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Adverse Drug Reaction Reporting by Patients in the Netherlands

Three Years of Experience

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Abstract

Background: There has been discussion about the acceptance of adverse drug reactions (ADRs) reported by patients to spontaneous reporting systems. Lack of experience with patient reporting in real life was one of the main drawbacks in this debate. This study covers 3 years of experience with patient reporting in daily practice. We compared patient reports with reports from healthcare professionals. Although patients have the opportunity to report ADRs in several countries, little is published in the literature about the contribution that patient reports have in practice. To our knowledge, this paper is the first to describe long-term experiences with patient reporting as part of a spontaneous reporting system.

Methods: The number of reports received, age and sex of the reporters, characteristics of the most frequently reported drugs and characteristics of the ADRs (most frequently reported ADRs, seriousness, outcome) in a 3-year period (April 2004–April 2007) were compared between patient reports and reports from healthcare professionals.

Findings: During this 3-year period, the Netherlands Pharmacovigilance Centre Lareb received 2522 reports directly from patients, concerning 5401 ADRs. In the same period, healthcare professionals submitted 10 635 reports, concerning 16 722 ADRs. Differences were found in the categories of seriousness and outcome of the reported ADRs between patients and healthcare professionals. Conversely, similarities between patient reports and reports from healthcare professionals were found in age, sex, most frequently reported ADRs and most frequently reported drugs.

Interpretation: Our study highlights clearly that valuable differences between ADR reports from patients and reports from healthcare professionals exist. Differences in interpretation by patients and healthcare professionals may cause the observed disparities in seriousness and outcome of reported ADRs. However, the similarities between patient reports and reports from healthcare professionals in most frequently reported ADRs and most frequently reported drugs are striking.

After 3 years of experience with patient reporting, we conclude that patient reporting in spontaneous reporting systems is feasible and that it contributes significantly to a reliable pharmacovigilance.

Background

Recently, interest for patient reporting of adverse drug reactions (ADRs) has been growing. Patients' understanding of illnesses is on the increase and many patients wish to be involved in decisions regarding his or her disease and therapy.[1]

Patients can provide first-hand information about their experiences with drugs and possible ADRs. Therefore, patients are a valuable source of information. For instance, patient reports may provide information on over-the-counter drugs or alternative and complementary medication, about which the doctor is unfamiliar. Patients may be able to give more detailed information about the impact of an experienced ADR on their quality of life. There is also the possibility that patients, because they lack medical knowledge, are more likely to report associations that may seem unlikely from a medical point of view, but can turn out to be a true signal. A drawback of unfiltered information from patient reports is the lack of medical confirmation, which might impede the interpretation of possible ADRs.

In most countries, only healthcare professionals such as general practitioners and specialist doctors are allowed to report ADRs. However, in an increasing number of countries, other healthcare professionals, such as pharmacists and nurses, are also allowed to report ADRs.[2,3] The reporting of ADRs by patients is accepted only in some countries, e.g. the US, the Netherlands and Denmark.[4] Recently, the UK and Sweden also started accepting patient reports.[5] In 2006, Blenkinsopp et al.[6] wrote a review on patient reporting of suspected ADRs. They concluded that although patient reports are collected in several countries, there is a lack of publications about patient reporting of suspected ADRs in the literature. Most previously published studies were small, and none of them involved spontaneous reporting by patients.[6] In the Netherlands, patient reports are considered just as important as reports from healthcare professionals in the spontaneous reporting system, but the lack of experience with patient reports makes it difficult to address the fundamental question regarding their intrinsic value. The need for evaluation of patient reporting is emphasized in several publications.[4,6]

Patient Reporting in the Netherlands

Since 1 April 2003, patients have been able to submit reports of possible ADRs directly to the Netherlands Pharmacovigilance Centre Lareb. Initially, there was discussion about the acceptance of patient reports.[4] Patient reporting was tested during a 1-year trial, and impressions were favourable.[7] Patient reports usually contained sufficient medical information to be useful to pharmacovigilance.

