ORIGINAL RESEARCH ARTICLE

Drug Saf 2011; 34 (3): 253-266
0114-5916/11/0003-0253/$49.95/0

Reporting Patterns Indicative of Adverse Drug Interactions

A Systematic Evaluation in VigiBase

Johanna Strandell,[1,2] *Ola Caster*,[1,3] *Andrew Bate*,[1,4] *Niklas Norén*[1,5] and *I. Ralph Edwards*[1]

1 Uppsala Monitoring Centre, Uppsala, Sweden
2 Department of Drug Research/Clinical Pharmacology, Linköping University, Linköping, Sweden
3 Department of Computer and Systems Sciences, Stockholm University, Stockholm, Sweden
4 School of Information Systems, Brunel University, London, UK
5 Department of Mathematics, Stockholm University, Stockholm, Sweden

Abstract

Background: Adverse drug interaction surveillance in collections of Individual Case Safety Reports (ICSRs) remains underdeveloped. Most efforts to date have focused on disproportionality analysis, but the empirical support for its value is based on isolated examples. Additionally, too little attention has been given to the potential value of the detailed content of ICSRs for improved adverse drug interaction surveillance.

Objective: The aim of the study was to identify reporting patterns indicative of suspected adverse drug interactions before the drug interactions are generally established.

Methods: A reference set of known adverse drug interactions and drug pairs not known to interact was constructed from information added to Stockley's Drug Interactions Alerts between the first quarter of 2007 and the third quarter of 2009. The reference set was used to systematically study differences in reporting patterns between adverse drug interactions before they are generally established and adverse drug reactions (ADRs) to drug pairs that are not known to interact, in the WHO Global ICSR Database, VigiBase. The scope of the study included pharmacological properties such as common cytochrome P450 metabolism, explicit suspicions of drug interactions as noted by the reporter, clinical details such as dose and treatment overlap, and the lower limit of the 95% credibility interval of a three-way measure of disproportionality, Omega_{025} (Ω_{025}), based on the total number of reports on two drugs and one ADR together. Analyses were carried out including and excluding concomitant medicines.

Results: Five reporting patterns were highlighted as particularly strong indicators of adverse drug interactions before they are known: suspicion of interactions as noted by the reporter in a case narrative, the assignment of the two drugs as interacting or through an ADR term; co-reporting of effect

increased with the drug pair; and, finally, an excess total number of reports on the ADR together with the two drugs, as measured by Ω_{025}. Overall, the inclusion of concomitant medicines led to a larger number of true adverse drug interactions being highlighted, but at a substantial decrease in the strength of most indicators. Notably, the inclusion of concomitant medicines completely eliminated the value of Ω_{025} as an indicator of adverse drug interactions, in this systematic evaluation.

Conclusions: Reported suspicion of interactions as noted by the reporter in a case narrative, the assignment of the two drugs as interacting or through an ADR term; co-reporting of effect increased with the drug pair and by the Ω_{025} each provide unique information to highlight adverse drug interactions before they become known in the literature. To our knowledge, this is the first systematic analysis demonstrating the value of disproportionality analysis for adverse drug interactions using a comprehensive reference set, and the first study to consider a broader basis including clinical information for systematic drug interaction surveillance.

Background

Adverse drug reactions (ADRs) constitute a major health problem for individuals as well as for the community. Drug interactions have been reported to be the cause of 16.6–59.1% of all ADRs.[1,2] Suspected ADRs can be reported on Individual Case Safety Reports (ICSRs), otherwise known as spontaneous reports and synonymously referred to as *reports* in this study. ICSRs are widely used in the early detection of suspected ADRs related to single drugs, although they have had limited use in the surveillance of previously unknown adverse drug interactions. Until now, there have been isolated case reviews of suspected adverse drug interactions,[3-8] and most of the methodological research related to drug interaction surveillance has focused on the development of disproportionality measures.[9-14]

A general definition of a drug interaction is when 'the effects of one drug are changed in the presence of another drug, herbal medicine, food, drink or by some environmental chemical agent'.[15] This definition also covers theoretical drug interactions without clinical relevance, but in this study we focus on drug interactions with the potential to cause one or more adverse events of clinical significance, which we refer to as *adverse drug interactions*.

In the small number of published case series reviews that concern suspected adverse drug interactions, the following clinical information has been highlighted as potentially suggestive that a suspected drug interaction might have caused the adverse event: metabolism through the same cytochrome P450 (CYP) enzyme, two drugs explicitly reported as interacting, suspicion of interactions as noted by the reporter in a case narrative, or through an ADR term referring to a drug interaction, and plausible time relatedness of drug therapy.[4-8] ADR terms relating to altered therapeutic effect have also been proposed as potentially indicative of drug interactions;[16] however, to our knowledge there has been no attempt to use such information systematically for drug interaction surveillance.

In VigiBase, a disproportionality measure, Ω (Omega), based on an additive baseline model, is used to highlight excess co-reporting of two drugs and one ADR.[11] This measure has shown promising results in more limited investigations[7,11] but has not previously been evaluated relative to a comprehensive reference set of adverse drug interactions.

Large-scale methodological research does require reliable references. The lack of gold standards is a major challenge in the attempt to systematically evaluate algorithms to support ADR surveillance.[17] Retrospective evaluation against established safety issues is one option. For drug interactions, there are several reference sets available, and one of the more comprehensive is Stockley's Drug Interactions,[15] which we have used in this analysis. A main limitation of any evaluation against established associations is that the real aim of safety surveillance is early detection. Reporting patterns shift as previously unknown associations become established and known to health professionals and patients. This may be especially important for adverse drug interaction surveillance, which is based on reporters' suspicion that a drug interaction may have caused an adverse event. For that reason, we have made a special effort to focus our analysis on time periods *prior* to when each adverse drug interaction first becomes available in the reference source.

Prior to this study we identified potential information (*indicators*) on case series that has been noted as supportive of a drug interaction in its early discovery. As this information has not been evaluated on a larger scale, the aim of this study was to systematically examine each individual indicator's propensity for highlighting suspected adverse drug interactions on ICSRs, using a reference set of known adverse drug interactions and drug pairs not known to interact.

