ORIGINAL RESEARCH ARTICLE

Drug Saf 2010; 33 (9): 775-788
0114-5916/10/0009-0775/$49.95/0



# Adverse Drug Reaction Reporting in the UK

## A Retrospective Observational Comparison of Yellow Card Reports Submitted by Patients and Healthcare Professionals

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## Abstract

**Background:** In the UK, spontaneous reporting of suspected adverse drug reactions (ADRs) by healthcare professionals has been in operation since 1964 through the Yellow Card Scheme (YCS). From 2005, patients themselves have been able to submit Yellow Card reports.

**Objective:** To compare patient characteristics, suspected drugs and suspected ADRs reported by patients with those reported by healthcare professionals using the YCS.

**Design and Setting:** Retrospective observational study in the UK.

**Methods:** Participants were patients reported to the Medicines and Healthcare products Regulatory Agency (MHRA), either by themselves, a representative or a healthcare professional, as having one or more suspected ADRs between October 2005 and September 2007. The main outcome measures were ADRs and time taken to report.

**Results:** In total, 26 129 Yellow Card reports from patients and healthcare professionals were received from the MHRA for the 2-year study period (19.8% patient and 80.2% healthcare professional). More Yellow Card reports were made for female than male patients ($p < 0.001$). Patients reported a significantly higher number of suspected ADRs per report than healthcare professionals (median [interquartile range {IQR}] of 3 [2–5] vs 2 [1–3], respectively; $p < 0.001$). A higher proportion of patient reports (16.1%) contained more than one suspect drug than healthcare professional reports (9%; $p < 0.001$). Healthcare professional reports had a higher proportion of ADRs that caused hospitalization (18.8% vs 12.9%), were life threatening (11.1% vs 6.2%) or caused death (2.6% vs 0.7%) than patient reports (all $p < 0.001$). Patient reporters took a significantly longer time to report their reaction than healthcare professionals (median [IQR] of 104 [27–463] vs 28 [13–75] days respectively; $p < 0.001$). Direct comparisons of the seriousness of the ADRs

were not possible because of important differences between patient and healthcare professional versions of the Yellow Cards.

**Conclusions:** This is the first substantial, published study in the UK to compare Yellow Card reports from patients and healthcare professionals. Whilst patients report more suspected ADRs to more suspect drugs than healthcare professionals, healthcare professionals tend to report more serious reactions that result in hospitalization, are life threatening or cause death. Further research is required to investigate the extent to which the extra information from patient reporters contributes to signal identification when assessing drug safety.

## Background

Pharmacovigilance is vital to patient safety as rare, serious and/or unexpected adverse drug reactions (ADRs) often appear only when drugs are used in everyday practice by many people. Spontaneous reporting of ADRs is one method used in pharmacovigilance, and in the UK this is facilitated through the Yellow Card Scheme (YCS), which was established in 1964 as a consequence of the thalidomide disaster.[1]

Patient reporting of ADRs has been an important topic of debate in recent years.[2-4] Perceived benefits of patient ADR reporting include the promotion of patient rights; acknowledgment that patients may have different perspectives and experiences than healthcare professionals; and benefits to healthcare organizations from patient involvement.[5] It is recognized that there is substantial under-reporting of ADRs by healthcare professionals, thus adding patients to the range of potential reporters may increase spontaneous reporting and earlier detection of important ADRs.[6-8] It has been suggested that patient reporting avoids the filtering effect of reporting by a healthcare professional.[8] On the other hand, concerns about patient reporting include possible difficulties among patients with differentiating between suspected ADRs and known problems associated with the underlying condition being treated by the suspected drug; an inability to accurately describe the ADR; and the costs of processing extra ADRs for perhaps little benefit.

Whilst patient reporting of ADRs is available in an increasing number of countries, e.g. the Netherlands, Sweden,[9] Denmark[10] and the US,[11] few comparisons have been made between patient and healthcare professional ADR reports. The Netherlands Pharmacovigilance Centre, Lareb, compared 3 years of patient ADR reports with those from healthcare professionals.[12] They found differences in the seriousness of ADRs (significantly more life-threatening ADRs and disability reported by patients) and their outcome (significantly more outcomes mentioned by patients) between these two groups. However, similarities also occurred with the relative frequency of reported reactions and drugs suspected of causing the event. In the UK in 2006, the Medicines and Healthcare products Regulatory Agency (MHRA) presented a conference abstract of a basic evaluation of patient and healthcare professional reports received during the first 6 months of patient reporting.[13] Patients appeared to report more suspected ADRs to established drugs than healthcare professionals, who in turn submitted more reports about vaccines and new drugs. There was no significant difference between the two groups in the numbers that reported ADRs already labelled in the product information. The MHRA concluded that patient reports may be of similar quality to those from healthcare professionals, and that the former may enhance the YCS by providing information on a different range of suspected ADRs.[13]

This paper compares, using routine data collected over a 2-year period, patient characteristics, suspected drugs and suspected ADRs reported by patients with those reported by healthcare professionals using the YCS.

