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REVIEW ARTICLE

Postmarketing Safety Surveillance

Where does Signal Detection Using Electronic Healthcare Records Fit into the Big Picture?

Preciosa M. Coloma · Gianluca Trifirò · Vaishali Patadia · Miriam Sturkenboom

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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 postmarketing. Postmarketing 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-à-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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P. M. Coloma (✉)
Ee-2116, Department of Medical Informatics, Erasmus Medical Centre, PO Box 2040, 3000 CA Rotterdam, The Netherlands
e-mail: p.coloma@erasmusmc.nl

G. Trifirò · V. Patadia · M. Sturkenboom
Department of Medical Informatics, Erasmus Medical Centre, PO Box 2040, 3000 CA Rotterdam, The Netherlands

G. Trifirò
Department of Clinical and Experimental Medicine and Pharmacology, Section of Pharmacology, University of Messina, Messina, Italy

V. Patadia
Astellas Pharma, Deerfield, IL, USA

M. Sturkenboom
Department of Epidemiology, Erasmus Medical Centre, Rotterdam, The Netherlands

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].

Postmarketing 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].

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 analyse, postmarketing 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].

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 VigiBase™) [34] also examine disproportionality of

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
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

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

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 understanding 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].

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.

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.

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	
				Peripheral neuropathy	
				Extrapyramidal disorders	
				Confusional state	
				Mood changes (*depression, mania*)	
				Amnesias	
				Suicidal behaviour/attempt	
				Progressive multifocal leukoencephalopathy	
				Acute renal failure	

Table 2 continued

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

OMOP Observational Medical Outcomes Partnership

[a] Outcomes that are common to more than one of the initiatives are shown in italics

[b] Data from outpatient and inpatient electronic health records and registries will be added subsequently

5.1 The SENTINEL Network

The SENTINEL Initiative was established in 2008 after the US FDA Amendments Act mandated the creation of a new postmarketing 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 laboratory 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. 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 framework for running drug safety studies 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]. Subsequent efforts focused on development of novel 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].

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 databases 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 database 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.

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).

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

Table 3 Drugs withdrawn from the market for safety reasons in the last 10 years in the US/EU[a]

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
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

EM Erythema multiforme, *SJS* Stevens-Johnson Syndrome, *TENS* toxic epidermal necrolysis

[a] Details, including references, are given in Appendix 1 (Online Resource 1)

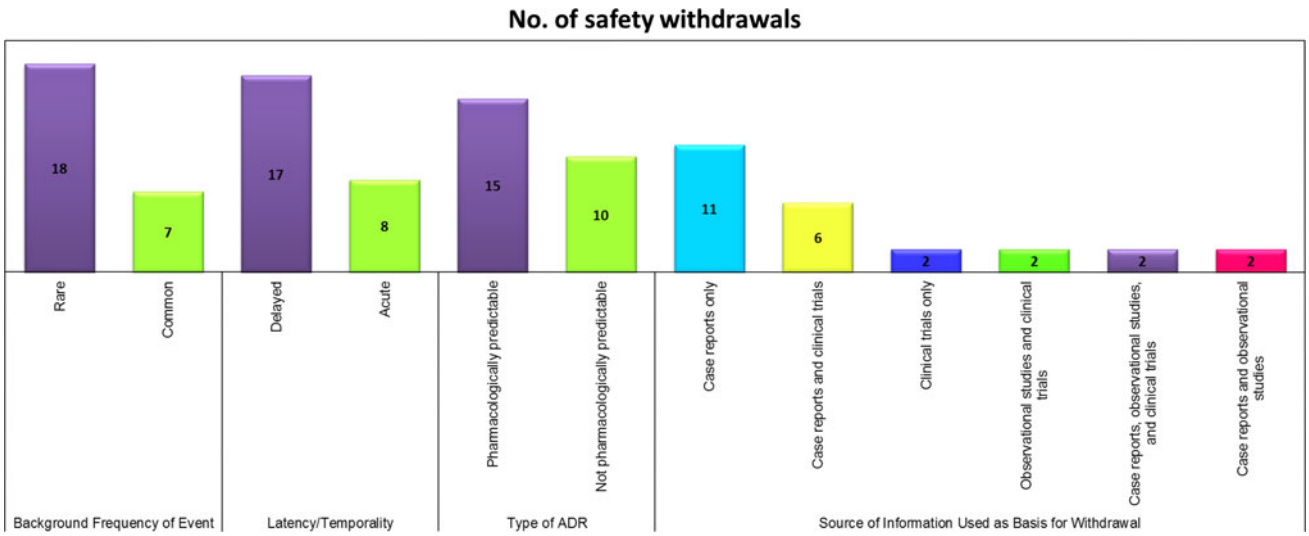

Fig. 1 Characteristics of drug safety withdrawals in the US and EU in the last 10 years. *Background frequency of event*: [100] where data are available, the following convention based on the European Commission's Guideline on Summary of Product Characteristics was used—common (>1/1,000) and rare (≤1/1,000). *Latency/temporality*: [101] mentioned in the reports or publications as being acute (i.e. occurring early in treatment) or delayed (i.e. observed some time after drug exposure, including the case where the drug is withdrawn before the reaction appears); no specific criteria for time period between beginning of exposure and onset of ADR were applied. *Type of ADR*: [101, 102] pharmacologically predictable/expected based on the drug's known pharmacological properties; not pharmacologically predictable/not expected based on the drug's pharmacological properties (includes idiosyncratic reactions). *Source of information used as basis for withdrawal*: details can be found in Appendix 1 (Online Resource 1). *ADR* adverse drug reaction

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 healthcare data. Some preliminary work has been done in this direction and will serve to benefit both SRS and EHR safety surveillance systems [105, 106]. Signal detection is only the initial step in the long and complex process of

postmarketing 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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