Data and Methods

To systematically identify reporting patterns indicative of suspected adverse drug interactions in VigiBase, a reference set of known adverse drug interactions and of drugs not known to interact was constructed based on Stockley's Drug Interactions Alerts,[18] which is a quick, ready-reference version of the more comprehensive literature source, Stockley's Drug Interactions.[15] A free-text extraction algorithm was used to map information in Stockley's to standard terminologies,[19] and link the reference data to reports in VigiBase. Known adverse drug interactions and ADRs to drug pairs that are not known to interact that occurred in both the reference set and VigiBase were evaluated with respect to the different reporting patterns of interest on the level of drug-drug-ADRs (DDAs). Data from VigiBase were specifically extracted from a point in time before the adverse drug interactions became acknowledged in the general literature and added to Stockley's Drug Interaction Alerts.

Study Indicators

To study reporting patterns of adverse drug interactions, information (*indicators*) that has been noted as potentially supportive of a drug interaction in its early discovery was identified prior to the study. The majority of indicators (12 of 14) were related to case report information in VigiBase; for example, whether certain ADR terms were ever co-reported with the DDA. The other two indicators were related to general pharmacological information on the drug pair: whether the two drugs have an acknowledged activity on the same CYP enzyme and whether they belong to the same Anatomical Therapeutic Chemical (ATC) group. The indicators were categorized into the groups 'primary' and 'secondary' prior to the study, based on the extent to which they may, on their own, support a potential safety signal. All indicators and the rationale for examining them are described in table I.

Primary Indicators

Primary indicators are those that may independently drive suspicion of an adverse drug interaction as they provide clinical information to suggest that a suspected drug interaction has occurred[7] (two drugs co-reported as interacting, the co-reporting of Medical Dictionary for Regulatory Activities [MedDRA®] interaction terms or a case narrative referring to an interaction) or appear as attributes of an altered therapeutic effect (co-reporting of decreased effect, increased effect or unexpected therapeutic effect[16]) or indicate excess reporting of the DDA relative to a statistical baseline model for no interaction, denoted as a positive Ω_{025} value, representing the

Table I. The 14 indicators examined for difference in reporting patterns between the two groups, known adverse drug interactions and drug-drug-adverse drug reaction (DDA) triplets not known to interact. *Report* should be read as one Individual Case Safety Report reporting the DDAs in VigiBase

Definition indicator	Description of indicator	Rationale
Primary indicators		
Empirical information		
Effect decreased	The DDA was co-reported with at least one of the following WHO-ART terms: 'Therapeutic response decreased', 'Drug level below therapeutic', 'Drug level decreased', 'Medicine ineffective', 'Medicine ineffective unexpected' on at least one report	The co-reported term indicates that the expected therapeutic effect has been decreased. This can be suggestive of a drug interaction[11]
Effect increased	The DDA was co-reported with any of the following WHO-ART terms: 'Therapeutic response increased', 'Drug level increased' on at least one report	The co-reported term indicates that the expected therapeutic effect has been increased. This can be suggestive of a drug interaction[11]
Interacting	Drug pair within the DDA was recorded as interacting on at least one report	The reporter suspects a possible interaction between the drugs reported as interacting
MedDRA® interaction	The DDA was co-reported with at least one of the following MedDRA® terms: 'Drug interaction', 'Labelled drug-drug interaction medication error', 'Inhibitory drug interaction', 'Potentiating drug interaction'	The reporter suspects the ADR to be a result of a possible interaction. At the time of the study, WHO-ART did not include interaction-related terms and therefore MedDRA® terms were used
Narrative information	The case narrative on at least one report with the DDA mentioned the word fragments 'interact' or interakt'	The reporter describes a possible interaction in the case narrative
Ω_{025}	Ω is a shrinkage observed-to-expected ratio for the number of reports of the ADR with the two drugs together. Ω_{025} is the lower limit of a 95% credibility interval for Ω	When Ω_{025} exceeds zero the DDA is reported reliably more often than expected if the attributable risks of the ADR from each drug would add together[14]
Unexpected therapeutic effect	The DDA was co-reported with the WHO-ART term 'Unexpected therapeutic effect' on at least one report	The co-reported term indicates that the expected therapeutic effect has been altered. This can be suggestive of a drug interaction[11]
Secondary indicators		
Empirical information		
Dechallenge	Positive dechallenge outcome is recorded for at least one of the drugs with the ADR on at least one report	A positive dechallenge can strengthen a potential relationship between one of the drugs and the ADR
Dose information	Dose information was provided for the drug pair on at least one report	The reporter might suspect and report doses to a greater extent if the ADR appears when normal doses are given
Overlapping treatment	Treatment of both drugs was definitely overlapping on at least one report	The drugs have definitely been used concomitantly
Rechallenge	Positive rechallenge outcome is recorded for at least one of the drugs with the ADR on at least one report	The re-occurrence of an ADR on re-introduction of one of the drugs can strengthen a potential relationship between the two
Sole two drugs	The drug pair were the only reported drugs on at least one report	To exclude influence from other possible interacting agents
Pharmacological information		
ATC	The drug pair is classified with the same chemical group (4th-level ATC code)	Could indicate an additive effect of the two drugs
CYP	The drug pair within the DDA are drugs that may induce, inhibit or be substrates in the phase I metabolism via the same CYP enzyme(s). CYP information is held in the VigiBase system with references from countries' drug reference sources,[20,21] original articles referred to on Indiana University's homepage (the so-called Flockhart table),[22] and Stockley's Drug Interactions[15]	Indicates a potential pharmacokinetic mechanism. Furthermore, drugs that undergo hepatic metabolism through the CYP enzymes are more likely to cause changes in other drugs' concentrations and therefore result in dose-related ADRs

ADR = adverse drug reaction; **ATC** = Anatomical Therapeutic Chemical; **CYP** = cytochrome P450; **MedDRA®** = Medical Dictionary for Regulatory Activities; **WHO-ART** = WHO Adverse Reactions Terminology.

