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ORIGINAL REPORT

The contribution of direct patient reported ADRs to drug safety signals in the Netherlands from 2010 to 2015

Florence van Hunsel[1] | Susan de Waal[1,2] | Linda Härmark[1]

[1] Netherlands Pharmacovigilance Centre Lareb, WHO Collaborating Centre For Pharmacovigilance In Education And Patient Reporting, 's-Hertogenbosch, The Netherlands

[2] Pharmaceutical Business Administration, Institute for Allied Healthcare, Utrecht University of Applied Sciences, Utrecht, the Netherlands

Correspondence
Florence van Hunsel, Netherlands Pharmacovigilance Centre Lareb, Goudsbloemvallei 7, 5237 MH 's-Hertogenbosch, The Netherlands
Email: f.vanhunsel@lareb.nl

Abstract

Purpose: The purpose of this study was to investigate the contribution of patient reports to signals sent by the Netherlands Pharmacovigilance Centre Lareb to the Dutch Medicines Evaluation Board and to determine if there are certain types of signals where patient report add a distinct contribution.

Method: All signals from 2010 until 2015 were included. First, we investigated how many patient reports were present in the signals and the characteristics of these reports compared to the health care professional and marketing authorization holders' reports.
In addition to source, the analysis included ATC code of the drug, MedDRA® system organ class and preferred term for the adverse drug reaction (ADR), seriousness of the ADR, and 7 other factors like reports on over-the-counter medication, and how often an ADR listed in the important medical event terms list was present.
Secondly, we determined the proportion of reports submitted by the individual groups to signals, in a cross-sectional manner.

Results: A total of 150 signals were included, including 1691 ADR reports. Our results show that 26.3% of all ADR reports in Dutch drug safety signals were reported by patients, and 30.5% of the patient reports in the signals contained one or more terms listed as important medical events. The proportion of reports by patients which were included the signals was 2% and 3.9% for health care professional reports and 0.2% for marketing authorization holders reports.

Conclusion: Patients had an important contribution to signals overall, but especially for ADRs related to generic drug substitution and psychiatric ADRs.

KEYWORDS

ADR, patient reporting, pharmacovigilance, signal detection

1 | INTRODUCTION

Spontaneous reporting of suspected adverse drug reactions (ADRs) remains the backbone of pharmacovigilance systems and has proven its worth in identifying drug safety signals.[1-3] In this context, a safety signal is defined as follows: information that arises from one or multiple sources (including observations and experiments), which suggests a new potentially causal association, or a new aspect of a known association, between an intervention and an event or set of related events, either adverse or beneficial, that is judged to be of sufficient likelihood to justify verificatory action."[4] In the Netherlands the spontaneous reporting system is maintained by the Netherlands Pharmacovigilance Centre Lareb, which assesses ADR reports on a case-by-case basis, analyses drug-ADR associations and disseminates drug safety signals to the Medicines Evaluation Board, the Dutch drug regulatory agency.[5] Of all signals disseminated by Lareb between 2008 and 2012, 90.7% resulted in one or multiple actions: in 87% a regulatory action and in 36% an (inter)national publication.[6]

In 2009 Lareb determined the contribution of patients' ADR reports to signal detection.[7] The proportion of patient reports contributing to signals was equal to the proportion of patient reports in the database. The study concluded that direct patient reports have contributed to drug safety signals in addition to health care professional (HCP) reports. No major difference in the nature of the reported ADRs (seriousness, type of ADR) between the signals with the highest and lowest percentage of patient ADR reports was found.[7]

The number of reports from patients to Lareb grew from 173 reports in 2003 to 8010 reports in 2015, while the number of HCP reports has remained stable.[8] In the past few years, since the 2012 pharmacovigilance legislation, Lareb has also widened the scope of their drug safety signals, including ADRs related to overdose, abuse, off-label use, misuse, and medication errors.[9] With this increasing number of patient reports and a broader focus in signal detection, we aimed to study the current contribution of patient reports to disseminated signals and in addition to determine if there are certain types of signals where patient reports add a distinct contribution compared to HCP and marketing authorization holders (MAH) reports.

KEY POINTS

- A total of 26.3% of ADR reports in Dutch drug safety signals are from patients.
- A total of 30.5% of the patient reports in the signals contained one or more terms listed as important medical events
- Patients had an important contribution to signals for ADRs related to drug substitution and psychiatric ADRs

2 | METHOD

2.1 | Selected signals

All signals sent to the Medicines Evaluation Board between 2010 and 2015 were included in this study, including overviews of drugs and their ADRs. Some of these signals were, in addition, also sent to the Healthcare Inspectorate if they contained information on unregistered drugs or off-label use. Signals were included if individual reports were described in the signal. Overviews where individual cases were not described and only accumulated data were presented were excluded from the analysis.

