

Novel data-mining methodologies for detecting drug-drug interactions: A review of pharmacovigilance literature

I. Heba, A. Amany, S. E. Ahmed, and S. Amr

Abstract— Pharmacovigilance (PhV) is an important clinical activity with strong implications for population health and conducting clinical research. The overarching goal of PhV is the timely detection of adverse drug events (ADEs) that are novel in their clinical nature, severity, and/or frequency. Until recently, the core of PhV is based on the systematic collection of valid safety data through spontaneous reporting systems (SRSs) that can be rigorously analyzed, interpreted, and acted upon as part of patient care. Data mining algorithms have been developed for the quantitative signal detection of ADEs from such databases. Drug-drug interactions (DDIs) constitute an important problem in the development of new drugs and postmarketing PhV which contribute to 6 - 30% of all ADEs. This article, therefore, reviews studies in which novel mining approaches and/or nontraditional data sources have been proposed for signaling DDIs. The authors provide a focused review of recent methodological innovations and alternative data sources used to support DDIs detection in the postmarketing period. We do not aim to elaborately examine all relevant work. Instead, we presented a synopsis of basic concepts, then following by the involved data-mining algorithms (DMAs) covering the computation of their statistical models, contributions, and major findings from published literature with respect to DDIs. Regarding data mining methodologies, the review is organized according to data source axis. Finally, the authors presented some of the challenges related to the currently used mining algorithms and suggestions for further research for drug interactions (DIs) surveillance are offered.

Keywords —pharmacovigilance, data mining, signal detection, disproportionality analysis, spontaneous reporting system, drug-drug interactions, Electronic Health Record, adverse event

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INTRODUCTION

The application domain: pharmacovigilance

Pharmacovigilance (PhV), also known as drug safety surveillance, it has been defined by the World Health Organization (WHO) as “the science and activities relating to the detection, assessment, understanding and prevention of drug-related problems” [1] PhV can be divided into two stages: (1) premarketing surveillance – information regarding adverse drug reactions (ADRs) is collected from pre-clinical screening and phases I to III clinical trials; [2] and (2) postmarketing surveillance – data accumulated in the postapproval stage and throughout a drug’s market life. Although the premarketing controlled randomized clinical trials (RCTs) are considered a hallmark of demonstrating the efficacy of a drug, they may not detect all safety issues related to a particular drug before its use in clinical practice. As they have well recognized limitations, represented in the limited number of study subjects included in the trials (compared with the size of patient populations that may be exposed to the drug once on the market), the limited duration of exposure to the drug per study subject (particularly in case of a drug intended for long-term use), limited or no data for potentially higher risk patient sub-populations that are often excluded from RCTs (e.g., patients with organ impairment, pediatric and geriatric patients, and women of childbearing age who may be treated during pregnancy and lactation), ethnicity restrictions in RCTs of chemotherapeutics [3]. Moreover, premarketing RCTs are not powered to detect rare (incidence of 1 in 10,000) or long-term (latency of > 6 months) adverse drug events [4]. In other means, the efficacy data of a drug is generally more robust and well-established based on premarketing RCTs, while less is known concerning safety profiles [4]. These limitations make it necessary that the marketing authorization holder of a drug and regulatory authority continue to collect, analyze, and interpret data relevant to patient safety that become available after the drug is introduced to market.

Interaction between drug substances is a major cause of morbidity worldwide and a leading source of treatment inefficacy. Drug-drug interactions (DDIs) may account for up to 30% of unexpected adverse drug events [5]. However, premarketing clinical trials focus on establishing the safety and efficacy of single drugs, and don’t typically investigate DDIs [6]. In premarketing trials, patients with multiple drug use are usually excluded. Even when DDIs are suspected DDIs are

suspected, sample sizes and cohort biases limit the ability to discover rare adverse effects [7]. Unfortunately, the interactions between drugs are difficult to study, and there are few predictive methods for discovery novel DDIs. Adverse drug reactions (ADRs) may occur when drug combinations target shared metabolic and pharmacological pathways altering the efficacy and safety profile of the drugs. In other means, the co-administration may alter significantly the safety and efficacy profile of a drug. Drugs may also interact with proteins that are not their primary therapeutic target. Unpredictable adverse events, due to DDIs, can be identified only through postmarketing surveillance and signal detection [8]. Depending on the seriousness of the DDI, different measures are carried out ranging from the introduction of warnings in drug labels to the withdrawal of drugs from the market. As an example, mibefradil, a calcium channel blocker approved by the FDA [9] in June 1997, was shortly withdrawn from the market due to dangerous and even fatal interactions with at least 25 other drugs, including common antibiotics, antihistamines, and cancer drugs, that prolong the QT interval [10]. In contrast, US FDA issued a warning in August 2008 about the possibility of developing major hemorrhagic events through the treatment combination of agrylin with aspirin [11]. In recognition of the challenge of postmarketing surveillance of interaction profiles between different drugs [5] and involvement in patient safety, research into application of data mining approaches on heterogeneous data sources, for DDIs discovery and prediction, have been adopted in recent years.

Data sources of PhV in support of signal detection

Several unique data sources are available for postmarketing PhV. Spontaneous reporting systems (SRSs) have served as the core data collection system for post-marketing drug safety surveillance since 1960s. These are passive systems composed of reports of suspected ADEs collected from health-care professionals, consumers, and pharmaceutical companies, and maintained largely by regulatory and health agencies. Among the prominent SRSs are; the FDA adverse events reporting System (FAERS) [12], the VigiBase co-managed by the World Health Organization (WHO) and the Uppsala Monitoring Centre, Uppsala (UMC), Sweden, which maintains the WHO Global Individual Case Safety Report Database, VigiBase [13], and EudraVigilance managed by the European medicines evaluation agency (EMA) which involving adverse event (AE) reports for medicinal products authorized in the European Economic Area (EEA) EMA [14]. In addition, there are other databases associated with spontaneous reporting such as, the vaccine adverse event reporting systems (VAERS) that is a US program for vaccine safety, co-managed by the Centers for Disease Control and Prevention (CDC) and the Food and Drug Administration (FDA) [15]. These databases are designed to support post-marketing safety surveillance program for drug and therapeutic biologic products. SRSs' structures adhere to the international safety reporting guidance issued by the International Conference on Harmonisation, ICH E2B [16]. Moreover, company safety databases that may allow for earlier detection of safety signals particularly for new products, as they are not subjected to the

delays associated with the public databases SRSs capture information on the drug(s) suspected to cause the adverse drug event (ADE). SRSs provide information on concomitant drugs, indications, suspected events, and limited demographic information in a structured format directly amenable to data mining.

