Drug Saf (2013) 36:565–572
DOI 10.1007/s40264-013-0063-5

ORIGINAL RESEARCH ARTICLE

A Potential Event-Competition Bias in Safety Signal Detection: Results from a Spontaneous Reporting Research Database in France

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Published online: 15 May 2013

Abstract
Background In spontaneous reporting databases, reports of well-established drug-event associations may mask alerts that arise from other drugs (drug competition bias). However, a symmetrical event-competition bias has not yet been explored whereby known events may mask an association with new events for a given drug or drug class.
Objective The objective of this study was to explore the effects of event-competition bias on safety signals generated from spontaneous reporting databases.
Methods The drug classes tested included statins, oral anticoagulants, antipsychotics and HIV antiretrovirals. For each, a type A reaction was selected, and its potential competitive effect on the generation of other safety signals for the drug was explored. These were rhabdomyolysis/myopathy for statins, haemorrhage for oral anticoagulants, extrapyramidal syndrome for antipsychotics and lipodystrophy for HIV antiretrovirals. Signals of disproportionate reporting (SDRs) were detected using the case/non-case approach in the French research spontaneous reporting database (which contains reports from 1 January 1986 to 31 December 2001), before and after removing all reports concerning these competitor events. SDRs were considered as potential signals if not reported in the literature before 1 January 2002 but confirmed since.
Results The whole database included 207,236 reports, 4,355 of which included statins as one of the suspected drugs. The removal of reports of rhabdomyolysis/myopathy concerned 8,425 reports among which 867 involved statins. After this removal, 11 new SDRs appeared for statins that had not been detected initially. Similarly, 15 SDRs were unmasked for oral anticoagulants, six for antipsychotics and nine for HIV antiretrovirals. After literature-based assessment, five of the 41 unmasked SDRs appeared related to potential safety signals confirmed after 2002.
Conclusion This study demonstrated that a masking phenomenon resulting from an event-competition effect could occur when performing signal detection using disproportionality analyses of spontaneous reporting databases. This should be taken into account when routine signal detection is performed.

On behalf of the Association Française des Centres Régionaux de Pharmacovigilance (CRPV).

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1 Introduction

Pharmacovigilance aims for the early detection of unrecognised adverse drug reactions (ADRs). Even if these can be detected through various study designs in clinical pharmacology (e.g., randomized controlled trials or pharmacoepidemiological studies) [1, 2], the main pillar of ADR detection remains spontaneous reporting of adverse reactions [3]. Its primary purpose is to provide early

warnings of ADRs not recognized prior to marketing. Even if other methods may be needed to quantify the potential risk once a signal has been identified, spontaneous reporting may provide sufficient information to sustain regulatory actions including drug withdrawal [4]. During recent decades, spontaneous reporting systems have increased their capacity to detect signals, mainly due to the development and the automation of disproportionality analyses in spontaneous reporting databases, which result in signals of disproportionate reporting (SDRs). These are based on the identification of drug-event pairs that are reported more often than would be expected as compared to other drug-event pairs [5, 6].

Several methods exist for the detection of SDRs, none of which constitutes a gold standard for signal detection [7–9]; their performances in signal detection are similar when more than three cases have been reported [10]. Though these methods were designed to have high sensitivity [11], competition between drugs could potentially mask interesting SDRs [12–14]. For instance, the well known association of anticoagulants with haemorrhagic accidents hinders the detection of SDRs associating haemorrhage with other drugs [15]. On the other hand, the symmetrical bias through which haemorrhages could mask the generation of SDRs concerning other events for anticoagulant agents has not been explored. This may also be true for many other cases where the presence of a frequent reaction could mask excess relative reporting of another, less common reaction with the same drug. The aim of the present study was therefore to investigate this potential event competition bias in signal detection for given drugs and to see whether it could lead to masking SDRs and hampering the detection of potential signals for these drugs.

2 Methods

2.1 Data Source

This analysis concerned all reports collected in the French pharmacovigilance research database, which includes all reports entered in the *Base Nationale de Pharmacovigilance* between January 1986 and December 2001 [16]. This research database includes all adverse drug reactions reported to the 31 French regional pharmacovigilance centres by health professionals during the period, but not those reported to manufacturers. The regional centre reviews and assesses each report before entering these into the database,, and for all ADRs the diagnosis and associated coding is checked as being accurate. In the French pharmacovigilance research database, ADRs originally coded with the WHO-ART in the *Base Nationale de Pharmacovigilance* were recoded to MedDRA® [1] (Medical Dictionary for Regulatory Activities, US 5th version) using the translation included with the preferred terms (PTs) or with the high level terms (HLTs) when the PT was missing. All drugs are coded according to the Anatomical Therapeutic Chemical (ATC) classification.

