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Impact of Safety Alerts on Measures of Disproportionality in Spontaneous Reporting Databases

The Notoriety Bias

Antoine Pariente,[1,2,3] *Fleur Gregoire*,[3] *Annie Fourrier-Reglat*,[1,2,3] *Françoise Haramburu*[2,3] and *Nicholas Moore*[1,2,3]

1 Department of Pharmacology, Universite Victor Segalen, Bordeaux, France
2 INSERM U657, Bordeaux, France
3 CHU de Bordeaux, Bordeaux, France

Abstract

Background: Disproportionality analysis of spontaneous reporting is increasingly used, but it may be influenced in unknown ways by safety alerts (notoriety bias).

Objective: To explore the consequences of safety alerts on reporting disproportionality.

Methods: Within the French national pharmacovigilance database, disproportionality of reporting was tested, using the reporting odds ratio (ROR) and its 95% confidence interval, before and after four safety alerts: valvulopathies with pergolide; tuberculosis with infliximab; strokes with atypical antipsychotics; and rhabdomyolysis with HMG-CoA reductase inhibitors (statins) [after cerivastatin withdrawal].

Results: No cases of valvulopathy were reported in association with pergolide before the safety alert and 63 cases were reported after the alert, (ROR 9400; 95% CI 4300, 20 000), of which five had occurred before the alert. Twenty-five reports mentioned rhabdomyolysis associated with statins (not including cerivastatin) before the safety alert (ROR 5.8; 95% CI 3.8, 9.0), and 63 did so after the alert (ROR 9.4; 95% CI 7.0, 13.0). Approximately 280 cases involving cerivastatin were reported after its withdrawal. There were two reports of tuberculosis associated with infliximab before the alert (ROR 1500; 95% CI 130, 18 000) and seven after the alert (ROR 430; 95% CI 110, 1700). There was one report of a stroke in association with atypical antipsychotic treatment before the safety alert (ROR 0.10; 95% CI 0.01, 0.63) and 16 after the alert (ROR 1.10; 95% CI 0.70, 1.90). After excluding events involving treatment with anticoagulant agents, the RORs for stroke in association with atypical antipsychotic treatment were 0.14 (95% CI 0.02, 1.00) before the alert and 2.0 (95% CI 1.2, 3.4) after the alert.

Conclusion: Disproportionality in spontaneous reporting databases increases after a safety alert because of increased reporting of the event of interest, including

reports of such events that occurred before the alert. This may overflow to increased reporting of the event in association with other drugs.

Background

Despite its recognised and well documented limitations, spontaneous reporting is an invaluable and proven way to identify safety signals. The primary purpose of spontaneous adverse drug reaction reporting is to provide early warnings of hazards that have not been recognised prior to marketing of the drug because of the limitations of clinical trials with respect to sample size, duration and extrapolation to routine practice. Once a signal has been generated, other methods will be used to quantify the potential risk, and if there is sufficient evidence of a public health issue, steps aimed at minimising the risks and informing users are taken by the regulatory authorities.[1,2]

Most countries have set up spontaneous reporting systems for adverse drug reactions. To improve the capacity of spontaneous reporting systems to detect signals beyond the examination of the individual case-reports, various frequency or probability-based methods have been devised to test for reporting disproportionality, i.e. that a drug-event pair is reported more often than would be expected. The statistical identification of abnormal or unusual reporting patterns that could indicate an increased risk for an adverse drug reaction relies on a number of different approaches, all of which give the same results as long as the number of reports exceeds four.[3,4] These approaches include Bayesian exploration, neural networks and, more simply, the reporting rates ratio where the computation is based on the relative risk (the Medicines and Healthcare products Regulatory Agency's proportional reporting ratio)[2,5] or the odds ratio (the case/non-case approach leading to reporting odds ratio [ROR] estimates).[6,7] These are all essentially based on the disproportionality of the reporting of a given event in association with a given drug or class of drugs compared with other events and other drugs (figure 1). Although this is a very powerful tool, it is not without its limitations.[8-10] The ROR depends both on the occurrence and the reporting of events and the interaction between these may be more complex than is apparent: events that occur may be reported or not, so that all signals based on disproportionality concern the relative reporting of events and not their occurrence. Increased relative reporting may be related to increased occurrence of the event, or to increased reporting of an event with a constant occurrence rate. Factors influencing reporting could then result in variations of a signal concerning an event that are unrelated to variations in its frequency of occurrence. Many factors affecting the rate of spontaneous reporting have been identified.[8,11,12] Several prerequisites have to be met for a health professional to report an adverse drug reaction. The probability of reporting increases with the apparent responsibility of the drug for the reaction and the identification of the drug-related character of the effect, the seriousness of the effect, the novelty of the drug and the time available to report the reaction.[11,12] In this context, the dissemination of an alert could alter the balance of reporting between reactions, and result in the spurious perception of a drug-effect association. This phenomenon is called notoriety bias and has been defined as a "selection bias in which a case has a greater chance of being

