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ORIGINAL RESEARCH ARTICLE

How Do Patients Contribute to Signal Detection?

A Retrospective Analysis of Spontaneous Reporting of Adverse Drug Reactions in the UK's Yellow Card Scheme

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Abstract

Background In 2005, spontaneous reporting of adverse drug reactions (ADRs) to the UK's Yellow Card Scheme (YCS) was extended to include patient reports. Here, we investigate the potential pharmacovigilance impact of patient reporting.

Objectives The aim of the study was to investigate the relative contribution of patient reporting to signal detection through disproportionality analysis.

Methods Data were analysed from all reports submitted directly to the YCS between October 2005 and September 2007. Three datasets of drug–ADR pairs were created: one for patient reports, one for healthcare professional (HCP) reports and one for all reports combined. The proportional reporting ratio (PRR) method was used to identify signals of disproportionate reporting (SDRs) in each dataset. The number of SDRs identified from patient and HCP reports were compared, as well as the type of ADR and suspect drug involved. A sensitivity analysis was performed to examine how combining the patient and HCP reports may affect the SDRs identified.

Results Data were received for 5,180 patient and 20,949 HCP reports, relating to 16,566 and 28,775 drug–ADR pairs, respectively, with 4,340 (10.6 %) pairs found in both datasets. A significantly higher proportion of the SDRs identified from HCP reports involved reactions classified as serious by the Medicines and Healthcare products Regulatory Agency (MHRA), compared with patient reports ($n = 931$, 48.0 % vs. $n = 185$, 28.5 %), or involved newly marketed drugs ($n = 596$, 30.7 % vs. $n = 71$, 10.9 %). The proportion of SDRs assessed as not listed on the Summary of Product Characteristics (SPC) was similar in each group ($\sim$15 %, based on a random sample). After combining the patient and HCP reports, 278 ($\sim$11 %) of the SDRs identified when each group was analysed separately no longer met the SDR criteria, including 12 potentially serious ADRs not listed on the product's SPC. On the other hand, the combined dataset identified an additional 508 SDRs that were not identified when patient or HCP reports were analysed separately. Approximately 10 % ($n = 47$) of these additional SDRs were assessed as serious ADRs and were not listed on the product's SPC.

Conclusions Although this study is limited to the UK experience, overall, the results suggest that patient reporting may provide a positive complementary contribution to that of HCPs. Patient reporting may make an important contribution to drug safety by identifying different SDRs not identified from HCP reports alone. The combination of reports from patients and HCPs, however, when used for the purposes of signal detection through disproportionality analysis, may result in the loss of some information. One possible strategy is to conduct such analyses using reports from patients and HCPs combined, as well as separately for each group.

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1 Background

Spontaneous reporting of adverse drug reactions (ADRs) to regulatory authorities or drug manufacturers remains one of the most important means of monitoring the post-marketing safety of medicines. The aim of spontaneous reporting schemes, such as MedWatch in the USA [1] and the Yellow Card Scheme (YCS) run by the Medicines and Healthcare products Regulatory Agency (MHRA) in the UK [2], is to ensure the early detection of signals of previously unrecognized ADRs. This is particularly important for rare, serious reactions to established drugs, or reactions to newly marketed medicines where knowledge about their safety profile is based upon relatively limited exposure information obtained during premarketing clinical trials. A number of important signals of ADRs have been identified through such schemes, for example, seizures with the smoking cessation drug bupropion, hyperglycaemia with olanzapine and hepatic disorders with atomoxetine [3].

Large spontaneous reporting schemes, such as the YCS, have such a large volume of reports that it is impractical to evaluate in detail every report received. Instead, priority is given to reactions deemed to be serious; that were previously undocumented, particularly in relation to newly marketed medicines; that occurred in pregnant women or children; and/or for which there appears to be a disproportionately high level of reporting (based on continuous analysis of the evolving database). Disproportionality analysis is a statistical tool that identifies signals of disproportionate reporting (SDRs) for drug–ADR combinations or 'pairs' that are reported more frequently than expected, based on the background reporting rate for both the drug and reaction of interest within the spontaneous reporting scheme's database. The merits and limitations of the different approaches used for disproportionality analysis used in signal detection have been discussed elsewhere [4]. The SDRs identified by these methods help prioritize ADRs that require a more exhaustive signal assessment, usually involving a clinical evaluation of individual cases reported, a search of the literature and an assessment of the pharmacological plausibility of a causal association.