## Methods

### Setting

Yellow Card reports are submitted to the MHRA by post, telephone or via the Internet.[14,15] The MHRA electronically records and reviews all information submitted so that major safety issues can be detected through signal identification.[16] Prior to 2005, only healthcare professionals and the pharmaceutical industry were able to submit Yellow Card reports. In January 2005, following an independent review of access to the YCS,[1] a pilot scheme was launched that allowed the general public (hereafter referred to as patient reporters) to report ADRs directly to the MHRA.[17] In October 2005, patient reporting was rolled out nationally through the YCS.[15,18] Patient-specific Yellow Card reports are made either by the patient who has, or is experiencing, the suspected ADR or a patient representative (e.g. parent or carer). They can be for prescribed and non-prescribed medicines. Patients can make a Yellow Card report online,[19] by telephone or via a Yellow Card form available from pharmacies. The MHRA website contains detailed information on patient reporting procedures.[20]

### Patient and Healthcare Professional Yellow Cards

Different versions of the Yellow Card reporting form exist for patient and healthcare professional reporters. Whilst many similarities exist, there are several important differences between forms. Both versions ask for personal information about the person experiencing the suspected ADR, including their age, sex and weight; details of the suspect drug, including its name, dosage, indication, start and end date of taking; and a description of the reaction. Although details of other concomitant drugs used are requested on both versions, there is only space for one other drug on the patient form, compared with five on the healthcare professional form. Other important differences between the two versions of

| | Patient yellow card | Healthcare professional yellow card |
|---|---|---|
| Current status of patient | Reporter asked 'How is the person feeling now?' and selects one of:<br>1. Recovered completely<br>2. Recovered but with some lasting effects<br>3. Getting better<br>4. Still has reaction<br>5. Other (there is space to give details) | Reporter selects outcome of the reaction:<br>1. Has recovered<br>2. Has recovered (but free-text indicates sequelae)<br>3. Is recovering<br>4. Is continuing<br>5. Other |
| | Please note that the MHRA recategorized these five options in the dataset to make them comparable across reporter types. They were recoded as:<br>1. Recovered/resolved<br>2. Recovered/resolved with sequelae<br>3. Recovering/resolving<br>4. Not recovered/not resolved<br>5. Free-text field | |
| Is the reaction serious? | Not asked | Reporter asked 'Do you consider the reactions to be serious?', and selects: yes or no |
| How serious is the reaction? | Reporter asked 'How bad was the suspected side effect?' and selects one of: mild or slightly uncomfortable; uncomfortable, a nuisance or irritation, but able to carry on with everyday activities; bad enough to affect everyday activities; bad enough to be admitted to hospital; life-threatening; or caused death | After answering yes to the question above, the reporter is asked to indicate why the reaction is considered serious, with the option of ticking any number of six boxes: life-threatening, hospitalized, caused death, congenital abnormality, involved persistent or significant disability or incapacity, and medically significant (with a request to give details as to why they felt that this was so) |
| Height of patient | Asked for | Not asked for |

**Fig. 1.** Main differences between the patient and healthcare professional Yellow Card reports. **MHRA** = Medicines and Healthcare products Regulatory Agency.

Yellow Card forms are highlighted in figure 1. The outcome of the suspected reaction is ascertained differently on the two versions, which the MHRA recategorizes using other information on the report to enable consistency across both reporter types (figure 1).

The MHRA (Foy M, personal communication) explained that there may be patients who completed a healthcare professional version of the Yellow Card form or who had their reaction reported twice, e.g. firstly by themselves, followed by a healthcare professional. With the latter, extra information in the healthcare professional report was merged with the patient report on the MHRA database.

### Defining a Serious Reaction

Another important difference exists with the categorization of the seriousness of the ADR. As detailed in figure 1, unlike the healthcare professional version, the patient Yellow Card form does not ask directly whether the patient considers the reaction to be serious. Instead, the patient is asked to indicate how bad the suspected side effect was (mild or slightly uncomfortable; uncomfortable; a nuisance or irritation, but able to carry on with everyday activities; bad enough to affect everyday activities; bad enough to be admitted to hospital; life-threatening; or caused death). The MHRA code a response of 'bad enough to be admitted to hospital', 'life-threatening' or 'caused death' as 'reporter considered reaction serious' on its database.

### Data

A retrospective observational study was conducted to compare patient and healthcare professional reports to the YCS. The MHRA provided anonymized data for all Yellow Card reports held on their database that were received from patients and healthcare professionals between October 2005 and September 2007 (excluding reports from the pharmaceutical industry).

The data included information about the category of reporter (e.g. patient, patient representative, doctor, pharmacist, nurse, etc.), age and sex of person experiencing the suspected ADR, names of suspect drugs, date drug commenced, free-text description of the ADR, the reaction terms used by the MHRA to code the ADR at the 'lowest level term' and 'preferred term' levels within the Medical Dictionary for Regulatory Activities (MedDRA®),[21] and the date, seriousness (according to the reporter) and reported outcome of the suspected ADR. In addition, the MHRA allocate an in-house classification known as 'dictionary serious' to individual preferred terms within the MedDRA® dictionary following assessment by medically qualified staff within the MHRA.

### Data Management and Analysis

The data from the MHRA were imported into a Microsoft SQL Server (2000) database where they were subject to quality control procedures and coded. Any data anomalies or queries were resolved through communication with the MHRA. At the point of data entry the MHRA screen for duplicate reports. Therefore, full systematic searching for duplicate reports was not undertaken; however, any duplicate reports identified incidentally were either deleted, merged as one report, or retained as separate reports relating to two separate reaction experiences in the same patient after consultation with the MHRA. Further variables were created in the database, including the word count used to describe the suspected reaction and the number of suspect drugs reported per report. For ADRs reported by telephone, the word count used to describe the reaction is not an exact transcription of the telephone conversation. However, the MHRA scientist taking the call records the relevant case information stated by the patients and it is transcribed to the database in the first person. Suspect drugs were manually categorized into groups based on the Anatomical Therapeutic Chemical (ATC) classification system.[22] Complementary therapies (i.e. containing herbal and/or homeopathic ingredients) were identified and allocated to a separate category.