Since April 2004, Lareb has accepted that ADRs reported by patients are of equal value to reports from healthcare professionals. However, although healthcare professionals can choose between reporting electronically or on paper, patients can only report electronically. The content of the electronic form and the paper form is identical. The well-structured reporting form on the Lareb (www.lareb.nl) with several mandatory fields ensures completeness of information. There is also no difference in the content of the electronic form available to healthcare professionals and patients, although the patient form contains more information and the language used is easy to understand. These electronic reports can be read automatically by our internal computerized assessment system. Each re-

port, either from a patient or a healthcare professional, is assessed on an individual basis by a Lareb assessor, doctor and pharmacist who have received special training for this purpose. Each reporter receives personal feedback on the ADR reported. With the help of a computer-assisted system, the process is highly efficient and a large number of reports can be assessed.

Patient reports are marked initially as not medically confirmed in the database, whereas healthcare professional reports are marked as medically confirmed. If needed, the assessor of a report is able to ask patients for permission to contact their healthcare professional for additional information. With this additional information, a report may then become medically confirmed.

On occasion, both the patient and their healthcare professional send in a report about the same ADR. With each new report, a check is run based on the patient's sex and date of birth. If there is a match between reports, the details of the reports are compared and duplicated reports can be combined.

Not all patients are able to fill in the reporting form, i.e. in cases of ADRs in children or patients who are deceased. In such circumstances, Lareb accepts reports filled in by relatives or acquaintances.

After the introduction of patient reporting, Lareb started a large campaign to inform patients that the opportunity to submit reports was available to them. This information is published on the Internet, by the general media, and especially in journals from patient and consumer organizations. Leaflets are also available in pharmacies to inform patients that they can report ADRs and how to report.

Aim of the Study

We conducted a study analysing 3 years of experience with patient reporting of ADRs to examine the value of patient reports to a spontaneous reporting system.

Methods

Patient reports received between 1 April 2004 and 1 April 2007 were compared with the reports from general practitioners, specialist doctors and pharmacists (referred to as 'healthcare professionals') received in the same period. We included all reports from patients and healthcare professionals that were sent directly to our national pharmacovigilance centre during the research period. We combined duplicated healthcare professional and patient reports.

The number of reports received, patient characteristics and information about the reported drugs and ADRs in this 3-year period were compared between patient reports and reports from healthcare professionals. Patient characteristics of interest were age and sex. We compared the most frequently reported drugs between the two groups. The ADR characteristics we investigated were (i) the most frequently reported ADRs; (ii) the seriousness of the ADR; and (iii) the outcome of the reported ADRs.

The seriousness of the reports was categorized using the criteria formulated by CIOMS, namely death, life-threatening factors, hospitalization or prolongation of hospitalization, disability/incapacity, congenital anomaly/birth defect and other ADRs considered serious by the reporter.[8] In order to determine the most frequently reported drugs, the drugs were divided according to the first three levels of the WHO Anatomical Therapeutic Chemical classification system.[9]

ADRs were coded according to the Medical Dictionary for Regulatory Activities (MedDRA) coding system, which refers to a group of MedDRA terms belonging to a System Organ Class.[10,11]

To establish possible significant differences, we used a chi-squared (χ^2) test. A t-test was used to establish possible significant differences in the male-female ratio between reports from patients and healthcare professionals. Statistical analyses were performed with SPSS (Chicago, IL, USA).

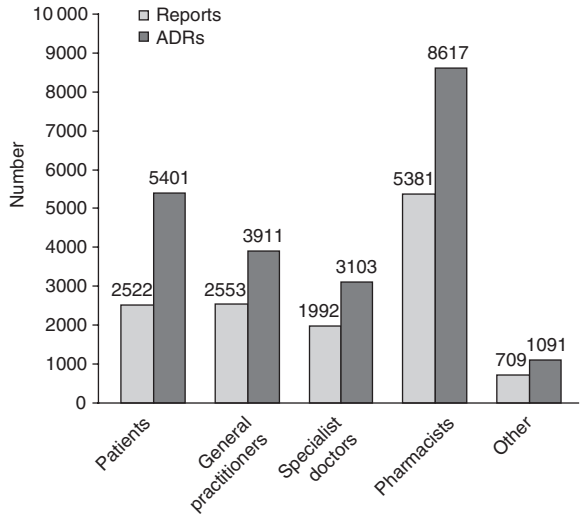

Fig. 1. Number of reports and adverse drug reactions (ADRs) stratified by source, in the period 1 April 2004 to 1 April 2007.