For each signal all the individual ADR reports that contributed to the signal were analyzed. The source of the reports was specified as patient, HCP, or MAH. Reports from the MAH can have either an HCP or a patient as the original source, but because these reports are not reported directly to Lareb but to the MAH, they are counted as a separate reporting group.

The HCP's reports were further divided into reports from general practitioners, specialist doctors, pharmacists, hospital pharmacists, and other HCPs (for instance, nurses, physicians without specialization, or physicians working in social medicine).

In addition to source, for each report in the signals, the following items where specified: SafetyreportID in the database, date of report, ATC code of the drug,[10] MedDRA® system organ class (SOC),[11] and preferred term (PT) for the ADR,[11] seriousness of the ADR according to CIOMS criteria,[4] and the following factors: presence of relevant laboratory values in the report, report on drug interaction, report on off-label use, report on medication error, report on generic drug substitution, report on drug use during pregnancy, and report on over-the-counter medication.

2.2 | Analyses

Two methods of investigating the contribution of patient reporting to signal detection were used.

First, we investigated how many patient reports were present in signals and the characteristics of these reports compared to HCP and MAH reports.

Mean with standard deviation and range of the number of reports per signal were calculated.

Descriptive analyses were used to describe the contribution of patient reports in the signals for the period 2010 to 2015, but also per year. For the PT level, we compared between patients and HCP and MAH reports how often an ADR listed in the important medical event (IME) terms list (MedDRA® version 19.1) was present.[12] A two-sided Pearson chi-square (X^2) test, significance based on $P < 0.05$, was used to compare variables between groups of reporters and to compare reported ADRs in patients vs HCP and MAH reports on MedDRA® SOC level.

Secondly, because the total number of reports per year for each source is known[8], we determined how many of the incoming reports per reporting group contributed to a signal, in a cross-sectional manner. Trend lines in Microsoft Excel® were used to look at the trends for the reporting between 2010 and 2015.

Data were analyzed using SPSS statistics version 22 software (IBM Corporation, Armonk, NY, USA).

3 | RESULTS

A total of 150 signals were included, containing 1691 ADR reports. On average a signal contained 11.2 ADR reports with a range from 2 to 78 reports and a standard deviation of 11 reports. There were 53 signals containing no patient reports and 1 signal consisting solely of patient reports.

The number of reports directly from patients in the signals rose from 16 (10% of total) in 2010 to 161 (28.3% of total) in 2015. In total 445 (26.3%) of 1691 reports in the period 2010 to 2015 were reported by patients. Pharmacists (n = 414, 24.5%) and general practitioners (n = 318, 18.8%) were other groups whose reports contributed to signals to a larger extend. In total HCPs contributed to 1169 reports in the signals (69.1%), and 77 (4.6%) reports in the signals were received via MAH (see Table 1).

There were 137 serious patient reports in the signals (30.8% of total patient reports), 224 (19.2%) serious HCP reports, and 73 serious MAH reports (94.8% of total), and differences between reporting groups are statistically significant (X^2 $P < 0.000$).

For reported ADRs, we compared on MedDRA® PT level how many reports included an ADR listed on the IME list (MedDRA® version 19.1). There were 104 patient reports with an ADR on the list (30.5% of total), and 214 HCP (22.5%) and 33 MAH reports (75.0% of total). X^2 $P = 0.018$ for patient vs HCP, $P = <0.000$ for MAH vs HCP and $P = 0.001$ for patient vs MAH. Patients reported a similar percentage of IME compared to HCP and MAH combined, $P = 0.135$ (see Table 2).

TABLE 1 Number of reports per reporting group in the signals (% of total) and total number of reports for those groups