lower limit of the 95% credibility interval for the three-way disproportionality measure Ω. [7]

Secondary Indicators

Secondary indicators may not, in isolation, raise a safety concern but could potentially be used to yield effective triages, perhaps in combination with primary indicators. This group includes specific pharmacological properties (drugs metabolized through the same CYP enzyme or belonging to the same ATC group) and other reported information, such as a positive outcome of a dechallenge or rechallenge intervention for at least one of the drugs, the presence of dose information for both drugs, overlapping treatment periods for the two drugs and the fact that only two drugs were reported.[5,7,8]

VigiBase

The WHO Programme for International Drug Monitoring is a cornerstone of global safety surveillance. It was initiated in 1968 for the early detection of previously unknown drug safety problems.[23] The Uppsala Monitoring Centre, Uppsala, Sweden, has been responsible for the operation of the WHO programme since 1978 and maintains and analyses its database, the WHO Global ICSR Database, VigiBase.[19] VigiBase is a vast resource of safety information that currently contains more than 5.7 million reports from 101 countries.

Reports are collected on a national basis by the individual member countries of the WHO Programme for International Drug Monitoring. Via each member country's national centre, the national reports are forwarded to, processed and stored in VigiBase. Each report includes at least one drug suspected of causing the adverse event, at least one suspected ADR, country of origin and an identification number. Ideally, the reports also include more detailed information such as a case narrative, therapy dates, dose information and information regarding the outcome of drug withdrawal and/or drug reintroduction. Drugs listed on the individual case reports should be stated as being (i) 'suspected' (drugs suspected for the reaction, but not explicitly as due to a drug interaction); (ii) 'interacting' (if an ADR is suspected of being related to a drug interaction between two or more drugs); or (iii) 'concomitant' (drugs used concurrently but not suspected by the reporter to have caused the adverse event). Drugs are classified to one of the above-mentioned categories by the primary reporter or through a second evaluation performed by the national centre. The individuals providing information on the reports are referred to as *reporters* in this analysis. VigiBase is heterogeneous with respect to origin of data and level of suspicion that a reported adverse event was due to a medicine. In particular, there may be regional variation in whether drugs believed to have caused an adverse drug interaction are assigned as interacting or suspected.

Stockley's Drug Interactions

Stockley's Drug Interactions[15] is a well known and comprehensive international source of drug interaction information. Part of this source is Stockley's Drug Interactions Alerts,[18] which is a quick ready-reference for drug interactions, including more than 40 000 clinically evaluated drug-drug, drug-alcohol and drug-food pairs. Stockley's Drug Interactions Alerts[18] categorizes and summarizes information regarding the interactions into a few sentences, indicating whether the drugs can safely be taken together, alter the therapeutic effect of one another, or may result in ADRs (this text is referred to as the *interaction text*).

Reference Dataset

Known Adverse Drug Interactions

A subset of known adverse drug interactions was constructed through free-text extraction of potential ADR terms from the interaction texts of drug pairs listed in the xml files of Stockley's Drug Interactions Alerts,[18] thus producing DDA triplets representing known adverse drug interactions.

Stockley's Drug Interactions Alerts covers drug interactions acknowledged from the early 1960s to the present time. In parallel to the entry of information on recently discovered adverse drug interactions, the electronic format has been

retroactively populated with historic data from 2003 onwards. To focus the study on newly discovered drug interactions, only drug interactions recently added in Stockley's Drug Interactions Alerts (first quarter of 2007 to third quarter of 2009) were included in the analysis. Each drug pair was linked to a particular 3-month period (quarter) in which the drug interaction first appeared.

Text Extraction

Each drug interaction text in Stockley's Drug Interactions Alerts[18] was automatically screened for ADR terms available in the WHO Adverse Reaction Terminology (WHO-ART).[19] The text was screened for 'preferred terms' and 'included terms', the latter being a more detailed description of a 'preferred term'. The 'included terms' were later replaced by their corresponding preferred terms and each 'preferred term' in combination with the drug pair formed a DDA. As WHO-ART terms are, in general, not written in natural language, verbatim matching was expected to miss many ADR terms. Therefore, a more sophisticated free-text extraction procedure was employed. First, both the free-text fields and the ADR terms were pre-processed; all non-alphanumeric characters, e.g. hyphens, and words not carrying any semantic meaning, so-called 'stopwords',[24] were removed. Furthermore, all individual words were replaced by their stems using a stemming algorithm.[25] Similar pre-processing schemes are standard in other text-matching procedures.[26] Additionally, ADR terms consisting of more than one word were permuted. This means that all possible orders of the individual words in the WHO-ART terms were matched against the free-text fields in Stockley's Drug Interactions Alerts. Preliminary tests revealed certain differences between WHO-ART and the medical language used in Stockley's Drug Interactions Alerts, which caused the extraction procedure to systematically miss terms. This was corrected by adding synonyms to a number of words used in WHO-ART. For example '*bleeding*' was a synonym for '*haemorrhage*'. The complete list of synonyms used can be found in table II.

Furthermore, all drugs within Stockley's Drug Interactions Alerts were mapped to their substance name in the WHO Drug Dictionary Enhanced.[19] Thus, all drugs and ADR terms in the analysis were mapped to standard terminologies.

Table II. Synonyms used for words in WHO Adverse Reaction Terminology terms

Original word or term	Synonym(s)
QT	QTc
Ferritin	Iron
Heart	Cardiac
Cardiac	Heart
GI	Gastrointestinal
Convulsion	Seizure
Anti platelet	Antiplatelet
International normalized ratio	INR
Nephropathy toxic	Nephrotoxicity, nephrotoxic
Hepatic	Liver
Estrogen	Oestrogen
Hepatotoxic effect	Hepatotoxicity, hepatotoxic
Increase	Potentiate, raise, elevate
Decrease	Lower
Haemorrhage	Bleeding
Myasthenia gravis-like syndrome	Myasthenia

Drug-Drug-Adverse Drug Reactions (DDAs) Not Known to Interact

To create a comparison group, pairs of drugs not known to interact were first formed by combining drugs that had occurred at least once in Stockley's Drug Interactions Alerts[18] but had never been listed together, and then adding ADR terms that had been extracted from Stockley's Drug Interactions Alerts in the construction of adverse drug interaction DDAs, as outlined above. The comparison group is referred to as '*DDAs not known to interact*'.

