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ORIGINAL RESEARCH ARTICLE

Key Elements in Adverse Drug Interaction Safety Signals

An Assessment of Individual Case Safety Reports

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Abstract
Background A large proportion of potential drug interactions are known from pre-authorization studies, but adverse drug reactions (ADRs) due to interactions (adverse drug interactions) are often first detected through astute observation in clinical practice. Individual case safety reports (ICSRs) are collected from broad patient populations and allow for the identification of groups of similar reports. Systematic screening for adverse drug interactions in ICSRs will require an understanding of which information on these reports can be suggestive of adverse drug interactions.
Objective The aim of the study was to identify what reported information may support the identification of drug interaction safety signals in collections of ICSRs.
Methods Three previously published safety signals of suspected adverse drug interactions were re-evaluated. To this end, 137 reports related to these signals were retrieved from the WHO Global ICSR Database, VigiBase™, and corresponding original reports were obtained from national pharmacovigilance centres. Criteria from an operational score for causality analysis of drug interactions of clinical cases, the Drug Interaction Probability Scale (DIPS), were applied to each of these reports with the aim of identifying what supportive information tends to be available in ICSRs. For three DIPS elements (plausible time course, resolution of the ADR after terminating the drug inducing the interaction without changes in affected drug therapy (positive dechallenge) and alternative causes of the reaction) we also compared the amount of information in VigiBase™ and in original reports, and in free text and structured data.
Results Commonly fulfilled DIPS elements on reports supporting an adverse drug interaction signal were plausible time course (50 reports; 36 %) and positive dechallenge (8 reports; 6 %). Alternative causes for the observed adverse reaction were observed in 72 (53 %) reports. We found limited differences between VigiBase™ and original reports for the structured data, although a substantial amount of additional information was available in free text in original reports.
Conclusions Information on plausible time courses and resolution of the adverse reaction upon withdrawal of the drug suspected to have induced the interaction may be a useful element in identifying suspected adverse drug interactions from ICSRs. Of these, plausible time course is by far the most commonly reported element in the three signals studied here. Our analysis also demonstrated the importance of sharing and analysing information available in free text where relevant clinical details are often available, such as those mentioned above, along with severity and dosage changes.

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1 Background

Adverse drug reactions (ADRs) [1] are a considerable health threat with immense consequences for patients and society [2–6]; drug interactions have been reported as the cause of approximately 20 % of ADRs [6, 7]. Even if a large proportion of potential drug interactions are

discovered in pre-authorization studies, drug interactions that result in ADRs (so-called adverse drug interactions) are often first detected through astute observation in clinical practice. Clinical case evaluation of a suspected adverse drug interaction can account for symptoms, signs, diagnosis, treatment and follow-up procedures for a patient. It is an important element in the early discovery of suspected adverse drug interactions, and in 2007 a scale for assessing the causality of a potential drug interaction in a patient, the Drug Interaction Probability Scale (DIPS) [8], was introduced. Individual case safety reports (ICSRs) are an alternative source of information to detect suspected adverse drug interactions. These reports summarize information on suspected ADRs, including those that may have been caused by drug interactions. However, causality assessment in this setting is more problematic without direct access to the patient and sometimes without access to medical records. On the other hand, ICSRs are collected from broad patient populations and allow for the identification of groups of similar reports. Depending on the qualifications and engagement of the reporter, much of the information required for causality assessment of suspected adverse drug interactions may be available in these reports.

Effective adverse drug interaction surveillance in large datasets requires a combination of expert clinical assessment and efficient algorithms. To date, most methods proposed for automatic adverse drug interaction screening are based exclusively on disproportionality analysis, which accounts for reporting rates but not the detailed information in the reports. However, recent results indicate that reported clinical and pharmacological information may be an important complement in automated adverse drug interaction surveillance [9]. This in turn requires a detailed understanding of what reported information tends to strengthen signals of suspected adverse drug interactions in the analysis of ICSRs.

The aim of this study is to identify what reported information may support the identification of adverse drug interaction safety signals based on ICSRs.

