluating various signal detection methods, as applied to EHR data, have shown that such methodologies perform well in the detection of previously known signals and, hence, may be useful in the identification of novel and previously undescribed signals [89–91]. Additionally, there is ongoing work with respect to substantiation of potential signals identified from EHR, using biomedical databases that provide plausible mechanisms that can explain identified drug-adverse event associations [92].

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6.1 Limitations

While EHR databases may provide a wealth of drug use information, there remain caveats in the interpretation of signals derived from mining EHR data. Since these data are not primarily intended for recording drug-related adverse events, potential associations are inferred outside the actual patient-physician encounter that leads to suspicion of an ADR—something that is inherent in SRS. Data mining methods that filter out alternative explanations for these associations (by controlling for bias and confounding) attempt to simulate the causality assessment performed by reporting physicians. The literature is replete with discussions on the merits and challenges of the secondary use of EHR, including how the type of database influences the structure and content of the data [58, 93]. Data in medical record databases are recorded in the course of clinical care and hence take a healthcare practitioner's view of what is going on with a patient. On the other hand, claims data- bases document information as a byproduct of fiscal transactions, and therefore provide an auditor's view of healthcare data, and coding of outcomes can be biased by differences (real or perceived) in reimbursement. Data derived from HMOs or social security systems could be affected by a lack of incentive to record sufficient data to allow proper case classification. Billing and reimbursement of claims for hospitalization is based on patients' diagnoses as coded according to diagnosis-related groups (DRG), for example, and one study has shown that there are differences in the classification and coding of diagnoses originally assigned by the physician and the hospital administration [94]. Drug use patterns derived from 'real- world' healthcare data are influenced by changes in clinical practice, including changes brought about by preferential prescribing and disease management guidelines, and may lead to underestimation of risks. It has been shown that even with large multi-country databases, the capability for signal detection may be low for drugs that are infrequently used and for very rare outcomes—situations wherein other surveillance systems, such as SRS and PEM, may provide better benefits [95]. Furthermore, before an EHR database is used for signal detection purposes, the decision makers should already anticipate the question of what happens if and when a signal is detected and whether the same data- base can be used for hypothesis confirmation studies related to the signal identified. Clarifying beforehand the options for further use of the data in such an event becomes imperative.

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7 How Signal Detection Using EHR Data Fits into the Big Picture

To better understand what could be the niche of EHR data in safety surveillance, we examined the nature and characteristics of safety signals triggering withdrawal of drugs from the market, particularly the type of data that provide the basis for these withdrawals. In Table 3 we give a summary of the drugs that have been withdrawn from the market for safety reasons in the US and the EU within the last 10 years. The year when the drug was initially marketed and the corresponding year when the drug was withdrawn, as well as the reason for the withdrawal, are shown. Of the 25 safety-based withdrawals in the US or the EU, ten (40 %) were for adverse cardiovascular events and seven (28 %) were for gastrointestinal, primarily hepatic, adverse events. Drugs acting on the gastrointestinal system comprised the majority (28 %, 7 out of 25) of all drugs withdrawn, while drugs acting on the neuropsychiatric and musculoskeletal systems each comprised 20 % (five drugs) and 17 % (four drugs), respectively. Eleven out of the 25 drugs (44 %) were withdrawn from both the US and EU markets. There are two drugs (trovafloxacin and rosiglitazone) that have been removed from the EU market, but remain available in the US with restrictions or black-box warnings [96, 97]. Likewise, there are two other drugs (natalizumab and pergolide) that have been withdrawn from the US, but are still marketed in the EU with labelling changes and additional risk minimization activities [98, 99]. We further describe in Fig. 1 the characteristics of these safety-based withdrawals in terms of background frequency [100], latency or temporality [101], type of ADR [101, 102] and source of information used as the basis for the withdrawal. Details on these drug withdrawals, including the sources of information used in Table 3 and Fig. 1, are given in Appendix 1 (Online Resource 1).

Figure 1 Characteristics of drug safety withdrawals in the last 10 years

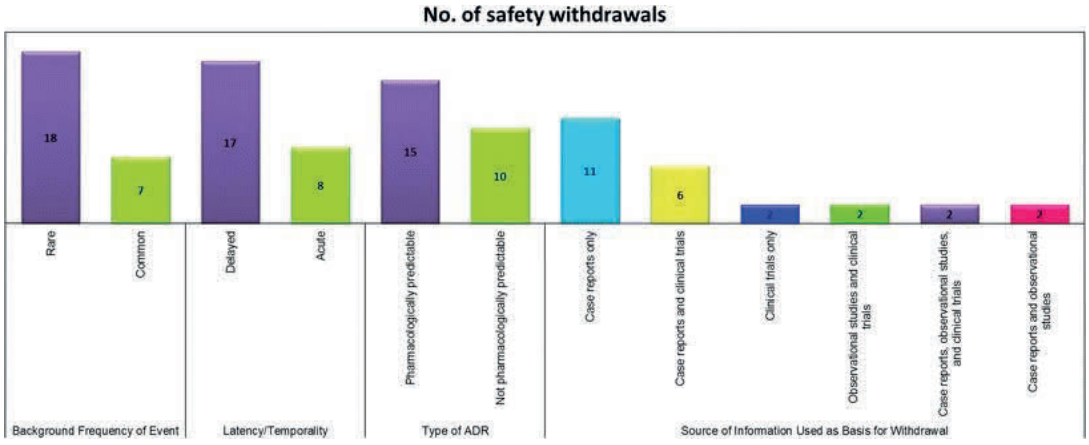

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Table 3 Drugs withdrawn from the market for safety reasons in the last 10 years in the US/EUa

Drug (trade name)	Year initially marketed (US/EU)	Year withdrawn (US/EU)	Reason for withdrawal
Cisapride (Propulsid®)	1993/1988	2000/2000 (UK) [EU—restricted indications only]	Fatal arrhythmia
Troglitazone (Rezulin®)	1997/1997 (not centrally authorized)	2000/1997 (UK)	Liver toxicity
Alosetron (Lotronex®)	2000/not marketed in the EU	2000; reintroduced in 2002 on a restricted basis	Ischaemic colitis, severe constipation
Trovafloxacin (Trovan®, Turvel®)	1998/1998	Still available in the US but with restrictions/2001	Liver toxicity
Cerivastatin (Baycol®)	1997/2001	2001/2001(UK), 2002 (EU)	Muscle damage leading to kidney failure
Rapacuronium (Raplon™)	1999/not marketed in the EU	2001	Severe bronchospasm
Etretinate (Tegison®)	1986/1983	2002/?	Birth defects
Levomethadyl (Orlaam®)	1993/1997	2003/2001	Fatal arrhythmia
Rofecoxib (Vioxx®)	1999/1999	2004/2004	Cardiovascular events (including myocardial infarction and stroke)
Valdecoxib (Bextra®)	2001/2003	2005/2005	Serious skin reactions (TENS, SJS, EM)
Thioridazine (Mellaril®)	1958	2005 (generic forms remain available in some countries, including the US)	Cardiac arrhythmias
Natalizumab (Tysabri®)	2004/2006	2005/still marketed, with additional risk management	Progressive multifocal leukoencephalopathy
Technetium fanolesomab (NeutroSpec™)	2004/not marketed in the EU	2005	Cardiopulmonary failure (respiratory distress, sudden hypotension)
Pemoline (Cylert®)	1975/1960s	2005/1997 (UK)	Liver failure

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Drug (trade name)	Year initially marketed (US/EU)	Year withdrawn (US/EU)	Reason for withdrawal
Ximelagatran (Exanta™)	2004—refused by the FDA/2003 (France; not centrally authorized)	2006	Liver toxicity
Pergolide (Permax®)	1988/1991	2007/still marketed with labelling changes	Cardiac valve damage
Tegaserod (Zelnorm®)	2002/2005—authorization refused	2007	Cardiovascular events (including myocardial infarction and stroke)
Lumiracoxib (Prexige®)	2003 and 2007—refused by the FDA/2005	2007	Liver toxicity, cardiovascular events
Aprotinin (Trasylol™)	1993/1974	2008/2007	Renal and cardiac complications, death
Efalizumab (Raptiva®)	2003/2004	2009/2009	Progressive multifocal leukoencephalopathy
Sibutramine (Meridia®)	1997/1999	2010/2010	Cardiovascular events (including heart attack and stroke)
Gemtuzumab ozogamicin (Mylotarg®)	2000/2007—authorization refused	2010	Lack of efficacy, increased risk of death (due to liver toxicity/veno-occlusive disease)
Propoxyphene (Darvon®, Darvocet®)	1957/1960s	2010/2009 (2005—UK, Sweden) [US]	Cardiac arrhythmia
Rimonabant (Acomplia®, Zimulti®)	Not marketed in the US/2006	2009	Psychiatric problems, including depression and suicide
Rosiglitazone (Avandia®)	1999/2000	Still marketed, but with black-box warning/2010 (suspended)	Cardiovascular events, including congestive heart failure, myocardial infarction and stroke

1. *EM* Erythema multiforme, *SJS* Stevens-Johnson Syndrome, *TENS* toxic epidermal necrolysis
2. [a]Details, including references, are given in Appendix 1 (Online Resource 1)

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It is apparent from Fig. 1 that the majority of safety- based withdrawals concern rare events that have a delayed onset and that cannot be predicted based on known pharmacological action. It is also clear that spontaneous reports have been an important resource contributing to the decision to take regulatory action, case reports (both published and unpublished) being the primary source of information in 11 of the 25 withdrawals (44 %). In two instances (8 %), clinical trials were the sole source of the safety information, but for the rest of the withdrawals a combination of case reports and/or clinical trials and/or observational studies contributed to the regulatory action. While all these data resources remain important and indispensable for safety surveillance, there remain gaps that may be filled by observational data derived from safety surveillance using EHR. Potential risk associated with drug use needs to be measured both in terms of risk to the individual and the population frequency, which requires knowledge of the level and duration of exposure. The longitudinal nature of routinely- collected EHR data may allow identification of adverse events that have a long delay between exposure and clinical manifestations (e.g. cardiac valvulopathy or cancer), especially in databases with long patient follow-up and low turnover. While most spontaneous reports usually involve newly marketed drugs, EHR data may be able to highlight new risks associated with old drugs (as a consequence of new indications of use or new generation of users), as well as adverse events that have high background incidence rates (such as acute myocardial infarction) and events that are not pharmacologically predictable and less likely to be suspected as drug-induced, thus less likely to be reported. Data from EHR further provide greater detail regarding patient demographics, drug use and utilization of healthcare services which permit evaluation of the benefit- risk profile of drugs, hence putting safety issues in a broader perspective and fostering sound regulatory decisions.

Clearly, regulatory decision making is a complex process and is based on more data than what are readily available from published medical literature [103]. From a regulatory perspective, would-be consequences might not allow delaying decisions until all the information is available, especially if this is the kind of information that only a definitive clinical study can provide. At times, the decision to intervene before knowledge is complete becomes imperative in order to avoid potentially harmful consequences. At the same time, the balance of the benefit-to-risk ratio still remains an important factor in the decision to withdraw a drug from the market. While it is often safety concerns about the use of a drug that draw attention, the availability of viable alternative treatments and the impact the withdrawal of such a drug would have on patients are equally important issues to consider [104]. Signal detection using EHR can complement and augment already existing SRS-based signal detection activities and vice-versa. Potential signals initially identified from spontaneous reports can be independently confirmed, refuted or further investigated using time-stamped, population-based health- care data. Some preliminary work has been done in this direction and will serve to benefit both SRS and EHR safety surveillance

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systems [105, 106]. Signal detection is only the initial step in the long and complex process of post-marketing safety surveillance. The evaluation of a signal may take years, from the earliest suspicion of a potential risk to an established mechanism of causation and fully understood phenomenon [107]. There remains the need to establish guidelines as to when and how to consider a signal likely to be substantial enough to warrant follow- up and verification using formal pharmacoepidemiological studies.

8 Conclusion

Initiatives exploring EHR-based signal detection systems are intended to complement, not replace, existing drug safety surveillance systems. Signal detection—whether using EHR databases or otherwise—is, by definition, exploratory. Every signal demands further investigation and the goal of any surveillance system should be to make judicious use of available healthcare data to highlight potential safety problems earlier. Identification and elucidation of drug safety signals is both an iterative and dynamic process. It is in the best interest of public health to integrate, and understand, evidence from all possibly relevant information sources on drug safety.

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Appendix 1. Characteristics of drugs withdrawn from the market in the US and EU for safety reasons

Drug	Reason for withdrawal	Source of information used as basis for withdrawal	Background Frequency	Latency/ Temporality	Type of ADR
Cisapride[1-6] (*Propulsid*®)	Fatal arrhythmia	Case reports	rare	acute	Pharmacologically predictable
Troglitazone[6-9] (*Rezulin*®)	Liver toxicity	Case reports, clinical trial data	rare	delayed	Not pharmacologically predictable
Alosetron[6, 10-11] (*Lotronex*®)	Ischemic colitis, severe constipation	Case reports	rare	acute	Pharmacologically predictable
Trovafloxacin[6, 12-15] (*Trovan*®, *Turvel*®)	Liver toxicity	Case reports	rare	delayed	Not pharmacologically predictable
Cerivastatin[5-6, 16-18] (*Baycol*®)	Muscle damage leading to kidney failure	Case reports	rare	acute, may be delayed	Pharmacologically predictable
Rapacuronium[5-6, 19-22] (*Raplon*^{TM})	Severe bronchospasm	Case reports	common	acute	Pharmacologically predictable
Etretinate[6, 23-26] (*Tegison*®)	Birth defects	Case reports	rare	delayed	Pharmacologically predictable
Levomethadyl[6, 27-29] (*Orlaam*®)	Fatal arrhythmia	Case reports	rare	acute	Pharmacologically predictable
Rofecoxib[5-6, 30-32] (*Vioxx*®)	Cardiovascular events (including myocardial infarction and stroke)	Clinical trial data	common	delayed (prolonged use)	Pharmacologically predictable
Valdecoxib[5-6, 33-35] (*Bextra*®)	Serious skin reactions	Case reports, clinical trial data	rare	acute, delayed	Not pharmacologically predictable
Thioridazine[6, 36-39] (Mellaril®)	Cardiac arrhythmias	Observational studies, case reports	rare	acute	Pharmacologically predictable

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Drug	Reason for withdrawal	Source of information used as basis for withdrawal	Background Frequency	Latency/ Temporality	Type of ADR
Natalizumab[5-6, 40-43] (*Tysabri*®)	Progressive multifocal leukoencephalopathy	Observational studies, case reports, clinical trial data	rare	delayed/ chronic	Not pharmacologically predictable
Technetium fanolesomab[5-6, 44] (*NeutroSpec*^{TM})	Cardiopulmonary failure (respiratory distress, sudden hypotension)	Case reports	common	acute	Not pharmacologically predictable
Pemoline[5-6, 45-48] (*Cylert*®)	Liver toxicity	Case reports	rare	delayed	Not pharmacologically predictable
Ximelagatran[6, 49-51] (*Exanta*^{TM})	Liver toxicity	Case reports	rare	delayed	Not pharmacologically predictable
Pergolide[6, 52-56] (*Permax*®)	Cardiac valve damage	Observational studies, case reports	rare	chronic	Pharmacologically predictable
Tegaserod[6, 57-59] (*Zelnorm*®)	Cardiovascular events (including myocardial infarction and stroke)	Case reports, clinical trial data	common	delayed (prolonged use)	Pharmacologically predictable
Lumiracoxib[6, 60-62] (Prexige®)	Liver toxicity, cardiovascular events	Case reports	rare	delayed	Not pharmacologically predictable
Aprotinin[6, 63-65] (TrasylolTM)	Renal and cardiac complications, death	Observational studies, clinical trials	common	acute	Pharmacologically predictable
Efalizumab[6, 66-70] (Raptiva®)	Progressive multifocal leukoencephalopathy	Case reports, clinical trials	rare	delayed/ chronic	Not pharmacologically predictable
Sibutramine[6, 71-74] (Meridia®, Reductil®)	Cardiovascular events (including myocardial infarction and stroke)	Case reports, clinical trials	common	delayed (prolonged use)	Pharmacologically predictable
Gemtuzumab ozogamicin[6, 75-78] (Mylotarg®)	Lack of efficacy, increased risk of death (due to liver toxicity/ veno- occlusive disease)	Clinical trial data	rare	delayed	Not pharmacologically predictable

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Drug	Reason for withdrawal	Source of information used as basis for withdrawal	Background Frequency	Latency/ Temporality	Type of ADR
Propoxyphene[6, 79-82] (Darvon®, Darvocet®)	Cardiac arrhythmia	Observational studies, clinical trial data, case reports	rare	acute	Pharmacologically predictable
Rimonabant[6, 83-86] (Acomplia®, Zimulti®)	Psychiatric problems (including depression and suicide)	Case reports, clinical trial data	rare	delayed	Pharmacologically predictable
Rosiglitazone[6, 87-92] (Avandia®)	Cardiovascular events (including congestive heart failure, myocardial infarction, and stroke)	Observational studies, clinical trials/meta-analyses	rare	delayed	Pharmacologically predictable

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Chapter 3

EU-ADR healthcare database network vs. spontaneous reporting system database: preliminary comparison of signal detection

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Abstract

The EU-ADR project aims to exploit different European electronic healthcare records (EHR) databases for drug safety signal detection. In this paper we report the preliminary results concerning the comparison of signal detection between EU-ADR network and two spontaneous reporting databases, the Food and Drug Administration and World Health Organization databases. EU-ADR data sources consist of eight databases in four countries (Denmark, Italy, Netherlands, and United Kingdom) that are virtually linked through distributed data network. A custom-built software (Jerboa©) elaborates harmonized input data that are produced locally and generates aggregated data which are then stored in a central repository. Those data are subsequently analyzed through different statistics (i.e. Longitudinal Gamma Poisson Shrinker). As potential signals, all the drugs that are associated to six events of interest (bullous eruptions - BE, acute renal failure - ARF, acute myocardial infarction - AMI, anaphylactic shock- AS, rhabdomyolysis - RHABD, and upper gastrointestinal bleeding - UGIB) have been detected via different data mining techniques in the two systems. Subsequently a comparison concerning the number of drugs that could be investigated and the potential signals detected for each event in the spontaneous reporting systems (SRSs) and EU-ADR network was made. SRSs could explore, as potential signals, a larger number of drugs for the six events, in comparison to EU-ADR (range: 630-3,393 vs. 87-856), particularly for those events commonly thought to be potentially drug- induced (i.e. BE: 3,393 vs. 228). The highest proportion of signals detected in SRSs was found for BE, ARF and AS, while for ARF, and UGIB in EU-ADR. In conclusion, it seems that EU-ADR longitudinal database network may complement traditional spontaneous reporting system for signal detection, especially for those adverse events that are frequent in general population and are not commonly thought to be drug-induced. The methodology for signal detection in EU-ADR is still under development and testing phase.

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Introduction

World Health Organization defines a drug safety signal as information on a possible causal relationship between an adverse event and a drug, which is unknown or incompletely documented [1]. Historically, spontaneous reporting systems (SRSs) for adverse drug reactions (ADRs) have been the cornerstone of signal detection in pharmacovigilance for the last four decades [2]. Cerivastatin and more recently rofecoxib stories highlighted the limitations of spontaneous reporting system with respect to the early detection of ADRs. The increasing availability of electronic healthcare records (EHRs) offers opportunities to investigate a wide spectrum of adverse drug effects and to detect signals closer to real time [3]. EHR databases present the additional advantage of large populations and long follow-up periods. A number of data mining techniques have been specifically developed for automatic detection of drug safety signals [2]. Currently, a number of ongoing international initiatives (SENTINEL [4], EU-ADR [5], PROTECT [6], and OMOP [7]) are aimed at testing the potential of signal detection using longitudinal electronic health record databases.

The EU-ADR (Exploring and Understanding Adverse Drug Reactions by integrative mining of clinical records and biomedical knowledge) project was funded by the European Commission and started in February 2008. The overall objective of the project was 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 led to the federation of different databases of EHRs, 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 is followed by signal substantiation through causal reasoning, semantic mining of literature, and computational analysis of pharmacological and biological information, all with the aim of finding possible pathways that explain the drug-event associations.

As regard to signal generation, in the EU-ADR project an event-based approach was adopted. A set of events warranting priority for monitoring in pharmacovigilance have been selected and inspected for their association with all possible drugs [8].

In this paper we describe the preliminary results of the comparison between EU-ADR healthcare network and two spontaneous reporting systems databases (Food and Drug Administration - Adverse Event Reporting System (FDA-AERS) and World Health Organization (WHO) Vigibase). As potential signal in the two systems, for the preliminary analyses we considered all the drugs being associated with the following six events that are deemed to be important in pharmacovigilance: Upper Gastrointestinal Bleeding (UGIB), Anaphylactic Shock (AS), Acute Myocardial Infarction (AMI), Rhabdomyolysis (RHABD), Acute Renal Failure (ARF) and Bullous Eruption (BE).

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1. Methods

1.1. Signal Detection in EU-ADR

The EU-ADR database network currently comprises of anonymized healthcare data from eight established European databases located in four countries: Health-Search (HSD, Italy). Integrated Primary Care Information (IPCI, Netherlands), Pedianet (Italy) and QResearch (United Kingdom) are general practice (GP) databases, while Aarhus University Hospital Database (Denmark), PHARMO (Netherlands), and the regional Italian databases of Lombardy and Tuscany are all comprehensive record-linkage systems in which drug dispensing data of a well-defined population is linked to a registry of hospital discharge diagnoses and other medical registries.

Due to the difference in coding schemes across various databases, the Unified Medical Language System (UMLS) was initially used as the terminology to define the events of interest [9]. Subsequently projection of the selected UMLS concept into different terminologies (i.e. READ, ICD9-CM, ICD10, and ICPC) was carried out.

In the EU-ADR project we adopted a distributed network approach that requires standardization of input files from the different databases. These input files (patient, drug, and event files) have been created locally by each database owner and have been subsequently elaborated through the purpose-built software called Jerboa© [10]. The software queries patient-level data in the different databases, which is later aggregated, and sent in encrypted format to a central repository for further analyses. For the analysis described in this paper, data from 1996 till 2010 has been contributed from six databases (QResearch and UNIMIB databases could not contribute data for this analysis). Several statistics were generated to detect all the associations between all the covered drugs and the six events of interest. Currently, the Longitudinal Gamma Poisson Shrinker (LGPS) posterior expectation of the incidence rate ratio higher than 2 and p-value<0.05 are the criteria that have been considered to distinguish between potential signals and non-signals [11]. The LGPS is a modification of the GPS method used in some spontaneous reporting system databases. These statistical approaches apply shrinkage to the frequentist estimates to reduce the chance of a false positive result. For the incidence rate ratios exposed time was compared with all non-exposed time including time exposed to other drugs. Based on empirically determined background incidence rates, for each event the minimum required amount of exposure was determined and the drugs not reaching this threshold were not tested as potential signals.

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1.2. Signal Detection in FDA-AERS and WHO

Food and Drug Administration (FDA) - Adverse Event Reporting System (AERS) and World Health Organization (WHO) spontaneous reporting databases have been used as comparators. The FDA-AERS database is a computerized spontaneous reporting database that was established in 1969 to support the FDA's post-marketing safety surveillance program and currently contains over 4 million reports of suspected adverse drug reactions (ADRs). FDA-AERS collects most of its reports from the USA.

The WHO spontaneous report database (Vigibase) was established in 1968 and is maintained by the Uppsala Monitoring Centre (UMC) [12]. VigiBase contains at the moment more than 4 million reports of suspected ADRs that are sent from the national centers of 95 countries participating in the WHO Programme for International Drug Monitoring.

Both databases collect reports from marketing authorization holders, healthcare professionals and consumers. Overlapping of the collected report in the two databases is present. The suspected adverse drug reactions are coded using the Medical Dictionary for Regulatory Activities (MedDRA). All the Preferred Terms (PTs) of MedDRA corresponding to the six events have been used.

As regard the drug coding, an internal mapping between the generic name and the ATC code has been created. A disproportionality analysis was performed using the above-mentioned PTs and the drug-ATC mapping in FDA-AERS and WHO database from the beginning (1968-9) through the 3Q2010 data. Empirical Bayes Geometric Mean (EBGM) was used to detect signals. A threshold of EB05>2 (with number of reports>0) was applied, with EB05 being the lower band of 95% Confidence Interval of EBGM [13].

As preliminary comparison for signal detection in SRSs and EU-ADR, for each of the six events we calculated the number of drugs that could be investigated, and we identified the potential signals. The number of drugs that can be investigated depends on the presence of at least one report of suspected ADR in spontaneous reporting databases and on the presence of at least one exposed case patient (i.e. patients exposed to the drug when the event occurred) in the EU-ADR database network.

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Table 1. Overview of signal detection in FDA-AERS and EU-ADR for the six events under consideration.

