

The proportion of patient reports of suspected ADRs to signal detection in the Netherlands: case–control study

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ABSTRACT

Aim To determine the contribution of patients' adverse drug reaction (ADR) reports to signals detection, through a study of the signals sent by Lareb to the Dutch Medicines Evaluation Board.

Methods The percentage of patient's ADR reports contributing to generate signals of adverse drug reactions was determined. A case–control design was used to study if the proportion of patient reports in associations that had been selected as 'signals' differed from non-signals. A logistic regression analysis was used to calculate the Odds Ratio with 95%CI for patient reports in the cases and controls.

Results The number of patient reports which contributed to a signal has increased from 0 reports in 2003 to 31 reports in 2008 (9% of total). Since 2005 patient reports have triggered particular associations to be selected as a signal. In 2007, 28% of all trigger reports were reported by a patient. The case–control analysis showed that patient reports were equally present in the reports used in signal formation (cases) as in the controls, reports not contributing to a signal. Odds Ratio (OR) was 1.10 (95%CI 0.81–1.49) and OR = 0.96 (95%CI 0.50–1.87) for the 'trigger reports'.

Conclusions The proportion of patient reports contributing to generate signals was equal to the proportion of patient reports in the database. Patient's reports of adverse drug reactions can provide a valuable contribution to the detection of signals in addition to healthcare professionals' reports. In the Netherlands, direct patient reports have added to the signals of adverse drug reactions sent to the Medicines Evaluation Board. Copyright © 2010 John Wiley & Sons, Ltd.

KEY WORDS — patient reporting; pharmacovigilance; signal detection; consumer reporting

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INTRODUCTION

The primary aim of a spontaneous reporting system (SRS) in pharmacovigilance is the timely detection of unknown adverse drug reactions (ADRs), or signal detection.¹ A signal can be defined as reported information on a possible causal relation between an adverse event and a drug, the relation being previously unknown or incompletely documented.²

In the Netherlands, spontaneous reports of ADRs are reported to the Netherlands Pharmacovigilance Centre Lareb from general practitioners, pharmacists, hospital pharmacists, specialist doctors, pharmaceu-

tical companies and since 1 April 2003 also patients. The number of patient reports has risen from 173 reports in 2003 (4.0% of total) to 1566 reports in 2009 (15.7% of total).³

Reporting of ADRs by patients has been incorporated into pharmacovigilance systems in a growing number of countries.^{4,5} The percentage of patient reports for other countries which have been published range between 7 and 15% of the total number of reports.⁴ Although some countries have published their experiences with patient reporting over the past few years,^{4,6–19} the contribution of reporting by patients to the detection of signals has not been quantified and it is not clear to what extent the source of the reports influences the selection of signals. Recently, potential signals of adverse drug reactions generated by patients

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compared to healthcare professionals were described in an abstract from UK.¹⁴

Several countries have indicated that patient reports can identify possible new ADRs that are not listed in the Summary of Product Characteristics (SmPC).⁴ There are no data showing the percentage of these reports by patients that are subsequently confirmed as ADRs.⁴

A pilot study with patient reporting in Sweden investigated the first 100 ADR reports by patients by the Medical Products Agency.²⁰ They found that part of the reports by patients concerned unlabelled reactions with a possible value to signal detection. They concluded that signals with impact on regulatory actions were received by consumers.¹² In the first 2000 calls to the Australian Adverse Medicine Events (AME) line, 5% of ADR reports were not listed in the SmPC.¹³ An evaluation of the first 6 months of patient reporting through the Yellow Card Scheme found that there were no differences between patients and healthcare professionals in the reporting of unlabelled ADRs.¹⁰ An analysis of patient reporting of ADRs the Danish ADR database from 2004 to 2006 showed that patients reported several categories of ADR that were not reported by health professionals.⁹ The Netherlands Pharmacovigilance Centre Lareb has previously reported on possible new signals, mainly based on patient reports.⁶ The contribution of patients' reports to signal detection in the Netherlands had not been evaluated yet.

According to Blenkinsopp *et al.*⁴ concerns have been expressed that patient reports might be inferior to those of healthcare professionals. A report having a patient as its source could be hampering factor in the selection of signals. On the other hand, there is also some evidence that new ADRs are reported by patients^{9,12} so the reporter being a patient could also be a positive factor in signal detection.

The aim of this study is to determine the contribution of patients' adverse drug reaction (ADR) reports to signals detection, through a study of the signals sent by Lareb to the Dutch Medicines Evaluation board.

METHOD

Since the main focus of the Netherlands Pharmacovigilance Centre Lareb is signal detection, the generated signals that Lareb send to the Medicines Evaluation Board (MEB) were chosen as the starting point for the analysis.