Although the SRSs play a vital role in supporting regulatory decisions for a long list of marketed drugs [17], those passive systems have well recognized limitations, such as missing or incomplete or unspecified data overreporting (adverse events known to be linked to certain drugs are more likely to be reported than other adverse events), duplication of reporting, limited demographic information (age and sex), date of report, fail to provide information about a denominator (i.e., the number of individuals consuming a particular drug) due to SRSs only contain reports of adverse effects, and misattribution causal ADEs links due to unmeasured confounding factors (e.g., disease-related AE, interacting drug(s)).

Other type of data sources for supporting post-marketing surveillance are pharmacoepidemiology databases such as: prescription event monitoring (PEM) in New Zealand [18], the medicine monitoring unit (Memo), general practice research databases (GPRD) in the UK [19] and PHARMO record linkage system in Netherlands. Pharmacoepidemiology is defined by WHO as: "the study of the use and effects/side-effects of drugs in large numbers of people with the purpose of supporting the rational and cost-effective use of drugs in the population thereby improving health outcomes" [20].

These databases have strengths including; 1) Large numbers of patients could provide sufficient power for the analysis; 2) The population could be linked to the corresponding medical, pharmacy and demographic information for a more complete analysis. 3) The detailed information could be followed for a long periods of time. The information in these databases includes demographics, medical diagnosis, treatment, hospitalizations etc., along with date and location of events. There are also options of free text, referral to hospital, all prescriptions (including date, formulation strength, quantity, indication for treatment for new drugs etc.). These databases have enabled researchers to investigate a wide range of hypotheses including PhV [21]. Their creation provides a great opportunity for active surveillance. The active surveillance has the potential to monitor safety signals prospectively when a new drug is marketed for detecting new AEs [22]. Limitations of using these databases in PhV include the following; first, although the availability of a substantial amount of comprehensive information in both structured and unstructured form, only a very small amount of structured data can be accessed by pharmacovigilance applications; Second, data integration from disparate clinical settings is extremely challenging, and the quality of integration can profoundly affects the outcome of pharmacovigilance research; third, real time surveillance is difficult due to the fact that the integration process usually lags behind [23].

For that said; the researchers recently have begun to focus on data sources that have not traditionally been used for PhV. Each of these sources offers promising prospects that may augment existing PhV approaches. Here we discuss some of these information sources.

Text mining of electronic health records (EHRs) could be very useful for detection of safety signal by applying natural language processing (NLP) systems such as MedLEE, BioMedLEE, SemRep, and MetaMap to identify, extract and encode information within EHR systems [24]-[27]. Information from these EHRs is often derived from a defined population with comprehensive, non-specific, capture of clinical important events, these data sources. An EHR is a type of longitudinal observational database (LOD) providing electronic record of patient health information generated by one or more encounters in any care delivery setting. This record includes both structured data, such as laboratory test results, and unstructured data such as narrative reports. As an example, the interaction of beta-blockers and warfarin could affect the risk of hemorrhage in CHF patients was found by using prescription and lab test data in the EHR [28]. The biggest advantage of using EHR systems for pharmacovigilance is the ability to perform active and real time surveillance. However, the majority of the records consist of unstructured narratives, such as discharge summaries, progress reports, or nursing notes which representing the main limitation to be accessed directly by pharmacovigilance applications.

Publically available chemical and biological knowledge bases such as STITCH (search tool for interactions of chemicals), and DDI DrugBank database [29], [30] provide the researchers the chance to create predictive models for potential DDIs. Such databases contain information on molecular structure, protein binding sites, biological pathways of drug action and metabolism, chemical structural similarities between drugs, and linkages between chemical substructures and specific toxicities. Leveraging this type of knowledge provide merits such as possibility to predict toxicological effects in the preclinical drug design stage in aim of decreasing late-stage attrition of new drugs due to toxicity [31]. Additionally, better predictive models can be created by linking chemical and biological knowledge with knowledge on post-marketed drug interaction adverse effects (DIAEs) or enriching subsets of drug interactions generated by other sources likely to be interested for further clinical studies [32].

Although screening the medical/ scientific literature by pharmaceutical companies on adverse reactions related to drugs they commercialize has become mandatory in European countries according to council regulation (EEC 2309/93) volume 9 of Eudralex (i.e., literature research is one of the required steps for standard management procedure in PhV centres), few studies have been conducted by drug safety researchers on mining biomedical literature for extracting new discoveries from the large amounts of biomedical knowledge available [33], [34]. Data mining algorithms (DMAs) in PhV have focused on coded and structured data and therefore miss important clinical data that is relevant to PhV. The biomedical

literature contains ADE-related information based on observations (e.g., case reports) and clinical studies. Analysis of biomedical literature for safety signal detection is challenging and labor intensive due to unstructured nature. Therefore, natural-language processing (NLP) techniques recently developed for extracting ADE-related information or direct/indirect drug interactions have gained large popularity[35]- [37].

The concept of “signal detection” in Pharmacovigilance

In pharmacovigilance, these methods are dedicated to hypothesis generation”, also called “signal detection/generation”, where signal being defined by WHO Uppsala Monitoring Centre (UMC) as: “reported information on a possible causal relationship between an adverse event (AE) and a drug, of which the relationship is unknown or incompletely documented previously” [1]. The term “signal” is primarily used to refer to marketed products. The signal may be a new issue never before seen with a drug, or it may be the worsening or changing of a known AE or problem (e.g., a previously unaffected patient group is experiencing this problem or it is now fatal in those it attacks, whereas before it was not or the incidence has increased, etc.).

The major aim of PhV is the timely detection of either new adverse drug reactions (ADRs) or a change of the frequency and/ or severity of ADRs that are already known to be associated with the drugs involved (i.e., signal detection). The whole process of risk/benefit evaluation depends on effective detection of signals. Signals may be “qualitative” (based on case by case analysis of observations by clinicians, case reports in the literature) or “quantitative” (based on data mining of observational databases, assessment of epidemiologic data, or clinical trials data). The detection of signals requires clinical assessment assisted by epidemiological and statistical analyses.