Results

During the 3-year period from April 2004 to April 2007, patients submitted 2522 reports concerning 5401 ADRs to Lareb (figure 1). Healthcare professionals submitted 10 635 reports, concerning 16 722 ADRs.

Patient Characteristics

Of the reports from patients, 63% of the patients were female compared with 61% in the reports from healthcare professionals. The difference between both groups was not statistically significant. The mean age of patients in the reports from patients was also similar (48 years) to that in the reports from healthcare professionals (49 years).

Type of Reported Drugs and Associations

The five drug categories most frequently reported by patients were successively HMG Co-A reductase inhibitors ('statins'), selective serotonin reuptake inhibitors, β-adrenoceptor antagonists ('β-blockers'), anticoagulants and proton pump inhibitors. As table I shows, the top five drugs reported by the different groups of healthcare professionals showed great similarity with that of patients. Statins were the most frequently reported drugs for patients, pharmacists and general healthcare professionals.

The five most frequently reported associations by patients included three associations of a statin associated with myalgia, one of a statin with arthralgia and one of paroxetine with weight gain. Other frequently reported associations by patients were paroxetine and decreased libido and paroxetine in association with fatigue.

Characteristics of the Reported Adverse Drug Reactions (ADRs)

There was a similarity between reports received from patients and reports from healthcare professionals concerning the System Organ Class for which the ADRs were most frequently reported. Nervous system disorders, psychiatric disorders, gastrointestinal disorders, musculoskeletal disorders and general disorders/administration-site conditions were the five most involved organ systems for patients and general practitioners. For pharmacists, skin and subcutaneous disorders were among the five most frequently involved organ systems instead of psychiatric disorders. For specialists, skin and

Table I. Five most frequently reported drug classes, stratified by source, in the period 1 April 2004–1 April 2007

Patients top five	% of total reported drugs in patient reports	GPs top five	% of total reported drugs in GP reports	Specialists top five	% of total reported drugs in specialist reports	Pharmacists top five	% of total reported drugs in pharmacist reports
Statins	8.2	Statins	6.9	Benzodiazepines	4.1	Statins	6.0
Serotonin reuptake inhibitors	4.7	β-Blockers	5.0	Proton pump inhibitors	4.0	Benzodiazepines	4.7
β-Blockers	3.6	Anticoagulants	4.5	Statins	3.3	Anticoagulants	4.5
Anticoagulants	3.5	Proton pump inhibitors	4.3	Anticoagulants	3.1	Proton pump inhibitors	4.3
Proton pump inhibitors	3.4	ACE inhibitors	3.5	Glucocorticoids	2.2	β-Blockers	3.1

GP = general practitioners; **statins** = HMG CoA reductase inhibitors.

subcutaneous disorders were among the five most frequently involved organ systems instead of musculoskeletal disorders.

Table II and table III show the ten most frequently reported ADRs for patients and health professionals. Patients reported myalgia most frequently. Myalgia is a well known ADR of statins, the drug class most frequently included in reports from patients. For health professionals, both headaches and rash were reported most frequently; myalgia ranked fourth in the top ten.

Overall, the seriousness of the reports was not significantly different between reports from patients (19.5%) and from healthcare professionals (21%). However, there were differences in the categories of seriousness (figure 2). Patients reported a significantly higher number of life-threatening ADRs (5.2% vs 2.7%) and disability (2.3% vs 0.4%). Moreover, patients reported significantly fewer ADRs leading to death (0.6% vs 1.5%) and hospitalization or prolongation of hospitalization (9.8% vs 12.0%). No significant differences in 'other' serious ADRs (6.4% vs 6.2%) or 'congenital anomaly' (0.1% vs 0.3%) were determined (χ^2 test: $p > 0.01$). Figure 2 shows the criteria of seriousness stratified by source. Overall, patients reported a significantly higher number of life-threatening ADRs (5.2% vs 2.7%) and disability (2.3% vs 0.4%) than health professionals.

There was a significant difference between patient reports and reports from healthcare professionals in the proportion of reports that included mention of the outcome of the ADR (87% vs 68%; χ^2 test: $p < 0.01$). Patients reported non-recovery (35.4%) from the ADR significantly more often than healthcare professionals (16.7%).