Using the signals sent to the MEB in the period 2003–2008 as a basis, we evaluated the contribution of patients' ADR reports to signal detection.

Signal selection at the Netherlands Pharmacovigilance Centre Lareb

Each incoming ADR report to a pharmacovigilance centre represents a possible association between one or more suspected ADRs and one or more suspected drugs, along with patient characteristics.¹ For the detection of signals at the Netherlands Pharmacovigilance Centre Lareb each ADR report undergoes a systematic individual review. Signal selection is carried out in a weekly meeting, where the assessed adverse drug reaction reports are reviewed on a case-by-case basis by trained assessors.²¹ Potential signals undergo a more detailed analysis.

A signal generally consists of multiple ADR reports. The ADRs in a signal can be reported by healthcare professionals, pharmaceutical companies and since 2003 patients.

Lareb works on behalf of the Dutch Medicines Evaluation Board (MEB) and the MEB is informed periodically about generated signals. On a three monthly basis the most relevant signals are published in a so-called 'quarterly-report' to the MEB. Associations described in the 'quarterly-reports' to the MEB may represent possible new signals of possible ADRs, drug interactions but also reviews of drugs that were marketed recently in the Netherlands²¹ or sometimes updates of older signals that still need attention.

The specific ADR report that triggered the particular association to be selected as a signal is called the 'trigger report' in this study. A trigger report is the last report received by Lareb before a signal is formed and published in a 'quarterly-report'.

For example, the 'quarterly-report' for the first quarter of 2006 (Figure 1), contained six signals of adverse drug reactions. In total the six signals contained 42 ADR reports of whom only one report per signal was the 'trigger report'.

Selected signals in this study

All signals sent to the Medicines Evaluation Board from the second quarter of 2003 until the fourth quarter of 2008 were included in this study, except for updates of previous quarterly reports. Mean and standard deviation (SD) of the number of signals in a 'quarterly-reports' and mean, standard deviation (SD) and range of the number of ADR reports in a signal were calculated.

For each signal in the quarterly reports, all the original ADR reports in the Lareb database which contributed to the signal were determined and the source of the reports was specified as patient,

Quarterly Report	Signals	Number of ADR reports per signal
2006-1	Moxifloxacin and severe iris disorders	2
	Olanzapine and hyponatraemia	3
	Sevoflurane and ventricular tachycardia	7
	Tamsulosin antagonists and anginal complaints	13
	Quetiapine and extrapyramidal effects	10
	AT ₁ -receptor antagonists and psoriasis	7

Figure 1. Example of a 'quarterly-report' consisting of several signals

healthcare professional or pharmaceutical company. The healthcare professionals' reports were further divided into reports from general practitioners, specialist doctors, pharmacists, hospital pharmacists and other healthcare professionals.

Other healthcare professionals include physicians without specialisation, physicians with their own pharmacy, National Immunisation Programme reports and reports from health professionals like nurse practitioners etc.

The percentage of patients' ADR reports was calculated for the whole study period and separately per year.

The proportion of patient reports and reports from other reporters, meaning healthcare professionals or pharmaceutical companies, that were considered a 'trigger report' was also determined per year and for the total study period.

In addition the eight signals of drug-ADR associations with the highest percentage of patient reports were determined.

Case-control design

In order to study if the percentage of patient reports in associations that had been selected as 'signals' differed from non-signals a case-control design was used. For each case, two controls were matched in calendar time because the amount of patient reports received by Lareb was variable over time.

Cases were all ADR-reports that contributed to a signal. Controls were all ADR-reports not contributing to a signal. The control reports were selected as the twentieth report before and after the ADR report chosen as a case. Selection was made on the basis on

the unique report number in the database. In this way cases and controls were matched in time.

Reporters in cases and controls were defined as either patient or *other*, meaning healthcare professional or pharmaceutical company.

A logistic regression analysis was used to calculate the Odds Ratio with corresponding 95% confidence interval for patient reports in the cases and controls. This was done for the dataset containing all cases and controls ($n=3330$ in total) and also for a dataset containing only the trigger reports with their controls ($n=324$ in total).

As well as analysing the whole study period, we also carried out the analysis for each individual year by stratification. SPSS 16.0 was used for statistical analysis.

RESULTS

The share of patient reports in signals to the Medicines Evaluation Board

Between the second quarter of 2003 till the fourth quarter of 2008, a total of 22 quarterly reports were included, containing 108 signals. In total there were 1110 ADR reports that contributed to a signal. The mean number of included signals in a quarterly report was 3.2 with an SD of 1.6. On average a signal contained 9.8 ADR reports with a range from 1 to 56 reports and an SD of 9.5.