Despite its inherent limitations, analysis of spontaneous reporting systems (SRSs) for suspected ADRs is a valuable tool in the detection of previously unknown ADRs [38]. Hypothesis generation of new possible adverse effects from such data is referred to as signal detection. The aims of data mining for quantitative signal detection are: to flag potential new signals that might be missed; to earlier identify AEs and decrease person- time expended per AE; to confirm signals that had been clinically first identified; to prioritise resources for signal detection when combined with more traditional methods; to probably distinguish a specific adverse drug effect of a molecule, not shared by its whole therapeutic family; to focus clinical review on the most likely candidates; to detect more complex associations in the data, which are hard to detect by manual review, in particular, drug– drug interactions and to aid prioritisation of potential signals. Safety data mining algorithms (DMAs) have shown high potentialities in the quantitative analysis of the very large PhV spontaneous reporting databases [39] - [43]. Data mining has become a powerful tool for knowledge discovery in biomedical informatics, and particularly useful for hypothesis generation in PhV.

Methodologies for signal detection within spontaneous reporting systems: basic concepts

Disproportionality analysis (DPA) methods for post-marketing drug safety surveillance, which are detailed in several publications, comprise the most widely used analytic methods for signal detection in SRSs [44], [45]. Also, DPAs are the most often data mining methods been described in PhV literature. They are based on measures of disproportionality that require comparisons of observed to expected proportions of drug-adverse event combinations (DECs). Disproportionality analysis (DPA) methodologies are generally be classified into two categories: frequentist and Bayesian. Both approaches use the entries of 2×2 contingency table (see Table I) to derive a statistical association / disproportionality measure. 2×2 contingency table is usually computed for each drug–event pair in the SRS. At the first level, each report generates n “D \times AE associations”, n being the number of drugs notifying one AE. At the aggregated level (the whole database being taken into account), the observed number of cases of each DEC is compared with the estimation of the expected number of cases. As the expected number of cases is calculated using data from the database only, these methods are also named “numerator dependent”. A safety signal is to be generated when there is a discrepancy between the observed number of a DEC within the database and the expected number of cases. In other words, these methods are using the “background noise” summarized in the marginal counts of 2×2 contingency table. Several methods are proposed to estimate the magnitude of the disproportion measure and its confidence interval. DPAs include Proportional Reporting Ratio (PRR) [46], [47], Reporting Odds Ratio (ROR) [45], Information Component (IC) [48], [49], and Multi-item Gamma Poisson Shrinker (GPS or MGPS) [50] are widely used, and currently employed by the Medicines and Healthcare products Regulatory Agency (MHRA), UK, the Netherlands Pharmacovigilance Centre Lareb, the World Health Organization (WHO), and the US FDA, respectively. Although the methodology of the aforementioned algorithms differs, they all share to what extent the number of observed cases differs from the number of expected cases. All of these algorithms calculate signal scores, i.e., the values for PRR, ROR, IC, and EBGM, to assess whether a drug is significantly associated with an adverse event or not.

Classical or frequentist approaches

Frequentist approaches of DPAs involve ROR and PRR. The common feature of these approaches is that they rely solely on information contained in the 2×2 table (table I) corresponding to the drug-event combination (DEC) of interest [51]. A limitation in such a binary approach (i.e. dividing ADRs into two classes: exposed versus non-exposed, as discussed in further detail below) is that with very small observed counts, if the expected count is small, the statistics will fail to screen out such associations, some of which may be false positives [51].

Table 1: Formal 2×2 contingency table

	Suspected event	All other events	Total
Suspected drug	a	b	a + b
All other drugs	c	d	c + d
Total	a + c	b + d	a + b + c + d

The ROR has been described in the PhV literature as an approach for disproportionality analysis of spontaneous data [52], [53]. The ROR was first established in the Netherlands Pharmacovigilance Foundation Lareb [45]. The ROR like traditional odds ratio; it is an estimate of incidence rate ratio, calculating the odds of the AE in those exposed to particular drug divided by the odds of the AE occurring in those not exposed to that drug [54]. The computation of the ROR is based upon the 2×2 table (see Table I). In practice, $ROR - 1.96 \text{ Standard Error (SE)} > 1$ with $p - \text{value} \leq 0.05$ are often used as the criteria to identify signals [55]. The ROR with 95% confidence interval (CI) is computed through the following formulae [56];

$$ROR = \frac{A/B}{C/D} = \frac{AD}{BC} \quad (1)$$

$$95\% \text{ CI} = e^{\ln(ROR) \pm 1.96 \sqrt{\frac{1}{A} + \frac{1}{B} + \frac{1}{C} + \frac{1}{D}}} \quad (2)$$

The PRR, as another metric of frequentist DPAs, was first used by Evans et al. in 2000 to demonstrate the risk of uveitis associated with the use of rifabutin [47], [57]. The PRR measures the strength of association between the suspected ADRs and the suspected drugs, behaving in a similar way to the relative risk (RR) [58]. The higher the value of the PRR is, the stronger the strength of the signal appears to be. The PhV literature suggests two common signal generation criteria for PRR method. The first one is a composite criterion requiring that the number of co-occurrences/observed cases (**a**) is at least equal to 3, PRR measure is at least equal to 2, and chi-squared measure (corresponding to a $p - \text{value of} \leq 0.05$) for this association is at least equal to 4 respectively: $a \geq 3$ and $PRR \geq 2$ and $\chi^2 \geq 4$ [59]. The second is that the lower bound of its 95% confidence interval has to exceed one: $PRR_{0.025} > 1$ [60]. The computation of PRR is same as the RR estimated in epidemiology and can be calculated using the 2×2 contingency table. PRR with 95% confidence interval (CI) can be calculated through the following formulae [61].

$$PRR = \frac{A/(A + C)}{B/(B + D)} = \frac{A(B + D)}{B(A + C)} \quad (3)$$

$$95\% \text{ CI} = e^{\ln(PRR) \pm 1.95 \sqrt{\frac{1}{A} - \frac{1}{A+C} + \frac{1}{B} + \frac{1}{B+D}}} \quad (4)$$

These approaches are easy to understand and more computationally efficient than Bayesian based approaches. However they show limitations involving; some have argued that, for small counts of a specific DEC, frequentist approaches are more liable to extreme values and therefore generating more false positives and also this type of approach

does not adjust the counts for exposure to the various drug combinations and thus does not provide an appropriate statistical context for studying drug interaction [61].

