Evaluation of patient reporting of adverse drug reactions to the UK 'Yellow Card Scheme'

Evaluation of patient reporting of adverse drug reactions to the UK 'Yellow Card Scheme': literature review, descriptive and qualitative analyses, and questionnaire surveys

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Executive summary

Health Technology Assessment 2011; Vol. 15: No. 20
DOI: 10.3310/hta15200

Health Technology Assessment
NIHR HTA programme
www.hta.ac.uk

Executive summary

Background

An adverse drug reaction (ADR) is a reaction to a drug and/or a combination of drugs which is harmful and unintended and which occurs at a dose that is normally used for prophylaxis, diagnosis or treatment.

The monitoring of ADRs through pharmacovigilance is vital to patient safety, as rare, serious and/or unexpected reactions often appear only when drugs are used in everyday practice by many people. Spontaneous reporting of ADRs is one method of pharmacovigilance, and in the UK this is undertaken through the Yellow Card Scheme (YCS). Since 1964, health-care professionals (HCPs) have been able to report ADRs, and in October 2005 the Scheme was opened up to patients or their representatives.

Yellow Card reports are submitted to the Medicines and Healthcare products Regulatory Agency (MHRA) by post or telephone or via the internet. The MHRA electronically records and reviews information submitted, so that important safety issues can be detected.

Whereas previous studies have shown differences between patient and HCP reports for the types of drugs and reactions reported, relatively little is known about the pharmacovigilance impact of patient reports. There have also been few studies on the views and experiences of patients/consumers on the reporting of suspected ADRs.

Aims

To evaluate patient reporting of suspected ADRs to the YCS in the UK by assessing the pharmacovigilance contribution of patient reports compared with those of health professionals; exploring the views of patient reporters and members of the public, and comparing study findings with those from existing schemes worldwide.

Objectives

To evaluate the pharmacovigilance impact of patient reporting to the YCS:

- Main research questions:
  - What are the characteristics of patient reports to the YCS; what types of drug and suspected adverse reactions do patients report and how serious are these?
  - What is the relative contribution to signal generation of patient reports compared with those made by health professionals?
  - What do patients' descriptions of suspected adverse reactions add in terms of richness of data compared with those from health professionals?

To elicit the views and experiences of patients and members of the public regarding patient reporting of ADRs:

- Main research questions:
  - What are the views and experiences of patients reporting to the YCS?
  - What are the views of members of the public on the YCS including user-friendliness and usability of different mechanisms of patient reporting?
  - What is the level of awareness of the YCS among members of the general public in Great Britain and what are their views on the convenience of three different ways of reporting (online, telephone, completing and mailing a paper form)?
  - How might the reporting system be improved?

To offer recommendations for improvement to patient reporting based on our research findings and literature from other countries.

Methods

Literature review and international survey of patient reporting systems:

- A range of methods was used to identify countries with patient reporting as part of their national pharmacovigilance activities, including a questionnaire to pharmacovigilance staff in 47 countries, personal communication with key contacts and literature review.
- A literature review was performed to identify comparative studies of patient and HCP ADR reports. A search was conducted of MEDLINE (Ovid), EMBASE (Ovid) and Pharm-line databases using both medical subject heading (MeSH) and text search terms. The search dates were from 1996 to May 2009.

Evaluating the pharmacovigilance impact of patient reporting through analysis of reports of suspected ADRs from the UK YCS:

- Anonymised data were provided by the MHRA for all patient and HCP reports received by the YCS between 1 October 2005 and 30 September 2007. To compare the two reporter groups, suspected adverse reaction terms were grouped within the hierarchical structure of the industry standard 'Medical Dictionary for Regulatory Affairs' (MedDRA, version 12) and suspect drug names were mapped to the most appropriate code within the Anatomical Therapeutic Chemical (ATC) drug classification system (2007 version).
- Patient and HCP reports were compared for a wide range of characteristics including age and gender of the patient on whom the report was being made; numbers and types of drugs and ADRs reported; time taken from ADR to making the report, and the recorded seriousness of the reports (based on the classification of reaction terms by the MHRA and whether reactions were considered life-threatening by the reporter, or caused hospitalisation or death).
- Signal generation analysis was undertaken on the whole database of patient and HCP reports. We identified signals of disproportionate reporting (SDRs), which are 'statistical signals' where the reporting rate for a suspected ADR in association with a particular medicine is disproportionate to that of other products in the database. We then investigated the effects (on SDRs) of including and excluding patient reports from the HCP database. We also did clinical causality assessments on selected drug–ADR pairs from patients and HCPs.
- We undertook a qualitative analysis of reports from patients and HCPs and purposively selected a wide range of different types of report. Focusing on the free text describing the ADRs, we undertook a content analysis to describe the characteristics of 230 patient and 179 HCP reports followed by a more detailed inductive qualitative analysis of the free text (which included 40 additional patient reports of drugs purchased over the counter and complementary therapies).

