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How Patient Reporters Identify Adverse Drug Reactions

A Qualitative Study of Reporting via the UK Yellow Card Scheme

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Abstract

Background: Direct reporting of suspected adverse drug reactions (ADRs) to authorities is increasing, but questions remain about how patients identify suspected ADRs and their ability to distinguish between ADRs and other symptoms.

Objective: The aim of the study was to determine how reporters to the Yellow Card Scheme (YCS) identify ADRs.

Methods: We carried out a qualitative analysis of data from three sources, obtained as part of a larger evaluation of patient reporting to the UK YCS: responses to open questions in postal questionnaires sent to all reporters during March 2008–January 2009 (method 1); telephone interviews with a purposive sample of these reporters (method 2); and the free-text field from completed Yellow Card reporting forms submitted during October 2005–September 2007 (method 3).

Results: Method 1 involved 1362 questionnaire respondents (67.8% of the 2008 patient reporters during the study period), 1167 of whom explained how they decided they had experienced an ADR. Temporality was the most common reason for the perceived association, given by 820 (70.2%) respondents. 478 (41.0%) provided information on two or more aspects of temporality, such as onset, changes with dose and re-challenge. A total of 383 (32.8%) respondents used information sources, such as patient information leaflets or discussions with health professionals to confirm associations, including 145 (12.4%) who had also reported a temporal association.

Telephone interviews with 27 reporters (method 2) provided detailed explanations of temporal associations, particularly experiences of rechallenge, and data from 230 Yellow Card reports (method 3) showed that, although

reporters are not required to explain reasons for their suspicions, 74.8% of submitted reports included a temporal association. These reports also showed evidence of causal theorizing and differential diagnosis.

Conclusion: In our study sample, most reporters to the YCS feel able to identify suspected ADRs adequately and describe processes of assessing causality that mirror those in standard algorithms designed for use by health professionals. These findings should help to reduce concerns among health professionals about the ability of patients to identify suspected ADRs when reporting to authorities.

Background

Pharmacovigilance is vital to patient safety as rare, delayed, serious and/or unexpected adverse drug reactions (ADRs) often appear only when drugs are widely used. Spontaneous reporting systems that support pharmacovigilance are in use in many countries, although most restrict reporting to health professionals. Direct reporting by patients may bring benefits, including the promotion of consumer rights and equity, acknowledging that consumers have unique perspectives and experiences, and healthcare organizations may benefit from consumer involvement.[1] Furthermore, additional reporting by patients may help to ameliorate the effect of underreporting by healthcare professionals,[2] potentially increasing overall spontaneous reporting rates and enabling earlier detection of ADRs.[3] Our research team has identified that the regulatory authorities of 46 countries accept spontaneous patient reports, although differing systems are used.[4] This includes the UK, where patients have been permitted to report suspected ADRs directly to the Medicines and Healthcare products Regulatory Agency (MHRA) since 2005, via the Yellow Card Scheme (YCS).[5] In the first 5 years of the scheme, patients have contributed 15.5% of reports, excluding those from the pharmaceutical industry.[6] Despite concerns that patient reports may create noise and prove a drain on surveillance systems,[7] a systematic review concluded that the benefits of direct reporting outweighed the costs.[8] The European Parliament is currently debating the inclusion of direct patient reporting of adverse events in the legislation on pharmacovigilance systems, and a report on collective experiences in Europe suggest that patient reporting provides a range of benefits, including greater detail of the burden of ADRs and involvement of the patient in their treatment.[9] More recently, three major comparisons of patient reporting with that of health professionals have been conducted, from the Netherlands, Denmark and the UK.[10-12]

Certainty about causality is not required for submission of a Yellow Card report, whether submitted by a patient or a health professional. However, questions remain about how patients identify suspect ADRs and their ability to distinguish between ADRs and other symptoms;[13] relatively little work has been conducted in this area. As direct patient reporting increases, the concerns about the ability of patients to identify ADRs for them to be of use in pharmacovigilance need to be addressed.

This study sought to determine how reporters to the YCS identify ADRs.

Methods

This work describes three parts of a large multi-methods study evaluating patient reporting through the YCS.