	Spontaneous reporting databases				EU-ADR		
	FDA-AERS		WHO VigiBase				
Event	**N. of drugs that could be studied**	**Potential signals N (%)**	**N. of drugs that could be studied**	**Potential signals N (%)**	**N. of drugs that could be studied**	**Potential signals N (%)**	**Potential signals in both systems, N**
Acute myocardial infarction	791	38 (4.8)	630	37 (5.9)	856	143 (16.7)	6
Acute renal failure	2,626	354 (13.5)	3,002	302 (10.1)	461	171 (37.1)	40
Anaphylactic shock	1,443	144 (10.0)	2,679	269 (10.0)	265	47 (17.7)	13
Bullous eruption	2,053	289 (14.1)	3,393	225 (6.6)	228	42 (18.4)	13
Rhabdomyolysis	1,302	94 (7.2)	1,164	51 (4.4)	87	30 (34.5)	3
Upper GI bleeding	1,937	115 (5.9)	2,419	175 (7.2)	695	218 (31.4)	31

Legend: *N. of drugs that could be studied*=number of drugs that could be investigated as potential signals, which depends on the presence of at least one report of suspected adverse drug reactions in FDA-AERS and on at least one exposed case patient in EU-ADR. *Potential signal:* statistically significant association between drug and event, based on specific analyses as described in paragraphs 1.1 and 1.2.

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2. Results

Table 1 shows for each event the number of drugs that could be tested as potential signals and the number of signals being detected in the two spontaneous reporting databases and the EU-ADR system. The unit of analysis for signals is represented by single drug-event association. Overall, spontaneous reporting systems could explore, as potential signals, a larger number of drugs in association with the six events under study, in comparison to EU-ADR (range: 630-3,393 vs. 87-856). This difference was even higher for the events that are thought to be potentially drug- induced (i.e. BE: 2,053 in FDA and 3,393 in WHO vs. 228 in EU-ADR; ARF: 2,626 in FDA and 3,002 in WHO vs. 461 in EU-ADR). On the contrary, concerning the analysis for AMI a larger number of drugs could be investigated in EU-ADR (856) than SRSs (791 in FDA and 630 in WHO).

Overall, higher proportion of potential signals is detected in EU-ADR as compared to SRSs (17-37% vs. 5-14%). For the signal generation new methodologies are currently under development in EU-ADR. The potential for signal detection in both EU-ADR and spontaneous reporting systems varies across events. The highest proportion of signals detected in SRSs was reported for BE, ARF and AS, while for ARF, UGIB and RHABD (for this event however a very low number of drugs could be tested) in EU-ADR.

3. Conclusion

The potential of EU-ADR database network for drug safety signal detection is promising particularly for those adverse events that have high frequency (i.e. acute myocardial infarction) in general population. Data mining of longitudinal electronic medical records may particularly complement traditional analyses on spontaneous reporting systems in the signal detection, especially for those frequent adverse events that are not traditionally thought to be drug induced. The implementation of additional analyses in the EU-ADR system is still ongoing. In the final EU-ADR system, a panel of statistical analyses will allow a greater precision of signal detection. In addition, automatic search in the scientific literature and summary of product characteristics will filter out the already known signals among those being initially identified in EU-ADR. On the other hand, signals will be substantiated by a computer-assisted exploration of biological plausibility in the context of current biomedical knowledge to reduce the false positive signals.

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Chapter 4

Evaluating performance of electronic healthcare records and spontaneous reporting data in drug safety signal detection

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Abstract

Background

Electronic reporting and processing of suspected adverse drug reactions (ADRs) is increasing and has facilitated automated screening procedures. It is crucial for healthcare professionals to understand the nature and proper use of data available in pharmacovigilance practice. Objectives To (a) compare performance of EU-ADR [electronic healthcare record (EHR) exemplar] and FAERS [spontaneous reporting system (SRS) exemplar] databases in detecting signals using ‘‘positive’’ and ‘‘negative’’ drug-event reference sets; and (b) evaluate the impact of timing bias on sensitivity thresholds by comparing all data to data restricted to the time before a warning/regulatory action.

Methods

Ten events with known positive and negative reference sets were selected. Signals were identified when respective statistics exceeded defined thresholds. Main outcome measure Performance metrics, including sensitivity, specificity, positive predictive value and accuracy were calculated. In addition, the effect of regulatory action on the performance of signal detection in each data source was evaluated.

Results

The sensitivity for detecting signals in EHR data varied depending on the nature of the adverse events and increased substantially if the analyses were restricted to the period preceding the first regulatory action. Across all events, using data from all years, a sensitivity of 45–73 % was observed for EU-ADR and 77 % for FAERS. The specificity was high and similar for EU-ADR (82– 96 %) and FAERS (98 %). EU-ADR data showed range of PPV (78–91 %) and accuracy (78–72%) and FAERS data yielded a PPV of 97 % with 88 % accuracy.

Conclusion

Using all cumulative data, signal detection in SRS data achieved higher specificity and sensitivity than EHR data. However, when data were restricted to time prior to a regulatory action, performance characteristics changed in a manner consistent with both the type of data and nature of the ADR. Further research focusing on prospective validation of is necessary to learn more about the performance and utility of these databases in modern pharmacovigilance practice.

Introduction

Access to real-world 'big data' is becoming easier for healthcare professionals. What is their utility to clinicians in pharmacovigilance (PV) practice? What confidence can be placed in these data as actionable and therefore valuable from a PV perspective? Answers to these questions require systematic interrogation of available data with corresponding assessment of performance. A new body of PV work is emerging, which, over time, will transform information into knowledge and provide better understanding of pharmaceutical product safety profiles, thereby protecting public health.

Regulatory agencies worldwide demand rigorous evaluation of safety data prior to approval of new prescription medications, but due to inherent limitations of clinical trials, the full safety profile of a product is not known prior to long-termuse in large populations [1–3]. Therefore, post-marketing data is collected and monitored to identify emerging safety issues [4– 6]. The process is called signal detection wherein a ''signal'' is defined as ''information that arises from one or multiple sources (including observations and experiments), which suggests a new potentially causal association, or a new aspect of a known association, between an intervention and an event or set of related events, either adverse or beneficial, that is judged to be of sufficient likelihood to justify verificatory action [7].'' In practice and by definition, this process is hypothesis-generating and entails further evaluation of relevant data [8].

Over the past decade, electronic reporting and processing of suspected adverse drug reactions (ADRs) has increased and has facilitated automated screening procedures. Focus has shifted from individual case assessment to analysis of aggregate data which are compiled into spontaneous reporting systems (SRS). Computerized data mining techniques are one way to detect safety signals [9]. Globally, the two most widely used SRS databases are the United States (US) Food and Drug Administration's (FDA) Adverse Event Reporting System (FAERS) [10, 11], and the World Health Organization's (WHO) VigiBase^{TM} [12, 13]. Despite the clear value of such aggregate data, SRS data are known to be incomplete, under/ over-reported or selectively reported [7, 14, 15]. Moreover, information on total patient exposure (i.e., ''background'' or ''denominator'') is usually inadequate.

To overcome some of these shortcomings, electronic health records (EHRs) are being explored as a data source for signal detection [16–18]. Ongoing initiatives include: US FDA's Sentinel Initiative [19], the Observational Medical Outcomes Partnership (OMOP) [20, 21], the ''Pharmacoepidemiological Research on Outcomes of Therapeutics by a European Consortium''

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(PROTECT) project, and the ‘‘Exploring and Understanding Adverse Drug Reactions by integrative mining of clinical records and biomedical knowledge’’ (EU-ADR) project [22].

FAERS and EU-ADR databases were chosen for this study as SRS and EHR exemplars, respectively. The use of FAERS is long-standing (dates to 1969) and well-documented. The relatively new EU-ADR project (2008–2013), networks several clinical databases located in four countries, and has the goal ‘‘to develop an innovative computerized system to detect adverse drug reactions (ADRs), supplementing spontaneous reporting systems’’.

Since SRS cases are known to be reported more frequently by consumers, lawyers, and healthcare professionals following action from a regulatory agency [23], and EHR data can be affected by risk minimization measures that often influence prescribing practices (e.g., safety warnings, health policy interventions), an impact analysis was conducted.

Aim of the study

The specific objectives of this study are to (a) compare performance of EU-ADR (EHR exemplar) and FAERS (SRS exemplar) databases in detecting signals using pre- defined ‘‘positive’’ and ‘‘negative’’ drug-event reference sets (respectively, ‘‘positive samples/sets’’ and ‘‘negative samples/sets’’); and (b) evaluate the impact of timing bias on sensitivity thresholds by comparing all data to data restricted to the time before a warning/regulatory action.

Methods

Design

Events warranting priority for PV monitoring were selected and evaluated for association with all marketed drugs. Positive and negative reference sets were then constructed using methodology previously described [24, 25]. Standard data mining algorithms were used to interrogate the two databases with thresholds set according to current PV practice (described below). Performance metrics include sensitivity, specificity, precision and accuracy, which were calculated for all results.

Positive reference sets were evaluated for suitability regarding timing bias. Seven were chosen for the data restriction analysis. Assuming regulatory action or media attention impacts reporting or prescribing behavior, statistical threshold sensitivity for both databases was assessed.

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Reference sets and impact analysis samples

Ten events were selected from 23 previously ranked by significance in pharmacovigilance and public health [24]. These events, Acute Liver Injury (ALI); Acute Myocardial Infarction (AMI); Acute Renal Failure (ARF); Anaphylactic Shock (AS); Bullous Eruption (BE); Cardiac Valve Fibrosis (CARDFIB); Neutropenia (NEUTROP); Pancytopenia (PANCYTOP); Rhabdomyolysis (RHABD); and Upper Gastrointestinal Bleeding (UGIB) represent a range of clinical course and combination of ADRs easily recognized due to known pharmacology (Type A) or relatively common idiosyncratic reactions (Type B).

For each event, drugs were defined ‘‘positive’’ if they were known from the literature, product labels, or Summary of Product Characteristics (SPC) to be associated with the event and drugs not known to be so associated were defined ‘‘negative.’’ For positives, MEDLINE citations naming the drug-event pair were reviewed. For negatives, there had to be no MEDLINE citations with co- occurrence of the drug-event pair and no explicit mention of such adverse event in the product label/SPC. Negative sets were further qualified using VigiBase to exclude associations flagged as potential signals. Sets were validated by two physicians proficient in clinical medicine, epidemiology and PV. A third expert arbitrated any differences. Forty-four positive and 50 negative sets were defined.

The impact of reporting timeframe on threshold sensitivities was conducted by selecting a subset of the positive samples that (1) had sufficient exposure data in EU-ADR [24]; and (2) were flagged as signals after the year 2000 (EU-ADR histories date to 1995). FAERS data were restricted using the date the reports were entered in the database. Start and end dates varied across each drug-event association, as they were dependent on time on market and date of first warning/regulatory action. Seven drug-event pairs were chosen: AMI/-Valdecoxib, Rosiglitazone, -Rofecoxib, ALI/Nimesulide, NEUTROP/Valproic Acid, PANCYTOP/Allopurinol and RHABD/Atorvastatin.

Databases

The EU-ADR network was chosen as the EHR exemplar and has follow-up data ranging from 1995 to 2010 on over 20 million patients [22]. Drug exposure was estimated using date of dispensing/prescription and delivery systems/ dosing regimen, according to characteristics of each data- base. Due to event coding heterogeneity, harmonization using Unified Medical Language System® (UMLS) concepts, related codes and labels corresponding to events of interest was

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conducted and database owners constructed queries for data extraction (‘‘Appendix 1 in Electronic supplementary material’’). Data were processed locally and then pooled utilizing Jerboa™ (accesses multiple health care databases without sharing identifiable data). Results were analyzed and harmonized, if necessary, by a team of experts (described by Avillach et al. [26]).

FAERS, containing over seven million reports at the time of this study, was chosen as the SRS exemplar. Events are coded using the Medical Dictionary for Regulatory Activities (MedDRA) with narratives excluded from the public version [27]. MedDRA, including Standardized MedDRA Queries (SMQs) version 11.1, was reviewed to identify terms corresponding to UMLS concepts. For events lacking SMQs, custom groupings of MedDRA terms were defined per UMLS concept (‘‘Appendix 1 in Electronic supplementary material’’).

Signal generation

For the EU-ADR database, the Longitudinal Gamma Poisson Shrinker (LGPS), the posterior expectation of the incidence rate ratio [relative risk (RR)-LGPS] was estimated for each drug-event pair. RR-LGPS>= 2 (p value < 0.05) defined a signal, except when the ‘‘Longitudinal Evaluation of Observational Profiles of Adverse events Related to Drugs’’ (LEOPARD) method identified such as potentially due to protopathic bias. Given the absence of validated thresholds in the EHR data, and the relative novelty of this approach, a second threshold of RR-LGPS >=1.5 (p value <0.05) was included in the analysis [28].

FAERS analyses were conducted on data up to and including 2Q2010 using Oracle Empirica™ Signal (Waltham, MA). The Gamma Poisson Shrinker (GPS) was used to compute EB05 (Empirical Bayes posterior Gamma Mixture 5th percentile; estimates lower point in 90 % confidence interval). A threshold of EB05 >=2 (p value <0.05) was selected based on extensive use and validation in PV practice [9].

Analysis

Signal detection sensitivity (i.e., true positive rate) was defined as the ability to detect (i.e., rediscover) positive reference samples (i.e., ‘‘true positives’’) and specificity as the absence of a signal for negative reference samples (i.e., ‘‘true negatives’’). Sensitivity was calculated by dividing the number of ‘‘rediscovered’’ positives by all positives in the reference set. Specificity (i.e., true negative rate) was calculated by dividing the number of negatives not detected by all negatives in the reference set.

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Figure 1: Derivation of performance metric calculations used in this study

Signal Detection in Test Database	Event-Drug Constructs (Reference Sets)	
	Positive Samples	Negative Samples
SDR Positive Result	(a) True Positive	(b) False Positive
SDR Negative Result	(c) False Negative	(d) True Negative

$$\text{Sensitivity} = \frac{\text{\# of True Positives}}{\text{Total \# of Positive Samples}} = \frac{a}{(a + c)}$$

$$\text{Specificity} = \frac{\text{\# of True Negatives}}{\text{Total \# of Negative Samples}} = \frac{d}{(b + d)}$$

$$\text{Precision} = \frac{\text{\# of True Positives}}{\text{Total \# of True Positives + False Positives}} = \frac{a}{(a + b)}$$

$$\text{Accuracy} = \frac{\text{Total \# of True Positives + True Negatives}}{\text{Total \# of Positive + Negative Samples}} = \frac{(a + d)}{(a + b + c + d)}$$

For evaluation of the diagnostic power or efficiency of the databases under study, precision or positive predictive value (PPV) and accuracy were also calculated. PPV was calculated by dividing the number of true positives by the total number of signals (i.e., true positives and false negatives). Accuracy was calculated by dividing the sum of true positives and true negatives by the sum of positive and negative reference samples. All four performance metrics, described in Fig. 1, were calculated for each drug-event pair in both databases.

As noted, SRS case reporting often increases after media attention/regulatory action and EHR data are affected by changes in prescribing practices. Since this study focused on retrospective analyses, the effect of these phenomena was evaluated by comparing data restricted to the years preceding first warning/regulatory action date with data from all years. RR-LGPS >=2 and EB05 >=2 values from both periods were compared within the respective databases.

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Results

Positive and negative reference sets are listed in Table 1. The presence (‘‘YES’’) or absence (‘‘No’’) of a signal is indicated for each drug-event combination. All performance metrics across the ten event categories are reported in Table 2. In aggregate across all events, the lower threshold in EU-ADR data increased sensitivity (RR-LGPS >=1.5, 73 % vs. RR-LGPS >=2, 45 %) and decreased specificity (RR-LGPS >=1.5, 82 %; RR-LGPS >=2, 96 %). When observed individually, RR-LGPS >=2.0 failed to detect 4 of 5 positive samples for ALI, AMI, AS and PANCYTOP (i.e., false negative rate is high); lowering the threshold to 1.5 ‘‘rescued’’ all but AS. The EB05 >=2 used for FAERS data yielded overall sensitivity 77 % and specificity 98 % (failed to detect 3 of 5 positive samples for both NEUTRO and AS).

Conversely, specificity using the same parameters was relatively high across all negative reference events. An EU- ADR threshold of RR-LGPS >=1.5 yielded a relatively high false positive rate (9 of 50; 1 each of 5 for ALI, BE and UGIB, and 3 each of 5 for ARF and RHABD). False positives dropped to 2 of 50 (both for ARF) with threshold of 2.0; FAERS analysis yielded 1 false positive among the 50 negative reference samples (ARF).

For each of the event groups, positive predictive value (PPV) and accuracy were also calculated. EU-ADR data showed RR-LGPS >=1.5 to RR-LGPS >=2.0 range of PPV (78 vs. 91 %) and accuracy (78 vs. 72 %), respectively. On the other hand, FAERS data yielded a PPV of 97 % with 88 % accuracy.

Signal detection results for selected positive samples comparing data from all years (yellow circles) to data restricted to the time before a regulatory action date (red circles) are shown in Fig. 2. In EU-ADR data from all years, RR-LGPS >=2.0 missed four of seven positives (i.e., false negatives); RR-LGPS >=1.5 missed only one. When data were restricted to before a regulatory action, six of seven were detected with RR-LGPS >=2, and all seven with RR-LGPS >=1.5. The greatest change was observed in PANCYTOP/allopurinol sample (from 6.3 to 23.2).

An opposite trend was observed with FAERS data. For all years, six of seven positives were detected as signals with relatively high EB05 values. For five of these, with data restricted to before regulatory action, the EB05 values were just slightly over the standard threshold of 2. The exception to this trend was the RHABD/atorvastatin positive sample where EB05 value showed greater than twofold increase between using all data (11) to using restricted data (28.4). The one positive sample, NEUTROP/valproic acid was not reported at all in FAERS data restricted to before a regulatory action.

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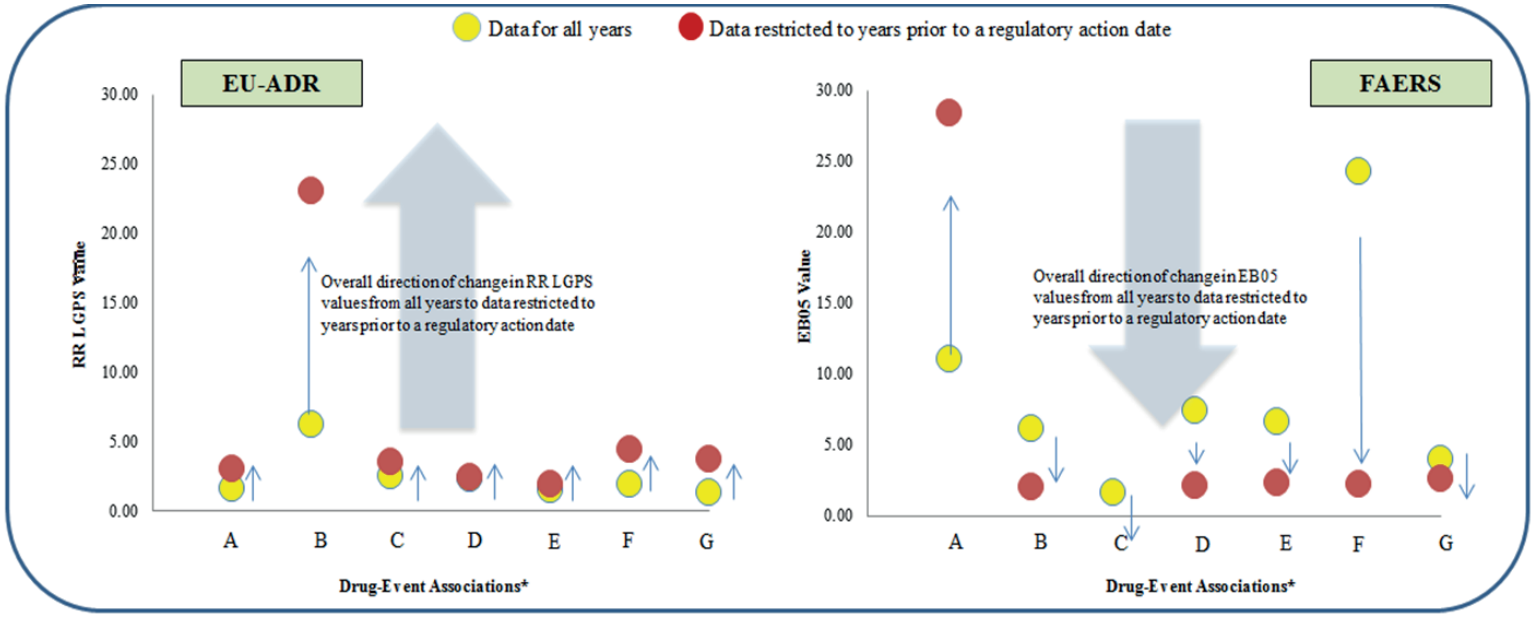
Figure 2: Signal detection results in the EU-ADR and FAERS databases using data from all years (yellow circles) versus data restricted to years prior to a regulatory action date (red circles).



Sample	Drug-Event Combination	EU-ADR data (RR-LGPS≥ 2.0)		FAERS data (EB05≥ 2.0)	
		All Years	Years before regulatory action	All Years	Years before regulatory action
A	RHABD-Atorvastatin	1.67	3.05	11.06	28.40
B	PANCYTOP-Allopurinol	6.27	23.15	6.12	2.04
C	NEUTROP-Valproic acid	2.59	3.52	1.66	
D	AMI-Valdecoxib	2.41	2.46	7.41	2.10
E	AMI-Rosiglitazone	1.55	1.95	6.66	2.36
F	AMI-Rofecoxib	1.92	4.46	24.29	2.19
G	ALI-Nimesulide	1.31	3.80	3.94	2.56

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Table 1: Positive and Negative Reference Sets with signal detection results from EU-ADR and FAERS analyses

Positive Reference Sets					Negative Reference Sets			
SDR in EU-ADR		SDR in FAERS EB05≥2	Drug(s)	Reference Event	Drug(s)	SDR in EU-ADR		SDR in FAERS EB05≥2
RR ≥1.5	RR ≥2					RR ≥1.5	RR ≥2	
YES	No	YES	Carbamazepine	Acute Liver Injury (ALI)	Formoterol	No	No	No
YES	No	YES	Valproic acid		Carteolol	No	No	No
No	No	YES	Nimesulide		Terazosin	No	No	No
YES	YES	YES	Amoxicillin and clavulanic acid		Levodopa and decarboxylase inhibitor	No	No	No
No	No	YES	Sulfasalazine		Glyceryl trinitrate	YES	No	No
YES	No	YES	Rofecoxib	Acute Myocardial Infarction (AMI)	Insulin (human)	No	No	No
YES	No	YES	Rosiglitazone		Ferrous sulfate	No	No	No
YES	No	No	Levonorgestrel and estrogen		Amoxicillin and enzyme inhibitor	No	No	No
No	No	No	Sumatriptan		Valaciclovir	No	No	No
YES	YES	YES	Valdecoxib		Gemfibrozil	No	No	No
YES	No	YES	Captopril	Acute Renal Failure (ARF)	Mometasone	No	No	No
YES	YES	YES	Ibuprofen		Levothyroxine sodium	YES	YES	No
YES	YES	No	Paracetamol		Fexofenadine	YES	YES	No
No	No	YES	Ciprofloxacin		Levodopa and decarboxylase inhibitor	YES	No	YES
YES	YES	YES	Lithium		Ferrous sulfate	No	No	No
No	No	No	Acetylsalicylic acid	Anaphylactic Shock (AS)	Mirtazapine	No	No	No
No	No	No	Paracetamol		Levothyroxine sodium	No	No	No
No	No	YES	Amoxicillin		Clonidine	No	No	No
No	No	No	Ciprofloxacin		Doxazosin	No	No	No
YES	YES	YES	Diclofenac		Oxazepam	No	No	No
YES	YES	YES	Carbamazepine	Bullous Eruption (BE)	Propafenone	No	No	No
YES	YES	YES	Sulfamethoxazole and trimethoprim		Atenolol	No	No	No
YES	YES	YES	Lamotrigine		Ipratropium bromide	No	No	No
YES	YES	YES	Allopurinol		Tiotropium bromide	YES	No	No
No	No	YES	Furosemide		Felodipine	No	No	No

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Table 1: Positive and Negative Reference Sets with signal detection results from EU-ADR and FAERS analyses (cont.)

