SYSTEMATIC REVIEW

Drug Saf 2012; 35 (10): 807-818
0114-5916/12/0010-0807/$49.95/0

Patient versus Healthcare Professional Spontaneous Adverse Drug Reaction Reporting

A Systematic Review

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Abstract

Background: Increasing numbers of national pharmacovigilance schemes are accepting adverse drug reaction (ADR) reports from patients. The extent to which patient ADR reports contribute to pharmacovigilance requires comparisons to be made with reports from healthcare professionals (HCPs).

Objective: This systematic review was conducted to identify all comparative studies of patient and HCP ADR reports to national pharmacovigilance schemes.

Methods: We conducted a systematic review (which complied with the PRISMA statement) and a narrative synthesis of the results. Electronic databases (1996–2011) were searched, including MEDLINE, EMBASE and PHARM-Line, and supplementary searching of reference lists of included studies, authors' personal reference lists and internet searches was carried out. Studies that compared patient and HCP ADR reports submitted to national reporting schemes were considered for inclusion. Independent, duplicate data extraction, quality assessment and risk of bias were undertaken.

Results: Of the 949 hits generated, three comparative studies were identified and included in this review. These studies were conducted on the national pharmacovigilance schemes in the Netherlands, Denmark and the UK.

Considerable variation was observed across the national schemes in terms of the proportion of total ADR reports submitted by patients. Some of this variation may be explained by the duration that the schemes have been in operation. The number of serious ADR reports as a percentage of total reports was similar for patients compared with HCPs within each study, but varied across studies. Similarities were shown with the Netherlands and the UK in terms of drugs reported. Both studies featured statins and proton pump inhibitors in the top five drugs.

Clear differences were shown between patients and HCPs in the body systems affected by ADRs as well as the therapeutic categories reported in both the UK and Danish studies. There was considerable similarity when considering the nature of ADRs reported. The Dutch study also showed similarities between patients and physicians in terms of the types of drugs for which ADRs were reported.

Conclusions: Despite the large and increasing number of national pharmacovigilance schemes that accept ADR reports from patients, few comparative studies have been undertaken of patient and HCP reporting. Comparison across schemes is challenging because of differences in reporting processes, the inclusion criteria of schemes and different reporter types. The true value of patient ADR reports to pharmacovigilance will remain unknown unless more comparative evaluations are undertaken. This systematic review has highlighted both similarities and differences between reporter behaviour, the implications of which, in terms of signal generation, require further exploration.

1. Background

Spontaneous adverse drug reaction (ADR) reports remain one of the most prolific methods of pharmacovigilance worldwide. However, there is substantial underreporting of ADRs by healthcare professionals (HCPs)[1] who may also fail to recognize ADRs reported by patients.[2] There is growing interest in the involvement of patients as reporters to pharmacovigilance schemes. The potential benefits of patient-reporting include the promotion of patient rights and equity, acknowledging that patients have unique perspectives and experiences, and that healthcare organizations would benefit generally from patient involvement.[3] Patients may provide different information compared with HCPs, including suspected reactions to over-the-counter medicines and different presentations of reactions, as well as providing a broader picture of ADRs and their impact on the individual.[1] As such, adding patients to the range of potential reporters may increase overall spontaneous reporting and may assist earlier detection of important ADRs. To date, at least 46 countries accept patient ADR reports to their national spontaneous reporting schemes.[4] The systematic review reported here was originally conducted to inform the evaluation of the Yellow Card Scheme.[4] It was subsequently updated and conducted as a systematic review of comparative studies of patient and HCP reports to national spontaneous reporting schemes.

2. Method

This systematic review was conducted to comply with the PRISMA statement.[5] Studies that compared patient and HCP ADR reports submitted to national reporting schemes were considered for inclusion. No study design, language or publication status restrictions were imposed. Studies were excluded if they presented ADR reports: made to non-national spontaneous reporting systems; restricted to specific drugs or therapeutic classes; or restricted to specific patient groups, e.g. paediatric patients, cancer patients.