Method 1 involved postal questionnaires that were distributed by the MHRA on our behalf to all members of the public who submitted a Yellow Card between February and December 2008. Questionnaires were sent out in batches each week between March 2008 and January 2009 following receipt of Yellow Cards. The questionnaire

included the open question ''What made you think that the medicine caused the side effect?'' Data from the questionnaire responses were categorized by two researchers independently then discrepancies discussed and agreement reached.

The questionnaires included an invitation to provide contact details to participate in a telephone interview (method 2). From those who agreed, a sample was purposively selected to include respondents of varying age, sex, educational attainment and reporting method. We used maximum variation sampling in order to obtain a wide range of opinions. In addition, we purposively selected some patients based on issues raised in the questionnaire, such as the perceived ease of reporting. The interview schedule covered a range of areas, including motivations for making the report, expectations about what would happen to their report and satisfaction or dissatisfaction with the process of reporting. An iterative process was applied to the interviews to ensure that people included had different perspectives based upon the preliminary analysis and emergent themes. Interviews were conducted by two experienced qualitative researchers, then data were recorded (with consent), transcribed verbatim and analysed using constant comparison.

Method 3 involved a qualitative analysis of the content of a sample of Yellow Card reports from patients, submitted during the period October 2005–September 2007. These reports were included for triangulation purposes, as our evaluation showed that some reporters often explained how they identified ADRs, although this is not requested on the Yellow Card forms. Purposive sampling was used to select reports concerning some of the most commonly reported drugs, 'black-triangle' drugs (products containing new active substances or in new formulations which have been recently licensed in the UK) and over-the-counter products. Data were read and coded by more than one researcher and where there was not full agreement over the codes or the interpretation of the data, these were discussed and reviewed. Approval was obtained from Warwickshire Research Ethics Committee for the large evaluation study, including these aspects of the work.

Results

Questionnaire Data (Method 1)

Questionnaires were distributed to 2008 reporters, of whom 1362 (67.8%) returned completed responses. Results from the questionnaire covering reporters' opinions and experiences of the reporting process, and their expectations and suggestions for improving the process are reported elsewhere.[14] Characteristics of respondents are shown in table I. In total, 1304 (95.7%) respondents were at least fairly sure that the side effect was due to the medicine. Most (1348 [99%]) had answered the open question. Of these, 181 (13.3%) were not analysable as 78 listed only symptoms and 103 were comments on other issues, such as the responses of health professionals, general views about side effects or inadequate descriptions of processes used to identify symptoms as ADRs, e.g. ''I felt it was obvious''; ''not had any problems before''.

Of the remaining 1167 respondents, most (689 [59.0%]) provided only one piece of information to explain causal association, but 382 (32.7%) provided two, 87 (7.5%) provided three and 9 respondents (0.8%) provided four. A total of 820 (70.2%) indicated temporality as the main reason for the perceived association, many involving several individual such associations.

Table I. Characteristics of patient reporters included in the study

Characteristic	Value
Questionnaire respondents (n = 1362)	
Age [y; median (IQR)]	56.5 (43, 67)
Females [n (%)]	910 (66.8)
White ethnicity [n (%)]	1274 (93.5)
Educational level further education or above [n (%)]	923 (67.8)
Interviewees (n = 27)	
Age [y; median (IQR)]	60.0 (49, 69)
Females [n (%)]	19 (70.4)
Educational level further education or above [n (%)]	15 (55.6)[a]
Yellow Card reports (n = 230)	
Age [y; median (IQR)]	44 (31, 55)
Females [n (%)]	156 (67.8)

a Missing data in four interviewees.

IQR = interquartile range.

''No previous symptoms prior to taking medicine. Symptoms eased following cessation of medicine but returned after second course of treatment.'' (Male, aged 68 years, postgraduate.)

In total, there were 195 (16.7%) comments that indicated the symptom was not present before the medicine was started, 320 (27.4%) that it began soon after starting the medicine, 275 (23.6%) that it reduced on stopping and a further 89 (7.6%) that it re-occurred on rechallenge. In addition, 37 respondents noted symptom changes with dose changes, 25 indicated symptoms started after medicine withdrawal and 29 on changing brand, as illustrated here.