Bayesian approaches

There are currently two major Bayesian techniques used for data mining in pharmacovigilance, the Information Component (IC) [48] and the multi-item Gamma-Poisson shrinker (GPS/MGPS) [50]. Bayesian approaches, based on 2×2 table, calculate an observed to expected ratio in which a database of adverse event reports is mined for the occurrence of significantly unexpected itemsets for relevant drug-AE or drug-drug-AE combination and/or syndromes. Both approaches calculate a Bayesian version of the relative reporting ratio (RRR) or O/E , along with a range of plausible values. For each itemset in the database, a RRR is defined as the observed count ' O ' for that itemset divided by the expected count ' E ' (for drug i and event j) as in the following formula [62];

$$RRR = \frac{\text{observed count 'O'}}{\text{expected count 'E'}} = \frac{N_{ij}}{E_{ij}} = \frac{a(a+b+c+d)}{(a+c)(a+b)} \quad (5)$$

The expected frequency would be the frequency expected under fully independent model, in which the likelihood of a given AE in a report is independent of drug(s) appear in the report. Bayesian approaches are based on Bayes' law to estimate the probability (posterior probability) that the AE occurs given the use of suspect drug by "shrinking" the measure toward the baseline of no association. This shrinkage to the null results in a reduction in spurious associations that have insufficient data to support them. Hence, Bayesian approaches show superiority to frequentist approaches when the available information is extremely limited.

Among the Bayesian approaches is BCPNN that was first adapted to drug safety signal detection by the WHO collaborative centre on pharmacovigilance (WHO-UMC) for International Drug Monitoring, Sweden [48]. Since 1998, WHO has implemented the IC using a Bayesian confidence propagation neural network (BCPNN) for screening international pharmacovigilance database (VigiBase) as part of the routine signal detection process [48], [49], [63], [64]. The BCPNN constructs a null 2×2 table for each AE in the database to achieve a desired null $O/E = 1$. A measure of disproportionality, called the Information Component (IC), and its credibility/ confidence interval is calculated for each drug-adverse reaction combination in the dataset. The IC is defined for a specific drug adverse reaction combination as [49], [65];

$$IC = \log_2 \left[\frac{\text{observed count} + 1/2}{\text{expected count} + 1/2} \right] \quad (6)$$

A signal for drug-ADR pair is detected if the lower limit of the 95% confidence interval ($IC_{0.25}$) exceeds zero. Positive values for $IC_{0.25}$ are highlighted for clinical review.

Another Bayesian approach is the multi-item gamma Poisson shrinker (MGPS) and its predecessor GPS which described by DuMouchel, also named "Dumouchel method" [42], [50]. MGPS is the DMA currently used by some drug regularity

authorities such as US FDA to interrogate signals of drug-AE associations in its SRS database, named as MedWatch [66]. Bayes computes a measure known as the empirical Bayes geometric mean (EBGM). EBGM, which is based on the whole database, is defined as a centrality measure of the posterior distribution of the true RRR in the population; also it is computed by the exponential of expectation value of logarithm of RRR under the posterior probability distributions for a true RRR, which can be represented as following [50], [67];

$$EBGM_{ij} = 2^{\log(RRR)} = 2^{E \log 2_{ij}} \quad (7)$$

MGPS computes an adjusted value of the observed-to-expected reporting ratio (RRR), corrected for temporal trends and for confounding by a particular stratum (e.g. age, sex) [68]. The posterior probability distribution supports the calculation of lower and upper 95% confidence limits (EB05, EB95) for the RRR. The EB05 metric, a lower one-sided 95% confidence limit of the EBGM, is used for signal detection when the EB05 is greater than or equal to the threshold value 2.0 [69]. Typically, the EB05 measure corresponds to the lower 5th percentile of the posterior distribution of RRR; meaning that there is a 95% probability that the true RRR exceeds the EB05.

Performance evaluation of DPAs most used in PhV

Although the comparative performance of DPAs, which are DMAs widely used in routine PhV, is beyond the objectives of this article, the authors believed that it is useful to be touched. Table II shows a comparison among the most frequently used disproportionality algorithms in PhV. Although several studies have been compared DPAs that are routinely applied to the SRSs, those studies mainly have focused on sensitivity. Shortcomings of these studies may be represented in; some have been conducted on a gold standard of limited size, most have focused on fixed thresholds for signal detection, some covered a limited time interval of study, and some examine a narrow spectrum of drug- AE combinations [70]- [72]. Also there are a paucity of studies comparing DPAs' performance in the context of trade-off between sensitivity and specificity [68]. The comparative performance of these methods can be summarized as follows:

- In general, frequentist forms of DPAs (e.g., ROR, PRR) seem to be more sensitive via highlighting a greater number of DEC than Bayesian forms of DPAs (e.g., IC, (M)GPS), while MGPS method has been shown to be the most conservative among DPAs [73];
- Bayesian approaches have showed superiority to frequentist approaches when the available information is extremely limited [45], [74];
- Some of the DECs obtained with frequentist DPAs may be false positives that can be attributed to confounding, thus requiring additional triage criteria for practical implementation, or further investigation by other methods [43];

- For DECAs which are highlighted by both frequentist and Bayesian DPAs, frequentist DPAs tend to do so earlier [75];
- ROR measure performs better than other DPAs from the standpoint of early and timely signal detection [76];
- Both ROR and PRR disproportionality metrics show near equivalence of performance and no obvious advantage of using the ROR over the PRR, in addition; LR-based approaches outperform DPA-based approaches across all levels of sensitivity/specificity [43], [77], [78].

In summary, no single method seems superior as this is highly situation-dependent due to heterogeneity in implementation choices, such as threshold election /titration and the triage logic for signals investigation.

Need for multivariate association approaches

While bivariate/two dimensional (2D) disproportionality analyses (DPA) represent the bulk of daily routine of PhV, higher dimensional associations are important for patient well-being. Although bivariate associations have shown to be adjunct for many of safety analyses, the reduction of ADE analysis to 2D dimensionality may result in missing clinically crucial information. Some studies showed that DDIs may account for up to 30% of all adverse drug events (ADEs) [5] and close to 50% in hospital patients [79]. Multivariate associations may involve detection of DDIs (e.g. drug₁- drug₂ – adverse event/(s)) or drug- induced syndromes in which a constellation of signs and symptoms (e.g. drug-event₁ –event₂ –event₃) exists.