An important limitation of spontaneous reporting schemes is the general under-reporting of ADRs by healthcare professionals (HCPs) [5]. Inclusion of patients or the public in the range of people supplying reports is likely to increase the number of reports. Concerns have been expressed, however, that patient reporting may increase problems of selective reporting (where the number of reports may be influenced by media coverage of problems with controversial or commonly used drugs). In addition, patient reports might flood the system with information about trivial or well-known ADRs, thereby compromising the ability to detect important safety issues [6]. The value of the system may also be undermined by the variable quality of the reports received from patients or the public. Despite these concerns, studies have suggested that patients may make a positive contribution, by reporting ADRs that are serious [7] or different to those reported by HCPs [8], or by reporting ADRs more quickly than HCPs [9].

Direct patient (or 'consumer') reporting of ADRs to regulatory authorities has been possible in the US and several European countries for a number of years [10]. This will soon extend to other countries in light of recent legislative changes in pharmacovigilance in the EU [11]. In the UK, patient reporting is a relatively recent initiative, commenced in 2005 and followed by an official launch and publicity campaign in community pharmacies in 2008.

The study presented here, funded by the National Institute for Health Research, was undertaken to evaluate the early experience of patient reporting in the UK. We have already published a comparison of patient characteristics, suspected drugs and suspected ADRs reported by patients and HCPs [12]. Here, we investigate the potential contribution that patient reporting may make to signal detection. Our objective was to investigate, quantitatively, the relative contribution of patient reporting to the identification of SDRs, firstly by comparing the pharmacovigilance importance of SDRs identified separately by patient and HCP reports, and secondly by exploring the effect of combining patient and HCP reports on the identification of SDRs.

2 Methods

2.1 Data Synthesis

Data were received from the MHRA for patient and HCP reports submitted to the YCS between October 2005 and September 2007. Reports from the pharmaceutical industry were not supplied. Three datasets were compiled: one consisting of all drug–ADR pairs present in the patient reports ('patient dataset'), one consisting of all drug–ADR pairs present in the HCP reports ('HCP dataset') and one consisting of all drug–ADR pairs in reports from both sources ('combined dataset'). A drug–ADR pair, for example, 'simvastatin and myalgia,' consisted of the suspected drug named in the report, coded at the lowest hierarchical level within the Anatomical Therapeutic Chemical (ATC) classification system for drug substances [13], and the appropriate ADR term, coded at the Preferred Term (PT) level within the hierarchical Medical Dictionary for Regulatory Activities (MedDRA®) [14]. MedDRA® terminology is the medical terminology developed under the auspices of the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH).

SDRs were generated using the proportional reporting ratio (PRR) method [15–17], computed within a Microsoft SQL Server (2000) database (Microsoft Corporation, Redmond, WA, USA).Within each of the three datasets, a PRR was calculated for each drug–ADR pair. On the basis of previously published arbitrary thresholds, an SDR was identified for a drug–ADR pair if the PRR was ≥2, the number of reports for the drug–ADR pair was ≥3 and the lower 95 % confidence interval (CI) for the PRR was ≥1 [15, 16].

2.2 Statistical Analysis

2.2.1 *Comparison of Signals of Disproportionate Reporting Identified in the Patient and Healthcare Professional (HCP) Datasets*

From the patient and HCP datasets we compared the proportion of drug–ADR pairs identified as SDRs, the proportion of SDRs involving ADRs that were recorded by the MHRA as 'serious' (based on MedDRA® PTs deemed by medical staff within the MHRA to indicate a serious issue) and the proportion of SDRs that involved a recently marketed medicine undergoing intensive surveillance by the MHRA (known as 'black triangle' drugs in the UK).