Case report

On occasion, both the patient and healthcare professional involved reported on the same suspected ADR to the same drug. In this case report, we

Table II. The ten most frequently reported adverse drug reactions (ADRs) for patients in the period 1 April 2004–1 April 2007

Adverse drug reaction	Number of reports	% of total number of ADRs (n = 5401)
Myalgia	193	3.6
Fatigue	171	3.2
Headache	159	2.9
Dizziness	144	2.7
Nausea	126	2.3
Depression	111	2.1
Weight increase	106	2.0
Rash	100	1.9
Arthralgia	96	1.8
Insomnia	80	1.5

describe an example of a duplicate report from a pharmacist and a patient.

A pharmacist reported headaches in a woman aged 44 years following withdrawal of octreotide (Sandostatin®)[1] 0.1 mg twice a day by subcutaneous injection for acromegaly, with a latency of days. The headache ceased within 5 minutes after the first re-administration of octreotide. The patient had experienced headaches during treatment in the previous years whenever she was late to administer the next dose of octreotide. Concomitant medications were levothyroxine and hydrocortisone. The pharmacist reported that the patient had not recovered from the ADR.

Two months later, we received an independent, direct notification from the patient herself. Her report contained the following information.

A female aged 44 years (height 170 cm; weight 89 kg) experienced headache and drowsiness following withdrawal of octreotide 0.1 mg three times a day for acromegaly with a latency of 2 days after octreotide had been withdrawn. The patient started injecting octreotide again to relieve the headaches. Concomitant medication was not reported. The patient reported that she had not recovered from the headache and drowsiness. Relevant medical history: surgery of the pituitary gland in 1991 and irradiation in 1996. In addition, the patient wrote in the open text part of the ADR notification form: "….My endocrinologist allowed me to stop treatment with Sandostatin® because my somatomedin level was stable at around 119 ng/mL and the 24 hour growth hormone curve showed levels between 1.8 and 8 mU/L. I had not taken Sandostatin® for six days but headaches were killing me all that time. I took up to 6 tablets of paracetamol a day with barely any effect on the headaches. I was also very drowsy during those days. As soon as I reported this to my endocrinologist he instructed me to start injecting Sandostatin® again. So now I am forced to inject Sandostatin® to prevent headaches. In retrospect, the moment for the next Sandostatin® injection was announced by headaches during all the previous years I was treated with Sandostatin®. I never needed a clock to know when my next injection was due!".

Discussion

Our study showed that some characteristics of patient reports (sex and age of the patient, the five most frequently reported ADRs and drugs) resembled those of healthcare professional reports, where-

Table III. The ten most frequently reported adverse drug reactions (ADRs) for healthcare professionals in the period 1 April 2004–1 April 2007

Adverse drug reaction	Number of reports	% of total number of ADRs (n = 16 722)
Headache	404	2.4
Rash	397	2.4
Dizziness	332	2.0
Myalgia	325	1.9
Nausea	301	1.8
Alopecia	287	1.7
Palpitations	241	1.4
Pruritus	233	1.4
Dyspnoea	226	1.4
Angioedema	216	1.3

1 The use of trade names is for product identification purposes only and does not imply endorsement.

as other characteristics (category of seriousness and outcome of the ADR) showed significant differences. Although in several countries patients have the opportunity to report ADRs, little is published in the literature about the contribution that patient reports have in practice. To our knowledge, this paper is the first to describe long-term experiences with patient reporting as part of a spontaneous reporting system.

Patients can report only through a reporting form on our website. Electronic reporting is possible in the Netherlands because Dutch consumers make use of the Internet extensively. In 2006, among people aged 65–75 years, 56% made use of the Internet on an almost daily basis. In younger age groups, this percentage was even higher at about 80% (source Dutch Central office for Statistics, www.cbs.nl). Electronic reporting has a number of important advantages. The structured reporting form facilitates the completeness of information; the report can be submitted to the centre only if all mandatory fields are filled in. Besides this, electronic reporting makes it easier to handle and assess a large number of patient reports. Furthermore, electronic reporting might increase the number of specific ADRs and concerns about specific drugs that patients do not wish to share with their healthcare professionals. The opportunity to write to an 'anonymous' organization may therefore be appealing especially to them.[12]

A possible drawback of patient reporting could be 'confounding by indication'. We try to be alert to this possibility in the medical assessment of the reports. For example, a consumer recently reported throat pain and ear pain in association with azithromycin, which was prescribed for the indications otitis and heavy coughing. In the computer-assisted system that is used for the assessment of the reports, reports with possible confounding can be 'marked'.