Positive Reference Sets				Reference Event	Negative Reference Sets			
SDR in EU-ADR		SDR in FAERS EB05≥2	Drug(s)		Drug(s)	SDR in EU-ADR		SDR in FAERS EB05≥2
RR ≥1.5	RR ≥2					RR ≥1.5	RR ≥2	
No Positive References for CARDFIB			No drug with sufficient exposure satisfied criterion for True Positive	**Cardiac Valve Fibrosis (CARDFIB)**	Fluvoxamine	No	No	No
					Methotrexate	No	No	No
					Irbesartan	No	No	No
					Furosemide	No	No	No
					Estradiol	No	No	No
YES	YES	YES	Thiamazole	**Neutropenia (NEUTROP)**	Sotalol	No	No	No
YES	YES	YES	Ticlopidine		Levothyroxine sodium	No	No	No
No	No	No	Captopril		Atorvastatin	No	No	No
YES	No	No	Carbamazepine		Isosorbide Mononitrate	No	No	No
YES	YES	No	Valproic acid		Tamsulosin	No	No	No
YES	No	YES	Ticlopidine	**Pancytopenia (PANCYTOP)**	Irbesartan	No	No	No
YES	No	YES	Carbamazepine		Fluvastatin	No	No	No
YES	YES	YES	Thiamazole		Latanoprost	No	No	No
No	No	YES	Allopurinol		Timolol	No	No	No
YES	No	YES	Captopril		Desloratadine	No	No	No
No	No	YES	Rosuvastatin	**Rhabdo-myolysis (RHABD)**	Estradiol	No	No	No
YES	No	YES	Atorvastatin		Doxazosin	No	No	No
YES	YES	YES	Pravastatin		Glimepiride	YES	No	No
YES	YES	YES	Simvastatin		Timolol	YES	No	No
					Glyceryl trinitrate	YES	No	No
YES	No	No	Acetylsalicylic acid	**Upper Gastro-Intestinal Bleeding (UGIB)**	Fexofenadine	YES	No	No
YES	YES	YES	Indometacin		Simvastatin	No	No	No
YES	YES	YES	Heparin		Dorzolamide	No	No	No
YES	YES	YES	Prednisolone		Goserelin	No	No	No
YES	YES	YES	Ibuprofen		Zopiclone	No	No	No

''YES'' indicates that the drug-event association was found to be a signal; ''No'' indicates that no signal was found

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Table 2: Performance metrics of signal detection using data from EU-ADR and FAERS

EVENT	EU-ADR (RR-LGPS≥1.5)						EU-ADR (RR-LGPS≥2.0)					
	True Positive Score	True Negative Score	Sensitivity	Specificity	Positive Predictive Value	Accuracy	True Positive Score	True Negative Score	Sensitivity	Specificity	Positive Predictive Value	Accuracy
ALI	*3/5*	*4/5*	*60%*	*80%*	75%	70%	*1/5*	*5/5*	*20%*	*100%*	100%	60%
AMI	*4/5*	*5/5*	*80%*	*100%*	100%	90%	*1/5*	*5/5*	*20%*	*100%*	100%	60%
ARF	*4/5*	*2/5*	*80%*	*40%*	57%	60%	*3/5*	*3/5*	*60%*	*60%*	60%	60%
AS	*1/5*	*5/5*	*20%*	*100%*	100%	60%	*1/5*	*5/5*	*20%*	*100%*	100%	60%
BE	*4/5*	*4/5*	*80%*	*80%*	80%	80%	*4/5*	*5/5*	*80%*	*100%*	100%	90%
CARDFIB	*N/A*	*5/5*	*N/A*	*100%*	N/A	100%	*N/A*	*5/5*	*N/A*	*100%*	N/A	100%
NEUTRO	*4/5*	*5/5*	*80%*	*100%*	100%	90%	*3/5*	*5/5*	*60%*	*100%*	100%	80%
PANCYTOP	*4/5*	*5/5*	*80%*	*100%*	100%	90%	*1/5*	*5/5*	*20%*	*100%*	100%	60%
RHABD	*3/4*	*2/5*	*75%*	*40%*	50%	56%	*2/4*	*5/5*	*50%*	*100%*	100%	78%
UGIB	*5/5*	*4/5*	*100%*	*80%*	83%	90%	*4/5*	*5/5*	*80%*	*100%*	100%	90%
Overall Performance	*32/44*	*41/50*	*73%*	*82%*	78%	78%	*20/44*	*48/50*	*45%*	*96%*	91%	72%

N/A not applicable (no positive reference samples were identified)

ALI acute liver injury, AMI acute myocardial infarction, ARF Acute Renal Failure, AS anaphylactic shock, BE bullous eruption, CARDFIB cardiac valve fibrosis, NEUTRO neutropenia,PANCYTOP pancytopenia, RHABD rhabdomyolysis, UGIB upper gastrointestinal bleeding

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Table 2: Performance metrics of signal detection using data from EU-ADR and FAERS (cont.)

EVENT	FAERS (EB05≥2)					
	True Positive Score	True Negative Score	Sensitivity	Specificity	Positive Predictive Value	Accuracy
ALI	*5/5*	*5/5*	*100%*	*100%*	100%	100%
AMI	*3/5*	*5/5*	*60%*	*100%*	100%	80%
ARF	*4/5*	*4/5*	*80%*	*80%*	80%	80%
AS	*2/5*	*5/5*	*40%*	*100%*	100%	70%
BE	*5/5*	*5/5*	*100%*	*100%*	100%	100%
CARDFIB	*N/A*	*5/5*	*N/A*	*100%*	N/A	100%
NEUTRO	*2/5*	*5/5*	*40%*	*100%*	100%	70%
PANCYTOP	*5/5*	*5/5*	*100%*	*100%*	100%	100%
RHABD	*4/4*	*5/5*	*100%*	*100%*	100%	100%
UGIB	*4/5*	*5/5*	*80%*	*100%*	100%	90%
Overall Performance	*34/44*	*49/50*	*77%*	*98%*	97%	88%

N/A not applicable (no positive reference samples were identified)

ALI acute liver injury, AMI acute myocardial infarction, ARF Acute Renal Failure, AS anaphylactic shock, BE bullous eruption, CARDFIB cardiac valve fibrosis, NEUTRO neutropenia,PANCYTOP pancytopenia, RHABD rhabdomyolysis, UGIB upper gastrointestinal bleeding

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Discussion

This is the first study evaluating the signal detection diagnostic performance of an EHR exemplar (EU-ADR) as compared with that of an SRS exemplar (FAERS). In overall results, sensitivity was comparable with respective thresholds RR-LGPS >=1.5 and EB05 >=2. However, within EU-ADR data there was marked improvement of sensitivity with a lower threshold (45 % RR-LGPS >=2.0, vs. 73 % RR-LGPS >=1.5). Therefore, signal definition may need to be adapted (i.e., customized) based on prior evidence for strength of association and type of event (i.e., Type A reactions with known pharmacology may require a lower threshold than idiosyncratic Type B events). For example, rosiglitazone was suspended in the EU due to increased AMI risk; the strength of this association was below 2 in observational studies and meta-analysis of randomized clinical trials [29, 30]. In this analysis, AMI/ rosiglitazone was a false negative with RR-LGPS >=2.0 but was detected with RR-LGPS >=1.5.

The specificity of signal detection was very high and at similar levels for the EU-ADR threshold RR-LGPS >=2 (96 %) and FAERS (98 %). This finding is reassuring as one critical issue concerning drug safety signal detection using EHR databases is the false positive rate. Once again, however, consideration must be given to the type of event and the data source. Specificity was lower for RR-LGPS >=1.5 (82 %) versus 2.0 (96 %), but stratification with the lower threshold into Type A and B events showed marked contrast of 68 versus 95 % specificity, respectively (data not shown). PPV and accuracy performance metrics showed similar behaviors. Namely, there are strengths and weaknesses in both types of data regarding signal detection performance based on event type and warrants future and more extensive study.

Another factor that was suspected to be significant is the timeframe of analysis. The comparison of data from all years to years before a regulatory action had a notable impact on sensitivity in both data sources. In EU-ADR data, RR-LGPS values of all seven samples increased, when data was restricted to before a regulatory action (see Fig. 2). The change in RR-LGPS reflects the expected change in prescribing behavior. Since regulatory actions are generally aimed at risk minimization, changing pre- scribing patterns (usually a reduction in prescriptions) and a corresponding decrease in the RR LGPS values is expected.

FAERS data exhibited the opposite effect wherein six of seven samples showed a decrease in EB05 values when data was restricted to before a regulatory action. FAERS contains reports for which an a priori association is suspected by the reporter (i.e., causality is assumed). Regulatory action/media attention usually increases reporting so corresponding EB05 increase

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is expected. This issue should be explored further with a larger number of drug- adverse event associations.

Also, performance of statistical algorithms was not the focus of this study. For FAERS, the data mining algorithm and threshold have extensive use and validation in PV practice over decades. However, despite the fact that RR- LGPS was validated for the EU-ADR project, it is relatively novel. Therefore, two thresholds were included, and results indicate that additional work is needed to develop optimal parameters.

This study had several limitations. Firstly, the study was limited to ten events and performance metrics were based on relatively small reference sets (44 positive and 50 negative). Although the diversity of adverse events and reference sets were strongly considered at the time of their creation [24], the findings may not necessarily apply to a broader range of drug-event associations.

Secondly, the negative reference samples were based on current safety data. Although unlikely, it cannot be ruled out that some ‘‘negative’’ drug-event associations may become ‘‘positive’’ in the future. Furthermore, VigiBase was used in selecting negative samples and FAERS was used for the analysis. Both FAERS and VigiBase are SRS and there is overlap of reports. This may have influenced high specificity observed in the FAERS analysis and should be considered for future research on performance assessment.

Thirdly, although FAERS contains non-US reports, most are from the US; all EU-ADR data are from EU countries. Thus, differences in medical practice and population characteristics could have impacted results. However, results of each were compared against reference sets which were selected with a global perspective and selections were not limited to associations observed only in one region.

Since VigiBase has a larger portion of non-US data, it could have been included in the analysis but was purposefully excluded as it was one of the information sources used for the selection of negative reference sets. Nevertheless, the unrestricted analysis was conducted with VigiBase (EB05 >=2). The sensitivity and specificity were similar to FAERS results (77 and 100 %, respectively; data not shown). Therefore, geographical variations in SRS databases do appear to impact performance results.

Healthcare professionals must understand the utility and value of EHRs and big data in pharmacovigilance practice. This retrospective study has shown favorable performance of EHR

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data compared with more traditional SRS data used in signal detection for marketed products. Perhaps the greatest significance of this study is that a framework has been established. Future research should focus on prospective validation of these data sources.

Conclusion

This retrospective evaluation against reference sets may have slightly favored the performance of FAERS and underestimated that of EU-ADR data as ‘‘diagnostic’’ signal detection tools. However, the value of both was clearly demonstrated by a time restriction analysis. Signal detection using data from all years, versus data restricted to before awareness of a regulatory action, lead to opposite, but expected trends in the statistics used to interrogate FAERS and EU-ADR data. Significantly, the performances of EU-ADR and FAERS data were similar and complementary. Additional research focusing on prospective validation of the EU-ADR system (and other EHR data sources) is needed.

Ethical approval

Ethical approval is not needed. This study was done using secondary data sources. No individual patient or healthcare professional identifying information was used.

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Appendix 1: Coding algorithms used for the identification of events in the EU-ADR network

EVENT	UMLS CUI	Medical term	ICD9CM	ICD10	ICPC2005	RCDv2	RCDv3 CTV
Acute Liver Failure (ALF)	C0151766	Liver function tests abnormal finding*	794.8	R94.5	B85001, A91017	44D2., R148., R148z	44D2., R148., R148z, XM1Ep
	C0239571	Fetor hepaticus					X76En, X76Ep
	C0001308	Acute and subacute liver necrosis (disorder)	570			J60.., J60z.	J60.., J60z.
	C0001364	Massive Hepatic Necrosis	570			J6002, J600z	J6002, J600z
	C0162557	Liver Failure, Acute	570			J6000	J6000, X3079
	C0267795	Subacute hepatic necrosis	570			J601., J601z	J601., J601z
		Subacute hepatic failure				J6010	J6010
		Subacute hepatic necrosis				J601., J601z	J601., J601z
	C0019151	Hepatic Encephalopathy	572.2			J622.	X0058
	C0085605	Liver Failure		K72.9	D97007	J62y.	X3076, X3077, X3078
	C0019158	Hepatitis	573.3	K75.9	D97008, D72002	J633z	X306T, J633z
	C0019193	Hepatitis, Toxic	573.3			J6330	J6330
	C0348754	Toxic liver disease		K71.9, K71		J635., Jyu76	J635., Jyu76
	C0451707	Toxic liver disease w ith cholestasis		K71.0		J6350	J6350
	C0451708	Toxic liver disease w ith hepatic necrosis		K71.1		J6351	J6351
	C0451709	Toxic liver disease w ith acute hepatitis		K71.2		J6352	J6352
	710	Toxic liver disease w ith chronic persistent hepatitis		K71.3			
	C0451711	Toxic liver disease w ith chronic lobular hepatitis		K71.4		J6354	J6354
	712			K71.5			
	713			K71.7			
	C0151766	Liver function tests abnormal finding	794.8	R94.5	B85001, A91017	44D2., R148., R148z	44D2., R148., R148z, XM1Ep
	C0400927	Hepatic failure as a complication of care					42

*ALT≥3x ULN (60 IU/L) OR AST≥3x ULN (40 IU/L) AND Total bilirubin≥2x ULN (1.2 mg/dL or 40 µmol/L) w ithin a period of seven (7) days of each other

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EVENT	UMLS CUI	Medical term	ICD9CM	ICD10	ICPC2005	RCDv2	RCDv3 CTV
Acute Myocardial Infarction (AMI)	C0155626	Acute myocardial inf arction	410, 410.9, 410.90	I21, I21.9	K75002	G30.., G30z.	XE0Uh, G30z.
		Electrocardiogram: myocardial infarction (finding)					
		Anteroseptal inf arction on electrocardiogram					
	C0428955	ECG: posterior/inferior infarct				3235	3235
	C0232325	Lateral inf arction on electrocardiogram				3236	3236
	C0428953	Electrocardiogram: myocardial infarction (finding)				323Z.	323Z.
	C0340324	Silent myocardial inf arction				G30..	X200a
Acute Renal Failure (ARF)	C0022660	Kidney Failure, Acute*	584, 584.9	N17, N17.9	U99005	K04.., K04z.	K04.., K04z.
	C0022672	Kidney Tubular Necrosis, Acute	584.5	N17.0		K040.	K040.
	C0003460	Anuria	788.5		U05001	1AC0., R0851	1AC0., R0851
	*serum creatinine ≥125 µmol/L w ithin 30 days of hospital discharge						
Anaphylactic Shock (AS)	C0002792	anaphylaxis		T78.2	A92005, A12004	SN50.	SN50.
	C0375697	Other anaphylactic shock	995	T78.0		SN500	X70w 1, X70vm
	C0161840	Anaphylactic transfusion reaction		T80.5		SP34.	SP34., X70vl
	C0274304	Anaphylactic shock, due to adverse effect of correct medicinal substance properly		T88.6		SN501	SN501

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EVENT	UMLS CUI	Medical term	ICD9CM	ICD10	ICPC2005	RCDv2	RCDv3 CTV
Bullous Eruption (BE)	C0235818	Bullous eruption					XM05i
	C0014742	Erythema Multiforme	695.1, 695.10	L51, L51.9	S99007	M151., M151z	XE1B0, M151z
	C0038325	Stevens-Johnson Syndrome	695.13, 695.12	L51.1	S99032, A12005	M1517	M1517, X50CE
	C0014518	Toxic Epidermal Necrolysis	695.15	L51.2		M1518	M1518
	C0085932	Skin Diseases, Bullous	694, 694.9	L13.9, L10- L14.9		M14.., M14z., Myu1.	M14.., M14z., Myu1.
Cardiac Valve Fibrosis (CVF)	C0003504	Aortic Valve Insufficiency		I35.1	K83001, K83002		X2017
	C0026266	Mitral Valve Insufficiency		I34.0	K83004	G540.	XE0Ux
	C0040961	Tricuspid Valve Insufficiency	397		K83012		XM00K
	C0034088	Pulmonary Valve Insufficiency	424.3	I37.1		G5430	X201L, G5430
	C0026265	Diseases of mitral valve	394.9, 424.0			G11.., G11z., G540z	XE0UY, G11z., G540z
	C1260873	Aortic valve disorder	424.1, 395	I35.9		G541z	G541z
	C0264774	Mitral and aortic incompetence	396.3			G133.	G133.
	C0264772	Mitral valve stenosis and aortic valve insufficiency	396.1			G131.	G131.
	C0340341	Aortic valve insufficiency NOS of specified cause, except rheumatic Incompetence of unspecified heart valve	424.1			G54z0	G54z0
	C0375259	Mitral and aortic valve disease	396, 396.9	I08.0		G13.., G13z.	G13.., G13z.
	C0155576	Multiple mitral and aortic valve involvement	396.8			G13y.	G13y.
	C1306822	Mitral valve insufficiency and aortic valve stenosis	396.2			G132.	G132.
	C0865572	Mitral valve stenosis w ith incompetence or regurgitation	394.2				

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EVENT	UMLS CUI	Medical term	ICD9CM	ICD10	ICPC2005	RCDv2	RCDv3 CTV
Neutropenia (NEUTROP)	C0027947	Neutropenia*	288.0, 288.00, 288.09		B84008	42J2.	42J2., Xa9E8
	C0001824	Agranulocytosis		D70	B84001	D400z	D400z
	C0398575	Other specified agranulocytosis				D400y	D400y
	C0398576	Acquired neutropenia NEC				D4008	XE14G
	C0272178	Drug-induced neutropenia	288.03			D4002	XE14C
	C2004273	Acquired agranulocytosis NEC				D4008	XE14G
	*Granulocyte count≤0.5 x 10^9/L OR Neutrophil count ≤ 1.5 x 10^9/L w ithin a period of seven (7) days						
Pancytopenia (PANCYTOP)	C0002874	Aplastic Anemia*	284.9	D61.9	B82001	D20., D20z.	D20., D20z.
	C0030312	Pancytopenia	284.1			D2016	X20CN, XE13v
	C0271907	Acquired aplastic anemia				D201., D201z	XE13t, XE13w
	C0271892	Acquired pancytopenia				D2015	D2015
	C0271909	Aplastic anemia due to drugs	284.89	D61.1		D2011	XE13u
	C0348890	Idiopathic aplastic anemia	284.9	D61.3		D204.	D204.
	C0029745	Other specified aplastic anemias	284.8	D61.8		Dyu21	Dyu21
Rhabdo-myolysis (RHABD)	C0035410	Rhabdomyolysis*	728.88			N2333	X70AI
	C1135344	Acute necrotizing myopathy	359.81				
	C1401301	Ischemia muscle	level 1				
	C0027080	Myoglobinuria	791.3	R82.1		R113.	X709S, R113.
	*serum creatine phosphokinase >10x normal accompanied by elevated serum creatinine levels w ithin 30 days of hospital discharge						

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EVENT	UMLS CUI	Medical term	ICD9CM	ICD10	ICPC2005	RCDv2	RCDv3 CTV
Upper Gastro-Intestinal Bleeding (UGIB)	C0041909	Upper gastrointestinal hemorrhage				J68z2	X30Be
	C0017181	Gastrointestina Hemorrhage	578, 578.9	K92.2	D15001	J68.., J68zz	J68.., J68zz, XE0bJ
	C0018926	Hematemesis	578	K92.0	D14003, D14001	J680., 1994.	J680., Xa1dj
	C0025222	Melena	578.1	K92.1	D15003, D15004 D15005	J681., 19E4.	XE0bl, XE0rH, X76f M
	C0239293	Esophageal bleeding	530.82			J10y0	Xa7TU, J10y0
	C0155967	Acute gastric ulcer w ith hemorrhage	531	K25.0		J1101	J1101
	C0155973	Acute gastric ulcer w ith hemorrhage AND perforation	531.2	K25.2		J1103	J1103
	C0155992	Acute duodenal ulcer w ith hemorrhage	532	K26.0		J1201	J1201
	C0155998	Acute duodenal ulcer w ith hemorrhage AND perforation	532.2	K26.2		J1203	J1203
	C0267288	Acute peptic ulcer w ith hemorrhage	533.00, 533.0	K27.0		J1301	J1301
	C0267294	Acute peptic ulcer w ith hemorrhage and perforation	533.2	K27.2		J1303	J1303
	C0267112	Acute gastric mucosal erosion			D86010		
	C0156073	Atrophic gastritis, w ith haemorrhage	535.11				
	C0156080	Other specified gastritis, w ith hemorrhage	535.41				
	C0156082	Unspecified gastritis and gastroduodenitis, w ith hemorrhage	535.51				
	C0155970	Acute gastric ulcer w ith perforation	531.1	K25.1		J1102	J1102
	C0155995	Acute duodenal ulcer w ith perforation	532.1	K26.1		J1202	J1202
	C0267291	Acute peptic ulcer w ith perforation	533.1	K27.1		J1302	J1302
	C0156042	Acute gastrojejunal ulcer w ith hemorrhage	534	K28.0		J1401	J1401
	C0156043	Acute gastrojejunal ulcer w ith haemorrhage, w ithout mention of obstruction	534				
	C0156048	Acute gastrojejunal ulcer w ith hemorrhage AND perforation	534.2	K28.2		J1403	J1403

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Appendix 2: MedDRA Terms used for the identification of events in the spontaneous reporting databases (version 11.1)

Acute Liver Injury: Hepatic disorders SMQ (broad)

Acute Myocardial Infarction: 'Acute myocardial infarction', 'ECG signs of myocardial ischaemia', 'Silent myocardial infarction'

Acute Renal Failure: 'Albuminuria', 'Anuria', 'Azotaemia', 'Blood creatinine abnormal', 'Blood creatinine increased', 'Blood urea abnormal', 'Blood urea increased', 'Blood urea nitrogen/ creatinine ratio increased', 'Creatinine renal clearance abnormal', 'Creatinine renal clearance decreased', 'Glomerular filtration rate abnormal', 'Glomerular filtration rate decreased', 'Hypercreatininaemia', 'Nephropathy toxic', 'Oliguria', 'Protein urine present', 'Proteinuria', 'Renal failure', 'Renal failure acute', 'Renal function test abnormal', 'Renal impairment', 'Renal tubular disorder', 'Renal tubular necrosis', 'Tubulointerstitial nephritis', 'Urea renal clearance decreased', 'Urine output decreased'

Anaphylactic Shock: 'Anaphylactic reaction', 'Anaphylactic shock'

Bullous Eruption: 'Dermatitis bullous', 'Erythema multiforme', 'Stevens-Johnson syndrome', 'Toxic epidermal necrolysis'

Cardiac Valve Fibrosis: 'Aortic valve disease', 'Aortic valve disease mixed', 'Aortic valve incompetence', 'Cardiac valve disease', 'Heart valve incompetence', 'Heart valve stenosis', 'Mitral valve disease', 'Mitral valve disease mixed', 'Mitral valve incompetence', 'Pulmonary valve disease', 'Pulmonary valve incompetence', 'Tricuspid valve disease', 'Tricuspid valve incompetence'

Neutropenia: 'Agranulocytosis', 'Band neutrophil count decreased', 'Cyclic neutropenia', 'Febrile neutropenia', 'Granulocyte count decreased', 'Granulocytopenia', 'Idiopathic neutropenia', 'Neutropenia', 'Neutropenic colitis', 'Neutropenic infection', 'Neutropenic sepsis', 'Neutrophil count abnormal', 'Neutrophil count decreased'

Pancytopenia: 'Aplastic anaemia', 'Bicytopenia', 'Bone marrow failure', 'Febrile bone marrow aplasia', 'Full blood count decreased', 'Pancytopenia', 'Panmyelopathy', 'Plasma cells absent'

Rhabdomyolysis: 'Muscle necrosis', 'Rhabdomyolysis'

Upper Gastrointestinal Bleeding
'Chronic gastrointestinal bleeding', 'Duodenal ulcer haemorrhage', 'Duodenitis haemorrhagic', 'Gastric haemorrhage', 'Gastric occult blood positive', 'Gastric ulcer haemorrhage', 'Gastric ulcer haemorrhage, obstructive', 'Gastric varices haemorrhage', 'Gastritis haemorrhagic', 'Gastroduodenal haemorrhage', 'Gastroduodenitis haemorrhagic', 'Gastrointestinal haemorrhage', 'Gastrointestinal ulcer haemorrhage', 'Haematemesis', 'Haematochezia', 'Haemorrhagic erosive gastritis', 'Melaena', 'Occult blood positive', 'Oesophageal haemorrhage', 'Oesophageal ulcer haemorrhage', 'Oesophagitis haemorrhagic', 'Peptic ulcer haemorrhage', 'Ulcer haemorrhage', 'Upper gastrointestinal haemorrhage'

Chapter 5

Using real-world healthcare data for pharmacovigilance signal detection – the experience of the EU-ADR project

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Abstract

A prospective pharmacovigilance signal detection study, comparing the real-world healthcare data (EU-ADR) and two spontaneous reporting system (SRS) databases, US FDA's Adverse Event Reporting System and WHO's Vigibase is reported. The study compared drug safety signals found in the EU-ADR and SRS databases. The potential for signal detection in the EUADR system was found to be dependent on frequency of the event and utilization of drugs in the general population. The EU-ADR system may have a greater potential for detecting signals for events occurring at higher frequency in general population and those that are commonly not considered as potentially a drug-induced event. Factors influencing various differences between the datasets are discussed along with potential limitations and applications to pharmacovigilance practice.