	Reports including effect of interest	Reports including other effect(s)
Reports including drug of interest	a	c
Reports including drugs other than the drug of interest	b	d

$$\text{ROR (95\% CI)} = \frac{a \times d}{b \times c}\left(e^{\pm \sqrt{\left(\frac{1}{a}+\frac{1}{b}+\frac{1}{c}+\frac{1}{d}\right)}}\right)$$

Fig. 1. The 2 × 2 contingency table used to calculate the reporting odds ratio (ROR).

reported if the subject is exposed to a factor known, thought, or likely to cause the event of interest".[13] We wanted to estimate the importance of the potential notoriety bias induced by safety alerts on signal estimates generated using the French Pharmacovigilance database, which includes adverse drug reactions that have been spontaneously reported by health professionals. For this, we considered four safety alerts concerning new signals where the drug(s) of interest had been on the market at least 1 year before the alert, and was not removed from the market after the alert. We wanted to examine different situations, concerning either events not usually associated with drugs (tuberculosis) or new to the specific drug class (stroke in association with antipsychotics), or events previously associated with a drug class, both notorious (rhabdomyolysis) and more obscure (cardiac valvulopathy). We selected alerts that had also been clearly identified and dated in the French market.

Methods

We considered safety alerts concerning infliximab and the risk of tuberculosis; HMG-CoA reductase inhibitors (statins) and the risk of rhabdomyolysis after the withdrawal of cerivastatin; pergolide and the risk of valvulopathy; and atypical antipsychotics and the risk of stroke in the elderly. Regarding infliximab and tuberculosis, on 28 December 2000, the French medicines agency, Agence Française de Sécurité Sanitaire des Produits de Santé (AFSSAPS), sent out a press release concerning this potential adverse drug reaction, with 28 cases of tuberculosis in association with infliximab having been reported worldwide.[14] At that time, health professionals did not generally consider tuberculosis as a potential adverse drug reaction. With respect to statins and rhabdomyolysis, on 8 August 2001, the pharmaceutical firm Bayer decided to withdraw cerivastatin from the market after the occurrence of cases of rhabdomyolysis in patients, some of which were fatal.[15] At that time, the risk of rhabdomyolysis was already known as a class effect of statins, linked to their pharmacological properties. In this case, the safety alert did not concern the drugs of interest, but another drug of the same class ('ripple effect'). In the case of pergolide and cardiac valvulopathy, a 'Dear Doctor' letter was sent out by Eli Lilly and Company Ltd on 23 September 2003[16] to inform prescribers of the possible occurrence of cardiac valvulopathy in patients receiving pergolide, following reports of 18 cases. At that time, the drugs considered to be involved in the occurrence of valvulopathy were other ergot alkaloids and several anorectics. Finally, regarding stroke in elderly patients receiving atypical antipsychotics, on 9 March 2004, the AFSSAPS sent out a press release[17] on the potential risk of this adverse drug reaction in elderly patients receiving olanzapine, clozapine, risperidone and sulpiride, following the results of clinical trials of the treatment of behavioural disorders in elderly patients with dementia.[18,19] At that time, most case reports of stroke were haemorrhagic events occurring during treatment with antiplatelet and anticoagulant agents.

This study used data from the French Pharmacovigilance database of case reports.[20,21] This database includes all adverse drug reactions reported to the French Regional Pharmacovigilance Centres since 1985, but not those reported to manufacturers.[20] All reactions are coded according to the WHO Adverse Reactions Terminology dictionary. The Regional Centre team review and assess every report before to entering them into the database. All available data are considered to include a diagnosis and coding that are as accurate as possible.

We used the case/non-case method to estimate the ROR associated with these drug/event combinations.[6] The ROR is the ratio of the odds of reports of ADRs in cases and non-cases.[7] If the confidence interval does not include 1, the ROR is considered to be significant and is interpreted as indicating an association between the drug(s) and the effect(s) of interest. This method can be thought of as akin to a variant of the database nested case-control method or the study of proportional mortality ratios used in cancer research.[11,22] Figure 1 gives details of the estimation of the ROR and its 95% confidence interval.