Among the information may be hidden in 2×2 table is confounding factors, also known as covariates or effect modifiers. The term “confounding” refers to a situation when one finds a spurious association or misses a true association between an exposure (i.e. drug) variable and an outcome variable (i.e. disease or adverse event) as a result of a third factor or group of factors referred to as confounding variable(s)” [80]. In other means, confounding may lead to safety signals of spurious associations, if not accounted for. Confounding may be addressed either through design stage of the experiment before data collection (e.g. randomization, matching) or in the analysis stage when the data already been collected (as in case of SRSs). Confounders may be the key to realize potential risk factors or high risk subgroups even in simple 2D associations between a drug and AE. There are several types of confounders, a simpler type, such as confounding by age, gender, and year, have been effectively handled by stratification and Mantel – Haenszel type adjustments where the overall expected count is the sum of the expected counts for each stratum, and is compared to the observed count [81], [82]. However adjustment of confounding by a large number of potential confounders can lead to the missing of signals in the application of data mining [83], [84]. Another limitation, stratification according to age, sex or other variables is not yet relevant; as the number of cases per associations is already low and thus many DECAs may

be unable to reach statistical significance. Additionally; there are other types of confounding involving DDIs, and confounding by co-reporting pairs of drugs, known as “innocent bystander” in which the reported event is associated with the indication for treatment. Adjustments of such confounding types by Mantel – Haenszel methods are not effective [82]. Multiple logistic- regression (LR) is more appropriate approach for such types where large numbers of covariates present. The LR may allow the estimation of a drug– event association by adjusting for the presence of potential confounders; hence it can be applied in the domain of PhV [84].

Methodologies to interrogate drug interactions (DIs) signals in spontaneous reporting databases

Newer approaches have been designed to facilitate identification of higher-order or multivariate associations that represent more complex safety phenomena such as drug–drug interactions (DDIs). In general, the detection of potential DDIs is based on the concept: when a suspected AE is reported more frequently in the combination of two drugs compared with the situation when reported in the absence of other, the drugs combination may indicate the existence of DDI. The currently proposed approaches for quantitative signal detection of DDIs in SRSs include frequentist, Bayesian, and regression approaches as discussed later in further detail.

DPA extensions

DPA extensions to search for mostly three-dimensional associations corresponding to DDIs have been proposed both in **MGPS**, and **IC** measures in which observed-to-expected ratios are calculated in a similar manner but based on three elements (*drug₁ – drug₂ – AE*) [85], [86]. As an example, MGPS has been investigated by Almenoff et al. for AE profiles of combinations between the calcium channel blocker verapamil and three classes of cardiovascular drugs with well-established safety profiles [85]. The authors have identified significant drug associations based on EBGm values for the two drugs and their lower limit of 90% CI being greater than the upper limit of the 90% CI estimate for each of the two drugs. The results suggest that MGPS as a disproportionality analysis is a promising tool for predicting safety profiles of potential drug interactions and safety problems in polytherapy situations.

Multivariate logistic regression (LR)

The LR is a type of predictive modeling that is used to relate a dependent variable with a set of independent variables which has been proposed by Van Puijenbroek [67], [87], [88]. This approach can be used to assess the effect of age, sex and co-

Table II characteristics of most commonly used signal detection algorithms

	Frequentist methods	Bayesian methods
Algorithms	Proportional Reporting Ratio (PRR), Reporting Odds Ratio (ROR)	Information Component (IC), Multi-item Gamma Poisson Shrinker (GPS or MGPS)
Description	ROR: a method to compute a measure similar to odds ratio to quantify the strength of association between a drug and event PRR: a method to compute a measure similar to relative risk to quantify the strength of association between a drug and event	IC: a method to compute logarithmic measure of relative reporting ratio (RRR). MGPS: a method to compute an adjusted value of the Observed-to-expected reporting ratio called empirical Bayes geometric mean (EBGM)
Published signal score thresholds	$ROR - 1.96 SE > 1$ with $p - value \leq 0.05$ $a \geq 3, PRR \geq 2,$ $\chi^2 \geq 4$ and $PRR_{0.025} > 1$	$IC_{025} > 0$ $EB_{05} \geq 2$
Regularity users	Netherlands Pharmacovigilance Foundation Lareb European Medicinal Agency (EMA) - EudraVigilance	WHO-UMC collaborative centre for International Drug Monitoring, Sweden - VigiBase US Food and Drug Administration (FDA) - FAERS
Advantages	More sensitive Easy to understand Easily applicable Adjustments for temporal trends and covariates in logistic regression analyses Earlier signal detection	More specific Configured for detecting higher-order associations (e.g. drug interactions, medical syndromes)
Limitations	Lower specificity leading to false positive signals that may require additional triage criteria	Lower sensitivity leading to false negative associations Showing superiority to be more conservative

morbidity on signal generation. In other mean, LR provides the appropriate statistical context for studying multiple covariates including drug interactions. The LR requires the predictors (drugs and other covariates such as sex and age) first to be selected in advance to be included in the regression model.

It computes RORs by dividing all records in the database into cases and non-cases according to different AEs, all records in cases defined as patients who reported ADRs of interest, while 'noncases' consisted of all other reports.

There have been two publications applying LR for the retrospective detection of DDIs using a SRS database [89], [90]. The first publication by Van Puijenbroek et al. demonstrated potential association between delay of

withdrawal bleeding during concomitant use of oral contraceptives (OCs) and antifungal itraconazole (I) using the Netherlands PhV foundation Lareb which maintains SRS in Netherlands [89]. This interaction had previously only been suggested by case reports after receiving 19 reports of delayed withdrawal bleeding in women receiving OCs; in 10 of these reports OCs and itraconazole (I) were used concomitantly. The analysis of this interaction is based on the concept that target ADR is reported more often on the combination of two drugs compared with the situation where either of these drugs has been used in the absence of the other one. RORs were adjusted for source of reporting (physician or pharmacist), year of reporting, and age. In constructing the logistic model, drug OC, drug (I) as well as the concomitant use of OC and (I) were coded, respectively, by the system according to AE of delay of withdrawal bleeding and the model would then look like:

$$\log(odds) = \beta_0 + \beta_2 A + \beta_3 S + \beta_4 Y + \beta_5 I + \beta_6 OC + \beta_7 OC * I \quad (8)$$

Where A= age, S= source, Y = reporting year, I = itraconazole, OC = oral contraceptive, $OC * I$ = the concomitant use of both drugs.