2.2 Drug-Event Pairs of Interest: Definition of the Case Studies for the Investigation of Event Competition

Following our hypothesis, to be a potential competitor an event should represent an important percentage of the reports for the drug studied and be rather specific for this drug. This would imply that the event is both strongly associated with the drug and has an important weight in the overall number of reports for the drug. Type A reactions, which are related to the pharmacological properties of drugs, a priori satisfy such criteria. As they mostly constitute class effects, we decided to retain as case studies, for the investigation of event competition, drug-event pairs made up of a drug class and a type A reaction related to that drug class.

We arbitrarily selected four drug class-type A reaction pairs as case studies. The events related to the type A reaction retained as a potential competitor were some of the most frequently reported adverse events for the drugs in the class. The four case studies for the exploration of event-competition included: statins (ATC code: C10AA) and rhabdomyolysis/myopathy [17], oral anticoagulants (B01AA) and haemorrhages [18], HIV antiretrovirals (J05AE, J05AF, or J05AG) and lipodystrophy [19], and antipsychotics (N05A) and extrapyramidal syndrome [20].

To identify all reports mentioning these events considered as potential competitors, we used the corresponding Standardised MedDRA® Queries (SMQs) [21]. The SMQs have been designed to help identify cases for approximately 180 medical conditions; they include terms that may relate to signs, symptoms, diagnoses, syndromes, physical findings, laboratory test, etc., associated with the medical condition or area of interest. The following SMQs were used to identify the reports related to the events considered as potential competitors: (i) rhabdomyolysis/myopathy: SMQ 20000002; (ii) haemorrhages: SMQ 20000038; (iii) extrapyramidal syndrome: SMQ 20000095; (iv) lipodystrophy: SMQ 20000177. As the objective was to identify all reports related to the potential competitor(s), SMQs selected for report removal were implemented using both narrow and broad terms.

[1] MedDRA® terminology is the medical terminology developed under the auspices of the International Conference on Harmonization of technical requirements for Registration of Pharmaceuticals for Human Use (ICH).

2.3 Data-Mining and Statistical Analysis for Signals of Disproportionate Reporting (SDR) Detection

To explore potential event competition in SDR detection for each drug class of interest, two data-mining procedures were performed. In the first, SDR detection was performed in the whole database. In the second, it was performed on a restricted database obtained after removing all the reports mentioning the events considered as a potential competitor for the drug of interest, whatever drugs are mentioned in the removed reports. The results of the two procedures were then compared for each drug class of interest to see if new SDRs appeared after removal of the report that would be likely to have been initially masked by an event-competition effect.

The data-mining algorithm chosen for SDR detection was the reporting odds ratio (ROR) of the case/non-case method [22]. To focus only on potential signals that would have been considered relevant for examination in a routine pharmacovigilance practice, only SDRs with three or more exposed cases were selected. In each procedure, SDR detection was performed for High Level Terms (HLTs) of the MedDRA® classification [23].

2.4 Potential Signal Identification: Literature-Based Assessment of Unmasked SDRs

To determine whether unmasked SDRs could be related to potential safety signals, for each unmasked SDR considered Medline was explored using the PubMed Mesh terms for the event and the drug in question to identify publications related to the identified drug class-event association. In all situations, as safety signal identification was not the objective of the present study, signals related to unmasked SDRs were only considered as potential as no medical assessment of the underlying cases had been made.

As this methodological study was performed retrospectively on a closed database (last data entered: 31 December 2001), this allowed the classification of unmasked SDRs as:

- *Already known signals*: the unmasked SDR was not considered as a potential signal as the relationship was already known and clearly documented as of 31 December 2001 [6].
- *Potential signals unknown, not later confirmed*: the unmasked SDR was considered as a pending potential signal as the relationship was not previously known on 31 December 2001 and had not been clearly documented later [6].
- *Potential signals unknown, later confirmed*: the unmasked SDR was considered as a potential signal as the relationship was not previously known on 31 December 2001 but had been clearly documented since [6].
- *Not assessable*: the unmasked SDR was considered as not assessable when related to codes not referring to events (e.g., "abnormal laboratory findings") as these SDRs could not be appropriately investigated using the literature. They were also considered as not assessable when the ADR was in relation to the indication(s) of the suspected drug, as they would thus require an assessment of the cases contributing to the SDR prior to literature examination.