Another possible bias could be reporting bias, i.e. reporting stimulated by media exposure of specific safety issues. In our study, no evidence for this type of bias in patient reports was found during the study period. In our experience, reporting bias through media exposure can affect both patients and healthcare professionals.[13]

Also, the possibility that litigation may drive patient reports could be a point of concern. In the Netherlands, this has not been an issue so far. However, we try to be alert to possible legal actions that might be involved with a report.

Patient Characteristics

Both patient reports and healthcare professional reports referred more often to female patients than to male patients. This could be explained by the fact that women are known to use more drugs than men.[14] Whether or not women are more likely to report an ADR is an issue for further research.

The mean age of patients who reported ADRs themselves was comparable with the mean age of patients reported on by healthcare professionals. Apparently, the fact that patients could only report ADRs electronically, while healthcare professionals could also report on paper, did not lead to a selection of younger patients, as was found in an earlier study.[7] Patients were more likely to report on symptoms that may be less easy to discuss with the doctor or pharmacist, for instance those relating to sexual matters. An alternate explanation is that patients find sexual ADRs, such as impotence, to be of greater concern than healthcare professionals do.

Reported Drugs and ADRs by Patients

The five drugs most frequently reported by patients and healthcare professionals showed similarity, but the ranking in the top five differed. Reported ADRs such as weight gain, decreased libido and fatigue were among the most frequently reported ADRs by patients, and this probably reflects the impact that these adverse effects have on the quality of life of users of drugs.

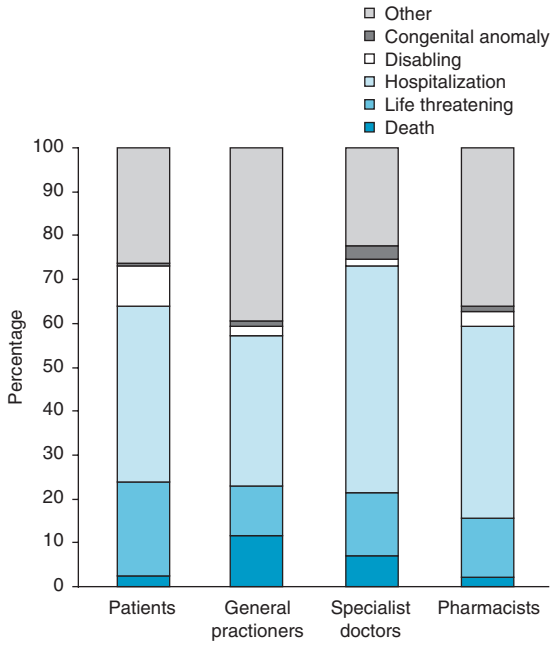

Fig. 2. Criteria of seriousness of reported adverse drug reactions (ADRs), stratified by source, in the period 1 April 2004–1 April 2007.

We did not find a significant difference in the percentage of serious ADRs in general between patients and healthcare professionals. However, we found differences between the two groups in the nature of seriousness. Patients often chose the rather subjective seriousness criteria 'life threatening' or 'significant disability'. When necessary, we asked patients for permission to consult their doctor or pharmacists. This could easily be obtained by e-mail, because all the reports were received electronically. In cases where patients are not able to fill in the report themselves, a relative can report for them. Nevertheless, the number of fatal ADRs is less for patient reports than for health professional reports.

Patients differed in their evaluation of the outcome of the ADR. They reported a non-recovery substantially more often than healthcare professionals. This could be explained by the impact non-recovery has on the patient, being a constant reminder for him or her to report. Differences in interpretation of full recovery could also be an issue. A physician could conclude that a patient was fully recovery after normalization of relevant laboratory values, whereas the patient could feel not recovered because of persistent fatigue. Here, patient reports can provide additional information about the impact of an ADR on daily life. Another explanation may be that patients report relatively soon after they experience the ADR, before full recovery could be anticipated.