Data Selection in VigiBase

For the purpose of analysing reporting patterns for DDAs not known to interact, and known adverse drug interactions in VigiBase, we restricted our test set to those DDAs that had been co-reported at least three times during the past 20 years with the two drugs listed as Suspected, Interacting or Concomitant (SIC). To further ensure a basic empirical support in VigiBase for each DDA included in the study, an

additional requirement was for the two drugs to have been reported as Suspected or Interacting (SI) on at least one report. The restriction to a time period of the last 20 years was made to avoid an identified quality issue in the categorization of drugs as interacting among older reports. Since drugs and ADRs in Stockley's Drug Interactions Alerts were mapped to standard terminologies, the determined DDAs could be compared with the reports in VigiBase.

Exclusion

This analysis did not aim to characterize drug interactions involving ethanol or nicotine, therefore DDAs including these substances were omitted from the analyses. Furthermore, DDAs comprising the following WHO-ART terms were excluded since they were part of potential indicators later used in the analysis: 'unexpected therapeutic effect', 'therapeutic response increased', 'drug level increased', 'therapeutic response decreased', 'drug level below therapeutic', 'drug level decreased', 'medicine ineffective' or 'medicine ineffective unexpected'.

The presence of duplicate reports may distort the analysis of ICSRs. In a previous study, large clusters of reports with many listed drugs and ADRs led to widely inflated measures of three-way disproportionality.[11] As a data pre-processing step, suspected duplicates were therefore automatically identified,[27] and only one report in a group of suspected duplicates was retained in the analysis (that with the greatest amount of information).

Validation

All DDAs from the set of known adverse drug interactions that fulfilled the selection criteria were manually confirmed with the original text in Stockley's Drug Interactions Alerts by a clinical pharmacologist (IRE). DDAs constructed from falsely extracted ADRs were not included in the subsequent analysis.

Timepoint of Extraction of VigiBase Data

Data for known adverse drug interactions were extracted from VigiBase up to the quarter prior to entrance of the DDA into Stockley's Drug Interactions Alerts. The quarter prior to entrance of information on an adverse drug interaction into Stockley's Drug Interactions Alerts was assumed to represent the most recent point in time at which the adverse drug interaction was not yet known.

Study-Specific Comparison Group

In order to provide a reference against which to evaluate the reporting patterns for known adverse drug interactions, a comparison group, specific to the present study, was constructed. The basis for this comparison group was the set of DDAs not known to interact [see 'Drug-Drug-Adverse Drug Reactions (DDAs) Not Known to Interact' section] subject to the exclusion criteria described above. For each of the remaining DDAs it was identified for what quarters, if any, the requirements on cumulative reporting of at least three SIC reports and at least one SI report were met. Finally, 20 DDAs not known to interact were randomly selected for each included known adverse drug interaction. The selection was matched on quarter of data extraction, so that the timepoint of data extraction was the same for each of the 20 DDAs not known to interact as it was for the corresponding known adverse drug interaction. Furthermore, each DDA not known to interact could only be randomly drawn once. The choice of selecting 20 comparison DDAs per included known adverse drug interaction was arbitrary; however, this number should be large enough, with a margin, to keep the sampling variability at a minimum.

Henceforth, the group of 'DDAs not known to interact' will refer to these specific DDAs just described. A crucial feature of this group is that it has, with respect to VigiBase reporting, been subject to the same inclusion and exclusion criteria as the group of known adverse drug interactions.

Performance Evaluation in VigiBase

Main Analyses

Known adverse drug interactions and DDAs not known to interact (defined above) occurring

in the reference set and VigiBase were systematically studied for differences in reporting of potential indicators of adverse drug interactions. Each indicator was binary by construction: either it was present for a DDA, according to the definitions in table I, or else it was not. Previous studies have shown that even drugs that have established interactions are often not reported as interacting or co-suspected of having caused a suspected ADR.[7,20] Therefore, with the exception of *'Interacting'*, the other 11 indicators based on empirical reporting patterns in VigiBase were evaluated both at the SI and the SIC level. Together with the two indicators referring to drug elimination pathway and ATC group, a total of 25 ($2 \times 11 + 3$) indicators were considered in the study.

For each individual indicator, the proportion of DDAs in the respective groups where the indicator was present was calculated (including 95% CI). Furthermore, for each variable, the ratio between the proportions in the respective groups was computed and used as proxy for the positive predictive value for that indicator. The overlap in the set of known adverse drug interactions highlighted by the most promising clinical reporting patterns and Ω_{025} was studied to establish the unique contributions of these qualitatively different approaches.

Sensitivity Analyses

The impact of two potential biases was assessed by means of sensitivity analyses. First, if data were extracted for the known adverse drug interactions at a point in time when they are already known, this might over-estimate the usefulness of reporting patterns that are more likely to occur for established adverse drug interactions, such as explicit remarks of suspected interactions. To assess the overall potential for such a bias, a random set of 57 known adverse drug interactions were reviewed to determine their support in the general scientific literature at the time of the study. Furthermore, a worst-case estimate of the ratio for the Interacting indicator was calculated by first reviewing the scientific support at entry into Stockley's of all DDAs highlighted with the interacting indicator, and then repeating the analysis for the Interacting indicator, including only those DDAs that could be verified as newly discovered. The Interacting indicator was chosen because it should be the most susceptible to this particular bias.

Second, the analysis of those indicators that are based on a feature being present on at least one report for a DDA could be subject to bias if the overall number of reports differs between known adverse drug interactions and DDAs not known to interact. To assess the potential impact of such bias, the analysis above was repeated with matching on the number of reports for the DDA. For indicators based on SIC reports and for the Interacting indicator, DDAs not known to interact were randomly selected based on matching with respect to quarter (as previously) and with respect to overall number of SIC reports. Correspondingly, for indicators based on SI reports, matching was performed with respect to quarter and overall number of SI reports.