''Never had it before. Didn't have it after stopped. Was worse on higher doses. Was better on lower doses.'' (Male, aged 32 years, graduate.)

''I had been taking Pfizer's Istin (amlodipine) for over six months and when I suddenly could not find it anywhere I was forced to take a generic version. Within half an hour of taking this I could feel symptoms which I had never experienced with Istin. I reported them immediately to the doctor.'' (Female, aged 63 years, further educational qualification.)

A further 22 comments related to the fact that the medicine was new and 78 others provided different timing-related issues.

''Newly on the medication – side effect happened twice. Knew it was related. Not happened again since I came off it.'' (Female, aged 41 years, graduate.)

''All symptoms occurred directly after taking the tablet, gradually clearing until next tablet taken. This was a once weekly tablet.'' (Female, aged 69 years, further educational qualification.)

A total of 383 (32.8%) respondents had used various information sources to confirm their suspicion of the association between the symptom and medicine, including 145 (12.4%) who had also reported a temporal association.

''Read about possible side effects on internet – commencement of taking medication coincided with my own medical problems. This was backed up by consultant.'' (Female, aged 65 years, postgraduate.)

There were 186 (15.9%) reporters who indicated a health professional had informed them of the association, 99 (8.5%) who had used the patient information leaflet (PIL) and 54 (4.6%) who stated they obtained information via the Internet. Many indicated that the information source was used to confirm their suspicions about the symptom cause, and 30 had confirmation both from one such source plus a health professional.

''My other medications have been taken for some years without causing unwanted side effects, and taking the 'new' medicine caused a problem immediately. When I looked at the list of known side effects, there it was!'' (Female, aged 47 years, graduate.)

''Side effects written on medication leaflet (looked after suffering them). Doctor confirmed this.'' (Female, aged 20 years, undergraduate.)

There were 21 respondents who cited other specific information sources, such as the *British National Formulary* or specific reports, possibly identified from the Internet, from sources such as the WHO or US FDA. Only 13 cited media sources and 12 cited friends, while 41 did not specify the information source.

''Read about the link between alendronate and heart palpitations. Checked with hospital pharmacy who said no (after my first admission with palpitations/black-outs). Then saw further info in national press.'' (Female, aged 61 years, postgraduate.)

Previous experiences were also considered relevant by 33 respondents, while concomitant drugs or diseases were mentioned relatively infrequently. Most commonly, this was to state that no other drugs were being used or that no other changes had occurred.

''Painful contraction of thigh & calf muscles which only started when I took indapamide (1.5 mg) one per day. Started after second tablet & ceased when dose stopped. A repeat occurrence on trial next week. Previously same reaction to bendrofluazide.'' (Female, aged 61 years, further educational qualification.)

Excipients were specifically identified by 20 respondents, and 22 related their symptom to an interaction.

''Sleepless nights after taking prescribed Simvastatin in white formula. Informed pharmacist

who changed tablets to pink formula & symptoms disappeared.'' (Male, aged 64 years, left school at 16 years of age.)

''I felt it was more of an interaction as I read in the note not to take ibuprofen tablets while I was on the medicine for high blood pressure. I felt the cramping in my legs got worse as a result of taking ibuprofen with the Cozaar.'' (Female, aged 70 years, left school at 16 years of age.)

Telephone Interview Data (Method 2)

A total of 27 telephone interviews were conducted; characteristics of interviewees are shown in table I. Interview data provided more detail, confirming the ability of patient reporters to link the ADR temporally with a particular medicine.

''I took this one capsule of the antibiotic and er I was talking to a friend on the phone and er within half an hour my tongue started to swell and I had to ring off because I couldn't speak ... and then I had mucous streaming from my nose and mouth. Oh it was awful, I felt sick and broke out into a rash all over my body which itched and felt hot.'' (Female, aged 72 years, no educational status given.)

Interviews also corroborated reporters' use of information sources about possible ADRs and that rechallenge provided them with further confirmation.