Considering the views and experiences of patients and members of the public regarding patient reporting:

- A questionnaire was developed for distribution by the MHRA to all patients reporting through the YCS between March 2008 and January 2009. The questionnaire elicited information on how patients found out about the YCS, their experiences of, and views on, reporting and their demographic characteristics.
- Semistructured telephone interviews were conducted with a purposeful sample of patient reporters selected from those who had completed questionnaires and given consent to further contact by the research team. The interviews explored motivations for reporting, expectations of, and satisfaction with, the reporting system and suggestions for improvements.
- Members of the public in Nottingham, UK, were invited to seven focus groups at which views on patient reporting of ADRs were explored. Participants were then observed completing Yellow Card reports for simulated ADR scenarios and detailed information was recorded on their experiences and suggestions for improvements.
- Eight questions were added to a national omnibus survey, which was carried out by the British Market Research Bureau by telephone over two weekends in January 2009, using a database of residential telephone numbers in Great Britain. Questions were developed to assess public knowledge of the YCS, previous experiences of side effects from medications, previous reporting of ADRs and preferred methods for reporting ADRs.

Results

Literature review and international survey of patient reporting systems:

- Forty-six countries were identified as having consumer reporting schemes. A number of studies of patient reporting of suspected ADRs were identified, including a recent systematic review. Since the time of that review, one large-scale comparative study from the Netherlands showed similarities in the classes of drugs most commonly reported by patients and HCPs, and similar proportions of reactions judged to be serious. Another large-scale comparative study from Denmark showed that, compared with other sources, patients reported different types of medicines for categories of ADR. No large-scale studies were found investigating the impact of patient reporting on generating potential signals for suspected ADRs.

Evaluating the pharmacovigilance impact of patient reporting through analysis of reports of suspected ADRs from the UK YCS:

- For the 2-year study period, 26,129 Yellow Card reports were received from the MHRA [5180 (19.8%) patient reports and 20,949 (80.2%) HCP reports]. Patient reports contained a significantly higher number of suspected ADRs per report than HCPs [median (interquartile range, IQR) of 3 (2 to 5) vs 2 (1 to 3), respectively; $p < 0.001$). A higher proportion of patient reports than of HCP reports contained more than one suspect drug (16.1% vs 9%, respectively; $p < 0.001$). The median (IQR) word count (excluding reports with zero word counts) used to describe the suspected reaction was significantly higher for patient reports than for HCP reports [45.0 (22.0 to 74.0) vs 15.0 (9.0 to 26.0), respectively; $p < 0.001$).
- Patients showed different patterns of reporting of drugs and ADRs compared with HCPs. Nevertheless, similar proportions of reports contained at least one reaction term that was classified as 'serious' by the MHRA (58.3% for patients vs 58.8% for HCPs; $p = 0.58$). The following were recorded more commonly in HCP reports than patient reports: 'caused hospitalisation' (18.8% vs 12.9%, respectively), 'life-threatening' (11.1% vs 6.2%, respectively)

and 'caused death' (2.6% vs 0.7%, respectively) ($p < 0.001$ for each comparison). Of the patient Yellow Card reports, 44.8% stated that the suspected ADR was bad enough to affect everyday activities. Patient reporters took a significantly longer time to report suspected ADRs than HCPs [median (IQR) of 104 (27 to 463) days vs 28 (13 to 75) days, respectively; $p < 0.001$], although there were missing data on 'time taken to report' for over 60% of patient reports.