3 Results

Between 1 January 1986 and 31 December 2001, 207,236 spontaneous reports of ADRs were collected in the database. Of these, 8,425 (4.1 %) concerned rhabdomyolysis/myopathy, 6,672 (3.2 %) haemorrhage, 2,406 (1.2 %) lipodystrophy and 6,438 (3.1 %) extrapyramidal syndrome according to the SMQ definitions.

3.1 Statins and Event Competition from Rhabdomyolysis/Myopathy

Of all the reports included in the database, 4,355 involved statins, of which 867 (19.9 %) concerned rhabdomyolysis/myopathy. After removing from the database all reports of rhabdomyolysis/myopathy whatever the drug incriminated, 11 new SDRs were detected for statins (Table 1).

Five SDRs were considered as *Already known signals*: sexual dysfunction and desire disorders, alopecia, cholestasis and jaundice, and skin reactions are well known to be associated with statins, which was clearly documented before 2002 [24]. The SDR concerning intestinal haemorrhages was also considered in this category: if no publication was found in Medline associating statins with intestinal haemorrhages before 2002, case reports of haemorrhagic disorders (e.g., purpura or petechiae) have been published before this date [25–28], and the potential interaction between lovastatin and warfarin (with haemorrhagic outcomes) has been known for a long time [29, 30].

Four SDRs were considered as *Potential signals unknown, not later confirmed*: no case report or other information on vasculitis induced by statins was found in the literature before 2002, and only one case report was found after this date, concerning an ANCA (anti-neutrophil cytoplasmic antibody)-positive systemic vasculitis induced by atorvastatin [31]. No cases or publications concerning gastrointestinal mobility disorders, leucocytosis or

Table 1 Proportion of reports removed when excluding events with known association with the drug class of interest, and number of unmasked signals of disproportionate reporting (SDR)

Drug class—event	All database reports [*n* removed/*n* total (%)]	Within reports for the drug class [*n* removed/*n* total (%)]	Unmasked SDR [*n*]
Statins—rhabdomyolysis/myopathy	8,425/207,236 (4.0)	867/4,355 (19.9)	11
Oral anticoagulant agents—haemorrhage	6,672/207,236 (3.2)	2,022/6,939 (29.1)	15
Antipsychotics—extrapyramidal syndrome	6,438/207,236 (3.1)	1,919/11,802 (16.3)	6
HIV antiretrovirals—lipodystrophy	2,406/207,236 (1.2)	2,406/9,509 (25.3)	9

scleroderma induced by statins were found in Medline, either before or after 2002.

One SDR that concerned "elevated cholesterol" was considered as *Not assessable*, as it was potentially in relation to one of the indications of statins.

Finally, the SDR concerning "breast signs and symptoms" was considered as *Potential signal unknown, later confirmed*: it could be related to cases of mastodynia, gynaecomastia or galactorrhoea. No publication was found associating statins with these events before 2002, but a recent publication showed a signal concerning statins and gynaecomastia [32] (Table 2).

3.2 Oral Anticoagulants and Event Competition from Haemorrhages

Of all the reports included in the database, 6,939 involved oral anticoagulants, of which 2,022 (29.1 %) concerned haemorrhages. After removing these reports of haemorrhages from the database, 15 new SDRs were detected for oral anticoagulants (Table 1).

Three SDRs were considered as *Already known signals*: cholestasis and jaundice [33, 34], vasculitis [35–37] and alopecia [38, 39] are well known to be associated with oral anticoagulants, which was clearly documented before 2002.

Six SDRs were considered as *Potential signals unknown, not later confirmed*: either before or after 2002, no publication was found that associated oral anticoagulants with autonomic system disorder, renal impairment, hypoglycaemic disorders, bladder infections and inflammation, potassium imbalance or leukocytosis.

The other six unmasked SDRs were considered as *Not assessable*: SDRs for liver function tests and abnormal abdominal findings concerned investigations without clear result; SDRs for cardiac disorders NEC (not elsewhere classified), cardiac conduction disorders, ventricular arrhythmias and cardiac arrest, speech and language abnormalities (potentially related to stroke) concerned potential indications of anticoagulant agents, and may include lack of efficacy (Table 2).

3.3 Antipsychotics and Event Competition from Extrapyramidal Syndrome

Of all the reports included in the database, 11,802 involved antipsychotics, of which 1,919 (16.3 %) concerned extrapyramidal syndrome. After removing all reports of extrapyramidal syndrome from the database, six new SDRs were detected for antipsychotics (Table 1).