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Introduction

In pharmacovigilance, a signal is defined as "information that arises from one or multiple sources (including observations and experiments), which suggests a new potentially causal association, or a new aspect of a known association, between an intervention and an event or set of related events, either adverse or beneficial, that is judged to be of sufficient likelihood to justify verificatory action" [1]. It is important to note that, by definition, a "signal" requires further evaluation, as this definition pertains to an unverified drug-event combination [2]. In pharmacovigilance practice, the process of signal detection is a hypothesis generation exercise and additional clinical evaluation is necessary to verify a causality relationship between the signal and the event [2,3]. In the last four decades, since the thalidomide disaster of the early 1960s [4] and continuing with the more recent reports of adverse drug reactions (ADRs) including nimesulide and cerivastatin, spontaneous ADR reporting systems (SRS) have been the cornerstone of signal detection in pharmacovigilance [5,6]. The SRS were implemented to collect data where a reporter had at least a suspicion that a drug caused an adverse event (i.e. causality is assumed) [7]. However, the rofecoxib story highlighted the significant limitations of the SRS with respect to early detection of ADRs, especially for those adverse events that are not commonly thought to be drug-induced and have multiple risk factors [8]. SRS suffer from underreporting, where approximately <10% of serious ADRs are reported [9]. At the same time, over- reporting and selective reporting of events that require risk management and risk minimization measures is also observed.

The increasing availability of electronic healthcare records (EHRs) offers important opportunities to investigate a wide spectrum of ADRs and to detect drug safety signals closer to real use and time as EHR databases record information for large populations and for long follow-up periods, irrespective of suspicion of causality [10]. A number of data mining techniques have been specifically developed for the automatic detection of drug safety signals using either SRS or EHR databases [11- 15]. Several international initiatives including the Observational Medical Outcomes Partnership [OMOP] [16,17]; the United State (US) Food and Drug Administration's (FDA) Sentinel Initiative [18]; the European Commission funded projects "Exploring and Understanding Adverse Drug Reactions by integrative mining of clinical records and biomedical knowledge" [EU-ADR] [19-20]; and the "Pharmacoepidemiological Research on Outcomes of Therapeutics by a European Consortium" [PROTECT] have focused on testing the potential of signal detection specifically using longitudinal electronic health record databases [21].

This article describes one of the many activities of the EU-ADR project concerning signal detection. The EU-ADR project, which ran between 2008 and 2013, led to the alliance of different

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administrative/claims and general practice databases, creating a resource of unprecedented size for drug safety monitoring in Europe (around 30 million persons from seven different databases). The overall scope of the EU-ADR project was to design, develop, and validate a computerized integrative system that utilizes data from EHRs and biomedical databases for the early detection of ADRs.

In this article we describe the results of a direct comparison (i.e. without using pre-defined reference standards of positive and negative controls) between EU-ADR and two SRS databases: the FDA's Adverse Event Reporting System (FAERS) and the World Health Organization's VigiBase™ (VigiBase). The objectives of this study were to (a) measure and compare the number of signals identified in EU-ADR database network and SRS databases; (b) evaluate the extent of concordance in signal detection between EU-ADR and SRS databases. The preliminary results were presented in 2011 [22].

Methods

Data Sources

Data from the EU-ADR database network, FAERS, and VigiBase were used for the analysis. The EU-ADR database network is comprised of seven established European healthcare databases located in three countries. Health-Search (HSD; Italy), Integrated Primary Care Information (IPCI: Netherlands), and Pedianet (Italy) are primary care databases, where both clinical information including medical diagnoses drug prescriptions are recorded. The Aarhus University Hospital Database (Aarhus, Denmark), PHARMO (Netherlands), and the regional Italian databases of Lombardy and Tuscany are comprehensive record-linkage systems in which drug dispensing data of well-defined populations is linked to a registry of hospital discharge diagnoses and other registries collecting clinical information. The main characteristics of the EU-ADR database network have been described in more detail by Coloma et al [23,24]. The data collected between the years 1995-2010 were used in this study [24].

The FAERS and VigiBase databases were utilized as a data source for spontaneous reports. FAERS was established in 1969 to support post-marketing safety surveillance programs in the US. At the time of this analysis, FAERS contained over seven million reports of ADRs from the US and worldwide; however, a large proportion of reports in the database are from the US [25]. The VigiBase consists of reports of adverse events received since 1968 from more than 100 member countries. At the time of this analysis, it contained over nine million reports of ADRs worldwide [26]. In both SRS databases, the reports originate from various sources including healthcare professionals, consumers, and

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pharmaceutical manufacturers. The adverse events are coded using the Medical Dictionary for Regulatory Activities (MedDRA) and patient narratives are not included in the public version.

Events under study

The study focused on the ten selected events that are deemed important in pharmacovigilance practice, as identified by a team of experts: Acute Liver Injury; Acute Myocardial Infarction; Acute Renal Failure; Anaphylactic Shock; Bullous Eruption; Cardiac Valve Fibrosis; Neutropenia; Pancytopenia; Rhabdomyolysis; and Upper Gastrointestinal Bleeding [19]. Because of the large heterogeneity in event coding between EHR databases in the EU-ADR network, harmonization of event definitions was required. The Unified Medical Language System® (UMLS®) concepts and related codes and labels corresponding to the ten events were identified, and using these codes and terms, database owners constructed their queries for the data extraction. The queries for the event data extraction from different EHR databases were analyzed by a team of clinical experts and, if necessary, were harmonized across all EHR databases. The detailed process is described by Avillach et al [27,28].

For the analyses in the SRS databases, the MedDRA dictionary including Standardized MedDRA Queries (SMQs) [version 11.1] was reviewed to identify MedDRA terms corresponding to the UMLS concepts for the ten events. An SMQ is a grouping of MedDRA terms that relate to a defined medical condition. If an SMQ was already available for an event of interest, then that SMQ was compared with the selected UMLS concepts to identify any missing MedDRA codes of interest. For an adverse event that did not have a corresponding SMQ, the complete MedDRA dictionary was reviewed to define custom grouping of terms per UMLS concept [Appendix 1].

Drugs under study

For comparison of drugs across EU-ADR and SRS databases, a list of drugs that could be assessed in both EU-ADR system and SRS databases was created, based on the following criteria: (i) the use of the drug resulted in at least one exposed case patient in EU-ADR with one or more of the ten selected events of interest; (ii) according to event-specific sample size calculations, the drug had a high enough exposure in EU-ADR to be able to detect relative risk=2 for each of the events; (iii) the drug was not prescribed as part of a combination therapy; (iv) the drug had at least one reported case in SRS. This process yielded 404 drugs. The analyses in this study were restricted to these 404 drugs. For each study drug, the drug names as registered in the SRS were mapped to Anatomic Therapeutic Chemical (ATC) classification system, which was used in EU-ADR.

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Signal detection

In EU-ADR database network, the posterior expectation of the incidencerate ratio [Relative Risk (RR) LGPS] was estimated for each drug-event combination using the Longitudinal Gamma Poisson Shrinker (LGPS) as a measure for signal detection [29]. All drug-event combinations in which RR LGPS was ≥2 with p-value <0.05 were considered a signal, except if "Longitudinal Evaluation of Observational Profiles of Adverse events Related to Drugs" (LEOPARD) identified such an association as potentially due to protopathic bias [14,29]. Protopathic bias is defined in this context as a more general bias which reflects reversal of cause and effect [30]. LEOPARD method detects and discards associations due to protopathic bias by comparing the rates of drug prescriptions in a fixed window prior and after the occurrence of an event [29].

The SRS analyses were carried out using a commercial software package (Empirica™ Signal System. Oracle, Waltham, MA). Data up to and including the 2nd quarter of 2010 in FAERS and 4th quarter of 2010 in VigiBase database were utilized in this study. The Gamma Poisson Shrinker was used to compute EB05, the 5th percentile of the empirical Bayes posterior distribution, which corresponds roughly to the lower point in a 90% confidence interval [31]. A threshold of EB05 was ≥2 used to detect a signal. The threshold of EB05 ≥2 was selected because of its extensive use in the pharmacovigilance practice [3].

Data analysis

The number of signals and proportion of signals out of total number of drug-event combinations in the database were calculated across the EU-ADR and the SRS databases. In addition, the signals across all events for each database were stratified and compared by the ATC codes using the 1st level, anatomical main groups. In order to measure agreement between data mining results from EU-ADR and SRS, all drug-event combinations for each event under study were classified using 2 x 2 table (**Table 1**). When a drug-event combination was detected as a signal in both EU-ADR and SRS or if a drug-event combination did not meet the threshold in both EU-ADR and SRS then the result for that drug-event combination was concordant. In contrast, when a drug-event combination was identified as a signal in EU-ADR but not in SRS, or vice versa, then that drug-event combination result was discordant. Kappa (k) statistics were calculated for each event to measure the extent of agreement across the drugs studied. In signal detection data analysis, typically a large number of drug-event combinations are screened to identify signals, however, the proportion of drug-event combinations resulting into signals is typically much smaller as compared to non-signals (i.e. cell *a* in Table 1 is typically much less than 50% of the sum of *a*+*d*). In this situation, using only the kappa value for interpretation of results would not be

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appropriate [32]. Therefore, we also calculated the proportion of positive agreement (P_{pos}) and proportion of negative agreement (P_{neg}), prevalence index (P_{index}), bias index (b_{index}), and prevalence adjusted bias adjusted kappa (PABAK). PABAK is a kappa adjusted for such imbalances in prevalence. The magnitude of PABAK was interpreted using the Landis and Koch scale: <=0=poor, 0.01-0.20=slight, 0.21-0.40=fair, 0.41-0.60=moderate, 0.61-0.80=substantial and 0.81-1.00=almost perfect [33].

Table 1. Classification of drug-event combinations using a 2x2 table

		Signal in SRS: yes	Signal in SRS: no	
Signal in EU-ADR	yes	a	b	a+b
	no	c	d	c+d
		a+c	b+d	N

Results

For each event under study, the proportion of drug-event combinations that resulted into a signal within the EU-ADR, FAERS, and VigiBase databases are shown in **Figure 1.** Overall, across the ten events, a higher proportion of drug-event combinations were identified as a signal in EU-ADR (22%) as compared to FAERS (12%) and VigiBase (9%). Acute renal failure had the highest proportion (41% for EU-ADR; 21% for FAERS; 12% for VigiBase). The lowest proportion was reported for cardiac valve fibrosis (3% across all three databases). When EU-ADR results were compared to those from FAERS, 10-20% more signals were identified in EU-ADR for acute events such as acute liver failure, acute renal failure, acute myocardial infarction, neutropenia, pancytopenia and upper GI bleeding. The highest difference was noted for acute renal failure (21% in FAERS and 41% in EU-ADR). A similar pattern but involving larger differences was observed when EU-ADR data were compared toVigiBase.

The measures of concordance between EU-ADR and SRS are shown in the **Tables 2 and 3.** The percentage of concordance was moderate to high in all ten events (59-94%). For both EU- ADR/FAERS and EU-ADR/VigiBase comparisons, the strength of concordance was highest for cardiac valve fibrosis and anaphylactic shock and the lowest for acute liver failure and acute renal failure. Despite the high percentage of concordance, low *k* was observed across all events. There was a high proportion of negative agreement resulting in a substantial imbalance in cells *a* and *d* in the 2 x 2 table. Therefore, PABAK values were used for interpretation of strength of agreement. The PABAK values were

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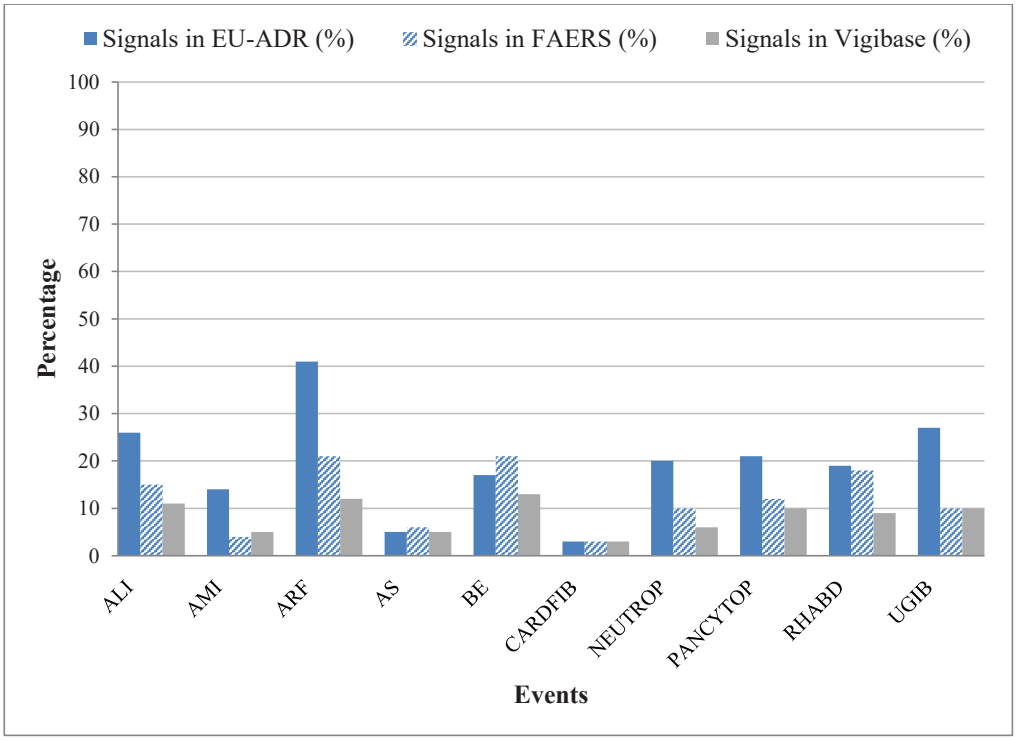
categorized as almost perfect for cardiac valve fibrosis and anaphylactic shock in both EU-ADR/FAERS and EU-ADR/VigiBase comparisons. The strength of concordance was slight and fair for acute renal failure and acute liver injury, respectively.

Figure 1. Proportion of drug-event combinations that resulted into a signal for ten events under study within EU-ADR and SRS databases



ALI=Acute Liver Injury; **AMI**=Acute Myocardial Infarction; **ARF**=Acute Renal Failure; **AS**=Anaphylactic Shock; **BE**=Bullous Eruption; **CARDFIB**= Cardiac Valve Fibrosis; **NEUTRO**=Neutropenia; **PANCYTOP**=Pancytopenia; **RHABD**= Rhabdomyolysis; and **UGIB**=Upper Gastrointestinal Bleeding

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Table 2. Measures of Concordance between EU-ADR and FAERS

Event	%	*k*	P_{pos}	P_{neg}	P_{index}	b_{index}	PABAK	Strength of concordance*
2x2 Table cells	*(a+d)/N*	**	*2a/ (N+a-d)*	*2a/ (N-a+d)*	*(a-d)/N*	*(b-c)/N*	(2(a+d/N)-1)	
ALI	68%	0.05	0.24	0.80	-0.59	0.11	0.37	Fair
AMI	84%	0.04	0.10	0.91	-0.82	0.10	0.68	Substantial
ARF	59%	0.09	0.34	0.70	-0.38	0.20	0.18	Slight
AS	91%	0.16	0.21	0.95	-0.88	-0.01	0.81	Almost Perfect
BE	80%	0.37	0.49	0.88	-0.61	-0.04	0.60	Moderate
CARDFIB	94%	0.08	0.11	0.97	-0.94	0.00	0.88	Almost Perfect
NEUTRO	79%	0.19	0.30	0.87	-0.70	0.11	0.57	Moderate
PANCYTOP	72%	0.00	0.16	0.83	-0.67	0.09	0.44	Moderate
RHABD	76%	0.20	0.35	0.85	-0.62	0.02	0.51	Moderate
UGIB	75%	0.22	0.34	0.85	-0.62	0.16	0.50	Moderate

ALI=Acute Liver Injury; **AMI**=Acute Myocardial Infarction; **ARF**=Acute Renal Failure; **AS**=Anaphylactic Shock; **BE**=Bullous Eruption; **CARDFIB**= Cardiac Valve Fibrosis; **NEUTRO**=Neutropenia; **PANCYTOP**=Pancytopenia; **RHABD**= Rhabdomyolysis; and **UGIB**=Upper Gastrointestinal Bleeding

%=Percentage of concordance*;* ***k***=Kappa Coefficient; ***Ppos***=Proportion of positive agreement; ***Pneg*****=** Proportion of negative agreement; ***Pindex***=Prevalence index; ***bindex***=Bias index; **PABAK**=Prevalence adjusted bias adjusted kappa

* PABAK categorization: <=0=poor, 0.01-0.20=slight, 0.21-0.40=fair, 0.41-0.60=moderate, 0.61-0.80=substantial and 0.81-1.00=almost perfect

***k*=(P_o- P_e)/(1-P_e) where P_o=(a+d)/N and P_e=((a+c)(a+d)+(b+d)(c+d))/N^2

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Table 3. Measures of Concordance between EU-ADR and Vigibase

Event	%	*k*	P_{pos}	P_{neg}	P_{index}	b_{index}	PABAK	Strength of concordance*
2x2 Table cells	*(a+d)/N*	**	*2a/ (N+a-d)*	*2a/ (N-a+d)*	*(a-d)/N*	*(b-c)/N*	(2(a+d/N)-1)	
ALI	67%	-0.03	0.13	0.80	-0.62	0.16	0.34	Fair
AMI	84%	-0.01	0.06	0.91	-0.83	0.09	0.67	Substantial
ARF	59%	0.06	0.24	0.72	-0.46	0.30	0.18	Slight
AS	92%	0.20	0.24	0.96	-0.90	0.01	0.85	Almost Perfect
BE	85%	0.43	0.52	0.91	-0.69	0.04	0.71	Substantial
CARDFIB	94%	0.10	0.13	0.97	-0.93	0.00	0.89	Almost Perfect
NEUTRO	81%	0.19	0.26	0.89	-0.74	0.14	0.62	Substantial
PANCYTOP	73%	0.01	0.14	0.84	-0.69	0.12	0.47	Moderate
RHABD	80%	0.21	0.31	0.88	-0.70	0.11	0.59	Moderate
UGIB	75%	0.23	0.34	0.85	-0.62	0.17	0.51	Moderate

ALI=Acute Liver Injury; **AMI**=Acute Myocardial Infarction; **ARF**=Acute Renal Failure; **AS**=Anaphylactic Shock; **BE**=Bullous Eruption; **CARDFIB**= Cardiac Valve Fibrosis; **NEUTRO**=Neutropenia; **PANCYTOP**=Pancytopenia; **RHABD**= Rhabdomyolysis; and **UGIB**=Upper Gastrointestinal Bleeding

%=Percentage of concordance*;* ***k***=Kappa Coefficient; ***Ppos***=Proportion of positive agreement; ***Pneg***= Proportion of negative agreement; ***Pindex***=Prevalence index; ***bindex***=Bias index; **PABAK**=Prevalence adjusted bias adjusted kappa

* PABAK categorization: <=0=poor, 0.01-0.20=slight, 0.21-0.40=fair, 0.41-0.60=moderate, 0.61-0.80=substantial and 0.81-1.00=almost perfect

**k=(P_O- P_e)/(1-P_e) where P_O=(a+d)/N and P_e=((a+c)(a+d)+(b+d)(c+d))/N^2

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Tables 4 and 5 present the frequency of drug-event combinations that resulted in signals in either the EU-ADR or SRS, but not in both. Of all drug-acute renal failure event combinations, about 30-35% generated signals in the EU-ADR but not in a SRS, while about 6-11 % of drug-acute renal failure combinations generated signals only in a SRS. Similarly, for acute liver failure, about 21-25% of drugs generated a signal only in EU-ADR and about 8-11% of drugs generated signals only in a SRS. In general, a higher number of signals were identified in EU-ADR vs SRS.

For each database, the proportion of drug-event combinations that resulted into a signal across all events by the ATC codes using the 1st level, anatomical main groups are presented in **Figure 2**. The proportion related to anti-infective for systemic use (1st level ATC Code J) was much higher in EU-ADR. Similar pattern was observed, however in a lesser magnitude, in drugs classified to nervous system (1st level ATC Code N) and respiratory system (1st level ATC code R).

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Table 4. Discordance between EU-ADR and FAERS

Event	Signal in EU-ADR	Signal in FAERS	%*
ALI	Yes	No	21
	No	Yes	11
AMI	Yes	No	13
	No	Yes	3
ARF	Yes	No	30
	No	Yes	11
AS	Yes	No	4
	No	Yes	5
BE	Yes	No	8
	No	Yes	12
CARFIB	Yes	No	3
	No	Yes	3
NEUTRO	Yes	No	16
	No	Yes	5
PANCYTOP	Yes	No	19
	No	Yes	9
RHABD	Yes	No	13
	No	Yes	11
UGIB	Yes	No	20
	No	Yes	4

ALI=Acute Liver Injury; **AMI**=Acute Myocardial Infarction; **ARF**=Acute Renal Failure; **AS**=Anaphylactic Shock; **BE**=Bullous Eruption; **CARDFIB**= Cardiac Valve Fibrosis; **NEUTRO**=Neutropenia; **PANCYTOP**=Pancytopenia; **RHABD**= Rhabdomyolysis; and **UGIB**=Upper Gastrointestinal Bleeding

*% of Yes EU-ADR and No FAERS = (b/N)x100;

*% of No EU-ADR and Yes FAERS=(c/N)x100

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Table 5. Discordance between EU-ADR and Vigibase

Event	Signal in EU-ADR	Signal in Vigibase	%*
ALI	Yes	No	25
	No	Yes	8
AMI	Yes	No	13
	No	Yes	4
ARF	Yes	No	35
	No	Yes	6
AS	Yes	No	4
	No	Yes	3
BE	Yes	No	9
	No	Yes	5
CARDFIB	Yes	No	3
	No	Yes	3
NEUTRO	Yes	No	17
	No	Yes	2
PANCYTOP	Yes	No	19
	No	Yes	7
RHABD	Yes	No	16
	No	Yes	5
UGIB	Yes	No	21
	No	Yes	4

ALI=Acute Liver Injury; **AMI**=Acute Myocardial Infarction; **ARF**=Acute Renal Failure; **AS**=Anaphylactic Shock; **BE**=Bullous Eruption; **CARDFIB**= Cardiac Valve Fibrosis; **NEUTRO**=Neutropenia; **PANCYTOP**=Pancytopenia; **RHABD**= Rhabdomyolysis; and **UGIB**=Upper Gastrointestinal Bleeding

*% of Yes EU-ADR and No FAERS = (b/N)x100;

*% of No EU-ADR and Yes FAERS=(c/N)x100

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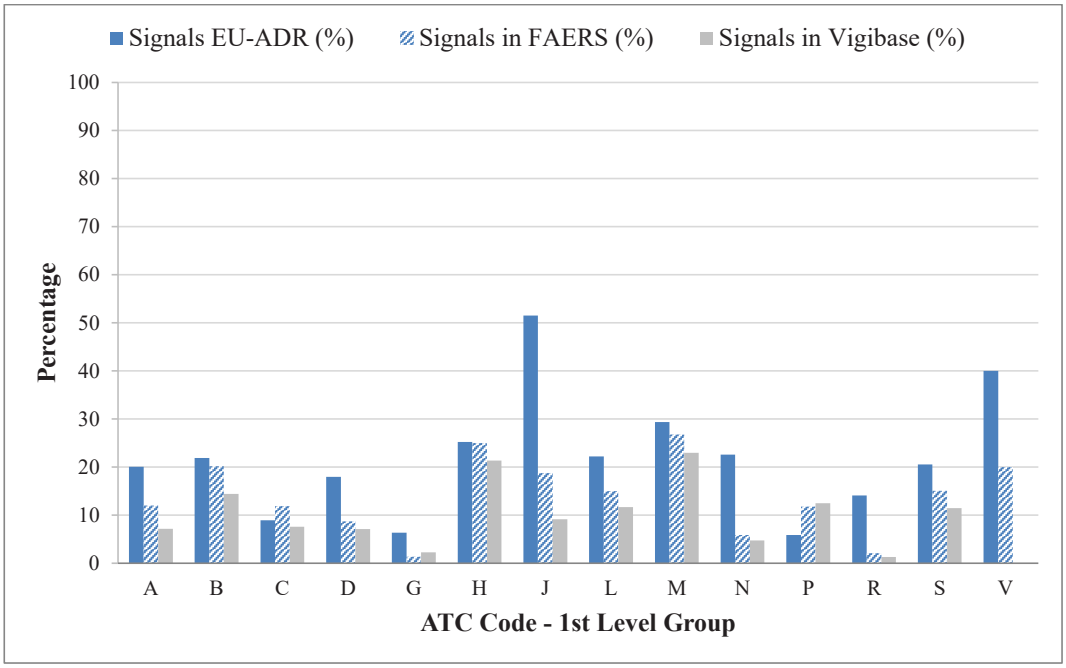
Figure 2. Proportion of drug-event combinations that resulted into a signal across ten events under study by 1st Level ATC Code within the EU-ADR network and SRS databases



ATC Code = Anatomic Therapeutic Chemical (ATC) classification system

A=Alimentary tract and metabolism, **B**=Blood and blood forming organs, **C**=Cardiovascular system, **D**=Dermatologicals, **G**=Genito urinary system and sex hormones, **H**=Systemic hormonal preparations, excl. sex hormones and insulins, **J**=Antiinfectives for systemic use , **L**=Antineoplastic and immunomodulating agents, **M**=Musculo-skeletal system, **N**=Nervous system , **P**=Antiparasitic products, insecticides and repellents, **R**=Respiratory system, **S**=Sensory organs, **V**=Various

Discussion

For the past fifty years, utilizing SRS for signal detection has been a cornerstone of the pharmacovigilance practice. This is the first study, of which we are aware, that has characterized agreement of signal detection using EHRs from EU-ADR database network and SRS databases. The results of this study show that general agreement exists between EU-ADR and SRS. The frequency of concordance between EU-ADR and SRS ranged from 59–94%. The greatest concordance between the EU-ADR and SRS was in the detection of cardiac valve fibrosis, anaphylactic shock, bullous eruptions and acute myocardial infarctions. Cardiac valve fibrosis has been known to be associated with the use of dopamine agonists for the treatment of Parkinson's disease and clinicians are alert to the potential for ADR and reporting may be more uniform [34-36]. Anaphylactic shock, bullous eruptions and acute myocardial infarctions are readily diagnosed as well as significant events. The other events may take

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longer to develop, require more testing and may not be as readily identifiable as drug-induced events. Reporting bias is a recognized weakness of SRS data and may result in underreporting in general or over-reporting of publicized events. These factors may account for the differences in concordance of results between EU-ADR and SRS.

