Drug Saf (2013) 36:267–276
DOI 10.1007/s40264-013-0028-8

ORIGINAL RESEARCH ARTICLE

Effect of Pharmacist Involvement on Patient Reporting of Adverse Drug Reactions: First Italian Study

Roberto Leone · Ugo Moretti · Paola D'Incau · Anita Conforti · Lara Magro · Riccardo Lora · Giampaolo Velo

Published online: 9 March 2013

Abstract
Background Adding patients to the range of potential reporters of adverse drug reactions (ADRs) may increase spontaneous reporting and contribute to the detection of signals, one of the primary aims of spontaneous reporting systems. Community pharmacies could have an important role in this context as a service for promoting patient reporting of ADRs.
Objectives The main objectives of the present study were to assess the potential impact of an intervention to promote patient reporting in community pharmacies in the Veneto region of Italy, and to compare the characteristics of patients' and general practitioners' (GPs) reports of ADRs.
Methods The study was conducted in the Veneto region of Italy and involved 211 pharmacists working in 118 community pharmacies. Each pharmacist was asked to select, during the study period, about 250 customers who had received at least one drug, and then to present the spontaneous reporting form to those who had experienced a suspected ADR. Patients were asked to complete the ADR report form and either give it back to the pharmacist, or send it by fax or mail, or else to fill in the form online.
Results In a 4-month period, 52,495 customers were interviewed by the pharmacists and 4,949 of them (9.4 %) referred a suspected ADR. The Pharmacovigilance Centre of the Veneto region received 2,311 citizen's ADR reporting forms related to the study (from 46.7 % of all patients interviewed who had experienced suspected ADRs). After quality control 1,794 of these reports were entered into the Italian Pharmacovigilance Database and were compared with the reports (226) sent by GPs in the Veneto region in the same period. Patients reported a higher percentage of known and non-serious reactions than did GPs. Drugs widely used in the community setting, and over-the-counter products, were the drugs most frequently reported by patients. In contrast, few reports involving reactions to antineoplastic agents or contrast media—drugs mostly used in a hospital setting—were sent by patients.
Conclusions Our study shows that patient reporting has the potential to add value to the pharmacovigilance system. The overall quality of the information provided in patients' reports was good. The differences between reports by patients and by GPs indicate different points of view that can enrich spontaneous reporting.

Electronic supplementary material The online version of this article (doi:10.1007/s40264-013-0028-8) contains supplementary material, which is available to authorized users.

R. Leone · U. Moretti · P. D'Incau · A. Conforti · L. Magro · R. Lora · G. Velo
Pharmacology Unit, Department of Public Health and Community Medicine, University of Verona, Verona, Italy

R. Leone (✉)
Department of Public Health and Community Medicine, Section of Pharmacology, University Hospital, p.le LA Scuro 10, 37134 Verona, Italy
e-mail: roberto.leone@univr.it

1 Introduction

In recent years, interest has been growing in the role of patients as potential reporters of adverse drug reactions (ADRs) [1–9]. ADR reporting by patients could greatly increase knowledge of the possible harm caused by medicines because their reports arise from direct experience of the effects of drugs. The added value of patients' reports may result from their different points of view and experiences of adverse effects, which complement ADR descriptions made by healthcare professionals.

It is recognized that under-reporting is a major drawback of spontaneous reporting systems of ADRs [10–12]. Adding patients to the range of potential reporters may increase spontaneous reporting, contributing to detection of signals, one of the primary aims of spontaneous reporting systems [4].

This topic was recently discussed at the European Medicines Agency (EMA), and the importance of patients as ADR reporters was emphasized in the new European legislation on pharmacovigilance (December 2010) [13, 14]. To date, the major nations actively involved in promoting ADR reporting by consumers are Australia, Canada, Denmark, the Netherlands, the USA and the UK [8, 13, 15]. The country in which patients make the greatest contribution to pharmacovigilance is the USA, where almost 50 % of ADR reports come from consumers [13].

In Italy, the possibility of direct patient reporting was formally introduced in April 1991 [16], but up to December 2009, few patient reports ($n = 206$) could be found in the Italian Pharmacovigilance Database [17]. Despite the limited number of reports, no action was ever taken to make known to the public the opportunity to report ADRs.

Recently the Italian consumers' organization 'Altroconsumo' promoted an internet survey about use of two topical immunosuppressants (tacrolimus and pimecrolimus). From 2006 to 2009, 566 citizens' web-based questionnaires were collected, which shows that if adequately stimulated, consumers respond in great numbers and provide accurate and detailed information [18]. Consumer involvement appears to favour the collection of better information on the adverse effects of drugs and also to give useful details about other problems with treatments, such as inadequate prescriptions or incorrect use of drugs, which would be very difficult to obtain otherwise.

Apart from the present investigation, to our knowledge no other study or survey directly involving patients in the spontaneous reporting system has been conducted in Italy. This shows the importance of developing intervention and education programmes aimed at patients to promote voluntary reporting of adverse reactions.

The role of community pharmacies in promoting ADR reporting by patients is of considerable value. Community pharmacies are geographically well distributed and easy to access, and may offer an informal environment well placed to provide services for patients who have to look after themselves [19, 20].

The main objectives of the present study were to assess the potential impact of an intervention to promote patient reporting in community pharmacies in the Veneto region, and to compare the characteristics of patient and general practitioner (GP) reports of ADRs.

2 Methods

This stimulated ADR reporting study was conducted in the Veneto region, Italy, and involved 211 pharmacists (10 % of all Veneto pharmacists) working in 118 community pharmacies (9 % of Veneto pharmacies), which were open to the public and evenly distributed across the region. Of these pharmacies, 59 % were located in urban areas (those with a population over 5,000 inhabitants) and 41 % in rural areas (with a population not exceeding 5,000). Since the study was based on stimulated spontaneous ADR reporting, Ethical Committee approval was not required.