2 Data and Methods

The WHO Global ICSR Database, VigiBase™ [10], contains more than 7.6 million reports of suspected ADRs from 110 countries (as at October 2012). The reports are collected on a national basis by member countries of the WHO Programme for International Drug Monitoring [11]. The programme was set up in 1968 to enable the detection of ADRs earlier than is possible on a national level. Nationally collected reports are transmitted by the pharmacovigilance centres to the Uppsala Monitoring Centre, the organization maintaining and analysing VigiBase™. The reports are harmonized in VigiBase and structured so that the transmitted reports can be systematically retrieved and analysed. Reported drugs may be assigned as 'suspected', 'interacting' if the ADR is suspected of being related to a drug interaction between two or more drugs, or 'concomitant' if the drug is used concurrently but not suspected by the reporter to have caused the ADR. This classification can be made by the reporter (the person sending the report) or through a second evaluation performed by the pharmacovigilance centre. Good reports carry a broad range of information such as dates of treatment, ADR onset dates and doses, along with information regarding the effect on the ADR of withdrawal of the medicine. Sometimes the information is available only as free text, possibly including a detailed description of the clinical course, therapeutic measures, outcome and additional relevant information in a report narrative.

To identify what detailed information in ICSRs tends to support drug interaction safety signals we re-evaluated a selection of three adverse drug interaction signals based (at least in part) on reports in VigiBase™. The signals selected for analysis were potentiation of warfarin's effect by glucosamine [12]; HMG-CoA reductase inhibitor ('statin')-induced rhabdomyolysis as a result of concurrent use of azithromycin [13]; and potentiation of the anticoagulant effect of coumarin derivatives (phenprocoumon and acenocumarol) by omeprazole [14]. See Table 1 for a summary of these signals. They were selected because they represent signals from different points in time (2006 and 2009) based on data from a variety of countries. The first two signals [12, 13] were based exclusively on reports in VigiBase™, while the third was a signal presented by The Netherlands Pharmacovigilance Centre LAREB based on Dutch reports with reference to related reports in VigiBase™ at the time [14].

For each signal, the analysis included reports in VigiBase™ with the two drugs (mapped according to the WHO Drug Dictionary Enhanced [10]) and the ADR (encoded in the WHO Adverse Reactions Terminology [WHO-ART] [10]) co-reported up to the time of the signal. No additional reports were included even if available at the time of this study. There were 33 reports of warfarin, glucosamine and increased International Normalized Ratio (INR) (reports up to March 2006) [12], 53 reports of statins, azithromycin and rhabdomyolysis (data up to July 2008) [13] and 51 reports of coumarin derivatives, omeprazole and increased INR, of which nine were the Dutch reports [14] on which that signal was originally based. Altogether, 137 reports from the three studies were included in the analysis. All VigiBase™ reports have a corresponding original report available at the national pharmacovigilance centre; as the original reports may provide more detailed information, these were retrieved and provided the basis for our primary analysis.

Table 1 Key information for each of the three published signals on which this analysis was based

Signal	Summary of key information
Potentiation of warfarin's effect by glucosamine [12], published in October 2006	A total of 33 reports of coagulation disorders under concurrent use of glucosamine and warfarin were included. The original publication focused on 22 of these, for which glucosamine and warfarin were reported as suspected or interacting ($n = 20$), or glucosamine was classified as concomitant but its importance was discussed in the narrative ($n = 2$). Of the 22 cases, increased effect of warfarin was documented in 21 patients and one case involved decreased effect
	• The reaction resolved upon discontinuation of glucosamine (with or without discontinuation of warfarin) in 17 of the 21 cases, including increased INR
	• Eleven patients had taken warfarin for a long time or continuously when the increased effect was established. After starting glucosamine, an increased INR was detected within 3 weeks in eight patients and within 1–6 months in five patients
	• Chondroitin was concomitantly used in 2 of the 22 patients
	• In one patient the increased INR occurred 3 days after having switched product from glucosamine hydrochloride 750 mg to glucosamine sulfate 1 g
Rhabdomyolysis as a result of azithromycin and statins [13], first published as a signal in SIGNAL document in July 2008 [20], official publication in September 2009	After exclusion of possible duplicates and follow-up reports, 53 cases from five countries remained
	• In 11 patients an interaction had been suggested by the reporter
	• Fourteen (26 %) patients had been using the statin for 3 months or more before the onset of rhabdomyolysis. Rhabdomyolysis occurred within 10 days from initiation of azithromycin in 10 of those patients
	• The reported statin doses were within the recommended daily doses [15, 16] with the exception of one patient
	• The observed number of cases reported for rhabdomyolysis with azithromycin and the individual statins was two to three times greater than the expected number of cases. The reporting over time showed that rhabdomyolysis under concomitant use of azithromycin and all statins as a group was reported more often than expected from the year 2000 and onwards in Vigibase™
Omeprazole and coumarin interactions [14], published in July 2009	In total, nine reports of potentiation of coumarin derivatives-induced coagulation effects associated with the use of omeprazole
	• INR values were increased within days after onset of PPI therapy
	• In three cases, INR was greater than six, which is a serious increase of anticoagulability
	• Instability of anticoagulation in the initial phase of coumarin treatment could be excluded since omeprazole was added to the coumarin derivatives in all nine reports