Descriptive statistics were calculated for Yellow Card reports from patients and healthcare professionals. Appropriate statistical tests compared the following variables across reporter type: age and sex of patients; reported seriousness of the suspected ADRs (as coded by the MHRA);

**Table I.** Characteristics of patients whose adverse drug reactions were reported through the Yellow Card System by reporter type[a]

| Characteristic | Patient report | | | Healthcare professional report | | |
|---|---|---|---|---|---|---|
| | male | female | all | male | female | all |
| Age (y) [median (IQR)] | 57.0 (40.0, 69.0) | 51.0 (35.0, 64.0) | 54.0 (37.0, 66.0) | 54.0 (32.0, 68.0) | 53.0 (34.0, 68.0) | 53.0 (33.0, 68.0) |
| Age missing [n (%)] | 402 (22.4) | 723 (22.3) | 1230 (23.7) | 506 (6.2) | 737 (6.2) | 1 371 (6.5) |
| Total [n (%)] | 1796 (34.7) | 3249 (62.7) | 5180 (100.0) | 8208 (39.2) | 11 935 (57.0) | 20 949 (100.0) |

a No sex was recorded for 3.9% of healthcare professional reports and 2.6% of patient reports.

**IQR** = interquartile range.

types and number of suspected ADRs using MedDRA® terms; word count used to describe the suspected reaction; number of suspect drugs per report and class of suspected drug using the ATC classification; time lag between suspected ADR and its reporting, and reported outcome of the suspected ADR. The time to report a suspected ADR for reactions occurring in the first and second year of the study period was also calculated by reaction outcome.

Continuous variables were compared using an independent t-test if they were normally distributed, otherwise the non-parametric Mann-Whitney U test was used. Associations between two categorical variables were examined using Pearson's chi-squared test. To minimize the chances of a type 1 error arising from multiple comparisons, a p-value of ≤0.01 was used to denote statistical significance throughout. Multiple logistic regression models were fitted to quantify the odds ratios (ORs) for reporting specific reactions (based on the system organ class of the MedDRA® classification system) between reporter type. The ORs were adjusted for the age and sex of the patient affected by the ADR. All statistical analyses were performed using SAS (v9) [SAS Institute, Cary, NC, USA].

## Results

### Characteristics of those Experiencing the Adverse Drug Reaction (ADR)

In total, 26 129 ADR Yellow Card reports were received from the MHRA for the 2-year study period. Of these, 5180 (19.8%) were patient reports and 20 949 (80.2%) were healthcare professional reports. Significantly more Yellow Card reports were made for female patients, whether reported by themselves or via healthcare professionals (both $p < 0.001$) [table I]. The median age of patients, as reported by either patients or healthcare professionals, was similar.

### Method of Reporting

There was a highly significant association between the method of reporting used and reporter type ($p < 0.001$). The most frequent method used to report an ADR was the paper Yellow Card form for both reporter groups (61.1% of patients and 62% of healthcare professionals). The Internet was the next most frequent method (13.6% vs 8.7%), followed by the telephone (2.7% vs 0.02%). The reporting method used was not documented for 22.7% of patient reports and 29.3% of healthcare professional reports.

### Reactions

Patients reported 20 358 ADRs in total whereas healthcare professionals reported 44 429 ADRs. Patients tended to report a significantly higher number of suspected ADRs per Yellow Card report than healthcare professionals (median [interquartile range {IQR}] of 3 [2–5] vs 2 [1–3], respectively) [table II].

The most frequent lowest level term reaction reported by patients was nausea (n = 458; 2.2% of all patient reactions reported), followed by headache (n = 440; 2.2%) and dizziness (n = 334; 1.6%) [table III]. Nausea (n = 987; 2.2%) and headache (n = 758; 1.7%) were also the two most frequently reported lowest level terms on the healthcare professional reports, followed by vomiting (n = 647; 1.5%).

Table IV presents the number of patient and healthcare professional reports that had at least

**Table II.** No. of reactions per report by reporter type

| No. of reactions | Patient reports | HCP reports | p-Value |
|---|---|---|---|
| Median (IQR) | 3 (2–5) | 2 (1–3) | <0.001[a] |
| 1 [n (%)] | 1120 (21.6) | 9475 (45.2) | <0.001[b] |
| 2 [n (%)] | 1041 (20.1) | 5405 (25.8) | |
| 3 [n (%)] | 812 (15.7) | 3070 (14.7) | |
| 4 or 5 [n (%)] | 1076 (20.8) | 2316 (11.1) | |
| >5 [n (%)] | 1131 (21.8) | 683 (3.3) | |
| Total [n (%)] | 5180 (19.8) | 20 949 (80.2) | |

a Mann-Whitney U test.

b Pearson's $\chi^2$ test = 2994.27; degrees of freedom = 4.

**HCP** = healthcare professional; **IQR** = interquartile range.

one of each type of reaction grouped according to the system organ classification of MedDRA®. More patient reports mentioned a nervous system problem (41.5%) than another organ system problem. The most common organ system affected in the healthcare professional reports was skin and subcutaneous tissue (23.2%). 'General disorders and administration site conditions' were the second most common problem in both patient and healthcare professional reports (39.8% and 23.1%, respectively).