Three were considered as *Already known signals*: the signal concerning "breast signs and symptoms" can be related to cases of mastodynia, gynaecomastia or galactorrhoea, which are well known adverse reactions of dopamine antagonists. Also, metabolic disorders and hepatic abnormalities have long been widely associated with antipsychotic use.

One unmasked SDR was considered as *Not assessable*: perception disturbances can be related to hallucinations, which may be symptoms of psychosis for which antipsychotics are indicated.

Finally, two were considered as *Potential signals unknown, later confirmed*: before 2002 only one case report in the literature relating cleft palate to maternal prochlorperazine intake has associated antipsychotic use with congenital abnormality [40], and no publication on gastrointestinal congenital abnormalities was found. However, in 2007 a descriptive analysis of spontaneous reporting data was published, which highlighted that, amongst the congenital defects reported in infants of mothers exposed to risperidone, lips and palate disorders were amongst the most frequently reported reactions [41]. This article also reported cases of gastrointestinal malformations (Table 2).

3.4 HIV Antiretrovirals and Event Competition from Lipodystrophy

Of all the reports included in the database, 9,509 involved HIV antiretrovirals, of which 2,406 (25.3 %) concerned lipodystrophy. After removing all reports of lipodystrophy from the database, nine new SDRs were detected for HIV antiretrovirals (Table 1).

Table 2 Signals of disproportionate reporting unmasked after removing reports of events related to the type A reaction selected as a potential competitor for each of the drug classes studied, classified according to the information available from Medline before and after 1 January 2002

Drug class of interest	Potential signals unmasked after removal			
	Already known (as of 1 January 2002)	Unknown, not later confirmed	Not assessable	Unknown, later confirmed
Statins	Sexual desire disorder	Vasculitide NEC	Elevated cholesterol	Breast signs and symptoms
	Alopecia	Gastrointestinal atonic and hypomotility disorders NEC		
	Cholestasis and jaundice	Leukocytoses NEC		
	Dermatitis and eczema	Scleroderma and associated disorders		
	Intestinal haemorrhage			
Oral anticoagulant agents	Cholestasis and jaundice	Autonomic nervous system disorders	Abdominal findings abnormal	
	Vasculitide	Renal failure and impairment	Liver function analyses	
	Alopecia	Hypoglycaemic conditions NEC	Cardiac disorders NEC	
		Bladder infections and inflammations	Cardiac conduction disorders	
		Potassium imbalance	Ventricular arrhythmias and cardiac arrest	
		Leukocytoses NEC	Speech and language abnormalities	
Antipsychotics	Breast signs and symptoms		Perception disturbances	Cleft lip and cleft palate disorders
	Metabolic disorders NEC			Gastrointestinal tract disorders, congenital NEC
	Hepatic enzymes and function abnormalities			
HIV antiretrovirals	Appetite disorders	Personality disorders NEC		Fractures and dislocations NEC
	Haemolytic anaemias NEC	Stillbirth and fetal death		Pathological fractures and complications
	Asthenic conditions	Inborn errors of porphyrin metabolism		
	Mononeuropathies			

NEC not elsewhere classified

Four unmasked SDRs were considered as related to *Already known signals*: appetite disorders, haemolytic anaemia, asthenias and neuropathies are well known adverse effects of antiretrovirals, which were clearly documented before 2002 [42–45].

Three unmasked SDRs were considered as related to *Potential signals unknown, not later confirmed*: no publication associating personality disorders with antiretrovirals was found, either before or after 2002. The data available before 2002 concerning birth defects in children born from a mother treated with antiretrovirals were not sufficiently powered to estimate the teratogenicity of these drugs [46, 47]. However, more recent data indicate that the birth defects rate is unchanged by HIV antiretroviral treatment during pregnancy [48, 49]. No publication associating congenital abnormalities in porphyrin metabolism with HIV antiretrovirals was found, either before or after 2002.

Finally, the last two unmasked SDRs were considered as *Potential signals unknown, later confirmed*: these two SDRs both concerned fractures (*Fractures and dislocations NEC*; *Pathological fractures and complications*). Only two case reports associating antiretrovirals with osteoporosis, osteopenia and fractures published before 2002 were found [50]. However, in a recent publication, the risk of fracture was found to be increased in patients taking antiretrovirals compared to drug-naïve subjects [51] (Table 2).