2.1 Data Sources and Search Strategy

Electronic search strategies were developed for MEDLINE (Ovid) and EMBASE (Ovid) databases (Appendix I; see Supplemental Digital Content [SDC], http://links.adisonline.com/DSZ/A74). The terms encompassed patient, adverse reaction reporting or monitoring, postmarketing, product surveillance and pharmacoepidemiology. These included Medical Subject Headings (MeSH) terms and keywords for each database. The search

period was January 1996 to May 2011, inclusive. The searches were last performed on 5 May 2011. The databases were searched and the abstracts were imported into RefWorks 2.0 (RefWorks, Cambridge, UK). Duplicate abstracts, i.e. exact match and close match, were identified and were manually deleted from the database. An additional search was conducted by the Royal Pharmaceutical Society librarian, on behalf of the authors, of the PHARM-Line database using specific keywords (Appendix II; see SDC). The PHARM-Line results were manually checked by one author (JI) and no additional abstracts of relevance were found. Four supplementary approaches were employed in addition to searching electronic databases. These included emailing pharmacovigilance contacts across 50 countries, searching reference lists of the included studies, use of the authors' personal reference lists and Internet searches using similar search terms to those used with the electronic database.

2.2 Study Selection

Duplicate independent screening was conducted by two authors (JI and MW), who both selected potentially relevant studies by screening titles and abstracts. This was followed by retrieval of full papers identified as being potentially relevant. The search results were reviewed independently by two authors (JI, MW) for relevant studies and consensus was agreed on the final selection of papers.

2.3 Data Extraction, Quality Assessment and Data Synthesis

Data were independently extracted and study quality independently assessed by two authors (JI, MW). Disagreements were resolved by consensus. A data extraction form was developed and independently piloted with one study and refinements were made before data extraction was performed. Assessment of risk of bias was conducted on the basis of selection bias, incomplete outcome data and selective reporting. These were assessed on a 4-point scale: low, medium, high and unclear. Duplicate assessment of risk of bias was performed (JI, MW) and consensus reached. Because of the heterogeneous nature of the data, meta-analysis of the data was not undertaken. The results are presented using a narrative approach and in the form recommended by the PRISMA statement.[5]

2.4 Ethical Approval

No ethical approval was required for this study.

3. Results

The combination of electronic searching of databases and hand searching generated a total of 949 hits (figure 1). Two publications were conference abstracts that described early evaluations of the UK Yellow Card Scheme,[6,7] which have been superseded by the recent evaluations of this scheme.[4,8] As such, only the full evaluations have been included in this review. Two publications presented comparative studies of data derived from the Danish[9] and Dutch[10] schemes. Additional publications were reports from the Canadian[11,12] and US[13] schemes presented as annual reports that did not include detailed methodological information.

3.1 National Spontaneous Adverse Drug Reaction (ADR) Schemes Represented in this Systematic Review

The five national schemes for which data were identified are presented in table I. Although the comparative studies of patient and HCP ADRs from three national schemes are the main focus of this review,[4,8-10] the characteristics of the five national schemes for which data were identified are described below.

ADR reporting was introduced in Canada in 1965 and patient ADR reports were accepted from this time.[12] In 2010, a total of 32 921 adverse reaction reports were submitted, but these were not limited solely to medicines.[11] Of these reports, 8733 (26.5%) were submitted by 'consumers' and 'patients', and 23 611 (71.7%) were submitted by HCPs. The number of domestic reports for ADRs in Canada has approximately trebled between 2001 and 2010, and was 19.7% higher in 2010 compared with the previous year.[11]

