



Patient reporting of adverse drug reactions

Falls in the numbers of spontaneous adverse drug reaction (ADR) reports from healthcare professionals (HCPs) have led to renewed interest in patient reporting of suspected ADRs. In addition, as paternalistic models of medicine have declined, excluding patients from reporting schemes has become politically unacceptable.

Evidence for the utility of patient reporting to discover new safety signals has been equivocal.^{1,2} Concerns have been expressed about the validity of patient reporting, with a *Lancet* editorial stating that patient reporting could “risk being seen as politically rather than scientifically driven”.³ Other concerns include trivial or poor reports creating “noise”, bias, and the effect of pressure groups.⁴

History and political context of patient reporting in the UK

Patient reporting to the UK's Yellow Card scheme was first examined in 1983 by a Committee on Safety of Medicines (CSM) Working Party on Adverse Reactions following the withdrawal of benoxaprofen.⁵ They concluded the expert medical opinion of the doctor treating the patient was essential, and advised patients to consult their doctor. The CSM hoped doctors would report appropriately.

In 2003 the National Audit Office examined the Yellow Card scheme as part of a wider review of the MHRA, and asked for the possibilities of patient reporting to be investigated.⁶ A pilot patient reporting system using the NHS Direct telephone service as an intermediary launched in April 2003, receiving a disappointing 39 reports.⁷ Patient groups also argued that the gate-keeping role of NHS Direct had prevented patients' qualitative experiences from being collected.

In 2004, *The Independent Review of Access to the Yellow Card Scheme* recommended the introduction of a direct patient reporting system.⁴ Re-launched in January 2005, and

rolled out nationally in October 2005, the revised patient reporting scheme included an electronic form for reporting ADRs, a telephone number, and a paper form. The scheme was re-launched again in February of 2008, using community pharmacies to raise public awareness. The MHRA has received about 9,000 reports to date from the various incarnations of their patient reporting scheme.⁸

An ongoing independent evaluation of the patient reporting scheme, funded by the MHRA, was started in September 2007; it will investigate the patient experience and involvement in the scheme, the scientific value of the reports, and the pharmacovigilance impact of patient reports.

Evidence for patient reporting

Patient self-monitoring schemes have been used in the past to some success by focusing on specific drugs of concern,⁹ and have been argued to be essential for obtaining reliable reports of effects from central nervous system drugs. Self-monitoring studies performed in the UK appear to find higher levels of ADRs compared with other post-marketing surveillance methods.¹⁰

Evidence suggests that patients can identify adverse reactions which are similar to, although sometimes less serious, than those reported by professionals and appear willing to report ADRs.¹⁰⁻¹³ Hospitalized patients may also be able to contribute to ADR reporting.¹⁴

Faster signal generation

The speed at which neuropsychiatric ADRs are detected by existing reporting systems has been criticised.¹⁵ A telephone information service in the Netherlands compared patient reports of ADRs to paroxetine, with health professional reports received by the regulator.¹⁶ The proportion of new unlabelled ADRs was similar for both patient and professional reports (21% vs 18%), but mean lag time for all ADRs was 229 days less for the patient reports, and 273 days less for nine new unlabelled ADRs.



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Quality of reports

Patient reports to the Netherlands phone service were considered crude and incomplete compared with professional ADR reports.¹⁶ E-mails elicited after a BBC documentary examining the safety of selective serotonin reuptake inhibitors (SSRIs) were found deficient in key data, such as name, sex, and age of the informant, dosage or duration of treatment, concurrent medication and diagnosis, although no formal reporting structure was in place to guide patients.¹⁷

Hammond *et al.*¹⁸ examined the quality of a sample (n=400) of patient reports and healthcare professional reports received by GlaxoSmithKline during 2003. They reported that the combined proportion of high and moderate quality reports were similar for patients (67.5%) and HCPs (61.5%) respectively. They suggested that consumer reports might be capable of providing reports that are useful in signal generation.

An evaluation of six months of MHRA patient reports (n=407) showed no difference in the number of serious ADRs compared with HCPs, although patients focused on well-established drugs, rather than newer agents. Patient reports were judged less complete, but there was no difference in causality assessments.¹⁹

The nature of patient reports

Patient reports capture the personal experience of ADRs in a way that professional reports cannot. The narrative 'richness' of such reports could guide regulatory authorities towards ADRs dismissed as trivial by HCPs. Patient reporting is likely to be influenced by the differing perception of risks that patients have and their interpretation of information provided to them about the safety of medicines.²⁰⁻²² There is evidence that patients are more likely to report symptoms, such as sexual dysfunction, which they may feel uncomfortable raising with a HCP.²³

Comparison of HCP Yellow Card reports and patient reports related to paroxetine, has showed patient reports to be much richer in terms of their description of the nature, severity, and significance of reactions than professionals' ADR reports.²⁴ This echoes evidence from the Swedish consumer organisation KILEN, who also found clear differences between HCP and patient reports. Withdrawal reactions, dependency, suicidal

behaviour, and "electric shocks" associated with sertraline were reported by patients, but no comparable reports were received from professionals.²⁵ Patient reports were overwhelmingly concerned with psychotropics and painkillers.

On other occasions patients may miss ADRs. A study comparing self-reported ADRs and those found by clinical examination by doctors in 404 patients over 75 years of age, found 11.4% (46) of patients identified ADRs, compared with 24% (97) of clinicians.²⁶ Only 7 patients had an ADR identified by a physician that was self-reported, and in only four cases was the ADR the same. Some ADRs may be discounted by patients as the effects of aging, or not recognized as being a possible effect of a drug. Physicians may neglect less clinically obvious effects or trivial effects that might be considered disturbing by patients.