In addition, a random sample of 300 SDRs from each dataset was selected to determine the proportion of SDRs involving ADRs not previously documented on the product's Summary of Product Characteristics (SPC). This sample size was sufficient to test the hypothesis that this proportion might be 10 % higher in the SDRs identified by HCP reports than in patient reports (30 % compared with 20 %), at the 5 % significance level with 80 % power. In practice, the SPC for a medicinal product changes over time and SDRs identified as individual reports come into the spontaneous reporting scheme. Our analysis, however, was based on a 'snapshot' of all reports made during a 2-year reporting period. It was not possible, therefore, to know for sure whether a particular ADR would have been documented on the SPC when an individual reaction was reported. Furthermore, the retrospective nature of our study meant that it was not always possible to identify when the SPC for a particular drug first documented a particular ADR. In order to provide an estimate of whether new information about SDRs was being revealed by each dataset, we used either the SPC version available at the beginning of the study period (2004) or the first available SPC for drugs launched on the UK market during the 2-year study period, rather than estimate which version was available when the reaction was reported.

Univariate comparisons were performed between the two datasets by calculating the difference in proportions along with 95 % CIs, calculated by normal approximation, and associated *p*-values.

2.2.2 *Sensitivity Analysis to Assess the Effect of Combining Data from Patient and HCP Reports*

The number of SDRs identified in the separate patient and HCP datasets was compared with that identified within the 'combined' dataset, to identify the number of SDRs that no longer met the SDR criteria (i.e. were 'diluted out'), after combining reports from both sources and the number of additional SDRs identified ('gained') by the combination. We also assessed what proportion of SDRs lost and gained were potentially serious, involved newly marketed medicines and were not listed on the product's SPC.

3 Results

There were 5,180 (19.8 % of all) reports supplied by patients and 20,949 (80.2 %) by HCPs. Figure 1 shows the number of drug–ADR pairs in the patient and HCP datasets

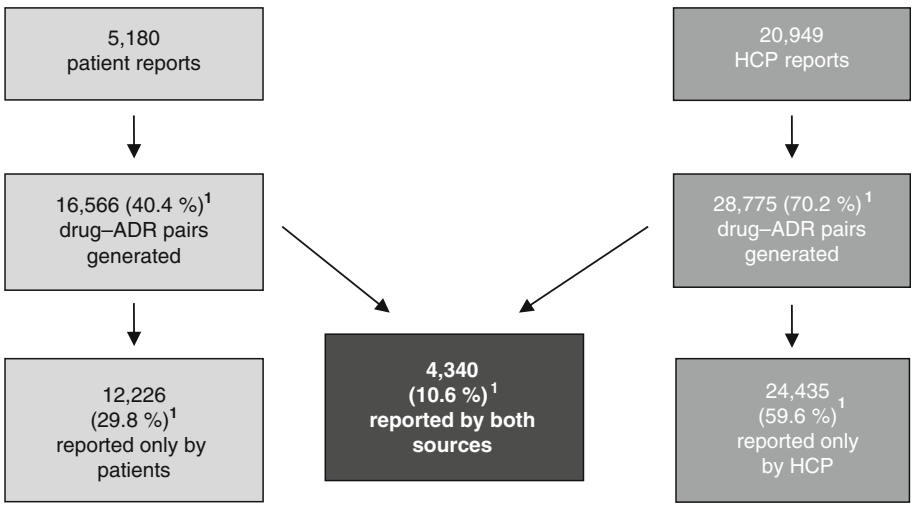

Fig. 1 Distribution of drug–adverse drug reaction (ADR) pairs by source of report. *HCP* healthcare professional