- For the signal generation analysis there were 16,566 drug–reaction pairs from patient reports and 28,775 from HCPs, with only 4340 (10.6%) pairs common to both groups. The HCP data set generated a significantly higher proportion of SDRs from the different drug–reaction pairs reported [1939 SDRs (6.7%) vs 649 (3.9%), respectively; difference in proportions 2.8%, 95% CI 2.4% to 3.2%]. Also, a higher proportion of HCP SDRs were for reactions classified as 'serious' by the MHRA compared with patient SDRs (48% vs 28.5%, respectively; difference in proportions 19.5%, 95% CI 15.4% to 23.6%) or for drugs undergoing intensive surveillance ('black triangle drugs') (30.7% vs 10.9%, respectively; difference in proportions 19.8%, 95% CI 16.6% to 23.0%). A similar proportion of SDRs in both groups (15%) were assessed as not being listed on the product's summary of product characteristics (SPC) and, therefore, potentially providing new information.
- After combining the patient and HCP data sets, an additional 508 SDRs were generated that were not produced by either data set alone, although 186 SDRs generated by the HCP data set alone were no longer present. The combined data set identified 47 SDRs for reactions classified as serious by MHRA, which had not previously recorded on SPCs, while eight generated by the HCP data set alone were no longer present. Among the sample of individual reports assessed for causality, most were assessed as having a 'possible' causal association, regardless of reporter group.
- The content analysis of text describing suspected reactions showed that patient reports were more likely than those from HCPs to include information about symptoms (93% vs 78%) and to stress the extreme nature of these (47% vs 17% of reports). They were also more likely to highlight the impact of the reaction on the patient (47% vs 12%), particularly the emotional impact (34% vs 7%) or social impact (27% vs 7%). Patients commonly reported on temporal associations, with 61% stating that the suspected ADR had followed the administration of the drug; 26% that it had improved on stopping the drug; 22% that it had occurred on withdrawal of the drug; and 7% that it had recurred on restarting the drug.
- The in-depth qualitative analysis demonstrated the richness of accounts from patients and provided numerous detailed and elaborate descriptions of suspected reactions. Patient Yellow Card reports also contained information on reasons for drugs being prescribed, reasons for reporting, how patients identified the ADR and responses from HCPs. Particularly striking were reports of reactions, often in relation to central nervous system drugs, that were extremely distressing, and sometimes frightening, including confusion, agitation, panic symptoms, mood swings, suicidal thoughts and electric shock sensations. Patient reports vividly described the effects of suspected ADRs on patients' lives, illustrating impact in terms of serious disruption to social and occupational functioning and marked emotional effects. By contrast, where HCPs did comment on the effects of suspected ADRs on patients' lives, the accounts were usually brief and rarely illustrated the profound impact recorded in patient reports.

Considering the views and experiences of patients and members of the public regarding patient reporting:

- There were 1362 evaluable responses to the questionnaire sent to 2008 patient reporters (68%). The most frequent reporting method was postal (59.8%), followed by online (32.8%) and telephone (6.3%). Online reporters were younger (median age in years of reporters: online 50 years, postal 61 years, telephone 63 years; $p < 0.001$) with a higher education level than those using other reporting methods (e.g. proportion of reporters with a degree:

online 48%, postal 28%, telephone 32%; $p < 0.001$). Almost one-half learned about the YCS from a pharmacy ($n = 667$; 49.0%). In response to a closed question, most respondents 1274 (93%) indicated that the report was 'fairly' or 'very' easy to complete, although in free-text comments 216 (15.9%) noted difficulties they had experienced. Suggestions for enhancements were made by 307 (22.5%). One-third ($n = 448$; 32.9%) expected feedback from the MHRA on their report and 828 (60.8%) would have liked feedback. Almost all respondents ($n = 1302$; 95.6%) would report again. Respondents indicated a need for increasing health professionals' awareness of patient reporting. Some stressed the importance of having a reporting mechanism that is independent of health professionals, so that patients' perspectives can be recognised.