4 Discussion

This study demonstrated that a masking phenomenon resulting from an event competition effect could occur when performing signal detection using disproportionality analyses of spontaneous reporting databases. This phenomenon is similar to that resulting from a competition between drugs, which has previously been reported [13–15].

The present study illustrates what signals could have been missed for four drug classes because of this competition bias. A third of unmasked SDRs (14/41) were likely to be false positives (those *not later confirmed*) as no additional external information emerged during the 10-year period following database lock. Conversely, the relevance of this unmasking is highlighted by the finding in the four case studies in the present paper that more than 10 % of the unmasked SDRs (5/41) were related to potentially "true signals", i.e. those unknown at the end of 2001, but later confirmed by the literature. It is of note that some were likely to involve serious ADRs (such as fractures and HAART, or congenital malformations and antipsychotics). In addition, it is likely that the SDRs classified as *non-assessable* could also constitute false-positive signals as they mostly refer to events related to the indication of the drug studied, suggesting that the association might result from an indication bias or treatment failure. If all of these *non-assessable* SDRs were false positives, the total proportion of false positives among unmasked SDRs would be around 85 %, making the efficiency if the unmasking technique as currently presented poor. This proportion could be lowered by using techniques that can minimize the number of SDRs related to indication bias or treatment failure [13, 22]. These techniques were not used in the present analysis, the purpose of which was to focus on the potential competition effect between events. The addition of these to the presented unmasking procedures should, however, be considered if willing to apply this technique to routine signal detection in a more efficient way.

This study presents several limitations owing to the methods retained for signal detection. The SMQs selected for identification of reports related to potential competitors were implemented using both narrow and broad terms, in order to provide good sensitivity for identification of competing events. A more specific identification of these events could have been obtained by implementing only those SMQs with narrow terms; however, this would have resulted in a loss of sensitivity in report removal and thus, potentially, in a loss of unmasking efficiency. The entire dataset (1986–2001) was considered to serve as a background for the ROR calculations, despite not all drugs of the classes of interest having been marketed for the complete period. This could have resulted in biases related to differences in trends of reporting between drug classes of interest and drugs from the complete dataset. As the oldest drug had been marketed long before 1986 for the oral anticoagulant class and antipsychotic class, while the oldest drug in the HIV antiretroviral drug class was launched in 1987 (zidovudine), and the oldest statin in 1988 (simvastatin), these differences and related potential biases were considered to be marginal in the context of this study. However, if investigating specifically a signal detected after unmasking in the context of an individual drug safety evaluation (and not in a methodological exercise such as that presented here), such differences in trends of reporting related to age of marketing of drugs should be studied [52].

Another limitation of the study is that assessment was performed unblinded to the existence of statistical association that could have affected judgement, but is also limited in that only four case studies were considered and therefore the generalizability of these results to other drug classes or to single drugs will need to be further investigated. A possibly more important aspect is that potential competitors were arbitrarily selected. In future, it will be necessary to define the criteria that could be retained to select the potential competitor events, and these should probably consider the strength of the association of the drug(s) with the event. This reflects the importance of the

disproportionality of reporting of this pair in comparison with the rest of the database and thus the importance of the constraint existing for the representation of other events for the drug. In addition, it should also consider the proportion of the reports for the candidate event among all those incriminating the drug or drug class of interest. Once the quantitative thresholds for such criteria are determined, this could allow an automated procedure for the minimization of the masking effect induced by event competition bias. Another point to consider is that the identification of events in the present paper was performed using MedDRA® High-Level Terms [23], which were considered as appropriate for a research focusing on a potential event competition bias in SDR detection, for a non-oriented data-mining approach. However, other alternatives could be considered if pursuing more oriented objectives in signal detection (e.g., events with a high rate of fatal cases).

5 Conclusion

The results of the present study confirm that competition and masking phenomena between events exist and can be a limit of signal detection using disproportionality analyses in spontaneous reporting databases. Further research is needed to better investigate the extent of this phenomenon and to define the criteria that would allow the adequate selection of the event(s) that could constitute potential competitors.

Acknowledgments The MedDRA® trademark is owned by the International Federation of Pharmaceutical Manufacturers & Associations (IFPMA) on behalf of the ICH.

The authors would like to thank all the members of the 31 French regional pharmacovigilance centres as well as the ANSM (Agence Nationale de Sécurité du Médicament) for the availability of the data. They also wish to thank Philip Robinson for his help in manuscript preparation. The authors declare no conflicts of interest for this study.

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