Results

Reference Data

The automatic text extraction identified a range of 373 unique WHO-ART preferred terms among the 40 606 unique pairs of interacting drugs in Stockley's Drug Interactions Alerts. After matching to the WHO Drug Dictionary Enhanced,[19] 40 124 drug pairs remained. One or more ADR terms were identified for 66% (n = 26 288) of the drug pairs, and the full reference dataset included a total of 50 538 adverse drug interactions. For the period of interest, 2007 to the third quarter of 2009, 7827 unique drug pairs and 16 664 adverse drug interactions were available.

Characteristics of DDAs Available in VigiBase

Of the 16 664 DDAs in the reference dataset, 665 (4.0%) were reported in VigiBase at least three times. However, the increased requirement on clinical suspicion, i.e. that at least one report include the two drugs co-reported as suspected or interacting, decreased the number of known adverse drug interactions in the study to 346.

Clinical review of the extracted ADR terms revealed 24 (6.9%) as false positives. False ADR terms were primarily related to the indication or mechanism of action of individual drugs, which were sometimes explicitly mentioned in the descriptive texts. Thus, the final analysis concerned 322 DDAs (1.9% of the 16 664) that represented known adverse drug interactions in this analysis. The comparison group consisting of DDAs not known to interact contained 6440 DDAs, corresponding to 20 DDAs per known adverse drug interaction, according to the previously defined study protocol.

Altogether, 208 unique drugs were represented among the known adverse drug interactions in VigiBase with the main groups of agents in ranked order: benzodiazepine derivatives, SSRIs, ACE inhibitors, selective β-adrenergic receptor antagonists and calcium channel antagonists. Individually, clozapine was most commonly represented, followed by fluoxetine, indapamide, venlafaxine, erythromycin, paroxetine, cisapride, thalidomide, atenolol and metoprolol.

The 322 known adverse drug interactions included 256 unique drug pairs, 47 of which were reported with more than one ADR term. In total, 58 WHO-ART preferred terms were represented among the known adverse drug interactions. These ADR terms primarily belonged to the 'Central and peripheral nervous system disorders' and various cardiovascular System Organ Classes (SOCs). Hypotension was the most common ADR, followed by somnolence, bradycardia, QT prolonged, dizziness, torsade de pointes, arrhythmia, convulsions and hyperkalaemia.

Performance Evaluation in VigiBase

The presence of each indicator for DDAs, including known adverse drug interactions and drug pairs not known to interact, respectively, are shown in figure 1 (primary indicators) and figure 2 (secondary indicators). Overall, these reporting patterns occur more commonly for known adverse drug interactions than for drugs not known to interact. The strongest indicators among the primary variables were a case narrative with the text 'interact' or 'interakt' (SI), followed by two drugs co-reported as interacting, a case narrative with the text 'interact' or 'interakt' (SIC), effect increased (SI), a drug interaction noted as an ADR term (SI) and an Ω_{025} measure exceeding zero (SI). Amongst the secondary variables, a positive dechallenge (SI) was the strongest indicator, followed by dose information provided for both drugs (SI), metabolism via the same CYP enzyme, only two drugs on the report (SI) and overlapping drug treatment (SI). Our study found poor discriminative power between known adverse drug interactions and DDAs not known to interact for the following indicators: effect decreased SI/SIC, Ω_{025} SIC and rechallenge SI. The absolute number of adverse drug interactions highlighted was greater when the analysis included drugs listed as concomitant, but the precision decreased. Our study found a limited overlap between Ω_{025} SI and other primary indicators, as shown in table III.

The sensitivity analyses provided reassuring results. Among randomly selected adverse drug interactions, more than 70% (43/57) were verified as emerging at their respective times of data extraction. For the adverse drug interactions highlighted by the Interacting indicator, 63.5% (40 of 63) were verified as emerging at the time of the study point. Seven of those 23 DDAs that already had some empirical support were only represented on isolated case reports. By excluding those DDAs (23 of 63) that had some support in the literature, the resulting worst-case estimate for the ratio of the Interacting indicator was 3.9, compared with the reported 5.7. The matching on total number of reports for DDAs caused only minor fluctuations in the resulting ratios for the promising primary indicators. For example, the ratios of Interacting and Narrative information (SI) increased from 5.7 to 6.0, and from 6.3 to 6.5, respectively. The ratios for Narrative information (SIC), Effect increased (SI) and MedDRA® interaction (SI) decreased slightly from 3.2 to 3.0, 2.4 to 1.7, and 2.4 to 1.6, respectively. For the most promising secondary indicators, the ratios decreased: from 2.9 to 1.5 for a positive dechallenge (SI), 2.4 to 1.3 for dose information for both drugs (SI), 2.1 to 1.5 for only two drugs on the report (SI) and 1.9 to 1.0 for overlapping drug treatment (SI).