Reporting group	Years																	
	2010			2011			2012			2013			2014			2015		
Patients	16	(1.04%)	1545	65	(3.11%)	2089	36	(1.38%)	2602	63	(1.59%)	3961	104	(2.37%)	4393	161	(2.01%)	8010	445	(1.97%)	22600
Pharmacists	44	(2.3%)	1914	73	(4.25%)	1717	48	(3.25%)	1479	54	(3.7%)	1461	78	(5.08%)	1536	117	(7.20%)	1626	414	(4.25%)	9733
General practitioners	56	(7.73%)	724	38	(4.97%)	764	34	(4.35%)	782	60	(6.05%)	992	52	(5.3%)	981	78	(8.96%)	871	318	(6.22%)	5114
Hospital pharmacists	1	(0.88%)	113	0	(0%)	157	2	(1.2%)	167	1	(0.42%)	236	4	(2.23%)	179	46	(22.22%)	207	54	(5.10%)	1059
Specialist doctors	21	(2.03%)	1037	31	(2.36%)	1314	32	(2.00%)	1600	47	(3.09%)	1522	47	(3.38%)	1392	86	(3.73%)	2308	264	(2.88%)	9173
Other health care professionals*	18	(7.86%)	229	8	(0.79%)	1016	8	(1.01%)	792	19	(2.78%)	683	15	(2.34%)	642	51	(3.27%)	1559	119	(2.42%)	4921
MAH	4	(0.12%)	3263	5	(0.11%)	4393	7	(0.10)%	6770	6	(0.07%)	8202	26	(0.21%)	12574	29	(0.30%)	9579	77	(0.17%)	44781
Total	160	(1.81%)	8825	220	(1.92%)	11450	167	(1.18%)	14192	250	(1.47%)	17057	326	(1.50%)	21697	568	(2.35%)	24160	1691	(1.74%)	97381

*Reports by nurses are grouped among the other health care professionals in this table, as Lareb did not specify nurses as a separate reporting group before 2015.

When comparing the ADRs in the signals on SOC level, the spectrum of SOCs as reported by patients and the HCP/MAH reports looked similar (see Figure 1). For the majority of SOCs, there is no difference in the reporting between patients and HCPs. However, in the signals patients statistically more often reported about psychiatric ADRs (X^2 P = 0.03) and HCPs/MAHs more about eye disorders (X^2 P = 0.01), immune system disorders (X^2 P = 0.01), and respiratory, thoracic, and mediastinal disorders (X^2 P = 0.02).

We compared the reports from the different reporting groups regarding presence of information of laboratory values, drug interactions, off-label use, medication errors, suspect drug being an over-the-counter product, ADR related to drug substitution, and drug use during pregnancy. There was only one report in the signals that specifically mentioned a medication error.

The ADR being related to drug substitution was the factor most reported (111 reports) and more often reported by patients than HCPs. In addition, for the other factors there were significant differences in the number of reports between groups, tested with a Pearson X^2 test (see Table 3).

When the reports in the signals were compared in a cross-sectional manner to the total number of incoming reports from each reporter group 2010 to 2015 (and separately per year), 3.9% of the HCP reports, 2.0% of patient reports, and 0.2% of MAH reports contributed to a drug safety signal. Table 1 shows the contributions per group. There was no large increasing trend in the proportion of by patient reports in the signals in this period, trend line $y = 0.0811\times + 1.6327$.

4 | DISCUSSION

Recent developments in pharmacovigilance emphasize the importance of the patient's perspective in drug safety.[13] Aspects of the contribution of patient reporting to pharmacovigilance go beyond a quantitative contribution and include more information on quality of life, severity of the ADR, and circumstances of use.[14-16]

Even though attitudes toward patient reporting are generally positive,[14,17] most information on the contribution of patient reports to signals is theoretical or anecdotal,[14,16,17] and there is still a limited amount of information available that actually quantify the contribution of patient reports to signal detection for a spontaneous reporting system.

In 2013, Hazell *et al*.[18] published an article on the contribution of patient reports to possible signals in the UK's Yellow Card scheme on the basis of a disproportionality analyses. More potential signals were gained then lost when patient and HCP reports were combined.

Our previous study from the Netherlands[7] found that there were 67 (6% of total) reports by patients that contributed to a signal in the period 2003 to 2008. 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.

Since this study, the number of ADRs reported directly by patients has taken a flight, and the fact that patients can contribute to signal detection is reflected by our current findings for the period 2010 to 2015; 26.3% of all ADR reports in Dutch drug safety signals originated from patients.