The second publication by the same authors assessed the statistical interaction between the use of diuretics and nonsteroidal anti-inflammatory drugs (NSAID), and showed significantly higher use in combination, suggesting decreasing in the efficacy of diuretics resulting in worsening of congestive heart failure (CHF) associated with their combination [90]. The authors calculated RORs and examined the effects of pairs of NSAIDs and diuretics using a logistic regression model with AE case reports of Netherlands PhV foundation LAREB (as in the following formula);

$$\log(odds) = \beta_0 + \beta_1 N + \beta_2 D + \beta_3 N \times D + \beta_{n-x} C_{n-x} \quad (9)$$

Where N = NSAIDs, D = diuretics, C_{n-x} = different covariates, i.e. age, source, and reporting year. The analysis showed that the use of diuretics or NSAIDs itself was not statistically significantly associated with an increased risk for onset or worsening of symptoms of CHF. However, the odds ratio of the statistical interaction term NSAIDs \times diuretics, was statistically significantly elevated (adjusted ROR 2.0; 95% CI 1.1 to 3.7).

Mining SRS databases by LR approach show some key limitations such as; building predictive model for a single AE and ignoring dependencies/ associations between AEs (like in syndromes), performing regression analyses to very- large-dimensions of predictors (> 10,000 drugs in SRSs), i.e. confounding by comedication by using all drugs in an SRS as regression predictors for an event, represent computational as well a theoretical barrier. However, new extension of logistic regression to very-large-dimensional data, known as Bayesian logistic regression (BLR), can carry out regression analyses with millions of predictors [91]. Caster et al. conducted a study on the WHO SRS (VigiBase) using the BLR algorithm to address confounding caused by co-medication and "masking effect" in which an increase in background reporting of a specific event can attenuate disproportionately values of true association to values of no association [92]. The authors

showed that BLR corrected several real examples of false-positive DECs due to confounding by comedication and also true DECs that were masked by media focus on the withdrawal of a drug causing rhabdomyolysis. In brief, LR/BLR approaches show distinct merits over methods that analyze bivariate associations related to drug safety such as; guarding against masking effects and false signals due to confounding by concomitant drugs, etc.

The Ω Shrinkage measure

The Ω Shrinkage measure was first described by Norén et al. [93] to screen drug interactions (DIs) in SRSs. The authors criticized the logistic regression method in missing some reporting patterns [93] strongly suggestive of potential DIs and they show that the Ω shrinkage measure is a more sophisticated method after conducting a confirmatory study using the WHO database [94]- [96]. The Ω Shrinkage measure calculates an observed-to-expected ratio as a measure of disproportionality and can be calculated according to equation;

$$\log_2 \frac{n_{111} + \alpha}{E_{111} + \alpha} \quad (10)$$

Where E_{111} is the expected value of the incidence of disease suspected to be derived from DI, and α is a tuning parameter, which is set at 0.5 [93] The logarithm of this equation for $\Omega = 0.025$ is a two-sided 95% lower confidence/credibility interval limit which acts as the threshold for generating DI signal when lower bound of its 95% confidence interval exceed zero: $\Omega_{0.025} > 0$ [93].

Qian Yifeng et al. [97] have developed a computerized system aiming to facilitate automated data acquisition, data arrangement and detection of potential DDIs. ADR reports was acquired automatically from the Shanghai ADR SRS which was developed by National Adverse Drug Reaction Monitoring Centre of China. The authors carried out a database-wide screen with three different methods the additive model and multiplicative model, the logistic regression method, and the Ω shrinkage measure method for the detection of possible drug interactions. The three methods were compared according to the detected suspicious DDIs during the database-wide screen. According to results; combinations detected, by at least two methods in average, may reflect the fact that the three methods are highly correlated. The performance of the described system was qualitatively validated by case studies in clinical practice for some of drug interactions detected. After its application in the Shanghai ADR SRS, the authors showed that their system could be a useful tool in detecting and analyzing potential drug interactions for routine surveillance.

Additive and Multiplicative model

The theory of multiplicative and additive models in the context of DDIs signal detection in SRSs has been elaborated by Thakrar et al. by which the detected drug interaction signals could be further identified by statistical test [98]. Referring to

their work, the formulations of the models are based on estimating measure of interaction (coefficient δ) by which the risk associated with drug combination is greater than that predicted for two drugs separately. Risk denote the risk (e.g. incidence rate, odds of developing the event, or percentage of subjects developing a particular event) of an adverse reaction associated with particular drug(s). The formal statistical testing of multiplicative model for interaction coefficient δ is done within the framework of log-linear regression as following:

$$\text{Log}(\text{risk of event}) = \alpha + \beta (\text{drug A}) + \gamma (\text{drug B}) + \delta (\text{drug A and B}) + \text{other covariates} \quad (11)$$

; Where the measure of interaction, the coefficient δ is the PRR associated with the drug combination.

Whilst the formal statistical testing of interaction coefficient of additive model is achieved as follows:

$$\text{Risk of event} = \alpha + \beta (\text{drug A}) + \gamma (\text{drug B}) + \delta (\text{drug A and B}) + \text{other covariates} \quad (12)$$

; Where the measure of interaction, the coefficient δ is the PRR difference associated with drug combination, A and B. The multiplicative model assumed the risk associated with a drug multiplies with the background risk, whilst the additive model assumed the risk associated with a drug adds to the background risk. For multiplicative model, under the assumption that null hypothesis is true (i.e., no interaction), the proportion of an event associated with the drug combination is the same as the product of the proportional risks of individual drugs in the absence of the other ($PRR_{AB} = PRR_A \times PRR_B$) (13). Similarly for the additive model, there is no interaction when the proportion of an event associated with the drug combination is the same as the add of proportional risks of individual drugs ($PRR_{AB} = PRR_A + PRR_B$) (14). DDI signal generated when $PRR_{AB}/PRR_A \times PRR_B > 1$ and $PRR_{AB} - PRR_A - PRR_B > 0$ for multiplicative and additive models respectively and also corresponding $value < 0.05$.