There were 67 reports by patients that contributed to a signal (6%) in the whole study period. The absolute number of patient reports which contributed to a signal has been increasing from 0 reports in 2003 when the pharmacovigilance centre had just started accepted

Table 1. ADR reports that contributed to signals from patients and other sources of the reports per year

Quarterly reports per year % ^a , N	Patient	General practitioner	Pharmacist	Hospital pharmacist	Specialist	Other healthcare professional*	Pharmaceutical company	Total
2003	(0)	15% (17)	20% (22)	1% (1)	21% (23)	2% (2)	41% (46)	111
2004	1% (1)	31% (50)	39% (63)	2% (3)	14% (23)	2% (3)	12% (19)	162
2005	5% (8)	38% (63)	31% (51)	2% (4)	14% (23)	4% (6)	7% (11)	166
2006	5% (8)	28% (42)	32% (49)	1% (1)	25% (38)	1% (2)	7% (11)	151
2007	12% (19)	18% (28)	38% (60)	1% (1)	20% (32)	2% (3)	9% (15)	158
2008	9% (31)	24% (86)	33% (119)	1% (3)	15% (56)	1% (4)	17% (63)	362
Total	6% (67)	26% (286)	33% (364)	1% (13)	18% (195)	2% (20)	15% (165)	1110

*Other Healthcare Professionals include physicians without specialisation, physicians with their own pharmacy, National Immunisation Programme reports and reports from groups like nurse practitioners etc.

patient reports, to 31 reports in 2008 (9% of total). The percentage of patient reports contributing to the signals was the highest in 2007, where 12% of all reports that were published in a signal were reported by patients.

Pharmacists and general practitioners reported 33 and 26%, respectively, of all the reports that were selected as a signal.

The absolute number and percentage of patient reports and reports from healthcare professionals and pharmaceutical companies that contributed to signals is shown in Table 1.

A patient report was first used in a signal of an adverse drug reaction in 2004; this was a report of arrhythmia and QT-prolongation on the ECG contributing to the signal about 'Cisapride and cardiac arrhythmia'.

Since 2005, reports by patients have contributed as reports that triggered particular associations to be selected as a signal. In 2005, 16% of all trigger reports had a patient as the source of the report. In 2007, 28% of all trigger reports were reported by a patient. The absolute number and percentage of trigger reports by patients and other sources is shown in Table 2.

Signals of drug-ADR associations with the highest percentage of patient reports are given in Table 3.

Case-control investigation of patient reports

In the study period from the second quarter of 2003 till the fourth quarter of 2008 a total of 1110 ADR reports

Table 2. Trigger reports of the cases grouped by patient and other (healthcare professional and pharmaceutical industry) reporters per year

Year	Number of patient 'trigger reports', (%)	Number of 'trigger reports' by other reporters, (%)	Total number of 'trigger reports'
2003	0 (0%)	14 (100%)	14
2004	0 (0%)	16 (100%)	16
2005	3 (16%)	16 (84%)	19
2006	3 (14%)	18 (86%)	21
2007	5 (28%)	13 (72%)	18
2008	4 (20%)	16 (80%)	20
Total	15 (14%)	93 (86%)	108 (100%)

contributed to the quarterly reports. These cases were matched with 2220 controls. The Odds Ratio (OR) for patient reports in the cases and controls was 1.10 (95%CI 0.81–1.49), $p = 0.56$.

The same analysis was performed for the 108 trigger reports with their 216 controls for the whole period. No significant difference was found either; OR = 0.96 (95%CI 0.50–1.87), $p = 0.91$. Results are shown in Table 4.

Differences in cases and controls were also analysed separately per year for 2003–2008. For 2003, an OR could not be calculated because there were no reports by patients in the signals sent to the MEB. No statistically significant differences were found for the years 2004–2008. ORs with their 95%CI were 1.00 (0.09–11.11) for 2004, 1.00 (0.42–2.39) for 2005, 0.71 (0.31–1.64) for 2006, 1.46 (0.79–2.72) for 2007 and 1.12 (0.71–1.77) for 2008.

DISCUSSION

To the best of our knowledge, this paper is the first to quantify the direct contribution of patient reports in signals generated by a pharmacovigilance centre.