All of the age- and sex-adjusted ORs between patient and healthcare professional reports by system organ class were statistically significant except for vascular disorders, infections and infestations, and injury, poisoning and procedural complications (table IV). In general, patients tended to report more ADRs in each system organ class, apart from cardiac disorders, where patients were significantly less likely to report a relevant ADR than a healthcare professional.

The median [IQR] word count used to describe the suspected reaction was significantly higher for patient reports (45.0 [22.0, 74.0]) than healthcare professional reports (15.0 [9.0, 26.0]; $p < 0.001$).

### Seriousness of Reaction

Over half (55.5%) of healthcare professional reporters considered their patient's reaction serious. Of the three subtypes of serious ADRs that were comparable between the two types of reporter, healthcare professionals reported a higher

**Table III.** The 20 most frequent lowest level term (LLT) reactions by reporter type

| Patient reported reactions (n = 20 358) | | Healthcare professional reported reactions (n = 44 429) | | |
|---|---|---|---|---|
| LLT | no. (% of reactions) | LLT | no. (% of reactions) | rank for patient reports |
| Nausea | 458 (2.2) | Nausea | 987 (2.2) | 1 |
| Headache | 440 (2.2) | Headache | 758 (1.7) | 2 |
| Dizziness | 334 (1.6) | Vomiting | 647 (1.5) | 6 |
| Depression | 300 (1.5) | Rash | 577 (1.3) | 10 |
| Diarrhoea | 280 (1.4) | Diarrhoea | 479 (1.1) | 5 |
| Vomiting | 242 (1.2) | Dizziness | 418 (0.9) | 3 |
| Tiredness | 230 (1.1) | Depression | 273 (0.6) | 4 |
| Anxiety | 196 (1.0) | Abdominal pain | 265 (0.6) | 44 |
| Itching | 178 (0.9) | Erythema | 262 (0.6) | 130 |
| Rash | 174 (0.9) | Shortness of breath | 256 (0.6) | 49 |
| Suicidal ideation | 156 (0.8) | Redness | 252 (0.6) | 108 |
| Appetite lost | 154 (0.8) | Chest pain | 249 (0.6) | 28 |
| Pain | 148 (0.7) | Pain | 222 (0.5) | 13 |
| Muscle pain | 145 (0.7) | Itching | 220 (0.5) | 9 |
| Joint pain | 133 (0.7) | Confusion | 214 (0.5) | 21 |
| Shaking | 133 (0.7) | Swelling | 213 (0.5) | 47 |
| Stomach pain | 131 (0.6) | Palpitations | 212 (0.5) | 22 |
| Constipation | 128 (0.6) | Anxiety | 211 (0.5) | 8 |
| Dry mouth | 127 (0.6) | Fever | 206 (0.5) | 55 |
| Sweating | 126 (0.6) | Sweating | 205 (0.5) | 20 |

**Table IV.** Comparison of the 15 most frequent System Organ Class reaction groups by reporter type as proportion of reporter type[a]

| Reaction | Patient reports [n (%)][b] | HCP reports [n (%)][b] | Patient vs HCP adjusted OR[c] (99% CI) |
|---|---|---|---|
| Nervous system disorders | 1626 (41.5) | 3912 (20.7) | 2.72 (2.47, 2.99) |
| General disorders and administration site conditions | 1561 (39.8) | 4371 (23.1) | 2.20 (2.00, 2.42) |
| Gastrointestinal disorders | 1266 (32.3) | 3722 (19.7) | 1.95 (1.76, 2.15) |
| Psychiatric disorders | 1213 (30.9) | 2312 (12.2) | 3.22 (2.89, 3.57) |
| Skin and subcutaneous tissue disorders | 997 (25.4) | 4391 (23.2) | 1.13 (1.02, 1.25) |
| Musculoskeletal and connective tissue disorders | 766 (19.5) | 1865 (9.9) | 2.22 (1.97, 2.50) |
| Respiratory, thoracic and mediastinal disorders | 498 (12.7) | 1598 (8.5) | 1.58 (1.37, 1.81) |
| Investigations | 488 (12.5) | 1713 (9.1) | 1.43 (1.24, 1.64) |
| Eye disorders | 353 (9.0) | 797 (4.2) | 2.25 (1.89, 2.67) |
| Metabolism and nutrition disorders | 284 (7.2) | 695 (3.7) | 2.05 (1.70, 2.47) |
| Vascular disorders | 182 (4.6) | 881 (4.7) | 1.00 (0.80, 1.23) |
| Renal and urinary disorders | 176 (4.5) | 609 (3.2) | 1.41 (1.13, 1.77) |
| Cardiac disorders | 163 (4.2) | 1025 (5.4) | 0.76 (0.61, 0.95) |
| Infections and infestations | 141 (3.6) | 711 (3.8) | 0.96 (0.75, 1.22) |
| Injury, poisoning and procedural complications | 128 (3.3) | 481 (2.5) | 1.29 (1.00, 1.68) |

a More than one reaction may be reported per report so they are not mutually exclusive.

b Numbers of patients and HCPs are lower due to those having missing values for sex and age, which were used to adjust ORs.

c ORs adjusted for age and sex of patient. The OR reference category is HCP.

**HCP** = healthcare professional; **ORs** = odds ratios.

proportion of each event than patient reports (caused hospitalization 18.8% vs 12.9%, life threatening 11.1% vs 6.2% and caused death 2.6% vs 0.7%; $p < 0.001$ for each). Similar percentages of both patient and healthcare professional reports contained at least one reaction term coded as 'dictionary serious' by the MHRA (patients 58.3% vs healthcare professionals 58.8%; $p = 0.58$).