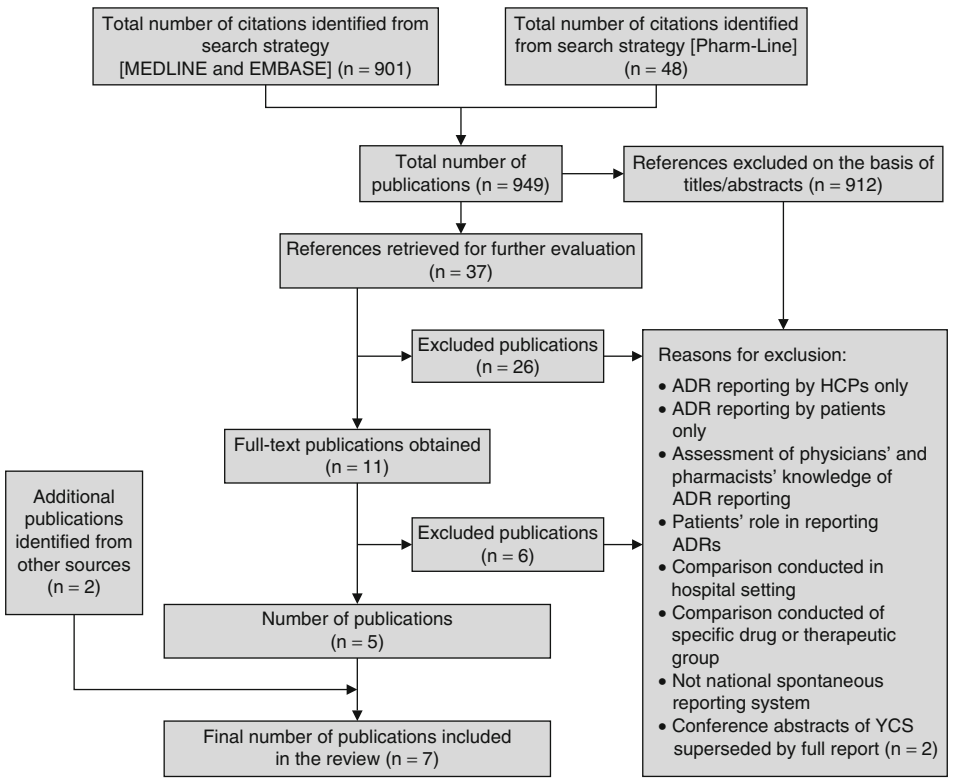

Fig. 1. PRISMA flowchart of literature searches and selection process. **ADR(s)** = adverse drug reaction(s); **HCPs** = healthcare professionals; **YCS** = Yellow Card Scheme.

In 1993, the MedWatch programme was introduced for patient and HCP reporting of ADRs in the US.[13] The proportion of total reports submitted by patients has increased since this time and of the 830 810 reports received from 'consumers' and HCPs in 2010, 48.6% were submitted by the former. Furthermore, between 2009 and 2010, the number of consumer reports increased by 47.9% compared with a 34.3% increase in HCP reports. No further information was presented to explain these considerable increases nor any other characteristics of the ADR reports submitted.

In Denmark, patient ADR reporting was introduced in 2003. The Danish Medicines Agency[15] is responsible for collecting all spontaneous reports, including all reports sent directly to pharmaceutical companies. Patient reports have risen steadily from 7% of the total number in 2003 to 30.6% (n = 1493) in 2009.[9,14] The Danish comparative study (table I) was based upon 544 patient reports (8.6% of total ADR reports) concerning 1700 ADRs, and 5775 HCP reports concerning 13 831 ADRs. The analyses of the data included only 'serious' (no definition given by authors) ADR reports, with 773 (9.6%) ADRs reported by patients and 7307 (90.4%) from HCPs.

In the Netherlands, the national pharmacovigilance scheme was founded in 1991 and is co-ordinated by Lareb[16] (the Netherlands Pharmacovigilance Centre). Patient reporting was introduced in 2004. In 2005, 819 (13%) of the 6305 ADR reports were received from patients, representing an 87% increase from the previous year.[10] The Dutch comparative study is based upon data received between 2004 and 2007, equating to 2522

Table I. Characteristics of comparative studies of patient and healthcare professional adverse drug reaction reports