Case and Non-Case Definition and Identification

For each effect of interest, all adverse drug reaction reports of that effect were classified as cases and adverse drug reaction reports of all effects other than the effect of interest were classified as non-cases.

Since pharmacologists and pharmacovigilance experts review all reports prior to entry into the database, it was not judged necessary to review individual case reports for misdiagnosis or misclassification.

Definition of Exposure

We examined cases and non-case reports for the presence of the selected drug(s), whether or not the drug was judged to be suspect in causing the effect.

To study the notoriety effect after cerivastatin withdrawal, we considered all statins except cerivastatin, as rhabdomyolysis was a known class effect of statins, and the occurrence of adverse drug reactions related to cerivastatin was supposed to be close to zero after this drug had been withdrawn from the market.

Study Periods

The alert for infliximab was sent out on 28 December 2000. The study periods for the drug-effect combination were from 28 December 1999 to 28 December 2000 and from 29 December 2000 to 29 December 2001. One-year periods were chosen because infliximab was launched in France on 13 August 1999, such that there was not a 2-year pre-alert period.

The withdrawal of cerivastatin was announced on 8 August 2001. We considered 2-year periods before and after this withdrawal: from 8 August 1999 to 8 August 2001; and from 9 August 2001 to 9 August 2003 for all statins marketed over that period of time.

The alert for pergolide and valvulopathies was sent out on 23 September 2003. The study periods considered were from 23 September 2001 to 23 September 2003 and from 24 September 2003 to 24 September 2005.

The alert for atypical antipsychotics and stroke was sent out on 9 March 2004. The study periods considered were from 9 March 2002 to 9 March 2004 and from 10 March 2004 to 10 March 2006.

Statistical Analysis

All reports of interest filed in the French Pharmacovigilance database during the periods of interest were described.

For each drug-effect pair, we estimated the ROR before and after the alert, considering equal time-periods of reporting. The 95% confidence interval was computed according to the usual formula used to compute confidence intervals for odds ratios. No other statistical testing was performed.

All analyses were conducted using Microsoft Office Excel 2003 software (Microsoft, Redmond, WA, USA).

Results

A total of 17 000–18 000 case reports per annum were filed in the French Pharmacovigilance database during the studied periods.

Between 28 December 1999 and 28 December 2000 (before the alert), 25 reports involving infliximab were filed in the database, of which two were cases of tuberculosis. One report cited tuberculosis in association with another drug. The ROR for tuberculosis in association with infliximab was estimated at 1500 (95% CI, 130, 18 000). Over the year following the AFSSAPS press release concerning infliximab (i.e. between 29 December 2000 and 29 December 2001), 105 reports cited infliximab, of which seven concerned cases of tuberculosis (table I). During the same period, three reports cited tuberculosis in association with other drugs, while the overall number of adverse drug reactions reported remained reasonably constant, resulting in a 3-fold increase in the rate of tuberculosis in association with other drugs between the two study periods. The ROR for tuberculosis with infliximab was then estimated at 430 (95% CI 110, 1700).

Table I. Reports of tuberculosis and other adverse drug reactions (ADRs) associated with infliximab and other drugs filed in the French Pharmacovigilance database, before and after the press release warning of a possible association between infliximab and tuberculosis

Reports	28 Dec 1999 to 28 Dec 2000		29 Dec 2000 to 29 Dec 2001	
	tuberculosis	other ADRs	tuberculosis	other ADRs
Infliximab	2	23	7	98
Other drugs	1	17 585	3	18 229
Total	**3**	**17 608**	**10**	**18 327**

Between 8 August 1999 and 8 August 2001, 1065 reports including statins were filed in the database (excluding reports in association with cerivastatin), of which 25 cited rhabdomyolysis. The ROR for rhabdomyolysis in association with statins, excluding cerivastatin, was 5.8 (95% CI 3.8, 9.0). Between 9 August 2001 and 9 August 2003, during the 2-year period following cerivastatin withdrawal, 1566 of the reports filed involved statins (281 further reports concerned cerivastatin). Among these reports, 63 were for rhabdomyolysis (table II). The ROR for rhabdomyolysis with statins other than cerivastatin rose to 9.4 (95% CI 7.0, 13.0) after cerivastatin withdrawal.

Between 23 September 2001 and 23 September 2003, 51 reports mentioning pergolide were filed in the database. None concerned valvulopathy. During the 2-year period following the Dear Doctor letter from Eli Lilly and Company, between 24 September 2003 and 24 September 2005, 89 reports involved pergolide, of which 63 concerned valvulopathies (table III). The ROR for valvulopathy with pergolide was then estimated at 9400 (95% CI: 4300, 20 000).