Nearly half (44.8%) of the patient Yellow Card reports said that the suspected ADR was bad enough to affect everyday activities, whilst 15.4% said it was uncomfortable or a nuisance and 2.6% said it was mild or slightly uncomfortable.

Some patients appeared to have completed a healthcare professional version of the Yellow Card or had a follow-up report by their healthcare professional merged with theirs. Because of the structure of the database, these occurrences were difficult to quantify.

### Drugs

A higher proportion of patient reports (16.1%) contained more than one suspect drug than healthcare professional reports (9%; $p < 0.001$). The median (IQR) number of suspect drugs reported was 1 (1, 1) for both reporter types, although they were statistically different, with the healthcare professionals reporting fewer suspect drugs ($p < 0.001$). The 20 most frequent suspect drugs reported by patients and healthcare professionals are presented in figure 2. Substantial differences were shown between patient and healthcare professionals in terms of the suspected drugs.

The ATC anatomical classification of suspect drugs on the patient and healthcare professional reports is presented in table V. The most frequent category of drug suspected of being linked to an ADR was for nervous system disorders for both patient (33.2%) and healthcare professional (26.2%) reports. This was followed by cardiovascular system drugs from patient reports (21.8%) and anti-infectives for systemic use from healthcare professional reports (19.4%). A statistically significant difference in the percentage of type of suspect drug between reporters was shown with drugs for the nervous system, the cardiovascular system, systematic hormonal preparations excluding sex hormones and insulins, anti-parasitic products, insecticides and repellents, herbals/complementary

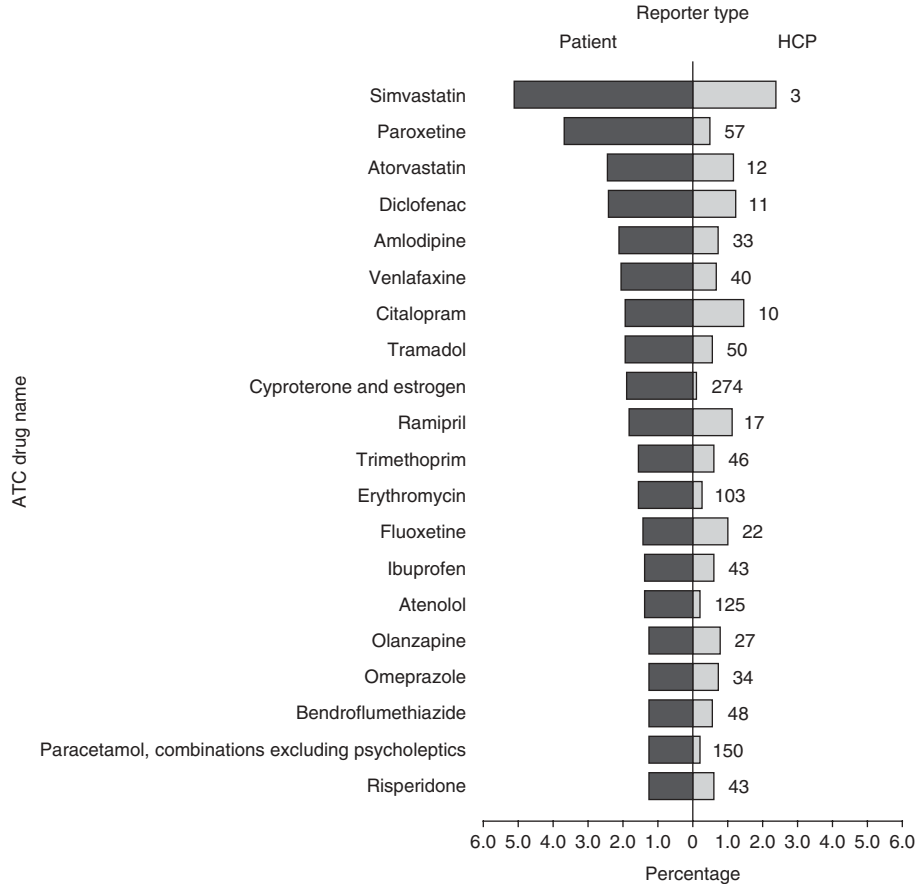


**Fig. 2.** The 20 most frequent suspect drugs reported by patients. The ordered rank of the drug for healthcare professionals (HCPs) is shown to the right of the bars. **ATC** = Anatomical Therapeutic Chemical.

medicine (which all had higher proportions in the patient than healthcare professional reports), anti-infectives for systemic use, antineoplastic and immunomodulating agents, drugs affecting blood and blood forming organs, and 'various' (all of which had higher proportions in the healthcare professional reports than the patient reports).