1 Percentage of all drug–ADR pairs reported, $n = 41{,}001$

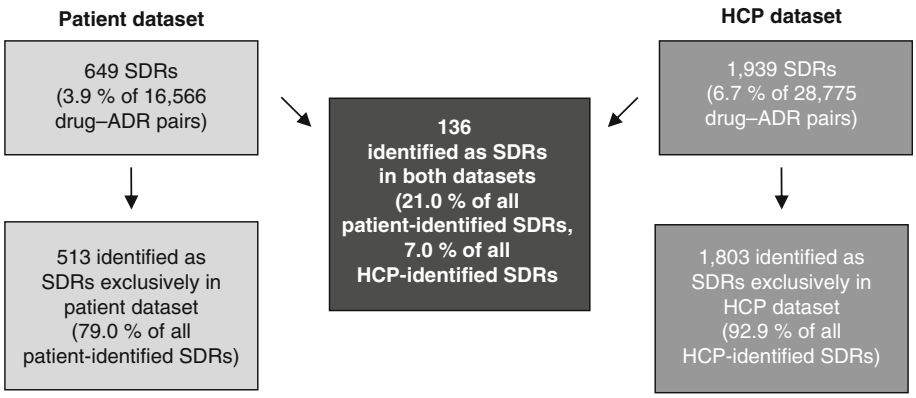

Fig. 2 Signals of disproportionate reporting (SDRs) identified by the patient and healthcare professional (HCP) datasets. *ADR* adverse drug reaction

and the proportion of these pairs derived exclusively from reports supplied by patients or HCPs, and those derived from reports from both sources. Patient reports produced 40.4 % of all of the drug–ADR pairs. Only 10.6 % of all drug–ADR pairs were reported by both sources.

Figure 2 shows the number of SDRs identified from drug–ADR pairs within the patient and HCP datasets. A significantly higher proportion of SDRs were identified from the drug–ADR pairs in the HCP dataset than in the patient dataset (6.7 % and 3.9 % of pairs, respectively; difference 2.8 %, 95 % CI 2.4–3.2). In total, 136 drug–ADRs pairs (21.0 % of those identified by the patient dataset and 7.0 % of those from the HCP dataset) were identified as SDRs in both datasets.

These results suggest that patient and HCP reports identify different SDRs. It is possible, however, that this is simply due to differences in the way in which reactions are described. Examination of the 649 SDRs identified by the patient dataset revealed that, in addition to the 136 SDRs also identified by the HCP dataset, a further 88 involved a similar or related reaction term to SDRs identified by the HCP dataset. For example, 'amlodipine and heart rate irregular' was identified as an SDR in the patient dataset while 'amlodipine and palpitations' was identified as an SDR from the HCP dataset. Nevertheless, 425 of the 649 (65.5 %) SDRs identified from the patient dataset were not identified from the HCP dataset.

Table 1 shows the characteristics of the drugs and reactions involved in the SDRs identified from the two sources. Compared with those identified from the patient dataset, a significantly higher proportion of the SDRs identified from the HCP dataset would have been deemed serious by the MHRA (difference in proportions 19.5 %, 95 % CI 15.4–23.6, $p < 0.05$) or involved a newly marketed drug (difference in proportions 19.8 %, 95 % CI 16.6–23.0, $p < 0.05$).

The majority of SDRs identified from reports from both sources involved ADRs that were either listed on the SPC for the suspect drug of interest or involved a similar clinical term (Table 2). There was no significant difference in the proportion of drug–ADR pairs assessed as not listed on the product's SPC (difference in proportions 2.0 %, 95 % CI −3.7 to 7.7, $p = 0.75$).

The distributions of SDRs across the different system organ classes are shown in Table 3. The SDRs identified from the patient dataset most commonly involved ADRs that were within the 'psychiatric disorders' system organ class ($n = 144$, 22.2 %), whereas those identified from the HCP dataset most commonly involved reactions within the 'general disorders and administration site conditions' system organ class ($n = 319$, 16.4 %). The drugs most commonly involved in SDRs identified from the patient dataset were those used for 'nervous system' conditions ($n = 253$, 39.0 %). This was also the case for the SDRs identified from the HCP dataset ($n = 482$, 24.9 %).