Between 9 March 2002 and 9 March 2004, 719 reports mentioning atypical antipsychotics were filed in the database, of which one was a case of stroke. The ROR of reports for strokes in association with atypical antipsychotics was estimated at 0.1 (95% CI 0.01, 0.63). During the 2 years following the press release concerning atypical antipsychotics and a risk of stroke in elderly patients, from 10 March 2004 to 10 March 2006, 860 reports mentioned atypical antipsychotics, among which 16 concerned strokes (table IV). A total of 630 reports involved strokes in association with other drugs. The ROR for stroke in association with atypical antipsychotic treatment was then estimated at 1.1 (95% CI 0.7, 1.9).

The safety alert concerning atypical antipsychotics did not specify the nature of the stroke. It was based on clinical trials, which mainly reported ischaemic strokes. Before this alert, the strokes reported as adverse drug reactions were usually haemorrhagic strokes, mainly in association with anticoagulant agents. We considered the ROR of strokes with atypical antipsychotics after excluding all reports concerning anticoagulant agents, in order to more specifically target ischaemic strokes (table V). When these reports were excluded, the ROR for strokes in association with atypical antipsychotics was 0.1 (95% CI 0.02, 1.0) before the alert and 2.0 (95% CI 1.2, 3.4) after the alert.

Discussion

Our results show that signals generated by disproportionality measures using spontaneous reporting databases can vary after a safety alert, whether this alert focuses on a rare event, an event not

Table II. Reports of rhabdomyolysis and other adverse drug reactions (ADRs) with HMG-CoA reductase inhibitors (statins) [except cerivastatin] and other drugs filed in the French Pharmacovigilance database, before and after withdrawal of cerivastatin from the market because of an excess risk of rhabdomyolysis

Reports	8 Aug 1999 to 8 Aug 2001		9 Aug 2001 to 9 Aug 2003	
	rhabdomyolysis	other ADRs	rhabdomyolysis	other ADRs
Statins	25	1 040	63	1 503
Other drugs	138	33 557	158	35 407
Total	**163**	**34 597**	**221**	**36 910**

Table III. Reports of valvulopathy and other adverse drug reactions (ADRs) mentioning pergolide and other drugs filed in the French Pharmacovigilance database, before and after Eli Lilly and Company Ltd's 'Dear Doctor' letter[16]

Reports	23 Sep 2001 to 23 Sep 2003		24 Sep 2003 to 24 Sep 2005	
	valvulopathy	other ADRs	valvulopathy	other ADRs
Pergolide	0	51	63	26
Other drugs	7	36 842	10	38 669
Total	**7**	**36 893**	**73**	**38 695**

usually considered to be an adverse drug reaction, an alert concerning an emerging drug-event association or, conversely, an alert concerning a well known class effect. This signal variation might not be due to a modification in the risk of the occurrence of events, which remains unchanged after safety alerts, but rather to a modification in the chance of recognition and reporting of events. The association between the drug and event of interest was demonstrated only after the alert for pergolide; it increased notably for statins and atypical antipsychotics. There were not enough reports regarding tuberculosis to comment on the results (three cases of tuberculosis with other drugs after the alert vs one before), although the proportion of tuberculosis cases among all reports mentioning infliximab actually decreased from 10% to 7%, whereas the proportion of reports for other drugs that were due to tuberculosis tripled. Even though reports concerning infliximab represented the majority of reports citing tuberculosis, the effect of the safety alert was to increase the reporting of tuberculosis in association with other drugs, as well as with infliximab, as if reporters did not consider tuberculosis a possible adverse drug reaction before the alert (whereas the emergence of tuberculosis is a classical adverse effect of immunosuppressants, such as corticosteroids). The recognition of this event as a possible adverse drug reaction after the alert could not only result in increased reporting concerning the drug of interest but also other drugs. This could illustrate a ripple effect following safety alerts: alerts could not only increase the reporting of the event for the drug of interest, but also for drugs other than those involved in the alert. Moreover, results concerning infliximab must be considered with caution because of the possibility of a Weber effect,[23] in that the reporting data were studied early in the post-marketing stage for this drug.

In a similar vein, increased reporting of valvulopathy after the alert with pergolide might also indicate ascertainment bias, whereby a patient with any cardiac-type symptom (shortness of breath for instance) might be more likely to be given a full cardiovascular work-up and a diagnosis (and report) of valvulopathy when taking an ergot derivative than with another drug. The same might be true of diagnostic tests for tuberculosis with infliximab.