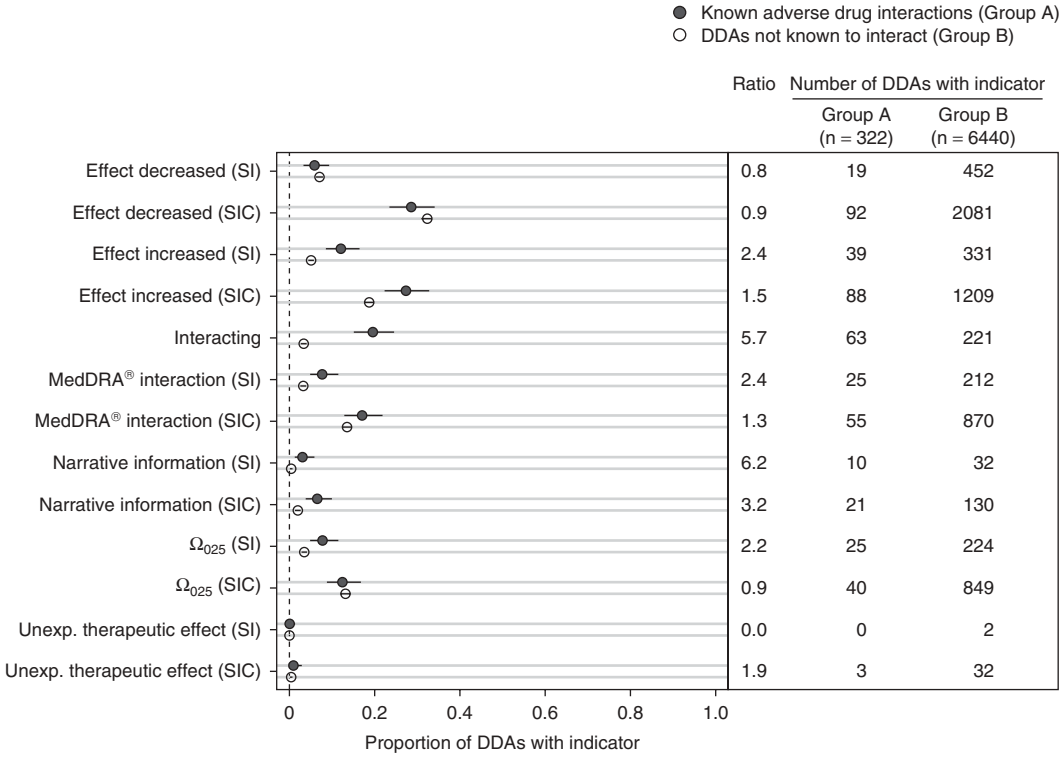

Fig. 1. The proportion (with 95% CIs) of drug-drug-adverse drug reactions (DDAs) occurring with the primary indicators, among DDAs constructed from known adverse drug interactions and drug pairs not known to interact, respectively. The ratio between the groups and the numbers behind the proportions are given in text. **Ω_{025}** = lower limit of the 95% credibility interval of the Omega (Ω) measure, a three-way measure of disproportionality; **MedDRA®** = Medical Dictionary for Regulatory Activities; **SI** = suspected or interacting; **SIC** = suspected, interacting or concomitant; **Unexp.** = Unexpected.

Discussion

Our study highlights important differences in the reporting patterns for adverse drug interactions and those of drugs not known to interact. Suspicions of a drug interaction by the reporter, as explicitly noted in a case narrative, as an ADR term, or the assignment of the two drugs as interacting, are much more common for known adverse drug interactions than for drugs not known to interact. The same holds for excess co-reporting of an ADR together with two drugs, as measured by the Ω measure and the co-reporting of enhanced therapeutic effect (effect increased), respectively. This analysis emphasizes the value for routine screening of detailed information on reports that have previously only been used in isolated adverse drug interaction safety signals.[4,6-8] Previous studies have indicated that reporters rarely provide explicit remarks on suspected drug interactions.[7,20] This was also reflected in our analysis but our results indicate that when such information is available it may be a good indicator of what becomes acknowledged as adverse drug interactions in the future. Our study also demonstrated that reporting patterns based on detailed clinical information tend to highlight other adverse drug interactions than those highlighted by excess reporting rates, which indicates that both approaches are required for effective drug interaction surveillance.

Whereas previous support for disproportionality analysis as an effective method to discover adverse drug interactions has been largely anecdotal, our study systematically demonstrated the Ω_{025} measure's ability to highlight adverse drug

interactions early. Underreporting is a fundamental challenge to effective ADR surveillance.[19,21] For drug interaction surveillance, an added complexity is that there may be underreporting at the level of individual medicines taken by a patient who has experienced a suspected ADR. Increased publicity for a specific drug-ADR combination may further amplify such effects[21] if the other medicines are assumed to be innocent bystanders to the implicated drug.[7] Failure to assign possibly interacting drugs as suspected or interacting will affect the analysis,[7,20] and this observation would motivate an analysis irrespective of the reporter's assigned level of suspicion. Our results do show that the inclusion of concomitant medicines leads to a larger proportion of true adverse interactions being highlighted, but at the expense of substantially decreased discriminatory power. Ω_{025} was by far a better indicator when the analysis was restricted to suspected and interacting drugs. This effect was primarily related to the reduction of false positives, e.g. positive Ω_{025} measures for DDAs not known to interact. This was unexpected since the baseline model used for Ω essentially requires information on all drugs taken.[11] A possible explanation for the deterioration in performance when including concomitant medicines could be the occasional listing as concomitant medication that is not truly concurrently used but reflects drugs that have been taken at previous times in the medical history of the patient.

This study included only a small proportion (1.9%) of all adverse drug interactions first extracted from the reference. Stockley's Drug