Patient Yellow Card reports were also split into those completed by patients themselves or by a representative, and healthcare professional Yellow Card reports were split into those reported by doctors, pharmacists, nurses or another health professional (e.g. dentist). Among the patient reports, a higher proportion of patients than representatives who completed the patient report reported drugs affecting the cardiovascular ($p < 0.001$), and genitourinary and sex hormone system ($p = 0.003$). In contrast, representatives reported a higher proportion of anti-infectives for systemic use ($p < 0.001$). Among healthcare professional reports, there were significant differences in the proportion of drugs in each ATC anatomical category reported by the four healthcare professional groups (except for antiparasitic products, insecticides and repellents). A higher proportion of nurses reported a suspected ADR for anti-infectives for systemic use (41.8%) or respiratory system drugs (5.6%) compared with any other healthcare professional group. A higher proportion of pharmacists reported a suspected ADR for a drug for the cardiovascular system (17.2%), musculoskeletal system (11.8%), blood

**Table V.** Anatomical Therapeutic Chemical (ATC) anatomical classification of distinct suspect drugs by reporter role

| | Patient report [n (%)] | | | HCP report [n (%)] | | | | | Patient vs HCP report[a] p-value |
|---|---|---|---|---|---|---|---|---|---|
| | patient (n = 4836) | representative (n = 344) | all (n = 5180) | doctor (n = 12 088) | pharmacist (n = 3690) | nurse (n = 2725) | other (n = 2446) | all (n = 20 949) | |
| Nervous system | 1604 (33.2) | 116 (33.7) | 1720 (33.2) | 3304 (27.3) | 897 (24.3) | 493 (18.1) | 789 (32.3) | 5483 (26.2) | <0.001 |
| Cardiovascular system | 1087 (22.5) | 44 (12.8) | 1131 (21.8) | 1936 (16.0) | 635 (17.2) | 101 (3.7) | 150 (6.1) | 2822 (13.5) | <0.001 |
| Anti-infectives for systemic use | 617 (12.8) | 86 (25.0) | 703 (13.6) | 1770 (14.6) | 533 (14.4) | 1139 (41.8) | 614 (25.1) | 4056 (19.4) | <0.001 |
| Alimentary tract and metabolism | 411 (8.5) | 21 (6.1) | 432 (8.3) | 1274 (10.5) | 300 (8.1) | 238 (8.7) | 145 (5.9) | 1957 (9.3) | 0.03 |
| Musculoskeletal system | 395 (8.2) | 16 (4.7) | 411 (7.9) | 889 (7.4) | 437 (11.8) | 41 (1.5) | 113 (4.6) | 1480 (7.1) | 0.03 |
| Genitourinary system and sex hormones | 267 (5.5) | 6 (1.7) | 273 (5.3) | 770 (6.4) | 97 (2.6) | 73 (2.7) | 100 (4.1) | 1040 (5.0) | 0.39 |
| Respiratory system | 181 (3.7) | 19 (5.5) | 200 (3.9) | 337 (2.8) | 119 (3.2) | 153 (5.6) | 53 (2.2) | 662 (3.2) | 0.01 |
| Blood and blood forming organs | 120 (2.5) | 12 (3.5) | 132 (2.6) | 375 (3.1) | 398 (10.8) | 66 (2.4) | 72 (2.9) | 911 (4.4) | <0.001 |
| Antineoplastic and immunomodulating agents | 118 (2.4) | 10 (2.9) | 128 (2.5) | 1022 (8.5) | 369 (10.0) | 320 (11.7) | 283 (11.6) | 1994 (9.5) | <0.001 |
| Systematic hormonal preparations, excluding sex hormones and insulins | 118 (2.4) | 6 (1.7) | 124 (2.4) | 164 (1.4) | 79 (2.1) | 27 (1.0) | 33 (1.4) | 303 (1.5) | <0.001 |
| Dermatologicals | 99 (2.1) | 13 (3.8) | 112 (2.2) | 298 (2.5) | 62 (1.7) | 29 (1.1) | 38 (1.6) | 427 (2.0) | 0.61 |
| Antiparasitic products, insecticides and repellents | 57 (1.2) | 7 (2.0) | 64 (1.2) | 85 (0.7) | 18 (0.5) | 25 (0.9) | 9 (0.4) | 137 (0.7) | <0.001 |
| Complementary therapies[b] | 48 (1.0) | 1 (0.3) | 49 (1.0) | 35 (0.3) | 35 (1.0) | 4 (0.2) | 7 (0.3) | 81 (0.4) | <0.001 |
| Sensory organs | 39 (0.8) | 5 (1.5) | 44 (0.9) | 86 (0.7) | 31 (0.8) | 17 (0.6) | 40 (1.6) | 174 (0.8) | 0.96 |
| Various | 36 (0.7) | 4 (1.2) | 40 (0.8) | 120 (1.0) | 39 (1.1) | 43 (1.6) | 90 (3.7) | 292 (1.4) | <0.001 |
| Unmapped[c] | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (0.01) | 1 (0.03) | 0 (0.0) | 0 (0.0) | 2 (0.01) | |

a Chi-squared tests comparing all patients and HCP reports.

b Complementary medicines are not part of the ATC anatomical classification but have been tabulated here to include all drug types.

c Unmapped includes suspect drugs that did not have a logical mapping in the ATC classification.

**HCP** = healthcare professional.

**Table VI.** Descriptive statistics of time taken to report an adverse drug reaction (ADR) by outcomes of reactions reported in the first and second year of the study