	UK[4,8]	Denmark[9]	Netherlands[10]	Canada[11,12]	US[13]
Year of publication	2010	2009	2008	2011	2011
Period of study/data collection	2005–7	2004–6	2004–7	2010	2010
Year patient reporting introduced	2005	2003	2004	Unclear	1993
'Patient' description	Patients, patient representatives	'Consumers' (patients, patients' relatives, other members of the public)	Patients, representatives, acquaintances.	Patients, consumers	Consumers
HCP description	Doctor, pharmacist, nurse or other HCP	Physicians, pharmacists, other HCPs (e.g. nurses, drug manufacturers, social and healthcare assistants), lawyers	General practitioners, specialist doctors, pharmacists	Physicians, pharmacists, health professionals, nurses, coroners, lawyers, dentists, naturopaths	Physician, pharmacist, other healthcare provider
Method of report submission					
Patient	Online, telephone, paper/post	Online, email, fax, post[14]	Electronic only	Online, telephone, fax, post	Online, telephone, fax, post
HCP	Online, telephone, paper/post	Online, email, fax, post[14]	Paper, electronic	Online, telephone, fax, post	Online, telephone, fax, post
Unit of analysis	Reaction coded using MedDRA®	Comparison of demographics, ADRs: most frequently reported, seriousness and outcome of ADR	ADR, serious reports only – CIOMS, category of ADR by SOC	NA	NA
Inclusion criteria	All reports	Serious ADRs only	All reports	NA	NA
Exclusion criteria	Reports from the pharmaceutical industry	NA	NA	NA	NA
No. of reports [N (%)]					
Patient	5180 (19.8)	773 (9.6) [total ADRs, i.e. serious and non-serious = 1700]	2522 (19.2)	NA	NA
HCP	20 949 (80.2) [comprising 12 088 doctors, 3690 pharmacists, 2725 nurses, 2446 other]	7307 (90.4) [total ADRs, i.e. serious and non-serious = 13 831]	10 635 (80.8) [comprising 2553 GPs, 1992 specialist doctors, 5381 pharmacists, 709 other]	NA	NA
Reporter sex – female (%)					
Patient	62.7	NS	63		

Continued next page

Table I. Contd

	UK[4,8]	Denmark[9]	Netherlands[10]	Canada[11,12]	US[13]
HCP	57.0	NS	61		
Reporter age [years]					
Patient [median (IQR)]	54.0 (37.0, 66.0)	NA	Mean 48.0	NA	NA
HCP [median (IQR)]	53.0 (33.0, 68.0)	NA	Mean 49.0	NA	NA
Outcome of ADR					
Recovering [patient/HCP; %]	28.4/16.8	NA	NA	NA	NA
Not recovered/resolved [patient/HCP; %]	36.4/22.2	NA	NA	NA	NA
Time taken to report [days (IQR)]	104 (27, 463)/ 28 (13, 75)	NA	NA	NA	NA

ADR(s) = adverse drug reaction(s); **GPs** = general practitioners; **HCP** = healthcare professional; **IQR** = interquartile range; **MedDRA**® = Medical Dictionary for Regulatory Activities; **NA** = not applicable (refers to reports where comparisons were not made); **NS** = not stated (refers to comparative studies where comparisons/data were not reported); **SOC** = System Organ Class.

(19.2%) and 10 635 (80.8%) ADR reports, and 5401 and 16 722 ADRs, from patients and HCPs, respectively.

In the UK, patient ADR reporting to the Yellow Card Scheme was introduced by the Medicines and Healthcare products Regulatory Agency (MHRA) in 2005.[8] Patients were responsible for 19.8% of reports submitted between 2005 and 2007. Of the three studies included in this systematic review, this comparative study included the largest number of reports from HCPs (n = 20 949; 80.2%) and patients (n = 5180; 19.8%).

Across the three studies, patients consistently reported higher numbers of ADRs per report than HCPs. This difference was reported as significantly different for patients compared with HCPs in the UK study[8] [median (interquartile range) of 3 (2–5) vs 2 (1–3), respectively; $p < 0.001$]. The UK study also identified that patient reports were more likely to contain more than one suspect drug than HCP reports ($p < 0.001$).

3.2 General Findings

3.2.1 Reporter Characteristics

Females were the largest group of reporters amongst HCPs and patients in the UK and Dutch studies. The age range documented in two of these studies (UK[8] and the Netherlands[10]) was similar between patients and HCPs (table I), but tended to be older in the Dutch study.

3.2.2 Drugs and ADRs Reported

Two studies[8,10] provided information on the drugs included in the ADR reports. The UK study listed the 20 most common drugs reported by patients, whilst the Dutch study[10] provided details of the five most common drugs reported by patients and HCPs (table II). Similarities were shown with the Dutch and UK studies in terms of drugs reported. Both studies featured statins and proton pump inhibitors in the top five drugs.