Thakrar et al.'s retrospective study [98] aimed to compare a multiplicative model and an additive model using known interactions of drugs using AE case reports from FDA's AERS. Both models were fitted to four known interactions and to four known non-DDI. The results showed that the additive model has better sensitivity in detecting DI signals and the multiplicative model may further help qualify the strength of the signal detected by the additive model.

Association rule mining

Unsupervised learning techniques have been used as exploratory data analysis to draw inferences of hidden patterns from a dataset. One of these techniques is association rule mining (ARM) [99] which is a well established data-mining technique for discovering interesting relationships hidden in large databases. The technique has been developed in computer science for over a decade and has been used in a variety of fields [100] - [102]. Recently, ARM has been applied in PhV for identification of complex or higher-dimensional drug safety patterns [103].

Apriori algorithm is a type of ARM that partially mitigates the challenge of hard computation of association rules [99]. Its principle is based on considering an item set frequent if its support exceeds the support threshold. An association rule is

an implication expression of the form $X \rightarrow Y$ where x is an item set, Y is an item set and x and y are disjoint. In the case of pharmacovigilance, X denotes a set of drugs and Y denotes a set of AEs. To account for directionality, the general Apriori algorithm works in two steps. The first step searches for item sets that exceed the minimum support, while in the second step, association rules are generated and filtered by selecting “confident” item sets (based on a threshold) from those found in the first step. In other means, an association rule is considered significant if it achieves both minimum support and confidence. The support of an itemset $S(X)$ is the number of records containing X . The support of an association rule $S(X \rightarrow Y)$ is equal to $S(X \cup Y)$. Low support may indicate that a rule has simply occurred by chance. The confidence of a rule $C(X \rightarrow Y)$ is equal to $(S(X \cup Y)) / (S(X))$ (15). Confidence determines how often items in Y appear in records that contain X . Confidence provides an estimate of $(Pr(Y) / (X))$ (16) the conditional probability of Y given X . Although association rules can be filtered by given minimum support and confidence, a variety of measures of “interestingness” have been proposed which can be used to filter these association rules [104]. Multi-item ADE associations are rarely reported in biomedical literature to identify plausible drug-drug interactions.

In a recent study, Harpaz et al. [105] applied an optimized and tailored implementation of the Apriori algorithm to mine a sample of AERS (full set of year 2008) reports with rules at least two drugs and one AE for drug interaction adverse effects (DIAEs) detection. Due to the inappropriateness of standard Apriori scores for PhV applications, the authors used the RRR score instead, with the additional constraint that each rule must have an RRR larger than any of its subsets. The latter constraint was used to exclude spurious associations [106]. The authors showed that ~35% of the DIAE rules corresponded to known associations, thereby demonstrating the potential value of their tailored Apriori algorithm for identifying statistically significant DDIs in SRSs for further investigation.

Methodologies for signaling DDIs using nonstandard data sources or linked multiple data sources

By integrating information from the FDA AERS and several EHRs sources, Tatonetti et al. [107] discovered a potentially new drug interaction between two widely used drugs—the antidepressant paroxetine and the cholesterol-lowering medication pravastatin—that can lead to unexpected increases in blood glucose levels. The finding that motivated their data-mining approach was the observation that side effects are not independent of each other and latent evidence for an (unreported) adverse event can be found by examining other (reported) side effects. By scanning the AERS for pairs of drugs that have matching side-effect profiles when taken together but not when taken individually, the authors created a candidate set of drug–drug interactions. The list of candidates was then narrowed down to the paroxetine–pravastatin interaction by conducting retrospective studies using EHRs from Stanford University Hospital, Vanderbilt University Hospital, and Partners Healthcare. The interaction was

confirmed by a prospective study in an insulin-resistant mouse model.

By linking information from DrugBank database and Human Protein Reference Database (HPRD), Huang J et al. [108] proposed a prediction model of pharmacodynamic DDIs (PD DDIs) using information from heterogeneous data sources which providing information such as drug targets, protein-protein interaction (PPI) network, and side effect similarity. They have predicted 9.626 potential PD DDIs at the accuracy of 82% and the recall of 62%. The proposed model provides opportunities for better understanding the potential molecular mechanisms and physiological effects underlying DDIs. For validation, the authors adopted two independent gold standard positives (GSPs) databases including DrugBank and STITCH [109]. The proposed approach may provide the necessary scientific evidence for the drugs during clinical trials, lead to relabeling drug interaction warning for marketed drugs, and avoiding harmful DDIs or enhancing beneficial drug combination in poly-medication prescriptions.

Villar et al. [110] proposed a model for DDIs based on molecular structure similarity. The authors compiled, from DrugBank database and the Interax Interaction Search engine on the DrugBank website [30], a reference set of drugs and mapped them to two-dimensional molecular fingerprints that represent the presence/ absence of specific structural features. Then, potential drug interactions were generated by screening drug candidates, the 50 most frequently sold drugs in 2009, via comparing their structural fingerprints with the reference set of fingerprints. Highly similar candidates were then retained as the final set of drug candidates. Using this approach, the authors achieved 68% sensitivity and 96% specificity using DrugBank database and Micromedex/Drugdex database as a gold standard reference databases [30]. Moreover, a database of 58 403 new predicted DDIs with structural evidence has been generated which could be useful for further study of possible candidates. This approach can be exploited by regularity authorities in detecting new DDIs that should be contraindicated.

By the same, Villar et al. [111] proposed a predictive method for DDIs on the basis of drug interaction profiles. This method is based on following the concept, if two drugs have similar interaction profile, the drugs with the non intersecting interactions will be DDIs candidates. The authors compiled, from DrugBank database, [112] a reference set of drugs (9.454 well-established DDIs) and mapped them to two-dimensional interaction fingerprints. The model could provide potential 17,230 DDI candidates comparing the interaction profiles of pairs of drugs either in the same or other pharmacological class. For instance, the model detected possible increased effect of antidiabetic Pioglitazone due to its interaction with macrolide antibiotic Clarithromycin.