Table 4 shows the impact of combining data from both sources. Most of the SDRs identified from the patient or HCP datasets when examined separately were also identified as SDRs in the combined dataset. However, 92 (14.2 %) and 186 (9.6 %) of the SDRs identified in the patient and HCP datasets, respectively, were no longer identified as SDRs in the combined dataset. Three of these SDRs involved serious ADRs to newly marketed medicines that were not listed in the product's SPC.

Table 1 Signals of disproportionate reporting (SDRs) identified by patient and healthcare professional (HCP) datasets involving a reaction classified as serious by the MHRA or involving a newly marketed drug

SDRs identified in each dataset	Patient dataset	HCP dataset
Number of SDRs identified	649	1,939
Number deemed serious by the MHRA (% of SDRs identified)	185 (28.5)	931 (48.0)
Number involving a newly marketed drug (% of SDRs identified)	71 (10.9)	596 (30.7)

MHRA Medicines and Healthcare products Regulatory Agency

Table 2 Sample of signals of disproportionate reporting (SDRs) identified by patient and healthcare professional (HCP) datasets assessed as providing potentially new information

SDRs assessed by comparison with SPC	Patient dataset	HCP dataset
Number of SDRs assessed	300	300
Number (%)[a] of ADRs documented on SPC	164 (54.7)	132 (44.0)
Number (%)[a] of ADRs with similar clinical term documented	73 (24.3)	80 (26.7)
Number (%)[a] of ADRs not documented	48 (16.0)	42 (14.0)
Number(%)[a] of ADRs that were documented during or after the period of study	11 (3.7)	33 (11.0)
Number (%)[a] of SDRs that could not be classified, e.g. involved ADRs with non-specific terms such as 'feeling abnormal'	4 (1.3)	13 (4.3)

ADR adverse drug reaction; *SPC* Summary of Product Characteristics

[a] Percentage of all SDRs assessed in the sample for each reporter dataset: $n = 300$ for patient reports, $n = 300$ for HCP reports

The combination of data from patient and HCP reports identified an extra 508 SDRs that were not identified by analysis of the patient or HCP datasets alone (Table 5). A small proportion of these involved serious, unlisted reactions to either newly marketed or established drugs ($n = 47$, 9.3 %). This included SDRs that may have been confounded by prescribing indications for the suspect drug, for example, 'diazepam and muscle spasms,' 'chloramphenicol and eyelid oedema' and 'donepezil and confusional state.'

4 Discussion

ADR reports supplied by patients and HCPs appeared to contain quite different data in terms of the clinical events reported and suspect drugs involved, with only 10 % of all drug–ADR pairs being reported by both sources. The SDRs identified from patient and HCP reports were also quite different. Some of the difference may have arisen from the way reactions are described by the different reporter groups. For example, a patient may report having a 'seizure' whilst using 'metoclopramide' whereas an HCP may report the same event as 'oculogyric crisis.' Nevertheless, even when comparisons were made using exact, similar or related terms for a particular reaction, two-thirds of the SDRs identified from the patient dataset were not identified in the HCP dataset. It may be possible to overcome terminology issues by performing the analysis at different dictionary levels. Although this was not examined in detail in this study, we found only a small increase in the degree of overlap between drug–ADR pairs when coded at the Higher Level MedDRA® term (15 %) compared with that for PTs (10 %) [data not shown].

Table 3 The top five most frequent system organ classes involved in the signals of disproportionate reporting (SDRs) identified in each dataset

System organ class	SDRs [*n* (%)][a]
Patient dataset	
Psychiatric disorders	144 (22.2)
Nervous system disorders	95 (14.6)
Gastrointestinal disorders	94 (14.5)
Skin and subcutaneous tissue disorders	67 (10.3)
General disorders and administration site conditions	66 (10.2)
HCP dataset	
General disorders and administration site conditions	319 (16.4)
Gastrointestinal disorders	234 (12.1)
Nervous system disorders	228 (11.8)
Skin and subcutaneous tissue disorders	204 (10.5)
Psychiatric disorders	194 (10.0)