''So I started taking that and about maybe 2 weeks into taking it and I started feeling sick. Reading on the instructions it just said that it can cause nausea but these are sort of like, when you read these instructions it's maybe, you know, one in however many people will have these .... Yes, so I started feeling sick as I say and I thought right, that will be fine, I'll just sort of ride through it and it just got worse until in the end I was being sick, violently sick. So I went back to my GP rather than the hospital because it was just every so often that I went to the hospital and he said, 'Right let's stop taking it.' So I stopped taking it on a particular Wednesday and then he said, 'Leave it a full week and then start taking the drug again and then we'll know whether it's that that's actually making you be sick'. So I started taking it on the Wednesday morning and I remember taking it at half past 8 just before going into work and by 9 o'clock I was being violently sick again and I was being sick about every 5 minutes.'' (Female, aged 47 years, left school at 16 years of age.)

''I think it was one day, two days and it was most pronounced, the symptom was pronounced and definite and I was very surprised. Stopped taking it for I think a few days, repeated it and got exactly the same results much to my amazement. It was more pronounced, most definite and repeatable.'' (Male, aged 61 years, further educational qualification.)

Yellow Card Data (Method 3)

Data from 230 patient Yellow Card reports were analysed; 148 concerning the five drugs most commonly reported by patients (citalopram, co-cyprindiol [ethinylestradiol/cyproterone], paroxetine, simvastatin and venlafaxine) and 82 concerning 'black-triangle' drugs. A total of 5180 reports were received by the MHRA over the period, thus our sample comprised 4.4% of the total reports. Characteristics of patients in whom ADRs were reported are given in table I. There were 172 (74.8%) reports that included at least one aspect of temporal association between the medicine and the symptom. Eighty-nine reports (38.7%) included only one item of information, 59 (25.7%) included two items, 21 (9.1%) included three items and three respondents (1.3%) included four items. Of these, 141 (61.3%) reports stated the symptom began soon after starting the medicine, 60 (26.1%) reports stated that symptoms reduced on stopping or dose reduction, and 15 reports (6.5%) stated that they re-occurred on rechallenge. A further 50 (21.7%) reports indicated that symptoms started after medicine withdrawal and 16 (7.0%) reports described other relationships to dose changes.

''Suspected side effects (from the start of treatment), gastrointestinal problems, dizziness/light-headedness on standing up, insomnia, weight gain, strange dreams, heightened awareness of colour.'' (Female, aged 43 years.)

''Unfortunately I had no indication that the contraceptive was having such an effect until I had been taking it for three years and decided to

have a break. Of course I would not like to spur severe accusations about Dianette however I strongly believe that the contraceptive was affecting my mood, giving me anxiety and panic attacks and quite bad depression on occasions, it seems too much of a coincidence that the anxiety and depression began after a few months of taking the pill and then evaporated not long after stopping. During the time I was on Dianette, in one burst of depression I took an overdose, it is for this reason that I would like to report what I think were side effects of what is generally thought of as a harmless drug.'' (Female, aged 19 years.)

''As I started to come off the medicine I started to feel anxious all over again despite feeling perfectly well prior to deciding to stop. Each time I have tried to come off the drug it has resulted in returning to the medication as the side effects have too much impact on my daily routine. I have been taking the medicine again and plan to start to gradually withdraw using a liquid replacement of the tablet in the immediate future. Hopefully, this will allow me to reduce the quantity very gradually and have less effect.'' (Female, aged 28 years.)

''I am presently taking 40 mg daily of this medication. On increasing the dose of citalopram, first to 60 mg and then reducing to 50 mg daily – I experienced severe agitation and a recurrent thought of ending my life. On 60 mg, I felt seriously suicidal, and had constant morbid thoughts and fixation. Increasing citalopram from 40 mg daily to 60 mg daily made my depression and anxiety much worse, therefore having the reverse effect on my mood-inducing suicidal feelings.'' (Female, aged 27 years.)

Furthermore, 23 (10%) showed evidence of causal theorizing and differential diagnosis, while 15 (6%) of reports included supportive evidence of the association provided by health professionals or objective data.

''Nose starts to tingle and the same effect moves down and around mouth and chin, it's just like the feeling if you have injection in your gum at the dentist. Wonder if it's a combination of both drugs – or one or the other – also it only happens when take medication late or forget.'' (Female, aged 45 years.)