| Reaction outcome | Time to report in first year (days) | | | No. of reports in first year | Time to report in second year (days) | | | No. of reports in second year | p-Value[a] |
|---|---|---|---|---|---|---|---|---|---|
| | median (IQR) | range | no. missing (%) | | median (IQR) | range | no. missing (%) | | |
| **Patient-reported ADR** | | | | | | | | | |
| Not recovered/ resolved | 195.0 (44.0, 852.0) | 2–14 994 | 675 (54.7) | 1234 | 147.0 (35.0, 644.0) | 2–5389 | 441 (67.6) | 652 | 0.08 |
| Recovering/resolving | 51.0 (13.0, 212.0) | 1–10 700 | 277 (49.2) | 563 | 88.5 (27.0, 331.0) | 2–4093 | 195 (63.9) | 305 | 0.01 |
| Recovered/resolved with sequelae | 247.5 (48.0, 670.0) | 6–5986 | 52 (53.1) | 98 | 306.5 (77.0, 925.0) | 9–2985 | 81 (61.8) | 131 | 0.91 |
| Recovered/resolved | 68.5 (21.0, 305.0) | 1–14 717 | 760 (52.8) | 1440 | 88.0 (24.0, 352.0) | 2–10 003 | 530 (71.3) | 743 | 0.54 |
| **Healthcare professional-reported ADR** | | | | | | | | | |
| Not recovered/ resolved | 35.0 (14.0, 105.0) | 0–4829 | 652 (27.7) | 2354 | 34.0 (14.0, 98.0) | 1–4328 | 1064 (46.4) | 2291 | 0.86 |
| Recovering/resolving | 20.0 (10.0, 46.0) | 0–5614 | 637 (20.3) | 3135 | 21.0 (11.0, 52.0) | 0–1642 | 960 (34.0) | 2822 | 0.02 |
| Recovered/resolved with sequelae | 99.0 (41.0, 107.0) | 7–203 | 2 (28.6) | 7 | 90.5 (30.0, 167.0) | 14–1655 | 7 (28.0) | 25 | 0.74 |
| Recovered/resolved | 33.0 (14.0, 81.0) | 0–3971 | 987 (23.1) | 4282 | 31.0 (14.0, 84.0) | 0–3092 | 1725 (39.7) | 4350 | 0.77 |

a p-Value from Mann-Whitney U test.

**IQR** = interquartile range.

and blood forming organs (10.8%), and systemic hormonal preparations (2.1%). Of all the healthcare professional groups examined, doctors reported a greater proportion of suspected ADRs of drugs for disorders of the alimentary tract and metabolism (10.5%) and of the genitourinary system and sex hormones (6.4%).

### Time Lag Between Suspect ADR and Reporting

Patient reporters took a significantly longer median [IQR] time to report their reaction to the MHRA than healthcare professionals (104 [27–463] vs 28 [13–75] days, respectively). The median time to report a suspected ADR for reactions occurring in the first and second year of the study period is presented in table VI by reaction outcome. The median time to report an ADR among patients who were still recovering or whose reaction was resolving was significantly longer in year 2 than in year 1, regardless of who reported the ADR. However, this data should be interpreted with caution as there were large amounts of missing data related to this issue in both groups of reporter.

### Reaction Outcome

A significantly higher proportion of healthcare professionals than patient representatives reported fatal outcomes to the reaction (2.6% vs 0.7%; $p < 0.001$) and a significantly higher proportion of healthcare professionals than patients reported that the patient was recovering or that the ADR was resolving (28.4% vs 16.8%; $p < 0.001$). More patients reported that they had not recovered or that the reaction had not resolved than healthcare professionals (36.4% vs 22.2%; $p < 0.001$). Both reporter types reported a similar proportion of patients who had recovered or whose ADR had resolved (42.1% of patients vs 41.2% of healthcare professionals; $p = 0.23$).

## Discussion

This study was based upon data from over 26 000 Yellow Card reports submitted to the MHRA in a 2-year period. One in five of these

reports were submitted by a patient. This study has shown that whilst patients report more suspected ADRs to more suspect drugs than healthcare professionals, healthcare professionals tend to report more serious reactions that result in hospitalization, are life threatening or cause death.

### Patient Characteristics

Our finding that 19.8% of the Yellow Card reports were made directly from patients is similar to other countries where direct patient reporting is possible. For example, in the Netherlands and the US, 19.2% and 15% of reports, respectively, were from patients.[3,12] A greater proportion of reports were for ADRs affecting female patients, irrespective of reporter type. This may be due to female polypharmacy,[23,24] or some other unidentified sex-specific risk factors.[25] The Dutch study had a very similar proportion of reports relating to women as ours, with 63% of events from patient reporters and 61% from a healthcare professional being for females.[12] The average age of patients reported via a patient reporter in our study was also similar to that of patients reported via a healthcare professional, as was found in the Dutch study.[12]

### Reactions

Patients tended to report a significantly higher number of suspected ADRs per Yellow Card report than healthcare professionals. This could have either a detrimental or beneficial impact on signal identification. If patients report many events of relatively mild severity this could diminish (or extinguish) important signals that may have been detected if only healthcare professional-reported ADRs were used. Conversely, the reporting of serious events by patients, e.g. to a new medicine, may enhance and accelerate signal detection.[26]

Our study showed that patients were almost 3-fold more likely than healthcare professionals to report ADRs categorized as affecting the nervous system. A recent study in Denmark also found that nervous system disorders were reported more often by patients than from other sources, i.e. healthcare professionals and drug manufacturers and lawyers (OR [95% CI] = 1.27 [1.05, 1.53]).[10] The top two lowest level term reactions reported, i.e. nausea and headache, were the same for both types of reporters. These findings differed from the Dutch study, which found that myalgia was the most frequent ADR reported by patients (3.6% of all ADRs).[12] Myalgia was reported by only 0.7% of patients in the UK and was the 14th most reported ADR. Only six of the top ten most frequently reported ADRs in the Netherlands were reported in the UK.