Routes of reporting

Examination of the characteristics of users of a telephone and internet drug information service for patients in the Netherlands has shown that males and young patients were more likely to use the internet-based service than the phone line service.²⁷

The Netherlands patient ADR reporting scheme argues that selective reporting by younger patients does not occur, despite only accepting electronic reports.²³ Currently, around 40% of MHRA patient reports are electronic.⁸ To maximize participation, differing routes of reporting should be offered.

International experience

A CSM Patient Reporting ADR Group concluded that although there was a lack of evaluations of patient reporting, international experience suggested new ADRs had been discovered,⁷ and provided evidence for patient reporting in Australia, Denmark, the US, the Netherlands, Sweden, and Canada. Further evidence for patient reporting in Denmark, Sweden, Australia and the US was presented at the recent International Society of Pharmacovigilance Annual Conference in Buenos Aires.²⁵

The Danish Medicines Agency has been accepting patient reports for six years, with 19% of all ADR reports being made by patients. ADRs related to the nervous system made up the majority of

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patient ADRs, and psychoactive drugs were reported in far higher proportions by patients than by professionals.

The Australian Adverse Medicine Events (AME) telephone service for ADRs uses pharmacists as expert intermediaries. One in four calls is forwarded to the Australian regulator. Again, central nervous system drugs are the most commonly reported drugs and psychiatric and neurological ADRs the most common reported reactions. The effect of news reporting on patient ADR reporting was demonstrated by the disproportionately high amount of zolpidem reports made, following media coverage of bizarre sleep walking and nocturnal sleep-related eating disorders associated with zolpidem.

Patient reports to the FDA's Adverse Event Reporting System (AERS) were 22% of all reports in 1998 and 46% of all reports by 2008. Patients reported more neuropsychiatric ADRs than HCPs. The top three drugs reported by patients from 2003–2007 were paroxetine, sertraline and levofloxacin, compared with warfarin, lisinopril and simvastatin from professionals.

The Netherlands Pharmacovigilance centre has accepted patient reports since 2003. They report that patient reports contain sufficient medical information for pharmacovigilance purposes. Failure of HCPs to listen to complaints about possible ADRs, or a lack of confidence that a report would be submitted were cited as key motivations for patients.²³ Patient reports make up 19% of reports and report more "life-threatening" ADRs (5.2% vs 2.7%) and ADRs associated with "significant disability" (2.3% vs 0.4%). HCPs reported more deaths (1.5% vs 0.6%) and admissions to hospital/prolonged hospital stay (0.4% vs 2.3%). Outcomes of the ADR, such as non-recovery, were more likely to be reported by patients. Patients also focused on reactions that impacted on their quality of life, such as weight gain, decreased libido and fatigue, than HCPs.

Herbal and OTC medicines

The increasing expansion of the range of Over-the-Counter (OTC) medicines available, their potency and the potential for unapproved use²⁸, makes the monitoring of OTC medication of particular importance.²⁹ Patient reporting of ADRs to OTC medicines, facilitated by pharmacists, has also been shown to find ADRs,

and inappropriate use of OTC medicines, that may be of interest to regulatory authorities.^{23,28,29}

Herbal medicines have also had increasing popularity in recent years. Interviews with users of herbal remedies have indicated 69% of users would not consult their GP in the event of a serious suspected ADR to a herbal product; 44% would not consult their GP with a serious reaction to an OTC medicine either.³⁰ Evidence from Australia suggests patients will self-report herbal ADRs.²⁵

Pharmacovigilance impact

It has been argued that the collective weight of patient reports is profound,¹⁵ but how should regulators deal with those effects deemed important by patients, if they are already acknowledged effects and further reports of which may have little immediate regulatory value? Opening up ADR reporting to patients creates an expectation that action will be taken. Registering the burden of non-serious ADRs that significantly decrease patients' quality of life may be easy, but communicating the information in a manner that will enable patients and prescribers to make informed decisions about the use of medicines may be more difficult.

Difficulties in coding patient reports have been noted⁷. Medawar and Herxheimer reported that coding of HCP reports of ADRs to paroxetine may have hidden the impact of ADRs on patients, such as the coding of "electric shock sensations" to the preferred term paraesthesia. While coding of ADR is essential in pharmacovigilance, care must be taken that the patient experience is not lost.

The FDA has reported that individual patient reports can trigger regulatory action. Receipt of a patient report of severe heart failure in a mitoxantrone-treated MS patient led to a review, revised warnings and an educational programme to inform prescribers of the risk of heart failure. A patient report of liver failure with tolcapone was pivotal in a series of cases submitted to the FDA, and led to the addition of liver failure in the product literature.²⁵

In the Netherlands examples of patient reporting contributing to new drug safety messages have been reported: inflammatory



bowel disease associated with isotretinoin, hyperparathyroidism associated with lithium, and pathological gambling associated with pergolide.²⁵

Conclusions

Patient reports complement professional reports of ADRs. Patients report a different spectrum of ADRs; neuropsychiatric reactions appearing to

be a particular concern. In addition, there are qualitative differences in the nature of reports that provide challenges to existing pharmacovigilance systems in terms of both coding and regulatory decision making. However, regulators value reports from patients. There is evidence that such reports have contributed to drug safety signals and regulatory decisions, which is the primary purpose of spontaneous reporting schemes.

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