The Danish evaluation[9] grouped drugs involved in ADRs by Anatomical Therapeutic Chemical classification and then compared the classification of patient reports with other sources (serious only) [table III]. The Danish evaluation also reported differences between patient and other types

Table II. Most frequently reported (as percentage of total reports) drugs and symptoms by reporter type

	Netherlands[10]	UK[4,8]a	UK[4,8]	Netherlands[10]			
	Patient (%)	Patient (%)	HCP (%)	HCP-combined (%)	HCP-GP (%)	HCP-specialist (%)	HCP-pharmacist (%)
Drug[b]/drug class							
Rank-1	Statins (8.2)	Simvastatin (5.2) [statin]	Varenicline (3.5)	NA	Statins (6.9)	Benzodiazepines (4.1)	Statins (6.0)
Rank-2	SRIs (4.7)	Paroxetine (3.7) [SRIs]	Pneumococcus, purified polysaccharides antigen conjugated (2.5)	NA	β-adrenoceptor antagonists [β-blockers] (5.0)	PPIs (4.0)	Benzodiazepines (4.7)
Rank-3	β-adrenoceptor antagonists [β-blockers] (3.6)	Atorvastatin (2.5) [statin]	Simvastatin (2.3) [statin]	NA	Anticoagulants (4.5)	Statins (3.3)	Anticoagulants (4.5)
Rank-4	Anticoagulants (3.5)	Diclofenac (2.4)	Rimonabant (2.1)	NA	PPIs (4.3)	Anticoagulants (3.1)	PPIs (4.3)
Rank-5	PPIs (3.4)	Amlodipine (2.2)	Etanercept (1.8)	NA	ACE inhibitors (3.5)	Glucocorticoids (2.2)	β-adrenoceptor antagonists [β-blockers] (3.1)
ADR (LLT) reaction [% (total no. of reports)]							
Myalgia/muscle pain	3.6 (193)	0.7 (145)	NA	1.9 (325)	NA	NA	NA
Tiredness/fatigue	3.2 (171)	1.1 (230)	NA	NA	NA	NA	NA
Headache	2.9 (159)	2.2 (440)	1.7 (758)	2.4 (404)	NA	NA	NA
Dizziness	2.7 (144)	1.6 (334)	0.9 (418)	2.0 (332)	NA	NA	NA
Nausea	2.3 (126)	2.2 (458)	2.2 (987)	1.8 (301)	NA	NA	NA
Depression	2.1 (111)	1.5 (300)	0.6 (273)	NA	NA	NA	NA
Weight increase	2.0 106)	NA	NA	NA	NA	NA	NA
Rash	1.9 (100)	0.9 (174)	1.3 (577)	2.4 (397)	NA	NA	NA
Arthralgia	1.8 (96)	NA	NA	NA	NA	NA	NA
Insomnia	1.5 (80)	NA	NA	NA	NA	NA	NA
Shortness of breath/dyspnoea	NA	NA	0.6 (256)	1.4 (226)	NA	NA	NA
Palpitations	NA	NA	0.5 (212)	1.4 (241)	NA	NA	NA
Itching/pruritus	NA	0.9 (178)	0.5 (220)	1.4 (233)	NA	NA	NA
Alopecia	NA	NA	NA	1.7 (287)	NA	NA	NA
Angioedema	NA	NA	NA	1.3 (216)	NA	NA	NA

a Percentages provided via personal communication from D. McLernon.

b Anatomical Therapeutic Chemical classification.

ADR = adverse drug reaction; **GP** = general practitioner; **HCP** = healthcare professional; **LLT** = lowest-level term; **NA** = not applicable/not reported; **PPIs** = proton pump inhibitors; **SRIs** = serotonin reuptake inhibitors.

of reporter regarding the types of medicines for which ADR reports were submitted.[9] Patients were more likely than HCPs to submit reports for medicines affecting some systems, but less likely to report others compared with HCPs. In addition, patients reported nine ADRs that had not been reported by other reporters, including dysgraphia, parosmia (a distortion of the sense of smell), and thromboembolic stroke, all of which are regarded as serious.

The UK evaluation[8] reported age and sex adjusted odds ratios between patient and HCP reports by System Organ Class, most of which were statistically significant except for vascular disorders, infections and infestations, and injury, poisoning and procedural complications (table III). When making comparisons between the Danish[9] and UK[8] evaluations in terms of system order class between patients and other sources, both evaluations found that patients were significantly more likely to report psychiatric disorders, nervous system disorders and infections and infestations (table III). However, this comparison should be treated with caution as the UK study included all ADR reports, whilst the Danish evaluation[9] reported only 'serious' reactions.