HCP healthcare professional

[a] Percentage of all SDRs generated in each reporter dataset: $n = 649$ for patient reports, $n = 1{,}939$ for HCP reports

In keeping with the findings of other studies [10, 18] on patient reporting, we found that the highest proportion of SDRs identified from patient reports were for psychiatric reactions or nervous system drugs. Many reasons for this can be speculated. For example, patients may place greater importance on such ADRs or they may not wish to discuss these problems directly with HCPs. On the other hand, HCPs may not acknowledge these problems as being ADRs and thus be less inclined to report such reactions.

A significantly higher proportion of the SDRs identified from HCP than patient reports were for ADRs deemed to be serious by the MHRA or involved newly marketed drugs. This is perhaps not unexpected since HCPs are encouraged to report these types of ADRs, whereas patients are not given explicit guidelines on what to report to the YCS. The majority of SDRs identified in our study were for non-serious reactions. In practice, these would not usually be prioritized by regulatory authorities for detailed assessment (unless they involved, for example, a child).

Table 4 Signals of disproportionate reporting (SDRs) identified before and after combination of data from patient and healthcare professional (HCP) reports, and those lost by the combination of data

SDRs identified in each dataset	Patient dataset	HCP dataset
SDRs identified before data combined (*n*)	649	1,939
SDRs remaining after data combined [*n* (% of SDRs identified in each dataset before combination)]	557 (85.8)	1,753 (90.4)
SDRs no longer present after data combined:		
Total 'lost' [*n* (% of SDRs generated before combination)]	92 (14.2)	186 (9.6)
Serious [*n* (% of lost SDRs)]	18 (19.6)	47 (25.3)
Involved newly marketed drug [*n* (% of lost SDRs)]	10 (10.9)	69 (37.1)
Not listed on SPC [*n* (% of lost SDRs)]	14 (15.2)	32 (17.2)
Serious, newly marketed and not listed on SPC [*n* (% of lost SDRs)]	0 (0.0)	3[a] (1.6)
Serious, established drug and not listed on SPC [*n* (% of lost SDRs)]	4[b] (4.3)	5[c] (2.7)

SPC Summary of Product Characteristics

[a] Levetiracetam/drug interaction, pregabalin/overdose and rimonabant/blood pressure increased

[b] Citalopram/aggression, doxazosin/muscular weakness, perindopril/hypertension and prednisolone/face swelling

[c] Anastrozole/depression, citalopram/hypoglycaemia, simvastatin/drug interaction, trimethoprim/chest discomfort and trazodone/myalgia

Even so, we have shown that patient reports can contribute to the identification of SDRs for serious ADRs, although perhaps, to a lesser extent than HCP reports.

Our assessment of a random sample of SDRs identified from the patient and HCP datasets showed that most of the reactions had been previously listed on the product's SPC (when using either exactly the same or similar clinical term). Nevertheless, both the patient and HCP reports identified SDRs for ADRs that were not previously recorded on the SPC. These findings suggest that patients may have an important contribution to make to signal detection of previously undocumented ADRs.

In practice, data from patient and HCP reports are combined by the MHRA for disproportionality analysis. Our study found that combining the data identified an additional 508 SDRs that would not have been detected by separate analysis of the patient and HCP datasets. On the other hand, approximately 278 of the SDRs identified in the separate datasets were 'diluted out' in the combined dataset. Although we explored the effect of adding patient reports to HCP reports, in terms of number of SDRs gained or lost, we were unable to examine in depth the relative importance of signals 'lost' or 'gained.' This would depend on a number of considerations, such as the level of use/exposure of the drug in the population, the type of population using the drug, the drug's indication and the degree to which patients may tolerate the reaction. A detailed impact analysis for each of the drug–ADR pairs in question would be required in practice but was beyond the scope of this project. Nonetheless, it would appear that there is more to be gained than lost by combining reports from patients and HCPs (provided that the additional new SDRs do not contain a lot of 'false positives,' which will overwhelm the system). It is important to note that pharmacovigilance centres will often use the traditional case-by-case approach to ensure that signals of rare, serious ADRs are not missed. For centres where quantitative methods have greater utility, further research is required to determine the optimal