This reporting risk modification could result from preferential reporting of highlighted events or increased diagnostic effort. This is consistent with the primary purpose of spontaneous reporting, which is to provide early warning for hazards that have not been recognised yet. Use of spontaneous reporting databases to quantify the risk for associations that are already known will lead to spurious estimates because notoriety could lead to disproportionality in reporting rates between effects. This bias is actually the consequence of one weakness of spontaneous reporting systems, under-reporting.

Table IV. Reports of stroke and other adverse drug reactions (ADRs) with atypical antipsychotics and other drugs filed in the French Pharmacovigilance database, before and after the press release warning of a possible association of atypical antipsychotics and stroke

Reports	9 Mar 2002 to 9 Mar 2004		10 Mar 2004 to 10 Mar 2006	
	strokes	other ADRs	strokes	other ADRs
Atypical antipsychotics	1	718	16	844
Other drugs	560	36 008	630	37 656
Total	**561**	**36 726**	**646**	**38 500**

Table V. Reports of stroke and other adverse drug reactions (ADRs) with atypical antipsychotics and other drugs filed in the French Pharmacovigilance database, before and after the press release warning of a possible association of atypical antipsychotics and stroke, after excluding cases associated with anticoagulant agents

Reports	9 Mar 2002 to 9 Mar 2004		10 Mar 2004 to 10 Mar 2006	
	strokes	other ADRs	strokes	other ADRs
Atypical antipsychotics	1	718	16	844
Other drugs	319	33 109	320	34 057
Total	**320**	**33 827**	**336**	**34 901**

Under-reporting results in an underestimation of the frequency of adverse drug reactions. This has no consequence in signal generation and risk evaluation if the under-reporting is random or constant for all adverse drug reactions. But under-reporting might be selective, which may introduce bias.[11] The effect of selective reporting becomes potentially disastrous if the number of reports of an adverse drug reaction is compared in an uncritical way between drugs.[5,8] We underline in this study that publicity surrounding adverse drug reactions can lead to such a bias because all the variations found in risk estimates could result from this phenomenon. Notoriety signals should then be thought of as one type of false signal generated by spontaneous reporting systems. In this regard, new signals from these systems should be scrutinised for a notoriety effect before they can be accepted.

Our results also demonstrate the high weight of existing associations and older alerts in the disproportionality estimates. Atypical antipsychotics exhibited a negative association with reports of strokes before the safety alert, and still did not show an association after the alert, when compared with all other drugs. However, when anticoagulant agents were excluded from the analysis (because of their well established relationship with haemorrhagic stroke), atypical antipsychotics were shown to not have a significant association with stroke before the alert and to have significant positive association after the alert. This could illustrate another consequence of notoriety bias: we know that the signal varies after a safety alert by changing the reporting equilibrium,[8] but what we do not know is when, if ever, the ratio returns to pre-alert values. This ignorance could imply that, by default, once a drug-effect or drug class-effect association has been demonstrated or publicised, associations of the same effect with any other drug should be studied but not those involving drugs already implicated in that effect.

Therefore, expert opinion on signal generation should be obtained before seeking new signals to eliminate existing associations, and after the emergence of new signals to eliminate potentials biases, which may include notoriety effects.

Notoriety or publicity surrounding an adverse effect related to a drug or a class of drugs might have other consequences. First of all, the more an effect is highlighted, the more it seems to be reported. This could explain why all reports of valvulopathies in patients receiving pergolide and most reports of stroke in patients receiving atypical antipsychotics were reported after the corresponding safety alerts (self-fulfilling alert). This could also explain the substantial number of adverse drug reactions involving cerivastatin that were reported after the withdrawal of this drug. In this last situation, the high number of reports recorded during the months following the withdrawal of the drug could also result from a carry-over effect: the alert causes health professionals to retrospectively report an event that occurred before the alert.

Conclusion

Knowledge of and publicity surrounding an alert will alter disproportionality measures in spontaneous reporting databases, which should therefore not be used to estimate the occurrence of known adverse drug reactions. This notoriety bias could also create a 'ripple' effect, altering the reporting balance of other drugs associated with the same effect.

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Correspondence: Dr *Antoine Pariente*, Département de Pharmacologie, INSERM U657, BP 36, Université Victor Segolen Bordeaux 2, Bordeaux, F-33076, France.
E-mail: Antoine.pariente@pharmaco.u-bordeaux2.fr