TABLE 2 Reports with an ADR listed on the important medical event terms list

		Reporter								
		Patient	General practitioner	Pharmacist	Specialist doctor	MAH	Hospital pharmacist	Nurse	Other	Total
Report with ADR on IME list	Yes	104	46	36	80	33	13	5	36	353
	No	341	272	378	184	44	41	5	73	1338
Total		445	318	414	264	77	54	10	109	1691

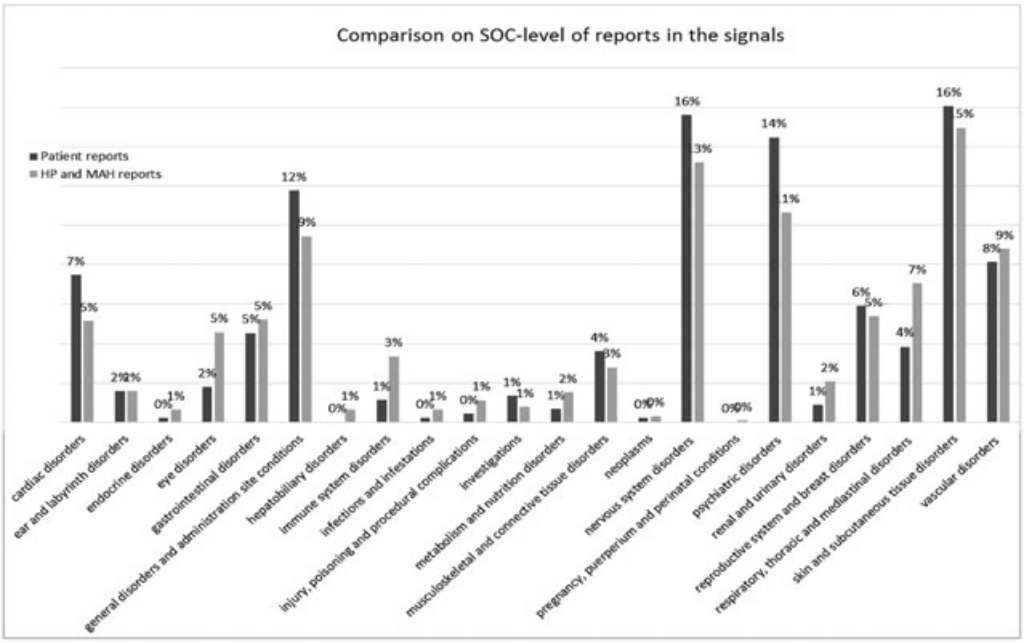

FIGURE 1 Comparison on SOC level of reports in the signals by patient to the HCP and MAH reports

Also, this study shows that many serious reports in the signals were reported by patients and that patient reports in the signals contained as many terms listed as IME[12] as combined HCP and MAH reports. There are differences in the reporting of IME however when all reporting groups are viewed separately. Especially MAHs and specialist doctor reported many IMEs. However, it should be noted that most IME are serious events, and Lareb currently only receives serious MAH reports. In general HCPs reported less IME's than patients.

The ADR being related to generic drug substitution was the factor most reported (111 reports) and more often reported by patients than HCPs. This is a type of drug safety issue where patients could be especially helpful. There were relatively many patient reports with laboratory values in the signals as compared to reports from other reporting groups; this was partly due to more standardized and intensive follow-up for a number of signals that contained a high percentage of patient reports. ADRs related to over-the-counter medicines were reported significantly more often by HCPs then patients. This is surprising as we expected beforehand that patient reports could fill a gap in the signal detection of "blindspots" in pharmacovigilance, including over-the-counter medicines and complementary medicines.[19,20] Experiences from other countries show that patients can provide additional information on these topics.[21] Drug interactions are more often reported by HCPs, especially pharmacists.

Reports from MAHs, hospital pharmacists, nurses, and other HCPs contained few of the factors we investigated, although off-label use was reported relatively often in the MAH reports. ADRs occurring during drug use in pregnancy were only reported 5 times in all signals.

Patients contributed to a varied set of signals, as we also found during our previous study.[7] Overall, the spectrum of the ADRs compared on MedDRA® SOC level was similar between patients and HCP/MAH, although there were significantly more reports on psychiatric ADRs by patients in the signals, especially related to the use of SSRIs. Also in Denmark, patients were more likely to report ADRs from the SOCs "psychiatric disorders" and in addition for "nervous system disorders" and "reproductive system and breast disorders" than other sources, in analyses of all reports.[22]

Signal detection is not about obtaining the exhaustive or full number of cases in a population but about obtaining sufficiently documented cases in real time to detect a signal as early as possible. Research has shown that in the Netherlands the information type and quality of patient reports is similar to HCP reports.[23,24] A previous study found that HCPs more often reported objective information compared with patients. Probably, they might recognize the importance of these elements more or are better equipped to provide it. However, clinical information like test results were not more often reported by HCPs, except for specialist doctors. Patient reported more subjective element of information, like information on the impact of