Table 3. Signals of drug-ADR associations with the highest percentage of patient reports

Quarterly report	Title of signal	Amount of patient reports (total amount of reports)	% of patient reports
2005.3.2	Pergolide and pathologic gambling	1 (2)	50
2007.1.2	Latanoprost and dizziness	2 (7)	29
2006.3.1	Topical tacrolimus and malignancies	1 (4)	25
2007.1.4	Valproic acid and pubertas praecox	1 (4)	25
2007.4.3	Fluorescein and anaphylactic reactions	1 (4)	25
2008.3.4	Paroxetine and restless legs	4 (18)	22
2008.3.5	Tramadol and flushes	2 (9)	22
2007.3.1	Venous thromboembolism and Yasmin [®]	7 (33)	21

Table 4. Odds ratios for reporters in the case and the control groups for the total dataset and a dataset containing trigger reports only

Period of quarterly reports	Case or control	Amount of reports by other reporters (<i>n</i>)	Amount of patient reports (<i>n</i>)	Total (<i>n</i>)	Odds Ratio (95%CI), <i>p</i> -value
Entire dataset	Control	2097	123	2220	1.10 (0.81–1.49), <i>p</i> = 0.56
	Case	1043	67	1110	
Dataset only trigger reports	Control	185	31	216	0.96 (0.50–1.87), <i>p</i> = 0.91
	Control				
	Case	93	15	108	

In the Netherlands, the contribution of patient reports to signal selection has increased throughout the study period from 2003 to 2008. In 2003, there were no reports by patients contributing to the signals that Lareb send to the Medicines Evaluation Board (MEB). This is not surprising since patient reporting had only become possible since 1 April 2003.

The signal with the highest percentage of patient reports was '*Pergolide and pathologic gambling*' in 2005. This signal consisted of only two well-documented reports, one by a neurologist and the second by a patient. Additional information revealed that the patients' neurologist recognised pathological gambling as a pergolide-associated ADR.

For the signals '*Topical tacrolimus and malignancies*', '*Valproic acid and pubertas praecox*' and '*Fluorescein and anaphylactic reactions*' in 2006 and 2007, 25% of the reporters were patients. In 2008, the signals describing the associations '*Paroxetine and restless legs*' and '*Tramadol and hot flushes*' were the signals with the highest percentage of patient reports. A characteristic of most of these signals is, that they contain relatively few ADR reports compared to the average of 9.8 ADR reports per signal.

No major difference in the nature of the reported ADRs between the signals with the highest and lowest percentage of ADR reports could be seen.

The case-control analysis shows that patient reports were equally present in the reports used in signal formation as in the controls. Apparently the presence of patient reports does not hamper the selection of signals forwarded to the Medicines Evaluation Board (MEB) but the percentage of patient reports that are used for the signals is proportional to the patient reports in the database.

Also for the trigger reports the amount of patient reports does not differ significantly for cases compared with the controls. Possible fluctuations of the amount of reports by patients were corrected for by matching cases and controls in time.

In this study the generated signals that were sent to the Dutch Medicines Evaluation Board (MEB) were chosen as a starting point for the analysis. A case-control design was chosen for the analysis because in this manner all ADR-reports that were used in generated signals to the MEB were taken into account. Alternatively, a cohort-design could be used to evaluate which percentage of all ADR reports by patients is used in generated signals.

Other studies

The impact of consumer reports on signal detection in the database of a pharmaceutical company was determined by Hammond *et al.*²² using a disproportionality analysis. It was concluded from this study that adverse event reports submitted directly to pharmaceutical companies by consumers can help significantly in the early detection of safety signals.²¹

In a recent abstract from UK, the authors compared signals of disproportionate reporting of ADRs generated by patient and healthcare professional (HCP) reports. A database of drug-reaction pairs for each reporter group was created. The Proportional Reporting Ratio (PRR) method was used to generate signals of disproportionate reporting for different reporting groups. Healthcare professionals' reports generated a significantly higher proportion of signals of disproportionate reporting overall compared to patients' reports but only 136 of these were common to both groups. A similar proportion of signals of disproportionate reporting in both groups were assessed as being 'unlabelled' ADRs during the study period (approximately 15%, based on a random sample). The authors concluded that patients' reports appear to generate signals of disproportionate reporting which are of potential clinical importance within the context of pharmacovigilance although this may be to a lesser extent than HCP reports.¹⁴ The same authors also

KEY POINTS

- Patient reports contribute proportionally to signal detection, in addition to health care professionals' reports.
- Patient reports have triggered the selection of certain signals in the Netherlands.

explored how signal detection in a database of healthcare professional reports may be affected by the addition of patient reports.¹⁶

Limitations

In this study, we have quantified the contributions of the different groups of reporters to the signals sent to the Dutch Medicines Evaluation Board. We have not investigated quality of the clinical information for each reporting group; this remains a subject for further study.

CONCLUSION

The proportion of patient reports contributing to generated signals was equal to the proportion of patient reports in the database. Patients' reports of adverse drug reactions can provide a valuable contribution to the detection of signals in addition to healthcare professionals' reports. In the Netherlands, direct patient reports have added to the signals of adverse drug reactions sent to the Medicines Evaluation Board.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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