INR International Normalized Ratio, *PPI* proton pump inhibitor

To determine what reported information may support the identification of a drug interaction safety signal, all reports in the study were analysed using selected elements in the DIPS causality assessment score for suspected drug interactions [8]. DIPS is proposed as a guide for practitioners evaluating drug interactions in an individual patient; it combines general information such as support in the literature that the drugs of interest may interact, and whether there is a plausible pharmacological basis for the interaction, with relevant properties of the clinical case at hand. Since the purpose of this study was to examine what information in ICSRs tends to support a safety signal, we used DIPS not as a method for causality assessment but as a basis to identify what elements of information pertinent to adverse drug interaction causality assessment tends to be available in ICSRs. For this reason, those components of DIPS that refer to general information, such as previous support in the literature and plausible pharmacological basis for the interaction, were excluded from the analysis (elements 1–3). The full set of DIPS elements is presented in Table 2. In DIPS, the drug responsible for acting on the drug causing the interaction is referred to as the precipitant drug, and the drug causing the interaction is referred to as the object drug. In this analysis we have referred to the former as the inducing drug and the latter as the affected drug.

In the evaluation of DIPS element 4 (consistency with the known or reasonable time course of the interaction—from here on referred to as 'plausible time course'), two aspects were considered: the pharmacological plausibility of the observed time course and the consistency across reports. A plausible time course was considered as: within 2 months after initiating glucosamine to a patient receiving

Table 2 Drug interaction probability scale [8] derived from the Naranjo adverse drug reaction probability scale (reproduced from Horn et al. [8], with permission)

	DIPS question	Yes	No	Unknown/ not applicable
1	Are there previous credible reports of this interaction in humans?	+1	−1	0
2	Is the observed interaction consistent with the known interactive properties of the precipitant drug?	+1	−1	0
3	Is the observed interaction consistent with the known interactive properties of the object drug?	+1	−1	0
4	Is the event consistent with the known or reasonable time course of the interaction (onset and/or offset)?	+1	−1	0
5	Did the reaction remit upon dechallenge of the precipitant drug with no change in the object drug?	+1	−2	0
6	Did the reaction reappear when the precipitant drug was re-administered in the presence of continued use of object drug?	+2	−1	0
7	Are there reasonable alternative causes for the event?	−1	+1	0
8	Was the object drug detected in the blood or other fluids in concentrations consistent with the proposed interaction?	+1	0	0
9	Was the drug interaction confirmed by any objective evidence consistent with the effects on the object drug (other than drug concentrations from question 8)?	+1	0	0
10	Was the interaction greater when the precipitant drug dose was increased or less when the precipitant drug dose was decreased?	+1	−1	0

DIPS Drug Interaction Probability Scale, *Precipitant drug* indicates the medicine believed to have induced the interaction, *Object drug* indicates the affected drug

existing warfarin treatment, within 16 days after initiation of azithromycin to a patient on existing statin therapy, and within 2 months after initiating omeprazole to a patient on existing treatment with coumarin derivatives. The longer time course for anticoagulants with glucosamine and omeprazole was allowed because the reported information depends on when the INR happened to be measured. For DIPS element 5 (reaction remission upon dechallenge of the drug inducing the interaction with no change in the object drug—from here on referred to as 'positive dechallenge'), reports were only considered to fulfill the criterion where the reaction dissolved on withdrawal of the drug inducing the interaction with no change of the affected drug. For DIPS element 6 (reappearance when the drug inducing the interaction was re-administered in the presence of continued use of affected drug—from here on referred to as positive rechallenge), reports were only considered to fulfill the criterion if DIPS element 5 was fulfilled and if the interaction reappeared when the drug inducing the interaction was re-administered under continued use of the affected drug. In terms of reasonable alternative causes for the reaction (DIPS element 7—from here on referred to as 'alternative causes'), reports that listed concomitant drugs or explicitly listed other possible causes of the ADR were assessed to have other alternative causes for the reaction. All other reports were assessed as 'unknown/not applicable', since it is not possible to rule out the existence of alternative explanations because ICSRs can never be relied on to contain all relevant information on a patient. For instance, there might be patients receiving statins who were particularly susceptible to rhabdomyolysis since their clearance was reduced because of the underlying infection (treated with azithromycin), even though this was not explicitly noted in the reports. For element 8 (detection of the object drug in the blood or other fluids in concentrations consistent with the proposed interaction—from here on referred to as 'drug concentrations'), reports were only considered to fulfill the criterion if drug levels were explicitly noted (e.g. in the narrative) for the affected drug and were consistent with the proposed interaction. For DIPS element 9 (confirmation of the drug interaction by any objective evidence consistent with the effects on the object drug—from here on referred to as 'objective evidence'), reports were considered to fulfill the criterion if they contained information on changed physiological parameters, such as elevated laboratory values or ADRs that are consistent with the pharmacological properties of the affected drug. For DIPS element 10 (greater interaction when the precipitant drug dose was increased or less when the precipitant drug dose was decreased—from here on referred to as 'dose response'), reports were only considered to fulfill the criterion if the dosage of the drug inducing the interaction had been increased with the dose of the affected drug unchanged, resulting in elevated physiological parameters such as laboratory values or an ADR.