3.2.3 ADR Symptoms

The symptoms associated with ADRs were reported in the Dutch[10] and UK[8] evaluations (table II). Both listed the top 20 symptoms presented by patients and HCPs. Four symptoms (nausea, headache, rash and dizziness) were reported in both studies by patients and HCPs. A further six symptoms (dyspnoea, palpitations, myalgia, depression, itching and fatigue) were documented to varying degrees by HCPs and patients across both studies.

3.2.4 Seriousness of ADRs

In terms of seriousness of ADRs (table IV), the Danish evaluation revealed highly significant differences between reporter type (patient, physician, pharmacists, lawyers, other HCPs) and the total number of serious ADRs that were reported ($p < 0.0001$).[9] However, no difference was shown between patient and HCP reports in terms of over-

Table III. Odds ratios for adverse drug reaction by System Organ Class for patients compared with healthcare professionals

System Organ Class reaction	UK[8] [OR (99% CI)][a]	Denmark[9][b] [OR (95% CI)][c]
Psychiatric disorders	3.22 (2.89, 3.57)	1.70 (1.31, 2.20)
Nervous system disorders	2.72 (2.47, 2.99)	1.27 (1.05, 1.53)
Eye disorders	2.25 (1.89, 2.67)	1.41 (0.90, 2.20)
Musculoskeletal and connective tissue disorders	2.22 (1.97, 2.50)	0.89 (0.63, 1.27)
General disorders and administration site conditions	2.20 (2.00, 2.42)	1.10 (0.88, 1.37)
Metabolism and nutrition disorders	2.05 (1.70, 2.47)	0.68 (0.40, 1.16)
Gastrointestinal disorders	1.95 (1.76, 2.15)	1.24 (0.99, 1.56)
Respiratory, thoracic and mediastinal disorders	1.58 (1.37, 1.81)	0.81 (0.58, 1.13)
Investigations	1.43 (1.24, 1.64)	0.71 (0.50, 0.99)
Renal and urinary disorders	1.41 (1.13, 1.77)	0.91 (0.50, 1.65)
Injury, poisoning and procedural complications	1.29 (1.00, 1.68)	1.19 (0.76, 1.88)
Skin and subcutaneous tissue disorders	1.13 (1.02, 1.25)	0.75 (0.56, 1.01)
Vascular disorders	1.00 (0.80, 1.23)	0.64 (0.37, 1.10)
Infections and infestations	0.96 (0.75, 1.22)	0.45 (0.23, 0.87)
Cardiac disorders	0.76 (0.61, 0.95)	1.17 (0.83, 1.67)

a Adjusted for reporter age and sex.

b Only 'serious' ADRs were analysed.

c Unadjusted OR. The OR reference category is HCP.

ADRs = adverse drug reactions; **HCP** = healthcare professional; **OR** = odds ratio.

Table IV. Level of seriousness of adverse drug reaction

Level of seriousness	Patient (%)			HCP (%)		
	UK[8]	Netherlands[10]	Denmark[9]	UK[8]	Netherlands[10]	Denmark[9]
Life-threatening	6.2	5.2	NA	11.1	2.7	NA
Death	0.7	0.6	NA	2.6	1.5	NA
Hospitalization	12.9	9.8	NA	18.8	12.0	NA
'Serious' reports as percentage of all reports	58.3[a]	19.5[b]	46[c]	58.8	21	52.8

a Serious defined as "dictionary serious" by the MHRA.

b Serious defined by CIOMS (deaths, life-threatening factors, hospitalization or prolongation of hospitalization, disability/birth defect) and "other ADRs considered serious by the reporter".

c Only 'serious' reports presented but 'serious' not defined. Significant difference between patients and HCPs ($p < 0.0001$) [Denmark only].

ADRs = adverse drug reactions; **HCP** = healthcare professional; **MHRA** = Medicines and Healthcare products Regulatory Agency; **NA** = not applicable/not reported.

all seriousness in the Dutch evaluation.[10] Differences were reported between reporter type and different categories of seriousness, i.e. patients reported significantly more disability than HCPs (2.3% and 0.4%, respectively), and more life-threatening reactions (5.2% and 2.7%, respectively). These results were in contrast to those of the UK evaluation,[8] which found that, compared with patients, higher proportions of reports from HCPs described ADRs that caused hospitalization, life-threatening symptoms and death. Over half of the ADRs reported by HCPs in the UK evaluation were classed as serious. The comparison of Danish and UK data regarding the outcome of ADRs shows that whilst considerable differences occurred between HCP groups, patients in the UK and Denmark were more similar (table IV).