The number of signals identified by EU-ADR and SRS was similar for so called “hallmark” drug-induced events (anaphylactic shock and bullous eruption) and for those events that have been highly publicized and causally linked to a drug (acute myocardial infarction, rhabdomyolysis, or cardiac valve fibrosis). For events falling outside of these criteria and those found in high frequency in the general population, a larger percentage of signals were found in the EU-ADR database compared to SRS databases. These events included acute liver injury, acute renal failure, UGIB, and neutropenia. These findings support the idea that data mining the EU-ADR system may be useful to detect hallmark drug toxicities as well as events that occur frequently in the general population.

There may be inconsistencies and underreporting associated with the data collected within the SRS. They are collected with assumption of causality between a drug and an event and are highly dependent on reporter’s ability to recognize such and their priority to report. However, in electronic health records databases, such as EU-ADR, regular practice, prescription, and test data are collected, irrespective of their relationship to adverse events. This could facilitate identification of signals for events that are likely to be confounded by many underlying factors, resulting in difficulty for a reporter to identify a causal link and also underreporting of events that are not deemed “important” in the eyes of the reporter.

When data were evaluated by ATC code, for codes J, N, and R the higher number of signals were identified in EU-ADR compared to SRS. Code J consists of anti-infective for systemic use. These are used frequently in the general population. Similarly, code N and R consist of medications related to nervous system and respiratory system, respectively. There could be two possible reasons for these significant differences in proportion between EU-ADR and SRS. First, prescription medications are recorded in the health records databases irrespective of their relationship to adverse events. Second, medications belonging to these ATC codes are prescribed for illnesses that are usually occurring in a higher frequency in the general population. Since in the EU-ADR data, human intervention was not required for reporting signals associated with these drug-event combinations, it is not surprising to observe a higher proportion in EU-ADR compared to SRS as potentially due to residual confounding. Further research should focus on evaluating ATC data at more drill-down level and also by event.

There were several limitations to this study, mainly related to the heterogeneity between SRS and EU-ADR systems. SRS contain a mix of European and non-European reports. The EU-ADR data

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was all European data. Also, the SRS data used MedDRA as an event coding dictionary, while EU-ADR data were originally coded using the local database coding practices. Thus, differences in medical practice, clinical judgment, cultural parameters, population characteristics and event coding practices could have had an impact on the study results. In addition, the scope of the study was limited to ten events and 404 drugs. As a consequence, the findings may not be generalizable to a broader range of drug-event combinations. Nevertheless, the selected events are diverse in terms of incidence, prevalence, severity and disease onset. Since the ten selected events were deemed important in the pharmacovigilance practice, it made harmonization of the definitions easier and achievable. In the future research, it would behelpful to see if the same came be achieved for other events and the impact of any coding differences on the results.

It is important to note that the focus of this study was not to compare performance of statistical algorithms utilized by each databases, but rather to measure and compare agreement in signal generation by data mining EU-ADR and SRS databases, in a setting akin to real-world pharmacovigilance practice. For SRS, the data mining algorithms and threshold (EB05>=2) were selected because of their extensive use and validation in pharmacovigilance practice. The RR-LGPS method was use in the EUADR analysis, as it was found to be the best method for signal detection using EHRs [14,29]. The threshold used for RR-LGPS is interpreted similar to EBGM. There are several other data mining algorithms that are utilized in the pharmacovigilance practice for SRS databases, but they were not included in this study. It would be helpful to replicate this study and understand the results using other data mining algorithms.

Our conclusions indicate that utilizing EHR for signal detection, such as the EU-ADR system might complement SRS in signal detection, particularly with events occurring at high frequency in the general population and those that are perceived as unlikely to be drug-induced. As EHR data are getting more accessible, a reviewer could use SRS as a first screening tool to detect signals and then utilize EHR data for selected drug-event combinations to further substantiate a signal. Signal detection in both EU-ADR and SRS systems would strengthen current signal detection activities by decreasing the influences of systematic bias when using one system. Further studies may clarify the possible advantages of signal detection using administrative claims and EHR databases as secondary data sources.

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Key issues

- The increasing availability of electronic healthcare records offers important opportunities to investigate a wide spectrum of adverse drug reactions and to detect drug safety signals closer to real use and time as these types of databases record information for large populations and for long follow-up periods.
- The EU-ADR project, which ran between 2008 and 2013, led to the alliance of different administrative/claims and general practice databases, creating a resource of unprecedented size for drug safety monitoring in Europe (around 30 million persons from seven different databases) and aimed at utilizing these data for the early detection of adverse drug reactions.
- The EU-ADR system may have a greater potential for detecting signals for events occurring at higher frequency in general population and those that are commonly not considered aspotentially a drug-induced event.
- Signal detection in both EU-ADR and spontaneous reporting system would strengthen current signal detection activities by decreasing the influences of systematic bias when using one system.

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** of considerable interest

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Appendix 1: MedDRA Terms used for the identification of the adverse events in the spontaneous reporting databases

Acute Liver Injury
Hepatic disorders SMQ (broad)

Acute Myocardial infarction
'Acute myocardial infarction', 'ECG signs of myocardial ischaemia', 'Silent myocardial infarction'

Acute renal failure
'Albuminuria', 'Anuria', 'Azotaemia', 'Blood creatinine abnormal', 'Blood creatinine increased', 'Blood urea abnormal', 'Blood urea increased', 'Blood urea nitrogen/creatinine ratio increased', 'Creatinine renal clearance abnormal', 'Creatinine renal clearance decreased', 'Glomerular filtration rate abnormal', 'Glomerular filtration rate decreased', 'Hypercreatininaemia', 'Nephropathy toxic', 'Oliguria', 'Protein urine present', 'Proteinuria', 'Renal failure', 'Renal failure acute', 'Renal function test abnormal', 'Renal impairment', 'Renal tubular disorder', 'Renal tubular necrosis', 'Tubulointerstitial nephritis', 'Urea renal clearance decreased', 'Urine output decreased'

Anaphylactic shock
'Anaphylactic reaction', 'Anaphylactic shock'

Bullous eruption
'Dermatitis bullous', 'Erythema multiforme', 'Stevens-Johnson syndrome', 'Toxic epidermal necrolysis'

Cardiac Valve Fibrosis
'Aortic valve disease', 'Aortic valve disease mixed', 'Aortic valve incompetence', 'Cardiac valve disease', 'Heart valve incompetence', 'Heart valve stenosis', 'Mitral valve disease', 'Mitral valve disease mixed', 'Mitral valve incompetence', 'Pulmonary valve disease', 'Pulmonary valve incompetence', 'Tricuspid valve disease', 'Tricuspid valve incompetence'

Neutropenia
'Agranulocytosis', 'Band neutrophil count decreased', 'Cyclic neutropenia', 'Febrile neutropenia', 'Granulocyte count decreased', 'Granulocytopenia', 'Idiopathic neutropenia', 'Neutropenia', 'Neutropenic colitis', 'Neutropenic infection', 'Neutropenic sepsis', 'Neutrophil count abnormal', 'Neutrophil count decreased'

Pancytopenia
'Aplastic anaemia', 'Bicytopenia', 'Bone marrow failure', 'Febrile bone marrow aplasia', 'Full blood count decreased', 'Pancytopenia', 'Panmyelopathy', 'Plasma cells absent'

Rhabdomyolysis
'Muscle necrosis', 'Rhabdomyolysis'

Upper Gastrointestinal Bleeding

'Chronic gastrointestinal bleeding', 'Duodenal ulcer haemorrhage', 'Duodenitis haemorrhagic', 'Gastric haemorrhage', 'Gastric occult blood positive', 'Gastric ulcer haemorrhage', 'Gastric ulcer haemorrhage, obstructive', 'Gastric varices haemorrhage', 'Gastritis haemorrhagic', 'Gastroduodenal haemorrhage', 'Gastroduodenitis haemorrhagic', 'Gastrointestinal haemorrhage', 'Gastrointestinal ulcer haemorrhage', 'Haematemesis', 'Haematochezia', 'Haemorrhagic erosive gastritis', 'Melaena', 'Occult blood positive', 'Oesophageal haemorrhage', 'Oesophageal ulcer haemorrhage', 'Oesophagitis haemorrhagic', 'Peptic ulcer haemorrhage', 'Ulcer haemorrhage', 'Upper gastrointestinal haemorrhage'

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Chapter 6

Can Electronic Health Records Databases complement Spontaneous Reporting System Databases? A historical reconstruction of the association of Rofecoxib and Acute Myocardial Infarction

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Abstract

Background

Several initiatives have assessed if mining electronic health records (EHRs) may accelerate the process of drug safety signal detection. In Europe, Exploring and Understanding Adverse Drug Reactions (EU-ADR) Project Focused on utilizing clinical data from EHRs of over 30 million patients from several European countries. Rofecoxib is a prescription COX-2 selective Non-Steroidal Anti-Inflammatory Drugs (NSAID) approved in 1999. In September 2004, the manufacturer withdrew rofecoxib from the market because of safety concerns. In this study, we investigated if the signal concerning rofecoxib and acute myocardial infarction (AMI) could have been identified in EHR database (EU-ADR project) earlier than spontaneous reporting system (SRS), and in advance of rofecoxib withdrawal.

Methods

Data from the EU-ADR project and WHO-VigiBase (for SRS) were used for the analysis. Signals were identified when respective statistics exceeded defined thresholds. The SRS analyses was conducted two ways- based on the date the AMI events with rofecoxib as a suspect medication were entered into the database and also the date that the AMI event occurred with exposure to rofecoxib.

Results

Within the databases participating in EU-ADR it was possible to identify a strong signal concerning rofecoxib and AMI since Q3 2000 (RR LGPS = 4.5 (95% CI: 2.84-6.72) and peaked to 4.8 in Q4 2000. In WHO-VigiBase, for AMI term grouping, the EB05 threshold of 2 was crossed in the Q4 2004 (EB05 = 2.94). Since then, the EB05 value increased consistently and peaked in Q3 2006 (EB05 = 48.3) and then again in Q2 2008 (EB05 = 48.5). About 93% (2260 out of 2422) of AMIs reported in WHO-VigiBase database actually occurred *prior* to the product withdrawal, however, they were reported *after* the risk minimization/risk communication efforts.

Conclusion

In this study, EU-EHR databases were able to detect the AMI signal 4 years prior to the SRS database. We believe that for events that are consistently documented in EHR databases, such as serious events or events requiring in-patient medical intervention or hospitalization, the signal detection exercise in EHR would be beneficial for newly introduced medicinal products on the market, in addition to the SRS data.

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Background

Rofecoxib is a prescription COX-2 selective Non-Steroidal Anti-Inflammatory Drugs (NSAID) for relief of osteoarthritis signs and symptoms, management of acute pain in adults and treatment of menstrual pain. The European Medicines Agency (EMA) and the United States Food and Drug Administration (FDA) provided approval for rofecoxib in 1999. In June 2000, Vioxx Gastrointestinal Outcome studies (VIGOR) was submitted to FDA which demonstrated an increased risk of cardiovascular thrombotic events, mostly driven by heart attacks (0.5 vs. 0.1% for rofecoxib and naproxen, respectively). [1] However, this finding was initially surprisingly attributed to cardio-protective effect of naproxen. In April 2002, this and other cumulated evidence on potential risks associated to rofecoxib led to the introduction of warnings on rofecoxib labeling concerning the increased risk of cardiovascular events (heart attack and stroke). [2, 3] Subsequently, in September 2004, the APPROVe study showed increased risk of myocardial infarction and stroke for the 12.5mg and 25 mg dose as compared to placebo after 18 months of treatment [1]. The same month, the manufacturer withdrew rofecoxib from the market because of concerns about increased risk of heart attack and stroke associated with long-term, high- dosage use. [1, 4] Subsequent to rofecoxib finding, there has been extensive research done on NSAIDs and cardiovascular risks.

This case triggered dialogue in the scientific community about how to improve the post-marketing surveillance of medicines with the aim of achieving early signal detection and ultimately regulatory intervention to ensure patients' safety. [4] In particular, several initiatives have assessed if mining electronic health records (EHRs) may accelerate the process of drug safety signal detection and strengthening. In the United States (US), in 2008, FDA has created the Sentinel System which is a national electronic system for medicinal product safety surveillance [5]. As of 2016, the Sentinel Distributed Database contained medical and pharmacy benefits data on 178 million members. [5]. Also in 2008, in the US, a public-private initiative called formerly Observational Medical Outcomes Partnership (OMOP) and currently Observational Health Data Sciences and Informatics (OHDSI) was established to research and educate stakeholders on the appropriate use of EHR for studying the effects of medicines. [6]

In Europe, Exploring and Understanding Adverse Drug Reactions (EU-ADR) Project Focused on using clinical data from EHRs of over 30 million patients from several European countries (The Netherlands, Denmark, United Kingdom, and Italy) during 2008- 2012 [7].

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The EU-ADR analyses has showed that signal detection using EHR could complement spontaneous reports that remain the cornerstone of drug safety signal detection, particularly with events occurring at high frequency in the general population and those that are perceived as unlikely to be drug induced [8, 9]. A retrospective study of EHR in the EU- ADR project demonstrated the value of using EHR data in signal detection and strengthening [9, 10].

In the current study we aimed to explore if the signal concerning rofecoxib and acute myocardial infarction (AMI) could have been identified in the EU-ADR distributed healthcare database project earlier than the spontaneous reporting system (SRS) and contribution of EU-ADR data in signal strengthening and possibly earlier rofecoxib withdrawal.

Methods

Data Sources

For this study, data from the EU-ADR project and the World Health Organization's VigiBase™ (WHO-VigiBase) which is an international spontaneous reporting database were used for the analysis. The EU-ADR project comprised seven established European healthcare databases located in four countries. Health-Search (HSD; Italy), Integrated Primary Care Information (IPCI: Netherlands), and Pedianet (Italy) are primary care databases, where both clinical information including medical diagnoses and drug prescriptions are recorded by general practitioners (IPCI and HSD) or family pediatrician (Pedianet) distributed all over the respective countries. The Aarhus University Hospital Database (Aarhus, Denmark), PHARMO (Netherlands), and the regional Italian databases of Lombardy and Tuscany are comprehensive record-linkage systems in which drug dispensing data of well-defined populations is linked to a registry of hospital discharge diagnoses and other registries collecting clinical information. The main characteristics of the EU-ADR project have been described in more detail by Coloma et al [7, 11]. The data collected between the years 1995-2010 were used in this study [11].

For the SRS analysis, the WHO-VigiBase database was used. This database consists of reports of suspected adverse drug reactions (ADRs) received since 1968 from more than 100 member countries. At the time of this analysis, it contained over nine million reports of ADRs worldwide till 2010 [12]. The reports originate from various sources including healthcare professionals, consumers, and pharmaceutical manufacturers. The suspected ADRs are coded using the Medical Dictionary for Regulatory Activities (MedDRA) and

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patient narratives (event history and details) are not included in the public version.

AMI search criteria

Due to the large heterogeneity in event coding between EHR databases in the EU-ADR data, harmonization of event definition was required. The Unified Medical Language System® (UMLS®) concepts and related codes and labels corresponding to AMI were identified, and using these codes and terms, database owners constructed their queries for the data extraction. The queries for the event data extraction from different EHR databases were analyzed by a team of clinical experts and, where necessary, were harmonized across all EHR databases. The detailed process is described by Avillach et al [13, 14].

For the analyses in the WHO-VigiBase databases, the MedDRA dictionary including Standardized MedDRA Queries [version 11.1] was reviewed to define custom grouping of terms for AMI which included the following preferred terms: 'Acute myocardial infarction', 'ECG signs of myocardial ischemia', 'Silent myocardial infarction'.

Rofecoxib-AMI association evaluation

In the EU-ADR project, the Longitudinal Gamma Poisson Shrinker (LGPS), the posterior expectation of the incidence rate ratio [Relative Risk (RR)-LGPS] was developed and estimated for drug-event pair. A RR-LGPS ≥ 2 p-value<0.05) was classified as a signal, except when the "Longitudinal Evaluation of Observational Profiles of Adverse events Related to Drugs" (LEOPARD) method identified such an association as potentially due to protopathic bias. [15, 16, 17]. The relative risks of AMI during exposure to rofecoxib as compared to non-exposure to the drug was calculated on quarter of year basis by measuring LGPS values,

WHO-VigiBase analyses were conducted on data up to and including 4th quarter of 2010 using Oracle Empirica™ Signal (Waltham, MA). The Gamma Poisson Shrinker (GPS) was used to compute EB05 (Empirical Bayes posterior Gamma Mixture 5th percentile; estimates lower point in 90% confidence internal). A threshold of EB05>=2 (p value<0.05) was selected based on extensive use and validation in PV practice [18]. The analyses were conducted two ways- based on the date the AMI events with rofecoxib as a suspect medication were entered into the WHO-VigiBase database and also the date that the AMI event occurred with respect to the exposure to rofecoxib. The data mining quarter date was used as a surrogate for the event date.

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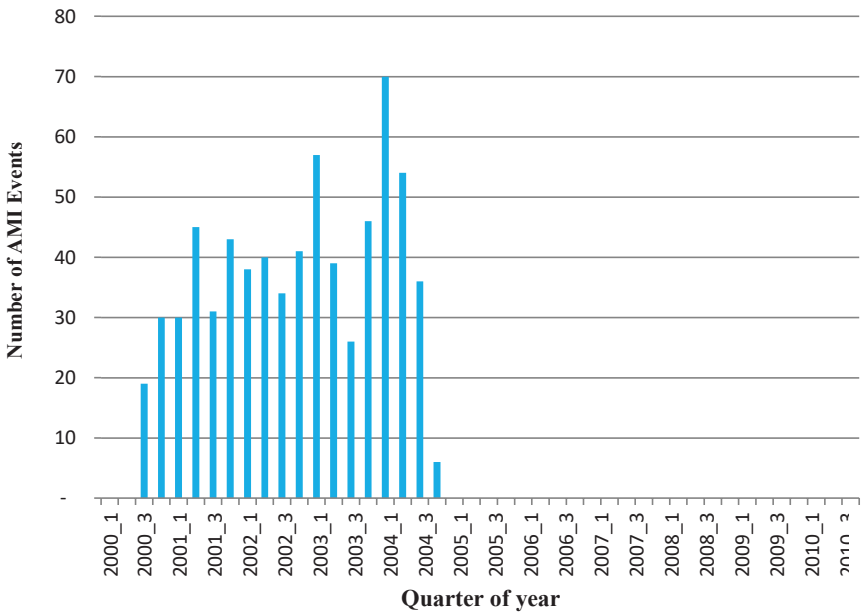
Results

EU-ADR analysis

A total of 685 AMI events during exposure to rofecoxib were captured in the databases participating in the EU-ADR project during the years 2000-2010 (**Figure 1**). The first AMI event during rofecoxib was recorded in third quarter of the year 2000 with total of 49 AMIs for the rest of that year. After withdrawal of rofecoxib there have not been any new AMI events during exposure, since 2005.

Figure 1: Frequency of Acute Myocardial Infarction (AMI) events occurring during exposure to rofecoxib in the EU-ADR database network



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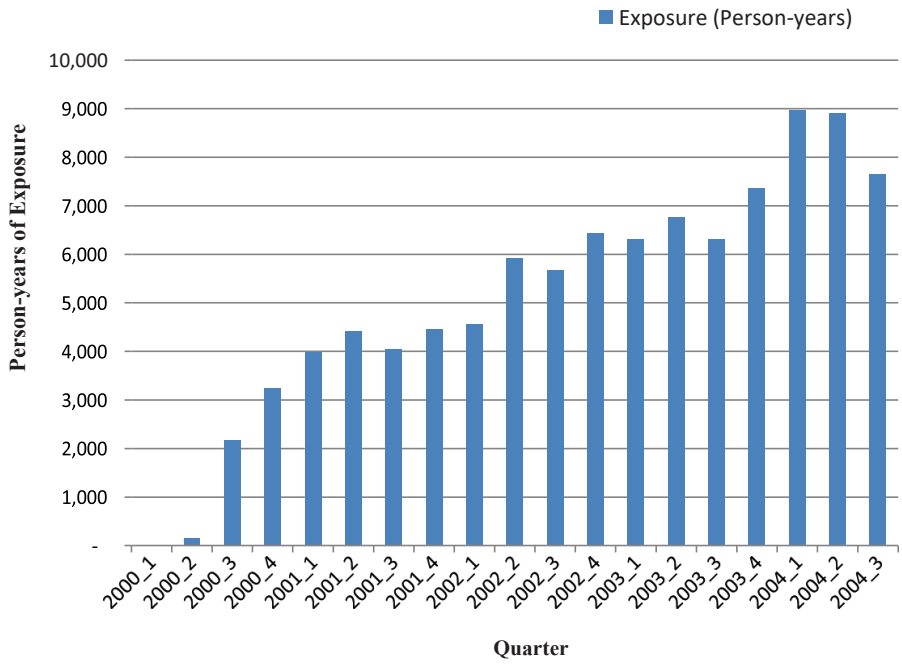
The rofecoxib market penetration in person-years of exposure in the participating EU databases is shared in **Figure 2**. Rofecoxib uptake began in the second quarter of the year 2000 with approximately 5,562 person-years of exposure in the year 2000. Its quarter- by-quarter exposure peaked in the first quarter of 2004 with 8,959 person-years of exposure. Subsequent to that, the exposure rapidly declined throughout 2004.

Figure 2: Rofecoxib exposure (person-years) cumulated over time in the EU-ADR database network



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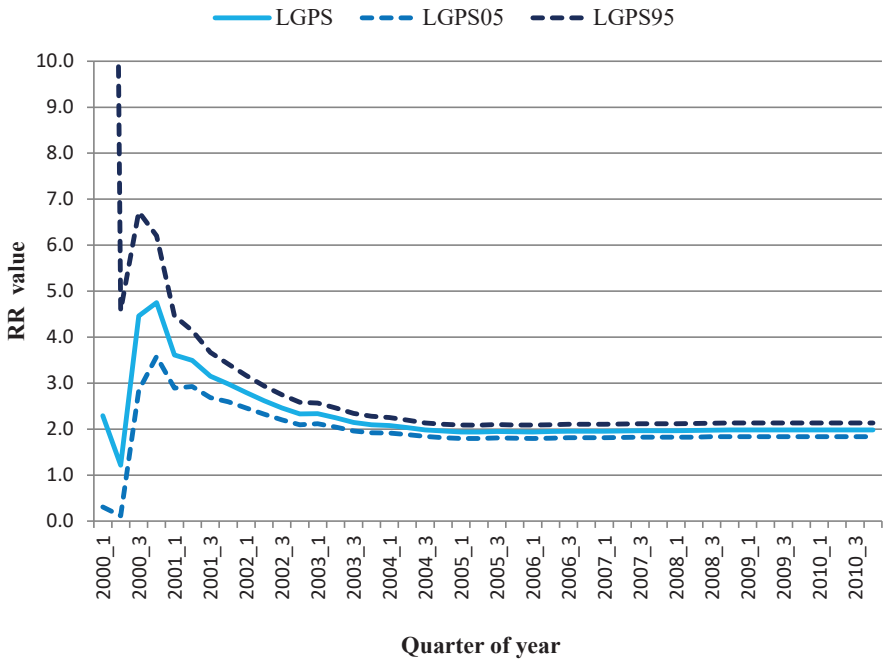
The databases in the EU-ADR project were able to identify a strong association concerning rofecoxib and AMI since the third quarter of 2000 (RR LGPS = 4.5; 95% Confidence Interval: 2.84-6.72) (see figure 3). The threshold of RR LGPS >= 2 was crossed early in 2000. The RR LGPS value increased to 4.5 in the third quarter of 2000 and peaked to 4.8 in the fourth quarter of 2000. The RR LGPS value ranged between 3 and 4 in the year 2001 and between 2 and 3 in the year 2002. It subsequently stabilized around 2 and stayed above the threshold of 2 until 2005.