The analysis was conducted in two steps. First, we examined to what extent the original reports fulfilled the DIPS elements (considering both free text and structured information). Second, we evaluated how much information was available in structured data on original reports and on VigiBase™ reports for three DIPS elements: plausible time course, positive dechallenge and alternative causes.

As a complement, we examined how many of the 137 reports included explicit notifications of suspected drug interactions provided by the reporter or the pharmacovigilance centre, and how often such notes coincided with the DIPS elements 'plausible time course', 'positive dechallenge' and 'alternative causes'. The following features were considered as a notification of a suspected drug interaction: assignment of the two drugs of interest as interacting, an ADR term referring to a drug interaction and notes of a drug interaction in the case narrative.

3 Results

Table 3 contains a complete listing for each signal with the number of reports that fulfilled each DIPS element (questions 4–10). These results refer to both structured and free text information on original reports. A plausible time to onset was noted in 50 reports (36 %), ranging from 27 % to 43 % for the three signals. A positive dechallenge for the drug inducing the interaction without change in the affected drug was suggested in eight reports, representing 6 % of all reports. The proportions of positive dechallenge varied between the signals: for warfarin and glucosamine such information was provided in 18 % of the reports, while there were no reports with statins and azithromycin where only azithromycin was withdrawn. The number of reports with both a plausible time course and positive dechallenge was seven (5 %), of which five were on warfarin and glucosamine, and two on coumarin derivatives and omeprazole. As could be expected from ICSRs that are specifically designed to collect information of suspected ADRs, objective evidence of ADRs were found in all 137 cases. In addition, physiological parameters such as elevated laboratory results were reported in 22 of the 33 reports of warfarin and glucosamine (elevated INR values), 28 of 51 reports of omeprazole and coumarin derivatives (increased INR values) and 37 of 53 reports of statins and azithromycin (elevated creatine phosphokinase).

Plausible alternative causes were noted in 72 reports (53 %) in the form of concurrent drugs that could have contributed to the reaction and/or explicit notations by the reporter of possible underlying factors.

The most infrequently fulfilled DIPS elements were altered dose response (one report), changed drug

Table 3 Response (given in number of reports) for the original reports for the Drug Interaction Probability Scale questions 4–10 for each of the case series analysed

		Warfarin (affected) and glucosamine (inducing) INR increased			Statins (affected) and azithromycin (inducing) rhabdomyolysis			Coumarin derivatives (affected) and omeprazole (inducing) INR increased		
		Yes	No	Unk/NA	Yes	No	Unk/NA	Yes	No	Unk/NA
4	Is the event consistent with the known or reasonable time course of the interaction (onset and/or offset)?	13	0	20	23	3	27	14	7	30
5	Did the reaction remit upon dechallenge of the precipitant drug with no change in the object drug?	6	0	27	0	0	53	2	0	49
6	Did the reaction reappear when the precipitant drug was re-administered in the presence of continued use of object drug?	3	0	30	0	0	53	0	0	51
7	Are there reasonable alternative causes for the event?	12	0	21	26	0	27	34	0	17
8	Was the object drug detected in the blood or other fluids in concentrations consistent with the proposed interaction?	0	0	33	1	0	52	0	0	51
9	Was the drug interaction confirmed by any objective evidence consistent with the effects on the object drug (other than drug concentrations from question 8)?	33 (22)[a]	0	0	53 (37)[a]	0	0	51 (28)[a]	0	0
10	Was the interaction greater when the precipitant drug dose was increased or less when the precipitant drug dose was decreased?	1	0	32	0	0	53	0	0	51