- Twenty-seven telephone interviews were conducted with patient reporters. Most became aware of the YCS by chance and many suggested that greater publicity was needed for patient reporting. Motivations for reporting included altruism and a desire to find out if others had experienced similar problems. Several suggestions were made for enhancements to reporting systems, including more space for writing free-text comments on the paper form.
- Forty participants took part in seven focus groups. After hearing an introductory presentation, a number of suggestions were made about improving publicity for the YCS. Usability testing with the 40 participants indicated that telephone reporting worked well, but identified specific suggestions for enhancing online and paper reports.
- From the national omnibus survey of 2028 adults, only 172 (8.5%) had heard about the YCS. The preferred method of reporting varied with the characteristics of respondents.

Conclusions

Patient reporting of suspected ADRs has the potential to add value to pharmacovigilance by:

- reporting different types of drugs and reactions to reports from HCPs
- generating new potential signals
- describing suspected side effects in enough detail to provide useful information on likely causality and the impact of ADRs on patients' lives.

These finding suggest that further promotion of patient reporting to the YCS is justified, along with improvements to reporting systems.

Implications for patient reporting

- In the authors' opinion, the following approaches may help to improve the timeliness and value of patient reporting for pharmacovigilance, increase the number of reports from patients, and improve patient experiences of reporting:
  - increase publicity for patient reporting
  - provide further guidance to reporters on what information to report
  - increase patient awareness of medicines for which the MHRA is undertaking intensive monitoring
  - change the design of paper reports and the online reporting system
  - provide general feedback to patient reporters on what the MHRA does with reports
  - explore possibilities for providing specific feedback to patients in relation to the medicines and suspected ADRs that they report.

- To aid future comparisons of reports submitted by patients and HCPs it important that similar information is collected from both groups, particularly with respect to categories of seriousness.
- According to patient accounts, some HCPs seem to be unaware that patients can submit their own ADR reports, and some appear to be dismissive of patients who report suspected ADRs. Education at an undergraduate and postgraduate level might help address these issues.

Recommendations for research

In order of priority, these are investigation of:

1. the pharmacovigilance impact of patient reporting in a long-term study, including the identification and tracking of regulatory action taken as a result of the contribution of patient reports
2. the optimum approach to signal generation analysis of patient and HCP reports
3. the burden of ADRs in terms of impact on patients' lives, and evaluating the extent to which patients' views and experiences of the seriousness of ADRs concur with those of regulatory bodies, such as the MHRA
4. the knowledge and attitudes of HCPs towards patient reporting of ADRs, and evaluating approaches aimed at addressing any learning needs identified
5. the value of using patient reports of ADRs to help other patients and HCPs who are seeking information on patient experiences of ADRs
6. the impact of increasing publicity and/or enhancements to reporting systems on the numbers and types of Yellow Card reports from patients.

Funding

Funding for this study was provided by The National Institute for Health Research Health Technology Assessment programme.

Publication

Avery AJ, Anderson C, Bond CM, Fortnum H, Gifford A, Hannaford PC, *et al*. Evaluation of patient reporting of adverse drug reactions to the UK 'Yellow Card Scheme': literature review, descriptive and qualitative analyses, and questionnaire surveys. *Health Technol Assess* 2011;**15**(20).

NIHR Health Technology Assessment programme

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The research reported in this issue of the journal was commissioned by the National Coordinating Centre for Research Methodology (NCCRM), and was formally transferred to the HTA programme in April 2007 under the newly established NIHR Methodology Panel. The HTA programme project number is 06/92/03. The contractual start date was in October 2007. The draft report began editorial review in June 2010 and was accepted for publication in February 2011. The commissioning brief was devised by the NCCRM who specified the research question and study design. The authors have been wholly responsible for all data collection, analysis and interpretation, and for writing up their work. The HTA editors and publisher have tried to ensure the accuracy of the authors' report and would like to thank the referees for their constructive comments on the draft document. However, they do not accept liability for damages or losses arising from material published in this report.

The views expressed in this publication are those of the authors and not necessarily those of the HTA programme or the Department of Health.

ISSN 1366-5278 (Print)
ISSN 2046-4924 (Online)
ISSN 2046-4932 (DVD)

Published by Prepress Projects Ltd, Perth, Scotland (www.prepress-projects.co.uk), on behalf of NETSCC, HTA.
Printed on acid-free paper in the UK by the Charlesworth Group.