Figure 3: Relative risk of AMI associated to rofecoxib use vs. non-use over time in the EU-ADR database network

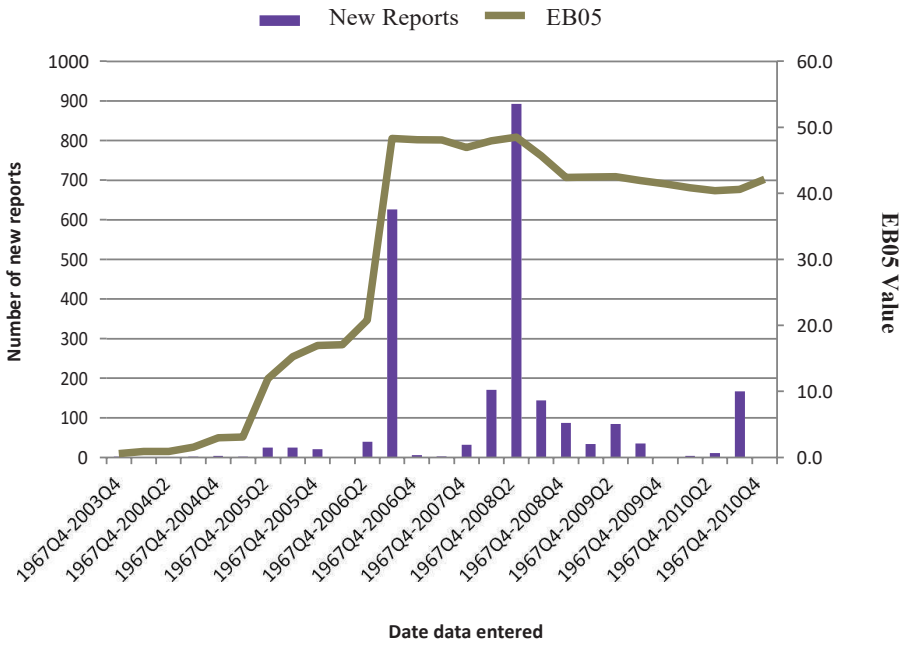


Relative risk (RR) was measured as Longitudinal Gamma Poisson Shrinkage (LGPS) value together with 95% confidence interval

WHO-VigiBase analysis

In the WHO-VigiBase spontaneous reporting system database, a total of 2,422 reports of AMIs were received with rofecoxib as a suspect medication. **Figure 4** shows the WHO-VigiBase data on rofecoxib and acute myocardial infarction per quarter by the date data were reported and entered in the WHO-VigiBase database. The first report of AMI with rofecoxib as a suspect medication was submitted in the fourth quarter of 2003, after the initial warning in 2002. There were two large increases in the number of new reports that were observed in the third quarter of 2006 and the second quarter of 2008. The EB05 threshold of 2 was crossed in the fourth quarter of 2004 (EB05 = 2.94). Since then, the EB05 value increased consistently and peaked in the third quarter of 2006 (EB05 = 48.3) and then again in second quarter of 2008 (EB05 = 48.5). It declined slightly after 2008 but still stayed in the range of 40-45.

Figure 4: Distribution of reports of AMI for which rofecoxib was the suspected drug as collected over time in the WHO- VigiBase spontaneous reporting database



EB05: Empirical Bayes posterior Gamma Mixture 5th percentile; estimates lower point in 90% confidence interval

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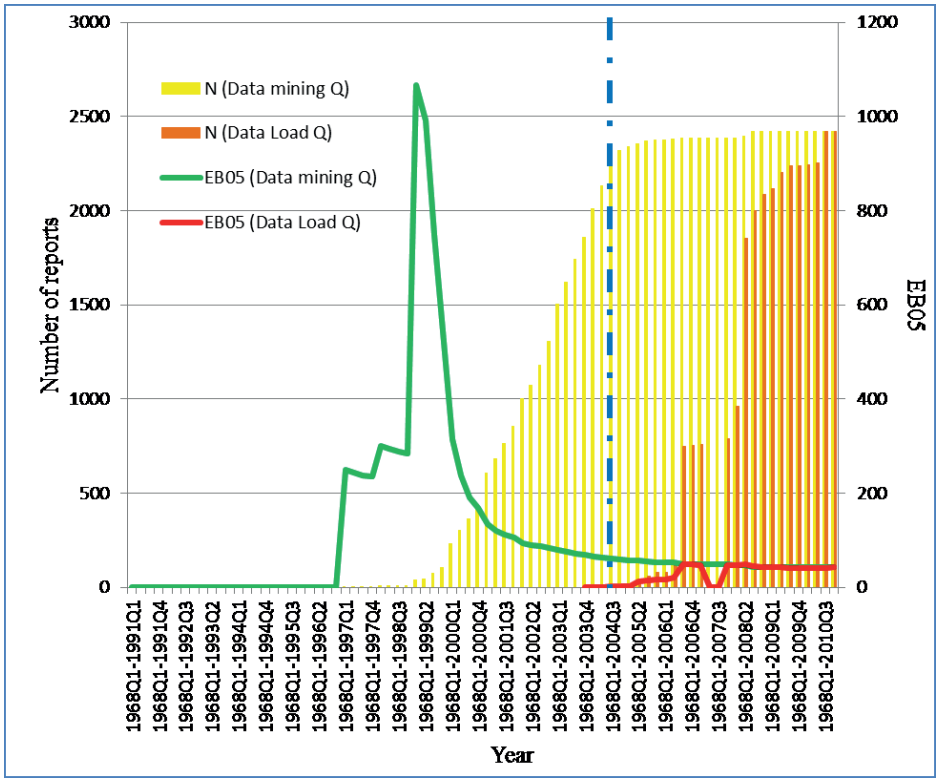
Figure 5 shows the WHO-VigiBase data on rofecoxib and acute myocardial infarction per quarter by the date data were entered in the WHO-VigiBase database (data load date) and also the date that the actual event occurred (data mining quarter date). The data from this chart shows that 93% (2,260 out of 2,422) of acute myocardial events actually occurred *prior* to the product withdrawal. However, they were reported *after* the risk minimization/risk communication efforts.

Figure 5: Acute Myocardial Infarction and Rofecoxib in WHO- VigiBase database



The yellow bars in the figure show the number of cumulative reports by quarter using the data mining quarter date. The orange bars represent the cumulative reports by the date they were reported and entered into WHO-VigiBase. The vertical blue line marks the date the manufacturer withdrew the product. The EB05 values using the data mining quarter is shown in green line and using the data load quarter is shown in red line.

Discussion

We demonstrated in this study that the AMI signal concerning rofecoxib could have been detected in the year 2000 (or 2001 at latest, taking into account the lag time in getting access to large database network) using the EU-ADR network of claims databases and EMRs, about 4 years before the signal was identified in the SRS data. The signal was not identified earlier in the WHO-VigiBase spontaneous reporting system. This is noteworthy since the association of AMI and rofecoxib was already documented in the VIGOR trial in which the finding on 3-fold increased cardiotoxicity in rofecoxib users vs. naproxen users was misinterpreted as protective effect of the latter drug. [19]

For the past six decades, for the marketed medicinal products, using spontaneously reported adverse events data has been the "gold standard" in the pharmacovigilance practice, even though, the limitations of these data are well recognized, including under- reporting in general and also over-reporting of highly publicized drug-adverse effects.

Healthcare professionals may not properly and readily attribute the onset of a multifactorial event like AMI to a medicine especially if that medicine is used for treating a disease which is per se a strong cardiovascular risk factor as it is the case for rheumatology diseases requiring coxib treatments. In the WHO-VigiBase database, initially, extremely low number of reports of suspected rofecoxib-associated AMI was reported. As a paradox, in the years following the rofecoxib withdrawal, a huge increase in the number of reports was observed. Data show that 93% of the reports concerned AMIs that occurred *prior* to the initial risk communications, however, was reported only after the rofecoxib was withdrawn from the market. These data show that the publicity of this topic was the driving force behind the increase number of reports observed *after* a risk was identified and not the true increase in the incidence of the drug-event combination.

It is possible, that once the risk was confirmed, communicated, and action taken by a regulatory agency, possibly healthcare professionals felt supported or even validated, in some instances, to report. In some cases, perhaps healthcare professional was even feeling compelled to report once a risk communication was distributed. Another major phenomenon to consider is that legal actions are common in North America, once a risk is communicated to public. Is the 'encouragement' from the lawyers driving patients and/or health care professionals to recall and report AMIs retrospectively? It will be interesting to tease out these reasons in future research.

EHR data are more immune to this type of reporting bias. The data are collected as a byproduct of the healthcare delivery practice and medical records system. They are not

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dependent on a healthcare professional or patient to, first, identify such an event and then report the event. The collection of the events and outcomes is less or not at all influenced by media or legal actions. Although not all events and outcomes are consistently captured in the EHR databases, serious events, such as AMI, have a greater chance to be collected and accurately coded.

As mentioned earlier, the SRS databases are used as a "gold-standard" in the pharmacovigilance practice for marketed products. However, the increased number of ADRs in the SRS after identification and communication of a risk brings minimal value to pharmacovigilance scientists. In fact, they contribute to "noise" in the SRS database. It is important for the pharmacovigilance scientists to understand this phenomenon when they are conducting data mining and signal detection for same medical concept but in different marketed product.

It is important to note limitations of this study. First, the study focused only on AMI as adverse event associated to with rofecoxib. As a consequence, the findings may not be generalizable to a broader range of drug-event associations, especially non-serious events which may not be captured consistently in the EHR system or drugs which are used in different therapeutic areas as compared to rofecoxib. In addition, WHO-VigiBase data were used for the SRS analyses. There are several other SRS databases that are widely used in the pharmacovigilance practice. The results may not be generalizable to other SRS databases. Another limitation is the fact that the LGPS method used on EHR data does not correct for confounding [20], and the increase observed might therefore reflect bias rather than a true signal. Lastly, true timing of the detection of AMI-rofecoxib association has to take into account the lag time between data generation and data access which may delay of 6 months or even 1 year the association identification in prospective evaluation. Future research should focus on these issues.

Conclusion

In this EU database network study covering a source population of 30 million persons, we were able to detect the AMI-rofecoxib association around 4 years prior to the drug withdrawal. If such a network was in place at that time it may have theoretically speed up the process leading to rofecoxib removal from the market. More specifically, the AMI-rofecoxib signal was initially identified in RCT but misinterpreted. As Platt stated in the Institute of Medicine meetings, large EHR and claims database networks may complement SRS and other sources for post-marketing drug safety evaluation, especially for those adverse events which are frequently captured in EHR databases and are not likely to be

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reported to SRS. [8] The US implemented Sentinel and the Canadian Network for Observational Drug Effect Studies (CNODES) has expanded capacity for drug safety surveillance. The EU has implemented several projects; however, none with sustainable system yet exist.

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Chapter 7

A reference standard for evaluation of methods for drug safety signal detection using electronic healthcare record databases

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Abstract

Background. The growing interest in using electronic healthcare record (EHR) databases for drug safety surveillance has spurred the development of new methodologies for signal detection. Although several drugs have been withdrawn post-marketing by regulatory authorities after scientific evaluation of harms and benefits, there is no definitive list of confirmed signals (i.e., list of all known adverse reactions and which drugs can cause them). As there is no true gold standard, prospective evaluation of signal detectionmethods remains a challenge.

Objective. Within the context of methods development and evaluation in the EU-ADR Project, we propose a surrogate reference standard of drug-adverse event associations based on existing scientific literature and expert opinion.

Methods. The reference standard was constructed for 10 top-ranked events judged as important in pharmacovigilance. A stepwise approach was employed to identify which among a list of drug- event associations are well-recognized (known positive associations) or highly unlikely ('negative controls') based on MEDLINE-indexed publications, drug product labels, spontaneous reports made to the World Health Organization's pharmacovigilance database, and expert opinion. Only drugs with adequate exposure in the EU-ADR database network (comprising approximately 60 million person-years of healthcare data) to allow detection of an association were considered. Manual verification of positive associations and negative controls was independently performed by two experts proficient in clinical medicine, pharmacoepidemiology, and pharmacovigilance. A third expert adjudicated equivocal cases and arbitrated any disagreement between evaluators.

Results. 94 drug-event associations comprised the reference standard, which included 44 positive associations and 50 negative controls for the 10 events of interest: bullous eruptions; acute renal failure; anaphylactic shock; acute myocardial infarction; rhabdomyolysis; aplastic anemia, pancytopenia; neutropenia/agranulocytosis; cardiac valve fibrosis; acute liver injury; and upper gastrointestinal bleeding. For cardiac valve fibrosis, there was no drug with adequate exposure in the database network that satisfied the criteria for a positive association.

Conclusion. A strategy for the construction of a reference standard to evaluate signal detection methods that use EHR has been proposed. The resulting reference standard is by no means definitive, however, and should be seen as dynamic. As knowledge on drug safety evolves over time and new issues in drug safety arise, this reference standard can be re-evaluated.

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Introduction

The growing interest in the utility of electronic healthcare records (EHR) for drug safety surveillance has spurred the development of new methodologies for quantitative and automated signal detection. Timely detection of safety signals remains a challenge because no single technique ensures identification of all drug-related adverse events, whether signal detection is done using spontaneous reports[1] or using healthcare records.[2] Generation of false alarms similarly constitutes a public health hazard, not only overwhelming regulatory agencies and diverting already scarce resources, but also triggering unwarranted warnings or even drug market withdrawals.[3] Thus, proper evaluation of signal detection methodologies calls for the creation of a reference standard, the purpose of which is to better define the predictive value of these new techniques, as well as their added value to the current pharmacovigilance armamentarium.

Signal detection in the context of pharmacovigilance

The World Health Organization (WHO) has defined 'signal' as 'reported information on a possible causal relationship between an adverse event and a drug, the relationship being unknown or incompletely documented.[4] An updated and more encompassing definition has been proposed recently based on a systematic review of how the term is being applied in current pharmacovigilance: a signal represents information that arises from one or multiple sources which suggests a new potentially causal association, or a new aspect of a known association, between an intervention and an event or set of related events, either adverse or beneficial, and is judged to be of sufficient likelihood to justify verificatory and remedial actions.[5] Although a 'gold standard' of confirmed signals, i.e., causal drug-adverse event associations, does not exist, a reference standard of recognized associations based on existing published scientific literature, regulatory actions (e.g., labeling changes or withdrawal of marketing authorization), as well as expert opinion may serve as suitable surrogate. In this paper we describe a reference standard that was put together in the context of methods development within the EU-ADR Project ('Exploring and Understanding Adverse Drug Reactions by integrative mining of clinical records and biomedical knowledge,' http://www.euadr-project.org), which aims to exploit information from various EHR databases in Europe to produce a computerized integrated system for the early detection of drug safety signals.[6] This reference standard was developed for the primary purpose of evaluating performance of methods for signal detection using EHR.

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Methodology

The EU-ADR network currently comprises anonymous healthcare data from eight established European databases located in four countries (Denmark, Italy, the Netherlands, and United Kingdom).[7] Clinical and drug dispensing/prescription data used for this paper represent data from 19 647 445 individuals with 59 929 690 person-years (PYs) of follow-up.

Adverse Events

In the EU-ADR Project we have chosen an event-based approach to active drug safety surveillance, focusing on events considered to be important from a pharmacovigilance and public health perspective. For the construction of this reference standard, we considered the following top 10 events which have been selected from a list of 23 events ranked on the basis of importance in pharmacovigilance using predefined criteria: (1) bullous eruptions; (2) acute renal failure;
(3) anaphylactic shock; (4) acute myocardial infarction; (5) rhabdomyolysis; (6) aplastic anemia/ pancytopenia; (7) neutropenia/agranulocytosis; (8) cardiac valve fibrosis; (9) acute liver injury; and (10) upper gastrointestinal bleeding.[8]

Drug selection

The procedure employed in the construction of the reference standard is outlined in Figure 1. It was first necessary to ensure that the drug-event associations to be included in the reference standard are identifiable in clinical practice and could be investigated in the EU-ADR network. That is, there should be adequate exposure to the drugs to permit detection of an association with the adverse event of interest, if present. In another publication we described the sample size calculations used to derive the total amount of PYs of drug exposure required to detect an association between a drug and a particular event over varying magnitudes of relative risk (RR), using one- sided significance level $\alpha = 0.05$ and power of 80%, given pooled population-based incidence rates (IR) estimated directly within the EU-ADR network.2 For this reference standard we employed in the calculations RR of at least 2 for all events except for rhabdomyolysis, bullous eruptions, and anaphylactic shock, where we used RR of at least 4. The latter was done to account for the very low background incidence rates of these events in the population (2.5/100 000 PYs for rhabdomyolysis, 5.7/100 000 PYs for anaphylactic shock, and 5.9/100 000 PYs for bullous eruptions). A series of steps was subsequently employed to select the positive drug-event associations and 'negative controls' among those potentially eligible (i.e., drugs with adequate amount of exposure to detect the association of interest) (see Figure1).

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Information retrieval from published literature

To streamline the scientific literature search, we utilized a tool developed within the EU- ADR Project that automatically searches MEDLINE-indexed publications concerning adverse drug reaction (ADRs).[9] A subset of MEDLINE was downloaded (via PubMed) and imported in a database including all the citations from December 1952 to February 2010 with the 'adverse effects' MeSH subheading. For each citation the PubMed identification (PMID), MeSH descriptors, major/minor subheadings, substances, date of creation of the citation, as well as publication type, were obtained. Co-occurrence of the drug (from 'substances' OR 'MeSH heading' fields) and the event (under the subheading 'adverse effects') in a citation were noted. Drug codes in WHO Anatomical Therapeutic Chemical (ATC) classification were first mapped to MeSH headings or supplementary concept records using standardized concept unique identifiers from the Unified Medical Language System (UMLS).[10] Drugs from the 'substances' field were taken into account only if their pharmacological action was qualified by the subheading 'adverse effects.' Taking the pharmacological action as an additional element for consideration was an attempt to establish a link between the adverse event of interest and the drug in the context of drug safety and not just a co-occurrence in a MEDLINE citation. This becomes particularly important when more than one drug is mentioned in the citation.[10]

Selection of known positive drug-event associations

The drug-event associations were ranked according to the number of MEDLINE citations with co-occurrence of the drug and the adverse event of interest. For the pool of positive drug- event associations, we considered those with the highest number of citations. This meant that more published evidence was available on these associations. Citations may refer to case reports, observational studies, clinical trials, reviews, or meta-analyses. The type of publication was taken into account in the evaluation of the evidence regarding each drug-adverse event association, as subsequently described. Supplementary information was obtained from the Summary of Product Characteristics (SPCs) or product labels.[11-16] The aim was to select five drugs which are positively associated with each event of interest. Whenever possible, drugs belonging to different classes were included in the pool. However, the need for minimizing ambiguity (i.e., by selecting strong and well- substantiated drug-adverse event associations) took precedence over the need for diversity in terms of drug class. Except for fixed-dose combinations, drug preparations with more than one active substance were excluded from the pool.

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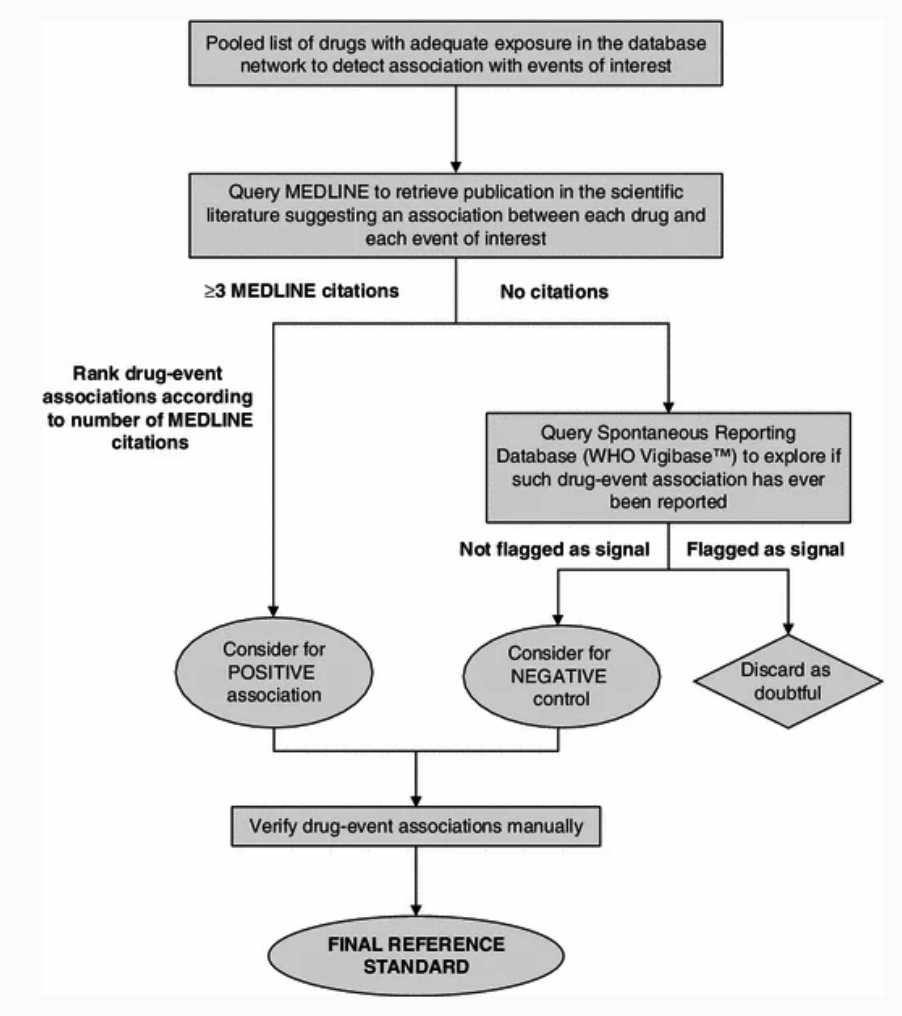
Figure 1: Flowchart showing the process of the construction of the reference standard



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Selection of 'negative controls'

A drug-event association was considered for the pool of 'negative controls' if there were no MEDLINE citations with co-occurrence of the drug and the event of interest and if there was no explicit mention of such adverse event in the drug product label. The pool of 'negative controls' was further evaluated using the WHO spontaneous reporting database (VigiBase) to exclude associations flagged as potential signal using standard data mining methodology. The list of potential signals from VigiBase (including data up to the fourth quarter of 2010) was generated using Oracle Health Sciences Empirica^{TM} Signal tool (courtesy of Astellas Pharmaceuticals). Bayesian disproportionality analysis was performed using preferred terms (PTs) mapped to the events of interest.[17] A value greater than 2 for the lower bound of the 90% confidence interval of the Empirical Bayes Geometric Mean (EB05) and the presence of at least one report were used as the criteria for flagging a signal.[18] The aim was to likewise obtain five drug-event associations as 'negative controls' per event of interest.

Evaluation of the evidence from literature

Table 1 shows the scheme that was used as guide to evaluate evidence from the literature. Manual verification of the positive associations and 'negative controls' was conducted by two physicians with proficiency in clinical medicine, epidemiology, and pharmacovigilance. A third expert arbitrated any disagreement between evaluators. The following indices of agreement between evaluators were assessed: (i) proportion of overall agreement; (ii) proportion of specific agreement; and (iii) kappa statistic, κ, for chance-corrected agreement. The earliest date of MEDLINE citation was also noted for each drug-event association.

Table 1: Levels of evidence used in the evaluation of drug safety information from the literature

Level of evidence	Description
I	Evidence from at least one (properly designed) randomized controlled trial or meta-analysis
II	Evidence from at least one observational study (e.g. cohort, case-control, case-crossover, self-controlled case series) OR from at least three published case reports from different sources and concerning different patients
III	Evidence from not more than two published case reports OR from unpublished reports in pharmacovigilance databases and no further substantiation in the literature
IV	Included in drug label (SPC) but no case reports or published studies
V	No evidence from published literature or from WHO spontaneous reporting database and not mentioned in the SPC

Recommendations: Levels I and II → positive association; Levels III and IV → cannot be determined → disregard as doubtful; Level V → 'negative control'
SPC: summary of product characteristics

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Results

The amount of drug exposure required to detect a potential signal in the EU-ADR database network for each of the events of interest is shown in Table 2. Overall, there were 893 drugs (i.e., unique ATC codes, 5th level – chemical substance) with enough exposure to permit detection of an association with at least one of the 10 events of interest. Out of the 893 drugs, the following are the number (i.e., count) of drugs for which there were at least three MEDLINE citations with co- occurrence of the drug and the corresponding event: acute liver injury, 21; acute myocardial infarction, 52; acute renal failure, 51; anaphylactic shock, 26; bullous eruptions, 47; cardiac valve fibrosis, 2; neutropenia/agranulocytosis, 30; aplastic anemia/pancytopenia, 21; rhabdomyolysis, 8; upper gastrointestinal bleeding, 54. Close to 1 200 abstracts and, when necessary, also the full- text journal articles pertaining to all 10 events were reviewed to arrive at a shortlist of potential positive associations and 'negative controls.' Specific citations in drug product labels concerning 'undesirable effects,' 'warnings,' and 'adverse reactions' were used to further restrict the shortlist of associations. Table 3 shows how the manual evaluation of a positive association for acute liver injury with valproic acid and for upper gastrointestinal bleeding with indometacin were done. The complete evaluation for all the positive drug-adverse event associations of interest can be found in the Appendix.