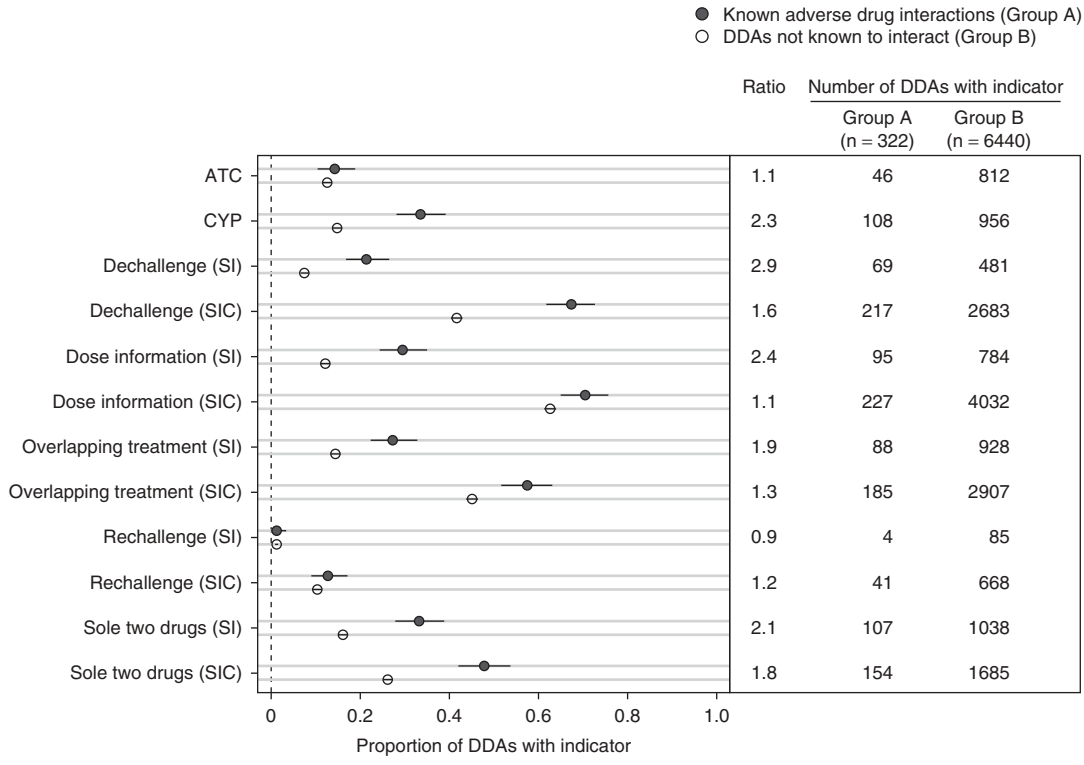

Fig. 2. The proportion (with 95% CIs) of drug-drug-adverse drug reactions (DDAs) occurring with the secondary indicators, among DDAs constructed from known adverse drug interactions and drug pairs not known to interact, respectively. The ratio between the groups and the numbers behind the proportions are given in text. **ATC** = Anatomical Therapeutic Chemical; **CYP** = cytochrome P450; **SI** = suspected or interacting; **SIC** = suspected, interacting or concomitant.

Table III. Dependence of Ω_{025} (SI) and other primary indicators measured by an overlap in drug-drug-adverse drug reactions (DDAs)

Primary indicator	Number of DDAs with indicator	Number of DDAs with indicator and Ω_{025} SI	Overlap in proportion
MedDRA® interaction (SI)	25	7	28.0
Narrative information (SI)	10	2	20.0
Interacting	63	10	15.9
Effect decreased (SI)	19	3	15.8
Effect increased (SI)	39	5	12.8
MedDRA® interaction (SIC)	55	7	12.7
Narrative information (SIC)	21	2	9.5
Effect increased (SIC)	88	5	5.7
Effect decreased (SIC)	92	5	5.4
Unexpected therapeutic effect (SI)	0	0	0.0
Unexpected therapeutic effect (SIC)	3	0	0.0
All primary indicators apart from Ω_{025} SI/SIC (unique)	182	17	9.3

Ω_{025} = lower limit of the 95% credibility interval of the Omega (Ω) measure, a three-way measure of disproportionality; **MedDRA®** = Medical Dictionary for Regulatory Activities; **SI** = suspected or interacting; **SIC** = suspected, interacting or concomitant.

Interactions Alerts constitutes a generally useful reference, including evaluated and evidence-based information on drug interactions, but, in contrast to VigiBase, it consists of drug interactions with variable clinical relevance, where some drug combinations are unlikely to occur in practice or have very limited clinical impact and others should never be concurrently used because of potential serious outcomes.[15] The restricted subset could also be a result of differences in medical language, where some medical terms are more frequent in literal language and were mapped to such WHO-ART terms, while the ADR terms listed on ICSRs might follow a different pattern. However, the manual review established that those ADR terms extracted by the text-matching procedure were accurate overall (<7% false positives).

Since the proportion of true adverse drug interactions among the DDAs that fulfill the study's inclusion criteria are unknown to us at this point, this analysis cannot estimate the true positive predictive value for any indicator. However, the high empirical support required for the comparison group (at least three reports, of which one with the two drugs listed as co-suspected) suggests that strong indicators in the study are likely to be strong indicators also prospectively.

Interactions due to additive effects do not fall under the strict definition of a drug interaction and are therefore not necessarily part of Stockley's Drug Interactions Alerts. Therefore, we suspect that a fair proportion of those DDAs not known to interact with both drugs listed as interacting (3.8%) correspond to additive effects. Additive effects may correspond to synergistic risk, which arguably should also be detected by an effective algorithm. Under that assumption, the inclusion of such DDAs in the comparison group could have underestimated the strength of some of the indicators in our study. Our sensitivity analyses indicated that whereas the presence of some established effects among the adverse drug interactions did have a minor effect on our analysis, even a worst-case scenario did not eliminate Interacting as a strong indicator. The second sensitivity analysis also provided us with reassuring results, as matching on the number of reports on each DDA affected the secondary indicators but not the promising primary indicators. We therefore conclude that this bias, too, is so minor as to not impact our conclusions.

This analysis does not intend to present the frequency of adverse drug interactions reported to VigiBase, nor the incidence of drug interactions in the population. Instead, we were interested systematically to study what reporting patterns in VigiBase characterize adverse drug interactions before they become known in the literature. At this point we have not demonstrated the full capacity of each indicator. We will pursue

more sophisticated predictive models that combine distinct reporting patterns in a separate study. Models built on the dataset at hand would ideally be evaluated based on independent information added in subsequent time periods. The analysis of the influence of concomitant medicines needs to be studied in more detail since these results conflict with previous findings[7,20] and conventional wisdom.

Conclusions

ICSRs carry valuable information indicative of what becomes recognized as an adverse drug interaction in the future. Our results demonstrate that a variety of reporting patterns make unique contributions in such an analysis: suspicion of interactions as noted by the reporter in a case narrative, the assignment of the two drugs as interacting or through an ADR term; co-reporting of effect increased; and, finally, excess co-reporting of the ADR together with the two drugs, as indicated by the Ω measure. To our knowledge, this study is the first large-scale evaluation to consider the value of detailed clinical information on reports and to demonstrate the value of three-way disproportionality analysis relative to a comprehensive reference set.