3.3 Quality Assessment

3.3.1 Risk of Bias

The three comparative studies had low risk of selection bias and incomplete outcome data. In terms of the risk of selective reporting, insufficient data were available for the Danish study, whilst the UK and Dutch evaluations were both assessed as having a low risk of bias.

3.3.2 Duplicate Reporting

In the Dutch evaluation, duplicate checks between the patient and HCP submitting a report for the same ADR was assessed by checking sex and date of birth, then the reports combined. In the UK study, duplicate reports were merged when identified. Additionally, the UK evaluation explored the extent to which duplicate reporting occurred between both types of reporter. Of the 5180 patient reports assessed, seven (0.1%) were identified as being possible duplicates of HCP reports. In addition, the MHRA systematically checks reports for duplication from different reporters. Where duplicate reports are suspected, the data are combined into one report for the 'primary reporter'. Furthermore, regarding the validity of patient reports that resulted in death, it was assumed that these were submitted by the patient's relatives or friends.

4. Discussion

This is the first systematic review to present comparative studies of patient and HCP ADR reports to national pharmacovigilance schemes. Despite the growing number of countries with patient ADR reporting, the number of identifiable comparative studies was disappointing. More detail could be provided with annual publications from national pharmacovigilance schemes, such as those from the US and Canada, to enable further comparisons to be made.

Considerable variation was observed across the national schemes in terms of the proportion of total ADR reports submitted by patients (table I). Some of this variation may be explained by the duration that the schemes have been in operation. If patient reporting is to become a

recognized component of national (and international) pharmacovigilance, more detailed exploration of patient engagement with existing schemes should be undertaken to identify which factors result in the higher reporting rates observed in the UK and the US. In addition, future initiatives to promote spontaneous reporting should address the variations shown in this review, i.e. higher reporting by female reporters (patients and HCPs)[4,8,9] and lower reporting behaviour by reporter type, e.g. pharmacists.[10]

4.1 Strengths and Limitations

Despite extensive searching and in the knowledge that at least 46 countries accept ADR reports from patients as well as HCPs, only three comparative studies were identified that fulfilled the inclusion criteria for this review. It was not possible to undertake like-for-like comparisons across the three included studies because of variations in the systems, reporting processes and analyses presented. The Danish evaluation[9] combined reports from lawyers with HCPs and this may have introduced bias as these reports could have been submitted due to differences in motivation. This analysis was also based upon data derived from a database with no validation of data extraction from actual ADR reports. The analysis was also limited to ADRs classified as 'serious' only. The Danish scheme[9] handled patient reports in the same way as HCP reports; 'patient status' was retained even if they were confirmed by a physician thereafter.

Although the authors of the Dutch evaluation[10] mentioned that patients reported specific reactions, e.g. libido, no supporting data were presented for this statement. No data were provided regarding the completeness of reporting and the number of ADR reports from patients who had contacted HCPs. HCP reports (unlike patient reports) were marked in the ADR system as medically confirmed, which could have led to disparities in assessing levels of seriousness and outcomes of ADR as patients may have interpreted symptoms differently from HCPs. The Dutch evaluation[10] did not present complete data in terms of numerators and the denominator varied (i.e. reports and ADRs), thus making comparisons and percentage calculations difficult.

When considering the UK scheme,[8] different versions of reporting forms were used by HCPs and patients. Concomitant drugs were requested with both forms but space was provided for one drug on the patient form compared with five on the HCP form. This could have introduced ascertainment bias. Different methods were used to categorize 'serious' for patients and HCPs. There was considerable missing data for age in patient reports compared with HCP reports (23.7% vs 6.5%, respectively) and missing data for reporting method (22.7% in patient reports vs 29.3% in HCP reports).