Table 5 Additional signals of disproportionate reporting (SDRs) identified in the 'combined' dataset not identified in either the patient or healthcare professional (HCP) datasets

SDRs identified in combined dataset	SDRs in combined dataset
SDRs identified from the combined dataset (*n*)	2,682
Additional SDRs 'gained' from the combined dataset:	
Total gained [*n* (% of all)]	508 (18.9)
Deemed serious by MHRA [*n* (% of additional)]	185 (36.4)
Involved newly marketed drug (% of additional)]	95 (18.7)
Not listed on SPC [*n* (% of additional)]	137 (27.0)
Serious, newly marketed drug and not listed on SPC [*n* (% of additional)]	10 (2.0)
Serious, established drug and not listed on SPC [*n* (% of additional)]	37 (7.3)

MHRA Medicines and Healthcare products Regulatory Agency, *SPC* Summary of Product Characteristics

method for using patient reports in disproportionality analyses. Consideration should be given to performing such analysis on patient and HCP reports separately alongside an analysis of a combined database, to ensure that important new signals are not missed.

4.1 Strengths and Limitations

Although we were unable to perform the analysis on the entire YCS database, we were able to evaluate a 'snapshot' of data for 26,000 reports accumulated over a 2-year period, soon after the launch of patient reporting in the UK. Thus, our study is the first large study to investigate how patient reporting of suspected ADRs in the UK may contribute to the generation of important new information used by regulatory authorities to assess drug safety. Our results may be limited to the UK experience, but similar findings in support of patient reporting in the context of signal detection have been reported elsewhere. van Hunsel et al. [19] performed a case-control study in which the proportion of patient reports was found to be similar among reports that contributed to signals and those reports that did not. It is likely that new EU legislation will lead to wider adoption of patient reporting. Thus it will be important to continue to monitor the potential impact of this reporter group in larger databases.

In our study, patient reports comprised around a fifth of all reports, but the proportion of patient reports in the entire YCS database is much smaller since data have accumulated since 1964 and include reports from the pharmaceutical industry. Hence, the contribution of patient reports to signal detection is likely to be smaller than implied by our results. This contribution, however, should increase over time as patient reports begin to represent an increasing proportion of all data available for analysis.

In our study, we have used disproportionality analysis as the primary means of identifying SDRs. In practice, a number of criteria are used in conjunction with disproportionality analysis to prioritize reports that require more detailed evaluation, including specific patient characteristics, reaction seriousness or the time of marketing of the suspect drug. Our analysis was based only on the PRR method, but there are several statistical approaches to disproportionality analysis, with different thresholds for filtering potentially important ADRs. Because of the anonymization of the dataset, we did not assess the extent of duplication of reports and relied upon internal processes at the MHRA for de-duplication. It is possible that there remained some residual duplication, but we do not believe this would be at a level to compromise the analysis.

The SDRs identified in this study should be regarded only as 'potential' signals of ADRs. An exhaustive signal assessment for each SDR identified was beyond the scope of this study. Ideally, our results should be replicated by the MHRA and in other pharmacovigilance databases using source data. Further research may also be warranted to compare the SDRs identified by patients with those identified by different HCP groups, for example, doctors, pharmacists and nurses.

5 Conclusions

Although this study is limited to the UK experience, overall the results suggest that patient reporting may provide a positive complementary contribution to that of HCPs. Our findings indicate that spontaneous reports provided by patients and HCPs are quite different in terms of the ADRs and suspect drugs involved. As a consequence, patient reporting may make an important contribution to drug safety by identifying different SDRs not identified from HCP reports alone. The combination of reports from patients and HCPs, however, when used in disproportionality analysis, may result in the loss of some information. One possible strategy is to conduct such analysis using all reports from patients and HCPs combined as well as separately for each group.

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