Potentiation of warfarin's effect by glucosamine (33 cases) [12]; statin-induced rhabdomyolysis as a result of concurrent use of azithromycin (53 cases) [13]; and potentiation of anticoagulant effect of coumarin derivatives (phenprocoumon and acenocumarol) by omeprazole (51 cases) [14]

Affected indicates the affected drug, *Inducing* indicates the drug likely to induce the interaction, *INR* International Normalized Ratio, *NA* not applicable, *Unk* Unknown

[a] Number of reports in brackets refers to the number of reports including important laboratory remarks for each association. For warfarin and glucosamine, and coumarin derivatives and omeprazole, the specific INR values were provided. For azithromycin and statins, creatinine phosphokinase was given

Table 4 Number of reports (original and VigiBase™) fulfilling a positive response for the Drug Interaction Probability Scale questions 4 (Is the event consistent with the known or reasonable time course of the interaction (onset and/or offset?), 5 (Did the reaction remit upon dechallenge of the precipitant drug with no change in the object drug?) and 7 (Are there reasonable alternative causes for the event?) for each of the case series

	Warfarin (affected) and glucosamine (inducing) INR increased		Statins (affected) and azithromycin (inducing) rhabdomyolysis		Coumarin derivatives (affected) and omeprazole (inducing) INR increased	
	Original	VigiBase™	Original	VigiBase™	Original	VigiBase™
Timecourse						
Total	13	9	23	4	14	10
Structured	9	9	4	4	14	10
Positive dechallenge						
Total	6	1	0	0	2	2
Structured	3	0	0	0	0	0
Alternative causes						
Total	12	12	26	21	34	34
Structured	12	12	21	21	33	33

Potentiation of warfarin's effect by glucosamine (33 cases) [12]; statin-induced rhabdomyolysis as a result of concurrent use of azithromycin (53 cases) [13]; and potentiation of anticoagulant effect of coumarin derivatives (phenprocoumon and acenocumarol) by omeprazole (51 cases) [14]

A positive response for question 7 stresses that the report contained information on possible alternative causes for the reaction

INR International Normalized Ratio

Table 5 Number of reports that included explicit notification on the original reports of suspected drug interactions, and those reports without any note of a suspected interaction, fulfilling a positive response for the Drug Interaction Probability Scale elements 'plausible time course', 'positive dechallenge' and 'alternative causes' of the reaction

Notes of interaction	Warfarin (affected) and glucosamine (inducing) INR increased	Statins (affected) and azithromycin (inducing) rhabdomyolysis	Coumarin derivatives (affected) and omeprazole (inducing) INR increased
Plausible time course			
Yes	11	8	8
No	2	15	6
Positive dechallenge			
Yes	3	0	2
No	3	0	0
Alternative causes			
Yes	5	6	5
No	7	20	29

Results are separated for each of the signals: potentiation of warfarin's effect by glucosamine (33 cases) [12]; statin-induced rhabdomyolysis as a result of concurrent use of azithromycin (53 cases) [13]; and potentiation of anticoagulant effect of coumarin derivatives (phenprocoumon and acenocumarol) by omeprazole (51 cases) [14]

INR International Normalized Ratio

concentration (one report) and positive rechallenge of the drug believed to have induced the interaction (three reports).

Table 4 compares the amount of information available in original reports and VigiBase™, and in structured form and free text, for three DIPS elements: plausible time course, positive dechallenge and alternative causes. On the whole, there were limited differences between VigiBase™ and original reports for the structured data. The only exceptions were positive dechallenge for warfarin and glucosamine, and plausible time course for coumarin derivatives and omeprazole. A fair amount of useful information in free text on original reports was not represented in structured format or transferred to VigiBase™.

This was particularly noticeable for plausible time course in the azithromycin signal. Furthermore, of the eight reports with positive dechallenge, none were recorded in structured format in VigiBase™ and only three were retrievable from the free text in VigiBase™.