The final reference standard consisted of 94 drug-event associations, which included 44 positive associations and 50 'negative controls' related to the 10 events of interest. Table 4 lists the positive associations, including the corresponding level of evidence. Majority of the positive associations were based on Level II evidence. The associations for which there was Level I evidence include that of nonsteroidal anti-inflammatory drugs (NSAIDs) and of heparin with upper gastrointestinal bleeding, the association of the statins with rhabdomyolysis, and the association of coxibs and of rosiglitazone with acute myocardial infarction. All 'negative controls,' by definition, have Level V evidence and are listed in Table 5. Both positive and 'negative control' associations comprised 68 unique drugs (i.e., ATC 5th level) belonging to 42 different pharmacological subgroups (i.e., ATC 3rd level). Only four drugs having sufficient exposure in the database network satisfied the criteria for a positive association with rhabdomyolysis, all of them being HMG-CoA reductase inhibitors (statins). Fibrates, as a class (ATC 4th level, chemical subgroup), comprised enough exposure to detect an association with rhabdomyolysis, but the individual drugs did not. For cardiac valve fibrosis, no drug with adequate exposure met the criteria for a positive association after review of the literature.

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Table 2: Amount of drug exposure required to detect a potential signal in the EU-ADR database network for the events of interest

Event	Required exposure (person-years)	No. of drugs with sufficient exposure to detect association and with ≥3 MEDLINE citations
Acute liver injury	32,769	21
Acute myocardial infarction	4,706	52
Acute renal failure	30,397	51
Anaphylactic shock	21,733	26
Bullous eruptions	20,823	47
Cardiac valve fibrosis	13,604	2
Neutropenia/agranulocytosis	82,697	30
Aplastic anaemia/pancytopenia	77,192	21
Rhabdomyolysis	49,593	8
Upper gastrointestinal bleeding	12,028	54

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Table 3: Example summary of manual evaluation of positive drug-event associations for valproic acid and indometacin

ATC code	Drug name	Event type	No. of MEDLINE notices	Labelled as AE in SPC [Yes/No]? (Source and label section)
N03AG01	Valproic acid	Acute liver injury	*Total no. of citations = 31*	Yes DailyMed[c] (boxed warning, adverse reactions) eMC[d] (special warnings and precautions for use, undesirable effects) Micromedex[e] (adverse reactions)
			Review[a] = 1	
			Clinical trial = 1 (RCT)	
			Epidemiological study = 1 (cohort study)	
			Case reports[b] = 28 (1 citation involving 3 cases, 1 citation involving 5 cases, 1 citation reviewing 31 cases, 2 other citations with literature review)	
M01AB01	Indometacin	Upper gastrointestinal bleeding	*Total no. of citations = 45*	Yes eMC[d] (undesirable effects) Micromedex (adverse reactions)
			Review = 13	
			Clinical trial = 16 (9 RCTs)	
			Epidemiological study = 5 (1 case control and 4 cohort studies)	
			Case reports = 11	

AE adverse event, ATC Anatomical Therapeutic Chemical, eMC electronic medicines compendium, RCT randomized controlled trial, SPC summary of product characteristics

a Review refers to both systematic and narrative reviews

b Case reports involve only one case pertinent to the drug of interest, unless specified

c Website for drugs currently marketed and approved by the US FDA (http://dailymed.nlm.nih.gov/)

d For drugs licensed in the UK (http://www.medicines.org.uk)

e The Micromedex family of international databases provides full-text drug and substance information (http://www.thomsonhc.com/micromedex2/)

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Table 4: Positive drug-event associations

	Positive associations.		
Event	**ATC**	**Name**	**Level of Evidence**
Acute Liver Injury	N03AF01	Carbamazepine	I
	N03AG01	Valproic acid	I
	M01AX17	Nimesulide	II
	J01CR02	Amoxicillin and clavulanic acid	II
	A07EC01	Sulfasalazine	II
Acute Myocardial Infarction	M01AH02	Rofecoxib	I
	A10BG02	Rosiglitazone	I
	G03AA07	Levonorgestrel and estrogen	I
	N02CC01	Sumatriptan	I
	M01AH03	Valdecoxib	I
Acute Renal Failure	C09AA01	Captopril	II
	M01AE01	Ibuprofen	I
	N02BE01	Paracetamol	I
	J01MA02	Ciprofloxacin	I
	N05AN01	Lithium	I
Anaphylactic Shock	B01AC06	Acetylsalicylic acid	II
	N02BE01	Paracetamol	I
	J01CA04	Amoxicillin	I
	J01MA02	Ciprofloxacin	I
	M01AB05	Diclofenac	I
Bullous Eruptions	N03AF01	Carbamazepine	II
	J01EE01	Sulfamethoxazole and trimethoprim	II
	N03AX09	Lamotrigine	I
	M04AA01	Allopurinol	I
	C03CA01	Furosemide	I
Cardiac Valve Fibrosis: No drug with sufficient exposure that satisfies criteria for True Positive			
Neutropenia/ agranulocytosis	H03BB02	Thiamazole	I
	B01AC05	Ticlopidine	I
	C09AA01	Captopril	I
	N03AF01	Carbamazepine	I
	N03AG01	Valproic acid	I
Aplastic anemia/ Pancytopenia	B01AC05	Ticlopidine	II
	N03AF01	Carbamazepine	I
	H03BB02	Thiamazole	I
	M04AA01	Allopurinol	I
	C09AA01	Captopril	I
	C10AA07	Rosuvastatin	I
Rhabdomyolysis	C10AA05	Atorvastatin	I
	C10AA03	Pravastatin	I
	C10AA01	Simvastatin	I
Upper Gastrointestinal Bleeding	N02BA01/ B01AC06	Acetylsalicylic acid	I
	M01AB01	Indometacin	I
	B01AB01	Heparin	I
	H02AB06	Prednisolone	I
	M01AE01	Ibuprofen	I

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Table 5: 'Negative control' associations

Event	ATC code	Name
Acute liver injury	R03AC13	Formoterol
	S01ED05	Carteolol
	G04CA03	Terazosin
	N04BA02	Levodopa and decarboxylase inhibitor
	C01DA02	Glyceryl trinitrate
Acute myocardial infarction	A10AD01	Insulin (human)
	B03AA07	Ferrous sulfate
	J01CR02	Amoxicillin and clavulanic acid
	J05AB11	Valaciclovir
	C10AB04	Gemfibrozil
Acute renal failure	R01AD09	Mometasone
	H03AA01	Levothyroxine sodium
	R06AX26	Fexofenadine
	N04BA02	Levodopa and decarboxylase inhibitor
	B03AA07	Ferrous sulfate
Anaphylactic shock	N06AX11	Mirtazapine
	H03AA01	Levothyroxine sodium
	C02AC01	Clonidine
	C02CA04	Doxazosin
	N05BA04	Oxazepam
Bullous eruptions	C01BC03	Propafenone
	C07AB03	Atenolol
	R03BB01	Ipratropium bromide
	R03BB04	Tiotropium bromide
	C08CA02	Felodipine
Cardiac valve fibrosis	N06AB08	Fluvoxamine
	L04AX03	Methotrexate
	C09CA04	Irbesartan
	C03CA01	Furosemide
	G03CA03	Estradiol

Event	ATC code	Name
Neutropenia/agranulocytosis	C07AA07	Sotalol
	H03AA01	Levothyroxine sodium
	C10AA05	Atorvastatin
	C01DA14	Isosorbide mononitrate
	G04CA02	Tamsulosin
Aplastic anaemia/pancytopenia	C09CA04	Irbesartan
	C10AA04	Fluvastatin
	S01EE01	Latanoprost
	S01ED01	Timolol
	R06AX27	Desloratadine
Rhabdomyolysis	G03CA03	Estradiol
	C02CA04	Doxazosin
	A10BB12	Glimepiride
	S01ED01	Timolol
	C01DA02	Glyceryl trinitrate
Upper gastrointestinal bleeding	R06AX26	Fexofenadine
	C10AA01	Simvastatin
	S01EC03	Dorzolamide
	L02AE03	Goserelin
	N05CF01	Zopiclone

ATC: Anatomical Therapeutic Chemical

Inter-evaluator agreement

The indices for agreement were computed across all drug-event pairs evaluated (179 drug- event pairs), including those which eventually did not get included in the final reference standard. The proportion of overall agreement (the proportion of cases for which both evaluators agreed across all evaluation categories) was 0.93 (95% confidence interval (CI) 0.89 to 0.97). The proportions of specific agreement were as follows: (1) 'positive' agreement 0.96 (95% CI 0.93 to 0.98); (2) 'negative' agreement 0.90 (95% CI 0.89 to 0.90). There were three instances where one evaluator considered a drug-event association 'undetermined' while the other considered it a positive association (paracetamol-anaphylactic shock, bromocriptine-acute myocardial infarction, and acetylsalicylic acid-bullous eruptions). Of these three instances only one was eventually included in the reference standard after arbitration (paracetamol- anaphylactic shock). There was a single case where one evaluator marked the association 'undetermined' while the other marked it as 'negative control' (prednisone-neutropenia/agranulocytosis). Arbitration was done by a third expert. There was no disagreement between evaluators in the final list of 'negative control' associations. The chance- corrected agreement kappa coefficient, was 0.83 (unweighted, 95% CI 0.74 to 0.92).

Discussion

In this paper we present a novel approach to identify a surrogate 'gold standard' for drug safety signal detection using a systematic and rigorous methodology, applied across various data sources and which could be extended to examine other drug-event associations. We put together a list of drug- adverse event associations known to be true and drug-event associations considered to be unlikely based on current published scientific literature, drug product labels, spontaneous ADR reports, and expert opinion. Although the rationale for creating this reference standard is to have one single index against which signal detection methods (as applied to EHR data) can be tested, this reference standard can be re-evaluated and adapted to different settings as needed.

In evaluating the evidence from the literature we only considered associations that were reported with use of the drug in therapeutic doses, which is consistent with the definition of an adverse drug reaction.[19] For acetylsalicylic acid, citations referring to both cardiovascular prophylactic (low-dose) and analgesic doses were considered. We considered, aside from case reports that described the clinical characteristics leading to suspicion of an ADR, publications that proposed (or elucidated) biologic mechanisms for the associations. Such publications came in the form of both narrative reviews and systematic reviews. We likewise considered associations that were described in the context of drug- drug interactions (e.g., aplastic anemia resulting from the synergistic interaction between azathioprine

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and allopurinol).[20] For the event acute renal failure, we disregarded associations which arose from rhabdomyolysis leading to renal failure, but considered the reverse situation (i.e., associations for rhabdomyolysis which resulted in renal failure). While randomized controlled trials (RCTs) and meta- analyses are considered supreme with respect to level of evidence, this is more true for evidence regarding efficacy, not so much for safety, of interventions.[21-24] This is apparent in Table 5, where most of the evidence pertaining to the positive associations came from observational studies and case reports (or reviews). The associations with Level I evidence are those that are well-known (e.g., association of the NSAIDs and of heparin with upper gastrointestinal bleeding), or well-investigated – either because of controversy or public health impact (e.g., the association of the statins with rhabdomyolysis, and the association of coxibs and of rosiglitazone with acute myocardial infarction). Interestingly, but perhaps not surprisingly, the most widely- investigated association was that between aspirin and upper gastrointestinal bleeding (259 MEDLINE citations overall, see Appendix). Most of the publications related to this association, including clinical trials, described the drug as a comparator to other drugs that are presumed (and proven) to confer a lower risk of the event.

There have been previous attempts to develop a reference standard with which data mining methods for safety signal detection can be evaluated, 'rules of evidence' being devised *ad hoc*.[25-27] In the creation of this reference standard we employed a systematic approach incorporating various sources of drug safety information, the process designed to be transparent and reproducible, thus also making it easier to update. Different sources have varying comprehensiveness and accuracy with regards to documenting drug-adverse event associations. Because RCTs may be restricted to specific populations and lack statistical power to detect rare events, they must be supplemented by non-experimental studies and other types of evidence, including case reports.[21-24] Rare or idiosyncratic events (e.g., bullous eruption- Stevens Johnson syndrome) and events occurring after chronic exposure (e.g., cardiac valvulopathy) are unlikely to be identified in clinical trials, but rather in case reports or observational studies.

There was only one disagreement between evaluators in the final list of positive associations ('undetermined' vs. 'positive' for the association paracetamol-anaphylactic shock; arbitration resulted in positive association). There was no disagreement between evaluators in the final list of 'negative control' associations. Although this high overall agreement between evaluators indicates that the resulting reference standard fulfills the pre-determined criteria, as the definitions of positive associations and 'negative controls' are based on existing knowledge at the time of this review, these associations (especially the 'negative controls') may be refuted as new data come along.[28] Hence, this reference standard should be considered dynamic and will need periodic re-evaluation. Adoption of this reference standard for use by other investigators can validate its applicability in other settings and

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will facilitate its further improvement.

While a reference standard, however rigorously constructed, may be able to permit evaluation and comparison of methods for signal detection, a method shown to successfully detect known drug-adverse events associations is not a guarantee that such method will also be able to detect signals, i.e., new, currently unknown, drug-event associations (problem of contemporary comparison).[29]

Limitations

Since the selection of drugs for the reference standard was dependent on the presence of adequate exposure to detect an association within the EU-ADR network (i.e., drugs that are more frequently used in the population were more likely to be chosen), this reference standard may not be as useful for evaluation in situations where the drug use patterns are expected to be different. In particular, the EU-ADR database network is unable to capture information on drugs which are primarily used in hospitals or specialist centers (e.g., anti-cancer drugs) and for this reason such drugs have not been included in the reference standard. This criterion also precluded the inclusion of known associations with drugs which have been withdrawn from the market for a long time before the accrual of healthcare data in the databases. Because of this, there was no drug that could be used as a positive reference for the event cardiac valve fibrosis; the use of the appetite suppressants fenfluramine and phentermine, as well as the dopamine agonists pergolide and cabergoline, were inadequately documented or no longer captured in the databases because of the decline in use (or eradication in practice) of these drugs.[30] The choice as to which drug-event pairs can be considered for the positive associations was primarily established on the basis of the number of publications (i.e., number of MEDLINE citations with co-occurrence of the drug and the event of interest). This meant that drugs that have been on the market longer – or were involved in high-profile or controversial issues – had a higher chance of being included in the reference standard.

Finally, the availability of a surrogate 'gold standard' is only one component of the evaluation process for signal detection methodologies.[3,31] Other issues that need to be considered in performance evaluation of these methods include standardization of event definitions, establishment of reliable and consistent criteria for adjudicating causality and expectedness of adverse events, as well as understanding variations in database content and quality.

Conclusion

A unique strategy for the construction of a reference standard to evaluate drug safety signal detection methodologies using EHR has been proposed. This reference standard should be considered dynamic and as knowledge on drug safety evolves over time and new issues in drug safety arise, this reference standard can be periodically re-evaluated. Our proposed strategy

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represents a novel contribution to pharmacovigilance, with opportunities for adaptation to evaluate harms and benefits for other suspected ADRs.

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Chapter 8

Summary, General Discussion, and Future Perspective

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Discussion

Spontaneous reporting systems in pharmacovigilance were established in the 1960s as a reaction to several severe adverse reactions to drugs (for example, thalidomide). Up until the early year 2000, spontaneous data sources such as the World Health Organization's Vigibase database (WHO-Vigibase), [2, 3] the United States (US) Food and Drug Administration's (FDA) Adverse Event Reporting System database (FAERS), [4-8] the US Vaccine Adverse Event Reporting System (VAERS), were the primary real-world data (RWD) sources available to pharmacovigilance professionals for signal detection. However, in the last 20-25 years, with the availability of high-capacity computers and the development of advanced analytics, pharmacovigilance has started to explore other types of RWD sources for signal detection, such as electronic health records (EHR), claims data and social media data. There are now varieties of these types of database available worldwide. Most of them are specific to a country or geographic area and differ from each other based on a medical practice of the institution and the country that they represent.

Historically, EHR data have been widely used for hypothesis testing by epidemiologists. However, the use of EHR data for signal detection or signal strengthening in pharmacovigilance is still a novel concept. Most studies thus far have developed new methods and compared them against reference sets to estimate the performance. In this thesis, the value of using EHR data for signal detection was evaluated and compare with signal detection through the spontaneous reporting system data.

Current role of EHR in signal detection

As part of the thesis, we evaluated utilizing EHR data compared to the spontaneous reporting system data for signal detection and signal strengthening using both retrospective and prospective methodologies. The spontaneous reporting system data still remains as the "gold standard" for signal detection conducted by regulatory agencies worldwide and manufactures. However, the limitations of these data are well known. The inconsistencies and underreporting associated with the data collected within the spontaneous reporting system have pushed pharmacovigilance professionals to explore new data sources such as EHR. As we know, the spontaneous reporting system data are collected with the assumption of causality between a drug and an event and therefore are highly dependent on reporter's ability to recognize such and their priority to report. This dependency could hinder the identification of signals for events that are confounded by many underlying factors and co-morbidities, resulting in difficulty for a reporter to identify a causal link.

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In this thesis, using a retrospective methodology, we started with pre-set drug-event combinations that were determined as signals based on experience with that product (by reviewing product information brochure) and literature publications [9]. The value of both EHR and spontaneous reporting system data was demonstrated by a time restriction analysis in the retrospective methodology (Chapter 4). The unrestricted evaluation (using data from all years) against reference sets, slightly favored the performance of spontaneous reporting system data and underestimated that of EHR data as ‘‘diagnostic’’ signal detection tools.

Prospective methodology mirrored the normal pharmacovigilance practice where signal detection was done as a hypothesis-generating exercise by looking for signals that were not previously known or there was a change in frequency or severity of the event for known signals. In this type of situation, the prospective analysis showed that EHR might have a more significant potential for detecting signals for events occurring at a higher frequency in general population and those that are commonly not considered as potentially a drug-induced event (Chapter 5).

In spontaneous reporting system databases, there is also underreporting of events that are not judged to be “important” in the eyes of the reporter. As described in Chapter 6, we observed that once the risk was identified and communicated to the healthcare community, there was a marked increase in the reporting of the adverse drug reactions (ADRs). Thus, the underreporting was observed in the spontaneous reporting system database until the detection of the risk; post- detection, increased reporting was observed. One of the most interesting findings was observed for the combination of acute myocardial infarction and rofecoxib. In the WHO-Vigibase database, the first reports that were collected were an extremely low number of suspected reports of acute myocardial infarction in association to rofecoxib. In the years following the rofecoxib withdrawal, a huge increase in the number of reports was observed. Data show that 93% of the reports were for the ADRs that occurred prior to the risk communication, however, were retrospectively reported. These data show that the publicity due to the risk minimization and risk communication was the driving force behind the increase number of reports observed after a risk was identified and not the true increase in the incidence of the drug-event combination. Therefore, the increased number of ADRs in the spontaneous reporting system data after identification of risk brings minimal value to the researchers. In fact, they contribute to "noise" in the spontaneous reporting system database. It is important for the pharmacovigilance professionals to understand this phenomenon when they are conducting data mining and signal detection for same medical concept but in different marketed product or product in the same drug class.

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EHR data are more immune to this type of reporting bias. The data are collected as a byproduct of the healthcare delivery practice and medical records system. They are not dependent on a healthcare professional or patient to, first, identify such an event and then report the event. The collection of the events and outcomes is less or not at all influenced by media or legal actions. Although not all events and outcomes are consistently captured in the EHR databases, serious events, such as AMI, have a greater chance to be collected and appropriately coded.

Future direction

Even though spontaneous data sources are typically used in pharmacovigilance for signal detection, based on research of this thesis, it is observed that conducting signal detection in both EHR and spontaneous reporting system would strengthen the current signal detection activities by decreasing the influences of systematic bias when using single data source. In a recently published opinion in the Journal of the American Medical Association, FDA has shared that as a part of the Sentinel initiative, it is routinely using real-world data (such as claims and EHR) for drug safety [10]. Active Risk Identification Analysis (ARIA) is FDA's active post-market risk identification and analysis system which is comprised of pre-defined, parameterized, reusable routine querying tools combined with the EHR in the Sentinel Common Data Model. [11] The FDA has also embarked on the next phase of the Sentinel initiative to explore utilization of this system and data for signal detection. The Robert J. Margolis, MD, Center for Health Policy at Duke University conveyed a public workshop in December 2018, under cooperative agreement with the FDA, to solicit broad stakeholder input (including academia and manufacturers), on potential frameworks for implementing signal detection using the Sentinel system and to discuss methodological approaches and opportunities, as well as challenges involved with operationalizing these approaches within Sentinel's distributed data network. [12, 13]

When thinking about practical implementation within regulatory agencies and manufacturers, it would be advised to systematically start with EHR data that are appropriate for the both products and patients. There is no one combined data source available globally. The best option would be to select one or several databases from the region(s) that covers most of the market share. For example, for manufacturers, if a product is primarily marketed in the EU, then EU specific EHR data source be the best and preferred option. As we know, signal detection is the hypothesis generation exercise. Multiple data sources are typically reviewed in drug safety to find signals. For a regulatory agency, database selection will depend on their country and/or geographical jurisdiction.

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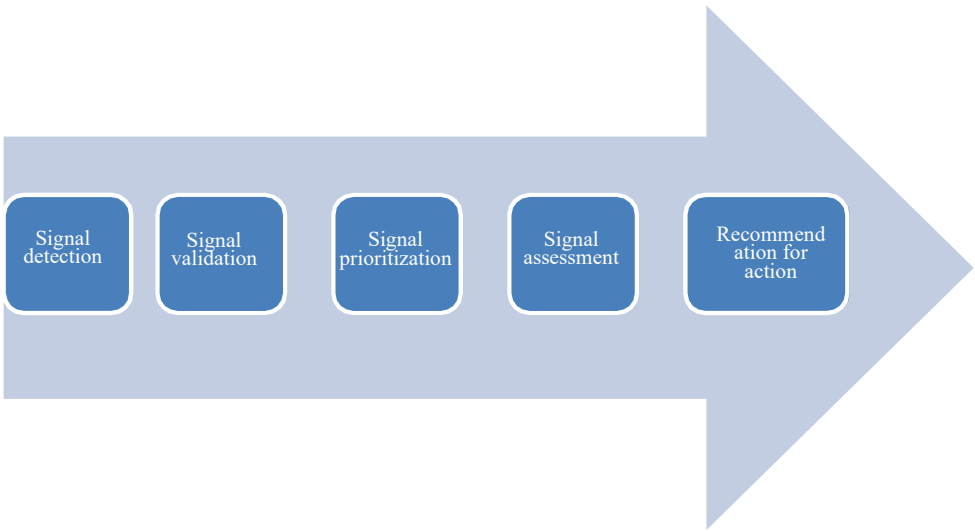
Lack of harmonization and consistent data structures are major limitations of the current EHR data sources, which prohibits pharmacovigilance professionals from integrating various data sources. There has been a lot of great work done under Sentinel, OMOP and OHDSI to develop common data models [12, 14, 15]. However, continuation of this work is needed if the pharmacovigilance community wants to fully utilize large EHR data across geographic regions for signal detection. There is also the need to have a reference standard for events of interest, such as the one created in the EU-ADR and OMOP projects to ensure that there is consistency in the definition of the outcomes that are included in the signal detection process (Chapter 7) [9, 14].

Another way EHR can contribute in pharmacovigilance is by providing multiple levels of evidence and thus help with signal strengthening in the prioritization step of the signal management process [16]. Figure 1 shows the typical steps in the signal management process. For example, if a signal is found in both the spontaneous reporting system and EHR data sources, then it could be given higher priority vs. detecting it only in the spontaneous reporting system. As we know, multiple criteria are used in the signal prioritization step.

Figure 1: Typical steps within the signal management process



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In general pharmacovigilance practice when a signal is detected and confirmed as a risk, either by a manufacturer or a regulator, using spontaneous reporting system data sources, sometimes analysis or study in EHR is proposed to further understand the risk (as part of epidemiology study). If EHR is included as a routine data source for signal detection (hypothesis generation exercise), then there is a discussion in the pharmacovigilance community if it would be appropriate to use the same EHR data source for signal evaluation and risk characterization (hypothesis testing). In other words, can you use the same data source for both hypothesis generation and hypothesis testing? There is a need to gain clarity on this in future research.

Due to technological advancement, we now have various frameworks (such as FDA's Sentinel Framework) and real-world data sources (such as PHARMO Database Network, Clinical Practice Research Datalink, Flatiron Health, etc.) available for signal detection [12, 17-19]. With the advancement of digital technology and digital wearables (such as a watch, apps, etc.), new types of real-world data are now available. One of the advantages of these types of data is that they can be tracked and evaluated in real-time. Future research should focus on incorporating these data into the signal detection process. There are already a few research publications on utilizing social media data for signal detection [20, 21]. They have had a mixed outcome on the utility of such data in the routine signal detection process. It would be helpful to the pharmacovigilance community to learn if there is a difference in structured vs. unstructured social media for signal detection. With the availability of machine learning techniques and advanced analytics, in future research, it would be useful to see if EHR and social media data could be layered on the top of the spontaneous reporting system data for real-world signal detection.