4.2 Reporting of Serious ADRs

The number of serious ADR reports as a percentage of total reports was similar for patients compared with HCPs within each evaluation but varied across evaluations. The comparison of national data from Denmark demonstrated that physicians and patients reported similar proportions of serious ADRs,[9] although almost all reports submitted by pharmacists were categorized as serious. As a result of the sole focus on serious ADRs, the data did not reflect the full range of ADRs reported by patients (and HCPs). The inclusion of non-serious ADRs would have enabled the extent of patient reporting for these types of ADRs to be assessed, as well as their impact on overall reporting rates and signal generation. In the Netherlands, whilst no difference was shown between HCPs and patients in terms of overall seriousness of reports, patients reported higher proportions of ADRs for specific categories, e.g. disability and life-threatening events.[10]

4.3 ADRs Affecting Specific Systems and Therapeutic Categories

Clear differences were shown between patients and HCPs in the body systems affected by ADRs as well as the therapeutic categories reported in both the UK and Danish studies[8,9] (table III). There was considerable similarity when considering symptoms of ADRs reported. The Dutch

study also showed similarities between patients and physicians in terms of the types of drugs for which ADRs were reported.[10]

4.4 The Value of Spontaneous ADR Reports from Patients

Spontaneous ADR reporting by HCPs is a valuable pharmacovigilance tool[1,17] and has contributed to the identification of major safety issues.[18] There is general acknowledgement that patient ADR reporting is the *right* thing to do and that it will enhance pharmacovigilance,[3,19,20] yet there remains a lack of clarity regarding the specific value of ADR reports from patients. Comparisons of patient and HCP reports have demonstrated important differences in terms of serious ADRs, identification of new ADRs, and the medicines and affected body systems included in reports. The interpretation of these differences and their implications for signal generation require further exploration and discussion. Only the UK study included an evaluation of the effect of patient reporting on signal generation, which demonstrated that when combined with HCP ADR reports, patient reports generated 47 new signals for serious reactions.[4] Future comparative studies should attempt to quantify the impact of patient ADR reports in signal generation. Further recommendations regarding reporting criteria of future comparative studies are presented in Appendix III (see SDC).

4.5 Harmonization Across Reporting Schemes

There is considerable variation amongst the processes used by national spontaneous reporting schemes that include patient reports. Whilst the US uses the same data collection form for patients and HCPs, the UK has two different versions, one for each type of reporter, with different categories of 'seriousness' in each. The importance of well-designed report forms has been emphasized previously[3]. Some systems accept reports solely for ADRs, whilst others include medicine- and product-related problems, including errors, e.g. Health Canada. To maximize the value derived from patient reports, national patient and HCP schemes should at least be compatible with one another, and ideally with other national schemes. It is timely for nations with existing patient reporting schemes to engage in a harmonization process regarding data collection, analysis and dissemination that would inform the future of patient reporting. Whilst the need for harmonization in Europe has at least been recognized,[21] a wider international approach should also be considered. There is also a need to promote pharmacovigilance in poor or developing countries,[22] preferably with patient reporting, which will require appropriate funding, training and public awareness for it to be successful.

5. Conclusions

Despite the large and increasing number of national pharmacovigilance schemes that accept ADR reports from patients, few comparative studies have been undertaken of patient and HCP ADR reports. The current evidence presented in this systematic review has identified both differences and similarities between reporter types. Comparison across schemes is challenging due to differences in reporting processes, the inclusion criteria of schemes and different reporter types. The true value of patient ADR reports to pharmacovigilance will remain unknown unless more comparative evaluations are undertaken. As the number of national pharmacovigilance schemes that accept patient ADR reports increases, the expectation is that more comparisons will be undertaken, particularly of the effect of patient reports on signal generation.

Acknowledgements

The authors would like to thank the Yellow Card Study Collaboration, which includes A.J. Avery, C. Anderson, C.M. Bond, H. Fortnum, A. Gifford, P.C. Hannaford, L. Hazell, J. Krska, A.J. Lee, D.J. McLernon, E. Murphy, T. Payne and S. Shakir. We also thank the Royal Pharmaceutical Society librarian for performing the search of the PHARM-Line database on our behalf.

The original literature review was conducted as part of a project funded by the National Institute for Health Research Health Technology Assessment (NIHR HTA) programme (project number 06/92/03) and was published in full in Health Technology Assessment Vol. 15, No. 20 (www.hta.ac.uk/1628). However, the systematic review reported here was conducted following this programme and was unfunded. All researchers were independent from the funder. The views and opinions expressed therein are those of the authors and do not

necessarily reflect those of the HTA programme, NIHR, NHS or the Department of Health. The original study sponsor did not participate in the study design; collection, analysis or interpretation of data; writing the report; or the decision to submit the paper for publication.

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