Discussion

This study has shown that a majority of the patients in our study sample who have reported suspected ADRs through the YCS use temporal associations to associate symptoms with medicines used. Additional information obtained from a variety of sources, mainly the PIL accompanying medicines and health professionals, are used by a proportion of reporters to confirm suspected associations. Such methods are in line with those used by health professionals themselves and with standard algorithms designed for assessing causality.[15]

This study triangulates data from three phases of a larger study, which involve written questionnaire responses, interviews and actual Yellow Card reports. Although the first two data sources were derived from the same population, the third was derived from reports submitted before any questionnaires were distributed. The questionnaire data were derived from a substantial proportion of all reporters to the YCS during the period of study, most of whom responded to the specific question concerning association of the symptom with the medicine. However, reporters to the YCS constitute a minority of the population who may experience ADRs, and respondents to our questionnaire were further self-selected. Furthermore, the large majority of respondents were White and more highly educated than the general UK population. Also, more females were involved in our study than males, although these differences tend to reflect the distribution of reporters to the YCS and, in the case of sex differences, the higher incidence of ADRs in women.[16,17] The interviews provided further opportunity to explain processes outwith the constraints of limited space on the questionnaire or the Yellow Card. The actual Yellow Card reports were selected from all those submitted to purposively obtain a variety of data and not specifically to include those that included information about how reporters identified the ADR. However, we acknowledge that this was a relatively small sample of total Yellow Card reports.

Other work has compared patient reports to those of health professionals, looking at reporter

characteristics, suspect drugs, seriousness of ADRs and time to report,[10-13] but little work has explored how patients identify and assess ADRs. Studies in both the US and the UK suggest that patients' understanding of ADRs based on their knowledge combined with timing issues, such as starting a new medicine, are factors that patients may use to attribute ADRs.[18,19] Our work, derived from a large population of patient reporters, confirms this. A study investigating patient experiences of suspected ADRs in primary care using a standardized generic symptoms checklist found that the majority identified a few symptoms that were probable/possible ADRs, while a small minority identified large numbers or symptoms unlikely to be ADRs.[20] Similarly, a hospital-based study using a single question identified that some patients are 'complainers', identifying multiple symptoms, while the majority identified only one or two complaints, and that a correct opinion about the relationship between complaints and medicines was found in 79% of patients.[21] Negative affect can result in patients feeling more susceptible to adverse effects,[22] which may contribute to this difference and to patients submitting reports. However, dismissive attitudes among health professionals were reported as being important among reporters to the Netherlands' scheme in its first 6 months.[23] Such attitudes have been seen in physicians in a small US study[24] and in our own evaluation of YCS reporters.[25] These could arise from doubts as to the validity of patients' ability to identify suspected ADRs, therefore further in-depth exploration of the processes patients use may help to reduce such concerns.

Further work is required involving patients who experience ADRs but do not report them to regulatory authorities, to determine whether similar processes are used. In particular, more work is needed on how patients undertake causal theorizing and differential diagnosis to take account of potentially confounding factors. However, the data suggest that reporters to the YCS feel able to identify suspected ADRs adequately and describe processes of assessing causality that mirror those in standard algorithms designed for use by health professionals. Our evaluation of the YCS also showed that patients report similar proportions of reactions classed as serious to reports from health professionals,[12] which was confirmed by MHRA in a larger sample.[6] Causality assessment in a sample of reports from both reporter groups found that similar proportions were possible ADRs.[4] In practice, reports from patients are assessed for causality and combined with those from health professionals in the Drug Analysis Prints available from the MHRA,[26] further illustrating their quality.

Conclusion

Most reporters to the YCS feel able to identify suspected ADRs adequately and describe processes of assessing causality that mirror those in standard algorithms designed for use by health professionals. These findings should help to reduce concerns among health professionals about the ability of patients to identify suspected ADRs when reporting to authorities. We therefore conclude that patient reports should be taken seriously.

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Janet Krska undertook the qualitative analysis of the questionnaire data, Claire Anderson and Elizabeth Murphy analysed the interviews and Yellow Card data, and Anthony Avery performed the quantitative analysis of the Yellow Card Data. Janet Krska and Claire Anderson drafted the article, to which all authors contributed. All members of the study group designed the overall study. Janet Krska is guarantor for the paper.

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