In our opinion, the differences between patient reports and reports from healthcare professionals in nature of seriousness and in outcome reflect the specific contribution of patient reports. As figure 2 shows, the percentage of serious reports from patients was higher than those from general practitioners and pharmacists, but lower than those from specialist doctors. The CIOMS criteria allow 'other' reasons to consider an ADR to be a serious,[8] giving insight into the effect an ADR has on a patient's daily life. Also the judgement about the final outcome reflects how the patient's perspective on recovery differs from that of the healthcare professional.

Contribution of Patient Reports to Pharmacovigilance

The involvement of patients in drug safety is demonstrated in cases associated with diethylstilbestrol, benzodiazepines, antidepressants and, more recently, hormone replacement therapy.[15] Patient reporting is in line with efforts towards providing quality in a health system where patients have a key position.

It should be emphasized that patient reports are not meant to replace reporting by healthcare professionals and that it is very important that healthcare professionals should not be deterred from reporting ADRs.[5] Healthcare professionals are a reliable source of ADR reports, although it is known that many physicians and pharmacists do not report.

Therefore, patient reports provide a good additional source of reports.

A recent study assessed patient opinions about how physicians responded when patients presented with possible ADRs. Patients reported that they, and not their physician, most commonly initiated the discussion about a possible relationship between the drug and symptoms. Physicians were also more likely to deny than affirm the possibility of a relationship, even for symptoms where there was strong support for a drug connection in published literature.[16] This problem was evident in our study period. Half of the patients who reported to Lareb during the 3-year period claimed that their healthcare professional did not take their complaint about a possible ADR seriously and was not inclined to report their experience.

Acceptance of patient reports will enhance the number of reported ADRs received in a certain time period, which increases the statistical power for signal detection and will contribute to signal detection of new ADRs.[16] We recently reported possible new associations based mainly on patient reports. In 2006, Lareb described three cases on inflammatory bowel disease associated with the use of isotretinoin. The first two cases were reported directly by patients, the third case was reported by a general practitioner.[17] In 2005, Lareb notified healthcare professionals about a case-report of hyperparathyroidism in association with lithium that was reported by the patient.[18] In the Dutch Drug Bulletin, we also underlined the serious implications that gambling addiction caused by drugs for the treatment of Parkinson's disease can have on a patient's daily life. We received two reports of pathological gambling in patients treated with the drug pergolide, one by a neurologist and one by a patient.[19] Reporting of this association to the Dutch Medicines Evaluation Board led to a change in the Dutch Summary of Product Characteristics (SPC) for pergolide, where pathological gambling is now mentioned as a possible ADR.[20]

Our case report about withdrawal headaches in association with octreotide illustrates the potential value of reports from patients and healthcare professionals. The reports of headache in association with octreotide were the first two such reports ever received by the Netherlands Pharmacovigilance Centre Lareb. Headaches are not listed in the Dutch SPC of Sandostatin®.[21] The US SPC of Sandostatin® does list headache under 'other adverse events' with a prevalence of 6% but does not mention withdrawal symptoms.[22] In fact, it is stated in the US SPC that "there is no indication that Sandostatin® (octreotide acetate) has potential for drug abuse or dependence".[22] However, case reports and case series have been published which show that patients experience 'rebound headache' caused by octreotide and that patients can experience drug dependence because of this.[23-26] The relationship between withdrawal of octreotide and 'rebound headache' is plausible in this case. Prescribers and users of octreotide should be alert to the possibility of such reactions.

Conclusion

Three years of experience with patient reporting has taught us that patient reports contribute substantially to the reporting of ADRs, both in quantity and quality. Reports from users of drugs are generally well documented reports with valuable information. The different point of view from patients, compared with healthcare professionals, is an interesting starting point for obtaining valuable information. Interpretation differences by patients and healthcare professionals may have caused the observed differences with respect to the seriousness and outcome of the ADR. On the other hand, the similarities in sex, age, most frequently reported ADRs and most frequently reported drugs are striking. We conclude that patient reporting in spontaneous reporting systems is feasi-

ble and that it significantly contributes to a reliable pharmacovigilance.

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