TABLE 3 Distribution of reported factors over the reporting groups

		Reporter			Total	Pearson chi-square*, *P*-value
		Patient	HCP	MAH		
Laboratory values	Present	26	22	0	48	Patient vs HPC *P* = < 0.000
	Not present	419	1147	77	1643	
Total		445	1169	77	1691	
Drug interactions	Present	5	35	2	42	Patient vs HCP *P* = 0.03
	Not present	440	1134	75	1649	
Total		445	1169	77	1691	
Off-label use	Present	11	30	8	49	Patient vs HCP *P* = 0.91 Patients vs MAH *P* = 0.001 HCP vs MAH *P* < 0.000
	Not present	434	1139	69	1642	
Total		445	1169	77	1691	
Medication errors	Present	0	1	0	1	—
	Not present	445	1168	77	1690	
Total		445	1169	77	1691	
OTC product	Present	8	51	2	61	Patients vs HCP *P* = 0.01
	Not present	437	1118	75	1630	
Total		445	1169	77	1691	
Drug substitution	Present	43	65	3	111	Patients vs HCP *P* = 0.003 Patients vs MAH *P* = 0.10 HCP vs MAH *P* = 0.53
	Not present	402	1104	74	1580	
Total		445	1169	77	1691	
Drug use during pregnancy	Present	2	2	1	5	—
	Not present	443	1167	76	1686	
Total		445	1169	77	1691	

*Only calculated if none of the cells had expected counts less than 5.

quality of life.[23] Both sets of elements can be important in the signal assessment. A recent study compared differences in clinical documentation on ADRs that were reported in duplicate, so-called paired reports of patient and HCPs. Differences in the clinical documentation of these ADRs were small.[24]

Although this study shows that patients have a valuable contribution to signal detection, there is much to gain both in the Netherlands and internationally. Most of the general public does not know that they can report ADRs themselves in the Netherlands.[14] In an international survey of National Competent Authorities' views and needs regarding patient reporting most respondents acknowledge that the general public can contribute to the detection or strength of drug safety signals (82.2% agree or strongly agree) and provide information that is not present in HCP reports (80.7% agree or strongly agree). Patient reports are used in signal detection in the majority of pharmacovigilance centers (n = 69, 64.5% of responding centers) and are also used to gain insight and knowledge about the impact of the ADR on daily life (n = 56, 52.3). However, some countries only collect reports from patients but do not use them actively (n = 30, 28%).[21]

The focus of this article was to look at the patient reports; however, it is important not to lose sight of the contribution of the HCPs. HCPs have the highest contribution to drug safety signals, both in number of reports in the signals as their relative contribution compared to all incoming reports (3.9% compared to 2.0% of patient reports and 0.2% of MAH reports).

5 | STRENGTHS AND LIMITATIONS OF THIS STUDY

The main strength of this study is that we can provide detailed insight in how patient reports have added to signal detection in the Netherlands. This study also has some limitations; we calculated the relative contribution to disseminated signals per reporting group by comparing reports in the signals to the total number of incoming reports from 2010 to 2015. This approach means that we cross-sectional compared reports in the signals with incoming reports, and we did not make a cohort out of all the ADRs reported in a specific year and wait how many would be included in a signal. Because drug safety signals sometimes take multiple years to build up, this latter approach would take many years, and a historic cohort would not capture the current contribution of patient reporting. In our previous study, we have looked at the contribution to safety signals per group with a case-control design, also elimination this latter issue.[7]

A few very large signals using mainly reports by patients were not taken into account because they did not describe individual cases.[15,25,26] These larger signals focused mainly on reports of ADRs after drug substitution or on off-label use. This means that the patient's contribution to these factors is underestimated.

Also, this current study was not designed to look at differences in the speed of signal detection between patients and HCPs; however, some of the signals in this study consisted mainly of patient reports and would have not been published without them. An example is a

signal of injection site pain and bruising due to blunt needles after patients were switched from one methotrexate product to another. However, there were more signals consisting mainly or solely from HCP reports.

This study looked only at the contribution to the disseminated drug safety signals. However, ADR reports, and hence also patient reports, are the basis of the knowledge system at Lareb and for many other important purposes[6] like publications in scientific, professional and patient journals, news items and to answers telephone calls on drug safety questions.

6 | CONCLUSION

This study aimed to revisit the contribution of direct patient reports to drug safety signals in the Netherlands. Our results show that 26.3% of all ADR reports in Dutch drug safety signals were reported by patients. A total of 30.5% of the patient reports in the signals contained one or more terms listed as IMEs. Patients had an important contribution to signals overall, but especially for ADRs related to generic drug substitution and psychiatric ADRs.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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