Recommendation for future: Need for disruptive innovation in pharmacovigilance

When spontaneous data collection systems were established in the 1960s, the goal was to collect information in "real-time" from the users and prescribers of the medications and to identify safety risks as soon as possible and implement risk mitigation and risk management strategies to protect public health. These principles remain unchanged and still echo the purpose of pharmacovigilance. In the last 60 years, what has changed though is the advancement in computer infrastructure, reduced cost of computing, digital technology, advanced analytics and the availability of machine learning and artificial intelligence. So, it is time to innovate and implement a system that will take advantage of the advancements and will help pharmacovigilance professionals to meet the goal of protecting public health effectively.

We need to explore new and innovative ways to collect good quality data in today's

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“real-time." Spontaneous reporting system data have been very successful in identifying risks, however, as we know <10% of the serious adverse drug reactions are reported to either a manufacturer or a regulatory authority [22, 23]. While conducting data analyses for this thesis, we have learned that there is low reporting of adverse events within the healthcare community for events that are already known or are linked to an indication. Furthermore, sometimes there is a long gap between event date, report date and signal detection review time. We need to think of ways to reduce or eliminate these issues. EHR data have better quality but still have time-lag of 3- 6 months. Furthermore, like claims data, EHR systems are not designed for pharmacovigilance [24]. Social media data are in real-time, but the quality and validity of this information are often questionable.

There is a critical need to have a major overhaul of the way we collect adverse events data which can be done by using a two-prong approach. First is to make reporting of adverse events easier and seamless for patients, care providers, and healthcare professionals. Mobiles are now used by approximately 5.1 billion people, about two-thirds of the world population. It is estimated that the worldwide smartphone adoption will reach 80% by 2025 [25]. We can develop a pharmacovigilance reporting system where an app (on mobile phone or tablet) links the prescription and adds features to show compliance as well as provides an ability to report an adverse event. Since it is linked to a prescription, the healthcare provider information and patient information is already available. This connectivity to prescription information will help manufacturer and regulatory agencies to follow-up with the healthcare provider and/or patient for additional follow-up. Secondly, link the app to patient’s EHR. This way, longitudinal information about the patient is available for signal evaluation and risk assessment.

Beyond data, we need to leverage advancement in analytics, machine learning and artificial intelligence for signal detection. Manufacturers and regulatory agencies are spending a huge amount of resources and funds for signal detection. In a recent scientific conference, EMA has shared that of 1 million ADRs collected, approximately 2000 signals were identified and only 2.1% of signals were validated and/or confirmed as a risk [26]. Our recommendation is to start leveraging new technologies so machine learning and predictive analytics can weed out most (if not all) of the noise and provide a shorter list of signals for a pharmacovigilance professionals to review, validate and assess. Machine learning can assist pharmacovigilance professionals to use their precious brain power on higher intelligence work. We can use advanced analytics to fine- tune methodologies for signal detection as well as for signal validation and prioritization. (Figure
2) With new technologies, it will be imperative to have the right education and training available for pharmacovigilance professionals. We will need to advance skill set to be able to leverage the

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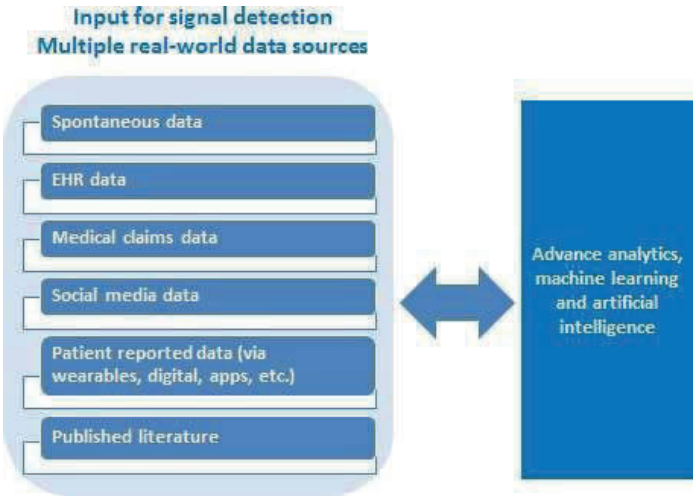
innovation described above. Universities and educational institutions should add courses on machine learning and artificial intelligence to their pharmacovigilance curriculum.

Figure 2: Real-world data sources plus innovative technologies and methods for signal detection



In the past 20 years, a lot has changed in the field of technology, but the basic premise of pharmacovigilance science is still the same – to help patients and improve public health. I hope that this thesis will add to the overall understanding of how we can utilize the real-world data in the signal management process. As we move forward, I would like to see innovation described above so we can serve the patients, consumers, healthcare providers, and caregivers in the best way possible.

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Nederlands Samenvatting

Spontane meldingssystemen voor geneesmiddelenbewaking zijn in de jaren zestig opgezet als reactie op verschillende ernstige bijwerkingen (ADR's) op geneesmiddelen (bijvoorbeeld thalidomide). Bijwerkingen zijn de vijfde doodsoorzaak in Europa met naar schatting 197.000 sterfgevallen per jaar en kosten de samenleving ongeveer 79 miljard euro per jaar. Naar schatting wordt in de Verenigde Staten (VS) jaarlijks ongeveer 3,5 miljard dollar uitgegeven aan extra medische kosten van bijwerkingen. Tot het begin van het jaar 2000, bronnen voor spontane rapportagesystemen (SRS), zoals de Vigibase-database van de Wereldgezondheidsorganisatie (WHO-Vigibase), de Adverse Event Reporting System-database (FAERS) van de Amerikaanse Food and Drug Administration, de US Vaccine Adverse Event Reporting Systeem (VAERS), waren de primaire real-world data (RWD) bronnen die beschikbaar zijn voor farmacovigilantieprofessionals voor signaaldetectie. Echter, in de afgelopen 20-25 jaar, met de beschikbaarheid van computers met hoge capaciteit en de ontwikkeling van geavanceerde analyses, is de geneesmiddelenbewaking begonnen met het verkennen van andere soorten RWD- bronnen voor signaaldetectie, zoals elektronische medische dossiers (EHR), claimt gegevens en sociale media-gegevens.

Historisch gezien werden EPD-gegevens veel gebruikt voor hypothesetests door epidemiologen. Het gebruik van EPD-gegevens voor signaaldetectie of signaalversterking bij farmacovigilantie is echter nog steeds een nieuw concept. In dit proefschrift werd de waarde van het gebruik van EPD- gegevens voor signaaldetectie geëvalueerd en vergeleken met signaaldetectie via de spontane rapportagesysteemgegevens. De gegevens van het EU-ADR-project, WHO-Vigibase en FAERS zijn in dit proefschrift gebruikt.

Hoofdstuk 2 gaf achtergrondinformatie over hoe signaaldetectie met EPD past in post-marketing veiligheidstoezicht. **Hoofdstukken 3 en 4** lieten zien hoe signaaldetectie met EPD SRS zou kunnen aanvullen. De waarde van zowel EPD als SRS werd aangetoond door een tijdsbeperkingsanalyse in de retrospectieve methodologie. De onbeperkte evaluatie (gebruikmakend van gegevens van alle jaren) ten opzichte van referentiesets was in het voordeel van de prestaties van SRS-gegevens en onderschatte die van EPD-gegevens als 'diagnostische' signaaldetectietools. Prospectieve methodologie weerspiegelde de normale farmacovigilantiepraktijk waarbij signaaldetectie werd gedaan als een hypothese-genererende oefening door te zoeken naar signalen die niet eerder bekend waren of er was een verandering in frequentie of ernst van de gebeurtenis voor bekende signalen. In **hoofdstuk 5** toonde de prospectieve analyse aan dat EPD een significanter potentieel zou kunnen hebben voor het detecteren van signalen voor gebeurtenissen die met een hogere frequentie voorkomen in de algemene bevolking en voor die welke gewoonlijk niet worden beschouwd als een

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potentieel door drugs veroorzaakte gebeurtenis. **Hoofdstuk 6** richtte zich op het belang van vroege detectie van een signaal. In dit hoofdstuk hebben we de tijd onderzocht om een signaal te detecteren. We gebruikten rofecoxib en acuut myocardinfarct om te bepalen of het signaal eerder dan SRS in de EU-ADR had kunnen worden geïdentificeerd en de bijdrage van EU-ADR-gegevens aan signaalversterking en mogelijk eerdere rofecoxibontwenning. Bij het evalueren van methoden voor signaaldetectie met behulp van EPD-databases, is het belangrijk om referentiestandaard voor het onderzoek te definiëren. Deze worden beschreven in **hoofdstuk 7**.

Hoewel SRS typisch wordt gebruikt in de farmacovigilantie voor signaaldetectie, wordt er op basis van onderzoek van dit proefschrift opgemerkt dat het uitvoeren van signaaldetectie in zowel EPD als SRS de huidige signaaldetectieactiviteiten zou versterken door de invloeden van systematische bias te verminderen bij gebruik van een enkele gegevensbron .

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Dr. Gianluca Trifiro`, my co-promoter, who has been a true mentor to me. It was a pleasure collaborating with him on the research methodologies, analyses, publications and presentations. I thank Gianluca for his patience and perseverance.

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PhD Portfolio

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PhD period: 2010 – 2020

PhD training

2012 – 2014 Master of Science in Pharmacovigilance and Pharmacoepidemiology, Bordeaux University, EU2P Program

Membership: International Society of Pharmacoepidemiology, 2010-2015, 2018-Present
Drug Information Association, 2015

List of publications

Manuscripts related to this thesis

Postmarketing safety surveillance. Where does signal detection using electronic healthcare records fit into the big picture?
Preciosa M. Coloma, Gianluca Trifiro`, ***Vaishali Patadia****, Miriam Sturkenboom*
Drug Saf. 2013 Mar;36(3):183-97.

Evaluating performance of electronic healthcare records and spontaneous reporting data in drug safety signal detection
Vaishali K Patadia*, Martijn J. Schuemie, Preciosa Coloma, Ron Herings, Johan van der Lei, Sabine Straus, Miriam Sturkenboom, Gianluca Trifiro`*
Int J Clin Pharm. 2015;37(1):94–104.

Using real-world healthcare data for pharmacovigilance signal detection – the experience of the EU-ADR project
Vaishali K Patadia*, Preciosa Coloma, Martijn J Schuemie, Ron Herings, Rosa Gini, Giampiero Mazzaglia, Gino Picelli, Carla Fornari, Lars Pedersen, Johan van der Lei, Miriam Sturkenboom, Gianluca Trifiro` on behalf of the EU-ADR consortium.*
Expert Rev. Clin. Pharmacol. 2015;8(1), 95–102.

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Can Electronic Health Records Databases complement Spontaneous Reporting System Databases? A historical-reconstruction of the association of Rofecoxib and Acute Myocardial Infarction
***Vaishali K Patadia**, Martijn J. Schuemie, Preciosa Coloma, Ron Herings, Johan van der Lei, Miriam Sturkenboom, Gianluca Trifiro`*
Frontiers in Pharmacology

EU-ADR healthcare database network vs. spontaneous reporting system database: preliminary comparison of signal detection
*Gianluca Trifirò, **Vaishali Patadia**, Martijn J Schuemie, Preciosa M Coloma, Rosa Gini, Ron Herings, Julia Hippisley-Cox, Giampiero Mazzaglia, Carlo Giaquinto, Lorenza Scotti, Lars Pedersen, Paul Avillach, Miriam C J M Sturkenboom, Johan van der Lei, EU-ADR Group* Stud Health Technol Infom. 2011;166:25-30

A reference standard for evaluation of methods for drug safety signal detection using electronic healthcare record databases.
*Coloma PM, Avillach P, Salvo F, Schuemie MJ, Ferrajolo C, Pariente A, Fourrier-Réglat A, Molokhia M, **Patadia V**, van der Lei J, Sturkenboom M, Trifirò G.*
Drug Saf. 2013;36 (1): 13-23.

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Details on PhD candidate's contribution to each publication

Chapter	Research topic	Data sources	PhD Candidate's contribution
2	Overview of signal detection using electronic healthcare records and how it fits in with traditional signal detection approach	N/A, Literature review	Provided information on the SRS systems, contributed to the writing and review of the publication.
3	Preliminary comparison of EU-ADR healthcare database network vs. spontaneous reporting system databases	EU-ADR, FAERS, and WHO-Vigibase	Provided analyses of FAERS and WHO-Vigibase. Worked with the first author on the publication.
4	Retrospective evaluating of performance of electronic healthcare record database and the spontaneous reporting system database	EU-ADR and FAERS	Worked with Promotor/co-promotor on the methodology and selection of codes for drug and events. Independently carried out analysis of FAERS data (including programming). Collaborated with the team working on EHR analysis on harmonization of codes Compared the results with EHR (EU-ADR) results. Wrote the entire manuscript and carried out reviews with other co-authors. Incorporated comments from co-authors. Submitted to the journal and lead the publication process. First author of the publication.

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Chapter	Research topic	Data sources	PhD Candidate's contribution
5	Prospective evaluation of utilizing electronic healthcare record database for pharmacovigilance signal detection and comparing it with results from the spontaneous reporting system databases	EU-ADR, FAERS, and WHO-Vigibase	Worked with Promotor/co-promotor on the methodology and selection of codes for drugs and events. Independently carried out analysis of FAERS and WHO-Vigibase data (including programming). Collaborated with the team working on EHR analysis on harmonization of codes Compared the results with EHR (EU-ADR) results. Wrote the entire manuscript and carried out reviews with other co-authors. Incorporated comments from co-authors. Submitted to the journal and lead the publication process. First author of the publication.
6	Exploration of time to signal and signal strengthening effect using electronic healthcare data	EU-ADR, and WHO-Vigibase	Worked with Promotor/co-promotor on the methodology and selection of codes for drugs and events. Independently carried out analysis of WHO-Vigibase data (including programming). Compared the results with EHR (EU-ADR) results. Wrote the entire manuscript and carried out reviews with other co-authors. Incorporated comments from co-authors. Submitted to the journal and lead the publication process. First author of the publication.
7	Development of a reference standard for evaluation of methods for drug safety signal detection using electronic healthcare record databases	EU-ADR	Provided information on the spontaneous reporting system to the lead authors. Reviewed the manuscript.

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Scientific presentations and posters related to the EU-ADR Project:

1. Drug-related upper gastrointestinal bleeding: comparison of signal detection between spontaneous reporting and longitudinal healthcare databases
   Patadia V., Schuemia M, Coloma P., Gini R., Herings R., Mazzaglia G., Picelli G., Scotti L., Pedersen L., Van der Lei J., Sturkenboom M., and Trifiro G.
   Poster at the annual meeting of the International Society for Pharmacoepidemiology, August 2010.
2. Comparison of EU-ADR data to signals from spontaneous data (FDA-AERS) wp6
   Patadia V and Trifiro G.
   Presentation at the EU-ADR Consortium meeting, October 2010
3. Preliminary comparison of drug safety signal detection between spontaneous reporting databases and EU-ADR longitudinal network
   Patadia V., Schuemia M, Coloma P., Gini R., Herings R., Mazzaglia G., Picelli G., Scotti L., Pedersen L., Van der Lei J., Sturkenboom M., and Trifiro G.
   Poster at the annual meeting of the International Society for Pharmacoepidemiology, August 2011.
4. Drug safety signals detected using electronic health records and spontaneous reporting systems data: the experience of EU-ADR project.
   Patadia V.
   Presentation at the meeting of the International Society for Pharmacoepidemiology, August 2012.

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Other work in the field of signal detection, pharmacoepidemiology, and pharmacovigilance:

PUBLICATIONS:

1. Data mining in pharmacovigilance: the need for a balanced perspective.
   Hauben M, **Patadia V**, Gerrits C, et al. Drug Safety 2005; 28 (10):835-842.
2. Perspectives on the use of data mining in pharmacovigilance.
   Almenoff J, Tonning J, Gould AL, et al. Drug Safety 2005; 28 (11):981-1007.
3. What counts in data mining?
   Hauben M, **Patadia V**, Goldsmith D. Drug Safety 2006; 29 (10):827-832.
4. Data mining in pharmacovigilance: lessons learned from phantom ships.
   Hauben M, Reich L, Puijenbroek EV, Gerrits C, and **Patadia V**. Euro Jour of Clinical Pharmacology 2006; 62 (11):967-970
5. Hepatitis b vaccination and multiple sclerosis: a data mining perspective.
   Hauben M, Sakaguchi M, **Patadia V**, and Gerrits C. Pharmacoepi and Drug Safety 2007; 16: 943–945.
6. Quantitative signal detection for vaccines.
   Hauben M, Madigan D, **Patadia V**, Sakaguchi M, Puijenbroek EV. Hum Vaccin. 2010 Sep 12; 6 (9): 20495343.
7. A business intelligence solution to pharmacovigilance signal tracking and management: One mid-size pharma's Experience
   Vaishali K. Patadia, David Nimke, Gudrun Stefansdottir, et al. Pharm Med (2015) 29:197–201.

SELECTED SCIENTIFIC CONFERENCE PRESENTATIONS/POSTERS:

1. A CASE-CONTROL STUDY ON MILK CONSUMPTION AND THE DEVELOPMENT OF EPITHELIAL OVARIAN CANCER
   Patadia V, Davis F, Rosenblatt K, Mallin K, Ramakrishnan R.
   Poster at Annual Meeting of the American Public Health Association in October 1999.
2. INFORMATION ON REQUIREMENTS AND CRITERIA FOR LICENSURE BY CREDENTIALS
   Patadia V, Morrissey R.
   Poster at Annual Meeting of the International Association of Dental Research in April 2000.
3. TRENDS IN THE UNITED STATES DENTAL SCHOOL GRADUATES BY GENDER AND RACE/ETHNICITY, 1988-89 TO 1998-99
   Patadia V, Morrissey R, Wagner K, Brown J.
   Poster at Annual Meeting of the American Public Health Association in November 2000.
4. DATA MINING IN PHARMACOVIGILANCE: MINING A LOW-GRADE ORE
   Gerrits C, Hauben M, **Patadia V**, Hornbuckle K.
   DIA Web seminar presented in April 2005.
5. COMPARATIVE SAFETY OF COLLOIDS: RESULTS ANALYSIS OF A DISPROPORTIONALITY
   Hauben M, Gerrits C, **Patadia V**, Van Puijenbroek E, Reich L.
   Poster at the 2005 meeting of the International Society for Pharmacoepidemiology.

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6. RETROSPECTIVE DISPROPORTIONALITY ANALYSIS ON PHANTOM SHIPS (DISCOUNTED DRUG-EVENT ASSOCIATIONS ORIGINALLY IDENTIFIED THROUGH TRADITIONAL PHARMACOVIGILANCE)
   Hauben M, Gerrits C, Van Puijenbroek E, **Patadia V**, Reich L.
   Poster at the annual meeting of the International Society for Pharmacoepidemiology in August 2005.
7. SOCIAL CIRCUMSTANCE ADVERSE EVENT TERMS IN MEDDRA: EXTENT OF CODING AND POTENTIAL IMPACT ON SIGNAL DETECTION
   Hauben M, **Patadia V**.
   Poster at the annual meeting of the International Society for Pharmacoepidemiology in August 2005.
8. DATA MINING: TO SHRINK OR NOT TO SHRINK?
   Gerrits C, Hauben M, **Patadia V**, Lester R.
   Poster at the annual meeting of the International Society for Pharmacoepidemiology in August 2005.
9. THE RELATIONSHIP BETWEEN HEPATITIS B VACCINE AND DEMYELINATING DISORDERS:
   A DATA MINING ANALYSIS OF A PHANTOM SHIPS ASSOCIATION IN VAERS
   Gerrits C, Sakaguchi M, Hauben M, **Patadia V**.
   Poster at the annual meeting of the International Society for Pharmacoepidemiology in August 2006.
10. COMPARING DATA MINING ALGORITHMS IN PHARMACOVIGILANCE: POINTS TO CONSIDER FOR PROSPECTIVE SURVEILLANCE
    Hauben M, Goldsmith D, Mahar S, **Patadia V**.
    Poster at the annual meeting of the International Society for Pharmacoepidemiology in August 2006.
11. A PRELIMINARY COMPARISON OF THE FDA ADVERSE EVENT DATABASE AND WHO ADVERSE EVENT DATABASE FOR PURPOSE OF DATA MINING
    Gerrits C, Sakaguchi M, Hauben M, **Patadia V**.
    Poster at the annual meeting of the International Society for Pharmacoepidemiology in August 2006 and the annual Euro-DIA meeting in March 2007.
12. SWITCHING FROM BRAND-TO-GENERIC WARFARIN: IS IT ASSOCIATED WITH UNDER AND OVER-COAGULATION? A RETROSPECTIVE ANALYSIS OF SPONTANEOUS ADVERSE EVENT REPORTS
    Gerrits C, Hauben M, and **Patadia V**.
    Poster at the annual Euro-DIA meeting in March 2007.
13. MINING PHARMACOVIGILANCE DATA
    Hauben M, **Patadia V**, Pearson R, and Madigan D.
    Minisymposium at SIAM Conference on Mathematics for Industry, October 2007
14. EPIDEMIOLOGY DURING DRUG DEVELOPMENT: APPLYING NATURAL HISTORY OF DISEASE TO UNDERSTANDING SAFETY
    Patadia V.
    Presentation at DIA's Safety Is Global: Contemporary Pharmacovigilance and Medical Product Risk Management Strategies conference, December 2008.
15. THE EVALUATION OF OFF-THE-SHELF DATA MINING PRODUCTS: POINTS TO CONSIDER
    Patadia V.
    Presentation at 2nd DIA conference on Signal Detection and Data mining, Nov 2009.

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WORK EXPERIENCE:

Sanofi Research and Development, Bridgewater, New Jersey, USA
Jan 2018 - Present
Head of Epidemiology Analytics and Innovation
Apr 2016 – Jan 2018
Senior Director, Center of Excellence Signal Detection Head
Feb 2015 – Apr 2016
Senior Director, Risk Management Officer, Global Pharmacovigilance and Epidemiology

Astellas Pharma Global Research and Development, Inc., Northbrook, Illinois, USA
Jun 2008 - Mar 2014
Director, Risk Management and Pharmacoepidemiology, Product Safety & Pharmacovigilance
Apr 2014 - Jan 2015
Director, Signal Detection and Management , Global Pharmacovigilance

Takeda Pharmaceuticals, Deerfield, Illinois, USA
Oct 2006 – June 2008
Associate Director, Global Pharmacoepidemiology and Outcomes Research

Amylin Pharmaceuticals, San Diego, California, USA
May 2005 – Oct 2006
Associate Director, Pharmacoepidemiology, Global Safety

Allergan, Inc., Irvine, California, USA
Apr 2004 – May 2005
Senior Signal Detection Specialist, Global Pharmacovigilance

Abbott Laboratories, Abbott Park, Illinois, USA
May 2000 – Apr 2004
Project Manager, Epidemiology: Global Medical Services, Global Pharmaceutical Research and Development

American Dental Association, Chicago, Illinois, USA
Apr 1999 - Apr 2000
Research Analyst II: Survey Research Department, Health Policy Research Center

University of Illinois at Chicago, Department of Epidemiology and Biostatistics, Illinois, USA
Sep 1997 - May 1999
Research Assistant - Ovarian Cancer Study

American Hospital Association, Chicago, Illinois, USA
Jun 1998 - Mar 1999
Data Analyst Intern in Health Research and Education Trust-Community Care Network Project

Chicago Center for Clinical Research (CRO), Chicago, Illinois, USA
Sep 1996 - Sep 1997
Research Assistant -Clinical Trials

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About the author

Vaishali Patadia grew up in India and emigrated to the United States of America in 1995. She has obtained her undergraduate degree in Human Nutrition and Dietetics from the University of Illinois in Chicago. She continued her studies in the same university and obtained her Master of Public Health degree in epidemiology in 1999.

She further pursued, in 2014, Master of Science degree in Pharmacovigilance and Pharmacoepidemiology from the Université de Bordeaux (Eu2P Program) and Master of Business Administration degree from Rutgers School of Business in New Jersey in 2019. As part of her doctoral research, Vaishali collaborated with the database partners and researchers working in the EU-ADR Project and at the Erasmus Medical Center in the Netherlands.

Vaishali is an effective leader with more than 20 years of international experience in patient safety and epidemiology, most of which is in the pharmaceutical industry. She has strong expertise in designing and implementation of signal detection, evaluation, and management processes. Her past achievements include building high-performing global teams and leading cross-functional matrix teams for execution of large-scale complex projects. Over the years, she has held various roles with increasing leadership and responsibilities in large to mid-size pharma and small biotech companies.

Vaishali enjoys traveling and exploring new cultures. She loves outdoors and long walks on the beach.

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