### Seriousness of Reaction

Our findings are in agreement with the study conducted in the Netherlands, which also found differences in the seriousness of the reported ADRs.[12] They found that, compared with healthcare professionals, patients reported significantly fewer reactions that caused hospitalization or death. As with our study, they found similarities in the most frequently reported reactions and suspect drugs reported by the different groups of reporter. On the other hand, the Netherlands study found that more patients than healthcare professionals reported life-threatening ADRs, which was the opposite of what we found. The authors stated that differences in seriousness and outcome of ADR may be due to differences in interpretation, and they concluded that patient reporting of ADRs is feasible and likely to make a reliable contribution to pharmacovigilance.

### Drugs

Over 16% of patient Yellow Card reports contained more than one distinct suspect drug, compared with 9% of healthcare professional reports. However, this may be due to the patients' lack of knowledge regarding which drug might have caused the reaction, leading to numerous drugs being reported. Simvastatin and citalopram were the only two drugs in the top ten suspect drugs reported by both reporter types. In contrast, the Dutch study found that statins were the most frequently reported drugs for patients, pharmacists and general healthcare professionals.[12] However, when drugs were grouped

into their ATC anatomical classifications, the three most frequently reported classes in our study were the same as the Danish study for both patient and healthcare reporters: nervous system, cardiovascular system and anti-infectives for systemic use.[10]

### Time Lag Between Suspect ADR and Reporting

For both reporter types, time to report a reaction did not differ substantially between reports submitted in the first and second year of the study when examined by reaction outcome, with the exception of those who were still recovering. For the patient reports, the second year showed the longer median time to report a reaction from which the patient was still recovering. This may have been due to retrospective patient reporting upon hearing of the new patient yellow cards. However, it should be noted that >60% of patient reporters had missing data for time to report, which may have introduced bias in this aspect of analysis.

### Strengths and Limitations of this Study

This is the first substantial, published study in the UK to compare all ADR reports from patients and healthcare professionals. A major strength has been collaboration with the MHRA, which enabled us to obtain and analyse all ADRs reported over a 2-year period. However, many reporters failed to complete all fields of the report and so there was a large proportion of missing data for some variables, including indication for the drug, reaction outcome and time to report a reaction. Sex and age were missing for 3.6% and 10%, respectively, of all reports. It is possible that some of the reports may have been triggered by media attention to safety concerns of specific drugs during the study period. Reporting systems such as the YCS are subject to confounding from such external influences, which is a limitation of all observational studies. It is conceivable that patient reporting may be more prone to this problem than healthcare professional reporting.

As shown in figure 1 there are several differences between the patient and healthcare professional yellow cards. The most notable difference, however, related to the perceived seriousness of the suspected reaction. Only three of the six options were comparable: caused hospitalization, was life threatening and caused death. In addition, some patient reports were found to have included the seriousness options only available on the healthcare professional reports. Therefore, one recommendation to improve ADR reporting is to create a single Yellow Card that could be used by patients and healthcare professionals alike. This would improve further research of ADR reporting since the reports from patients and healthcare professional would be directly comparable.

### Concerns with Patient Reporting

Although proponents have highlighted potential benefits from patient reporting of ADRs,[12,27-29] others have expressed concerns. These concerns include the ability of patients to distinguish between suspect ADRs and problems associated with the underlying condition being treated by the suspected drug; clarity of the ADR description;[2] the increase in resources involved; and a perceived undermining of healthcare professional status.[30] However, the significant rate of under-reporting of ADRs by healthcare professionals, estimated at a median of 94% (IQR 82–98%) across 12 countries, suggests that patient reporting should not be dismissed.[2,6]

Patients were found to report different patterns of reaction in terms of the number and seriousness of ADRs and the number of suspect drugs. These differences suggest that patients may have a contribution to make to signal identification. However, whilst patient reports may strengthen the detection of important ADRs, they may also have the effect of diluting them. There is known under-reporting of ADRs by healthcare professionals in general. Although patient reporting may help to rectify this, it could be at the detriment of healthcare professional reporting. Concentrating on one reporter type may give a false impression of the ADRs to specific drugs, thus it is important to consider both patient and healthcare professional reporting.

## Conclusions

Whilst patients report more suspected ADRs to more suspect drugs than healthcare professionals, healthcare professionals tend to report more serious reactions that result in hospitalization, are life threatening or cause death. Further research is required to investigate the extent to which the extra information from patient reporters contributes to signal identification when assessing drug safety.

## Acknowledgements

The Yellow Card Study Collaboration also includes Heather Fortnum, Alison Gifford, Janet Krska, Elizabeth Murphy, Tim Payne and Saad Shakir. Thanks to the Yellow Card Study Collaboration Advisory Group for their feedback. Thanks to the Medicines and Healthcare products Regulatory Agency for providing us with their data and assisting with any queries.

D.J. McLernon conducted the statistical analyses, drafted and finalized the paper. He is the guarantor for the paper. A.J. Lee, P.C. Hannaford, C.M. Bond, M.C. Watson and A. Avery contributed to and oversaw the design and conduct of the study, and contributed to the writing of the paper. L. Hazell prepared and coded the database, and contributed to the writing of the paper. All authors had full access to all of the data and can take responsibility for the integrity of the data and the accuracy of the data analysis.

This research was supported by the UK National Health Service Research & Development Programme Health Technology Assessment Programme (project number 06/92/03).

The views and opinions expressed therein are those of the authors and do not necessarily reflect those of the Department of Health. The study sponsor did not participate in the study design; in the collection, analysis or interpretation of data; in the writing of the report; or in the decision to submit the paper for publication. All researchers were independent from the funder. The authors have no conflicts of interest to report.

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