Acknowledgements

The authors thank Johan Hopstadius, Uppsala Monitoring Centre, for computational support presented in this study. We also thank the Royal Pharmaceutical Society for access to Stockley's Drug Interactions Alerts. Furthermore, the authors are indebted to the national centres that contributed data. The opinions and conclusions in this study are not necessarily those of the various centres, nor of the WHO.

No sources of funding were used to conduct this study or prepare this manuscript. The authors have no conflicts of interest relevant to this study. Andrew Bate is now a full-time employee of Pfizer; however, his major contribution to this manuscript was provided while he was employed at the Uppsala Monitoring Centre.

References

1. Davies EC, Green CF, Taylor S, et al. Adverse drug reactions in hospital in-patients: a prospective analysis of 3695 patient-episodes. PLoS One 2009; 4 (2): e4439
2. Pirmohamed M, James S, Meakin S, et al. Adverse drug reactions as cause of admission to hospital: prospective analysis of 18 820 patients. BMJ 2004 Jul 3; 329 (7456): 15-9
3. Henderson L, Yue QY, Bergquist C, et al. St John's wort (Hypericum perforatum): drug interactions and clinical outcomes. Br J Clin Pharmacol 2002; 54 (4): 349-56
4. Knudsen JF, Sokol GH. Potential glucosamine-warfarin interaction resulting in increased international normalized ratio: case report and review of the literature and MedWatch database. Pharmacotherapy 2008 Apr; 28 (4): 540-8
5. Netherlands Pharmacovigilance Centre, Lareb. Overview signals: omeprazole and coumarine interactions. July 2009 [online]. Available from URL: http://www.lareb.nl/documents/kwb_2009_3_omepr.pdf [Accessed 2001 Jan 6]
6. Ohlsson S, Holm L, Myrberg O, et al. Noscapine may increase the effect of warfarin. Br J Clin Pharmacol 2008 Feb; 65 (2): 277-8
7. Strandell J, Bate A, Hägg S, et al. Rhabdomyolysis a result of azithromycin and statins: an unrecognized interaction. Br J Clin Pharmacol 2009 Sep; 68 (3): 427-34
8. Yue QY, Strandell J, Myrberg O. Concomitant use of glucosamine potentiates the effect of warfarin. Drug Saf 2006; 29 (10): 911-1010
9. Almenoff JS, DuMouchel W, Kindman LA, et al. Disproportionality analysis using empirical Bayes data mining: a tool for the evaluation of drug interactions in the post-marketing setting. Pharmacoepidemiol Drug Saf 2003 Sep; 12 (6): 517-21
10. Egberts AC, Meyboom RH, van Puijenbroek EP. Use of measures of disproportionality in pharmacovigilance: three Dutch examples. Drug Saf 2002; 25 (6): 453-8
11. Norén GN, Sundberg R, Bate A, et al. A statistical methodology for drug-drug interaction surveillance. Stat Med 2008 Jul 20; 27 (16): 3057-70
12. Qian Y, Ye X, Du W, et al. A computerized system for detecting signals due to drug-drug interactions in spontaneous reporting systems. Br J Clin Pharmacol 2010 Jan; 69 (1): 67-73
13. Thakrar BT, Grundschober SB, Doessegger L. Detecting signals of drug-drug interactions in a spontaneous reports database. Br J Clin Pharmacol 2007 Oct; 64 (4): 489-95
14. van Puijenbroek EP, Egberts AC, Heerdink ER, et al. Detecting drug-drug interactions using a database for spontaneous adverse drug reactions: an example with diuretics and non-steroidal anti-inflammatory drugs. Eur J Clin Pharmacol 2000 Dec; 56 (9-10): 733-8
15. Baxter K, editor. Stockley's drug interactions. 7th ed. London: Pharmaceutical Press; 2006
16. Meyboom RH, Lindquist M, Flygare AK, et al. The value of reporting therapeutic ineffectiveness as an adverse drug reaction. Drug Saf 2000 Aug; 23 (2): 95-9
17. Hauben M, Norén GN. A decade of data mining and still counting. Drug Saf 2010 Jul 1; 33 (7): 527-34
18. Baxter K, editor. Stockley's drug interactions alerts (xml) [including data up to 2009-10-19]. London: Pharmaceutical Press, 2009
19. Lindquist M. VigiBase, the WHO global ICSR database system: basic facts. Drug Inf J 2008; 42 (5): 409-19
20. Strandell J, Bate A, Lindquist M, et al. Drug-drug interactions: a preventable patient safety issue? Br J Clin Pharmacol 2008 Jan; 65 (1): 144-6
21. Pariente A, Gregoire F, Fourrier-Reglat A, et al. Impact of safety alerts on measures of disproportionality in spontaneous

reporting databases: the notoriety bias. Drug Saf 2007; 30 (10): 891-8

22. Indiana University. Flockhart table (updated 19 August 2009) [online]. Available from URL: http://medicine.iupui.edu/clinpharm/ddis/table.asp [Accessed 2010 Oct 13]
23. Edwards IR, Olsson S. The WHO international drug monitoring programme. In: Aronson JK, editor. Side effects of drugs: annual 25. Amsterdam: Elsevier Science B.V., 2002: 589-98
24. Snowball [online]. Available from URL: http://snowball.tartarus.org/ [Accessed 2008 Jul 15]
25. Porter MF. An algorithm for suffix stripping. Program 1980; 14 (3): 130-7
26. Aphinyanaphongs Y, Tsamardinos I, Statnikov A, et al. Text categorization models for high-quality article retrieval in internal medicine. J Am Med Inform Assoc 2005 Mar-Apr; 12 (2): 207-16
27. Norén GN, Orre R, Bate A, et al. Duplicate detection in adverse drug reaction surveillance. Data Min Knowl Discov 2007; 14 (3): 305-28

Correspondence: Mrs *Johanna Strandell*, Uppsala Monitoring Centre, WHO Collaborating Centre for International Drug Monitoring, Box 1051, SE-751 40 Uppsala, Sweden.
E-mail: Johanna.Strandell@who-umc.org