Table 5 presents the number of reports that included explicit notifications of suspected drug interactions and at the same time fulfilled the DIPS elements 'plausible time course', 'positive dechallenge' and 'alternative causes'. A suspected drug interaction of the two drugs of interest was noted by the reporter in 41 original reports: 18 reports of glucosamine and warfarin; 11 reports of azithromycin and statins; and 12 reports of omeprazole and coumarin derivatives. With the exception of plausible time course for azithromycin and statins, DIPS elements supporting an adverse drug interaction (plausible time course and positive dechallenge) were more often provided on reports where suspicion of an interaction had been acknowledged. As expected, alternative causes were more often noted for reports without any note of a suspected interaction. Notably, two of the reports with both a plausible time course and positive dechallenge did not include explicit notes of suspected interactions.

4 Discussion

Our retrospective review of three adverse drug interaction signals identified two elements that often strengthen the suspicion that an ADR is due to a drug interaction. The first is a relatively short reported time course to the ADR from start of treatment with the drug believed to have induced the interaction in patients receiving existing treatment with the drug believed to have caused the ADR. The second is timely resolution of the reaction after withdrawal of the inducing drug (a so-called dechallenge intervention) while not changing the affected drug regimen. Plausible time course and favourable dechallenge interventions are also important in the analysis of ADRs and single drugs. However, suspected adverse drug interactions require much more detailed information and more specific interventions for reliable causality assessment. Even so, for the three published signals evaluated here, 36 % of the reports exhibited a plausible time course and 6 % reported a suggestive dechallenge intervention. Five percent of the reports had both suggestive time course and dechallenge interventions and may therefore represent potential index cases for adverse drug interactions in prospective safety surveillance using ICSRs.

The postmarketing pharmacovigilance reporting system may be a particularly powerful resource to detect rare and complex patterns such as those related to adverse drug interactions. However, the potential to use these reports in computerized screening for previously unknown adverse drug interactions has not yet been fully explored. The two newly identified elements in this analysis may serve as an important complement to the reporting patterns highlighted by Strandell et al. [9] as potential markers of suspected adverse drug interactions in ICSRs. These elements are an important complement to the explicit notes of suspected drug interactions. Indeed, we showed here that some of the reports with strongest support in favour of suspected adverse drug interactions do not include such notes by the reporter, which is in line with previous studies on this topic [9, 13, 18]. Underreporting is a general challenge to effective ADR surveillance. Most often, we think of underreporting as the complete lack of a report on a suspected ADR [10, 19], but inadequate information on possible interacting drugs or incomplete information on concurrent agents or other risk factors may be equally important. An important area for future research is computerized detection of suggestive time course and dechallenge interventions. This would require automated identification of the drug believed to have induced the interaction and the drug responsible for the interaction in each report. One possible approach would be to base this on the strengths of the associations between each drug and the ADR. However, an additional requirement for such automated screening is that the information on time courses and dechallenge interventions is available in structured format. In contrast, our results show that for a substantial proportion of reports, the relevant information is available only in free text. More complete encoding of the available information in structured data fields will facilitate computerized screening and is likely to improve the quality of reports available to the international community. This is exemplified by the information on dechallenge interventions in free text for warfarin and glucosamine, and time course for coumarin derivatives and omeprazole. For the latter, the majority of reports originated from European countries submitting reports in the E2b format, which transmit free text along with more details in structured format than was possible in the previous reporting format. Furthermore, the availability of free text is vitally important to effective clinical assessment and the potential basis for even more powerful automated screening using natural language processing in the future.

Differences in the amount of supportive information for the three signals do not only reflect variations in their level of documentation but can also relate to the seriousness of the ADR. For example, it would rarely be defensible to withdraw only azithromycin in a patient on concurrent statin treatment suffering from rhabdomyolysis. Consequently, positive dechallenge for the drug believed to have induced the interaction is unlikely to be observed for serious ADRs.

One limitation of this study is that only three signals were included, and that differences in characteristics were found even within this small sample. Review of additional adverse drug interaction signals is likely to generate further insights and refine the findings reported here. There is reason to believe that reporting elements that were rarely available in our study will be rare in general. For example, we believe rechallenge interventions of only the drug believed to have induced the interaction will be rare, in particular in the presence of serious ADRs, for the same reasons as when only one drug is used. The difference in the amount of information available in free text versus structured format may differ between organizations but was not limited to VigiBase™ or to individual countries participating in the WHO programme, and so can also be expected to be generalized.

5 Conclusions

Information on plausible time courses and resolution of the adverse reaction upon withdrawal of the drug suspected to have induced the interaction may be useful elements in identifying suspected adverse drug interactions from ICSRs. Relevant information to assess suspected adverse drug interactions from ICSRs is often available only in free text narratives, which is sometimes unavailable and can be challenging to analyse for large groups of reports.

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