A recent notable study of the successful detection of novel DDIs through mining of the FDA’s adverse event reporting system (AERS) has been conducted. By linking information from multiple sources (FDA AERS reports through April 2009 and clinical EMR data from Stanford hospital), Nicholas P

Tatonetti et al. [113] proposed a model to predict DDIs in adverse event reports. The authors first constructed profiles to 8 clinically severe adverse event (SAE) classes represented in cholesterol related events, renal impairment, diabetes, liver dysfunction, hepatotoxicity, depression, hypertension, and suicide which were defined through manual expert curation. To construct a predictive model, the authors divided AERS data into two independent sets: reports that listed exactly one drug and reports that listed exactly two drugs. They used the first for training SAE classes computationally and the second for validation. By performing a feature selection and fitting a logistic regression model, the authors identified 171 putative DDIs (for eight adverse event categories). The predictive performance of the model was validated by a hospital's EMR. Through EMR systems, the authors were also able to predict the positive association of paroxetine and pravastatin with increased blood glucose (22.6 mg/dl). The authors claimed that their algorithm may identify hundreds of novel interactions for further study, nevertheless the issue of underreporting in spontaneous reporting systems.

Jon D. Duke et al. [114] describe a novel approach for screening potential drug interactions that increase the risk of myopathy. Myopathy comprises a set of musculoskeletal conditions including muscle pain, weakness, and tissue breakdown (rhabdomyolysis). The authors used biomedical literature mining based on mechanistic properties to predict new DDI signals. Then they validated the resulted drug interactions, which are clinically significant, using a large electronic medical record database (EMR). The authors show that this approach predict five new DDI pairs associated with increased myopathy risk and their associated CYP-mediated metabolism enzymes.

Chung Am Choi et al. [115] examined the potential of using HIRA database as drug interactions (DIs) surveillance database. HIRA is a Korean national health insurance system, consisting of the health information of millions of Korean population including drugs and suspected adverse events (AEs), expressed as diagnoses. ICD-10 codes are used to code all kinds of occurring diagnoses. The authors apply Ω shrinkage measure in HIRA data to the well-known interaction between NSAID and diuretics. A significant disproportionate, correspond to an actual interaction between the two drugs, could be identified with Ω shrinkage measure (0.245) and its 95% lower credibility limit was above zero ($\Omega_{0.95} = 0.247$). This result showed the potential feasibility of HIRA database for DI research.

Closing Remarks, Future Perspectives, and Challenges

In this review, we have shown a portfolio of data-mining approaches and data sources proposed for the analysis and detection of postapproval DDIs. Each approach may renew interest to advance the science of DI surveillance by offering diverse prospects. To our knowledge, this article is the first review of published studies related to screening/detecting signals of DDIs in postmarketing drug safety surveillance programs.

Unfortunately, the interactions between drugs are difficult to study, and there are few predictive methods for discovery novel DDIs. These interactions are not necessarily adverse; sildenafil (Viagra) was developed to treat angina but is now used to treat erectile dysfunction. Some computational algorithms take advantage of these pleiotropic interactions of drugs for predicting off target effects and discovering novel protein targets. Nonetheless, discovering the off target interactions of drugs remains an active area of research.

Potential DDIs are evaluated for experimental drugs pre-clinically during development and then monitored by drug safety surveillance programs after they enter the marketplace. The development of predictive tools, to help study possible DDIs, is of great interest to pharmaceutical companies and regulatory authorities, such as the United States Food and Drug Administration (FDA) [11]. These organizations are interested in better methods to detect and assess drug interactions [116]. It is believed that integration of drug phenotypic, therapeutic, structural, and genomic similarities is promising for disclosing DDIs in drug development and postmarketing surveillance [117]- [119].

New opportunities have emerged to exploit diverse data sources that have not traditionally been used in postmarketing PhV, allowing for active paradigms of DI surveillance and detecting unknown DIs by performing pooled analyses. The purpose of DIs surveillance is to investigate the excess reporting of an event of interest on a combination of two drugs together which is more than reported by each individual drug. Although PhV research is now shifting away from the use of SRSs originating from the relative rarity of reporting DDIs to SRSs, this will not lessen the important value of data mining of SRSs; as SRSs represent the largest collection of population-based clinical data on DIs [120], [121]. The detection of DDIs is much more complicated than the detection of drug-event combinations because of the relatively lower incidence rates and background reporting rates in SRS and in addition, there are still no studies in literature suggesting that any of the proposed DDI detection methods (aforementioned in this article) have been implemented for routine PhV surveillance. Consequently, much effort is needed for developing, implementing and evaluating algorithms for discovering DDIs across disparate data sources for early DDI warnings and routinely DI surveillance.

A central challenge in DI surveillance research is the absence of established guidelines for evaluating the performance of DMAs for DDIs signal detection. Mainly, it is because of absence of gold standard for all possible DI safety profiles for marketed drugs. Consequently, more research is needed to conduct methodological research to evaluate the performance of various analytical methods and to gain better understanding of signaling characteristics of multivariate association measures. We believe that will help in identifying optimal signal-qualifying thresholds in purpose of titrating the threshold of the measure toward a desired level of sensitivity and specificity, and also avoiding costs associated with false-positive and false-negative signals.

In recognition of drug toxicity is a major cause of late-stage product attrition of drug discovery process, early identification about the DI safety profiles of new medicines remains challenging. In Traditional drug discovery, hundreds of new drug molecules are evaluated before a small number of candidates, which mostly relies on scientists' prior knowledge of the therapeutic area, are selected for subsequent laboratory safety testing in cells and animals. In summary, conventional drug development involves the hand-off of drug candidates from medicinal chemists into preclinical testing; followed by a transition to clinical study. Unforeseen DIs can have serious health consequences for patients that probably resulting in serious negative impacts on the whole drug development process. Consequently, there is a need for proposing data mining approaches to explore clinical safety knowledge and derive DIs of new drug candidates in early drug discovery via linking across multiple disciplines; encompassing preclinical, chemical structures, toxicology, drug metabolism, in vitro pharmacology and clinical safety information [122]. We think adopting this strategy in the drug discovery process will add values via providing a way to link clinical safety information to the experimental platforms used in early drug discovery, and enabling the analysis of potential safety issues of drug molecules in the early phases of the drug discovery process resulting in efficient triage of new drug candidates for further testing and elaboration [123].

Last but not least, Data mining does not provide sufficient evidence on causality and they are just adjunctive tool to formulate or strengthen or refine novel hypotheses. In other mean, well-organized clinical reviews remain crucial for further investigation and close surveillance of such safety signals, and data mining approaches should be incorporated into an overall signaling strategy as a first step in a more comprehensive process.

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