2.1 Study Development in Community Pharmacies

The study in community pharmacies took place over a 4-month period from April to July 2010. Each pharmacist was asked to select around 15 people per week aged $\geq$18 years and resident in the Veneto region, who had received at least one drug in the month before the selection day and whom the pharmacist considered capable of complying with the study.

To obtain a sample of people as representative as possible of all types of community pharmacy customers, the pharmacists were asked to select customers who came at different times of day. The number of people selected was calculated to obtain an appropriate number of ADR reports on the basis of the data in the literature, which show that ADRs occur in approximately 10 % of patients taking a drug [21] and that generally only 5–6 % of ADRs are reported [11]. At the time of recruitment, pharmacists recorded, on a dedicated monitoring form, the sex of the selected individuals, their age group (18–65 years or >65 years), and whether they had experienced an adverse event potentially related to a drug treatment during the previous month. Then the pharmacists presented the 'citizen's ADR reporting form' to patients who had experienced a suspected ADR. Patients were asked to complete the ADR report form and either give it back to the pharmacist, or send it by fax or mail, or else to fill in the form online. If the patient asked the pharmacist for help in filling in the form, it was mandatory that the pharmacist not interpret the patient's 'message', but to report whatever patients considered to be connected to the ADR. All the 'citizen's reporting forms' were sent to the Pharmacovigilance Centre of the Veneto region. For economic reasons, feedback confirmation letters were not sent to all patients who returned the ADR form, although an automatic reply was sent to those who reported through the web. Follow-up of reports was not carried out on a routine basis but it was possible if judged to be necessary.

2.2 Citizen's Adverse Drug Reaction (ADR) Reporting Form

In Italy, different ADR reporting forms exist for patients and healthcare professionals. The current citizen's reporting form was introduced in 2004 [22], and can be downloaded from the Italian Medicines Agency (Agenzia Italiana del Farmaco [AIFA]) website (http://www.agenziafarmaco.gov.it/sites/default/files/tipo_file07d6.pdf). This form, which is very similar to the previous one (introduced in 1991), still has important limitations in both the graphical aspects and the type of information requested. For this reason, in agreement with AIFA, a new version of the citizen's reporting form was used in our study (see the Online Resource for the form in Italian and its translation). The information requested from patients was organized in five sections, based on those on the UK Yellow Card Patient Reporting Form: (i) suspected side effects; (ii) medications; (iii) the prescriber; (iv) other relevant medical information; (v) personal information [23].

The reporting form contained all the data required for a report to be entered into the Italian Pharmacovigilance Database. In comparison with the official Italian form, the form we used contained more specific fields for collecting information about concomitant medications (including medicinal herbs, homeopathic remedies, supplements and other complementary medicines), outcomes of the reactions, and concomitant or previous diseases, including any drug allergies or side effects that had occurred in the past.

2.3 Data Entry and Management

In agreement with AIFA, the ADR reporting forms in which all the mandatory fields had been filled in were entered into the Italian Pharmacovigilance Database. Mandatory fields in the Italian spontaneous reporting database include at least one suspected drug and one adverse reaction, the patient's initials, age and sex, the date of onset of the reaction, the starting date of treatment and details about the reporter. As standard practice, reports were evaluated prior to insertion to assess causality, using the Naranjo algorithm [24], and to check whether ADRs were expected or unexpected, according to the Summary of Product Characteristics (SPC). Drugs were coded using national terminology and following the Anatomical Therapeutic Chemical (ATC) classification [25]. Drug reactions were classified using both MedDRA (Medical Dictionary for Regulatory Activities) [26] and WHO-ART (WHO Adverse Reactions Terminology) [27] systems.

The characteristics of ADR reports sent by patients were compared with those sent by GPs in the Veneto region, since they derived from the same setting, i.e. primary care. Specifically, GP reports regarding patients ≥18 years of age that had been collected over a 1 year-period (April 2010–March 2011) were included in this analysis. We excluded from the analysis patient or GP reports classified as doubtful or unclassifiable during the causality assessment. Patient and GP reports were individually compared in a search for potential duplicates, which was based on the patient's initial, age, sex, place of residence and the date of onset of the reaction.

The Italian Pharmacovigilance Database was also used to calculate the spontaneous reporting rate for the Veneto region. The reporting rate was calculated by dividing the annual number of reports in the Veneto region by the number of inhabitants.

All the percentages in the tables are shown with their 95 % confidence intervals. The Chi-square test was used to compare patient and GP reports. All calculations were made using Epi Info, a standard statistical software program developed by the Centers for Disease Control and Prevention, one of the major operating components of the Department of Health and Human Services, Atlanta, US (http://wwwn.cdc.gov/epiinfo/).

3 Results

3.1 General Description of Consumer Data

From April to July 2010, a total of 52,495 customers were interviewed by the community pharmacists, which means around 250 subjects for each pharmacist involved in the study. The sample of interviewees was representative of Veneto residents aged over 18 years ($n = 4{,}082{,}292$, data from the Italian census of 2010 [28]) with a confidence level of 99 % and a confidence interval 49.44–50.56.

Table 1 shows that 9.4 % of customers who were interviewed referred a suspected ADR to the pharmacist. The percentage of women who referred ADRs was higher than the percentage of men, whereas no difference was found between the two age groups.

The citizen's ADR reporting form provided by the pharmacist was rejected by 1,440 patients (29 %), with a higher percentage of men (35 %) than women (27 %) refusing, and a higher percentage of elderly (36 %) than adult patients (25 %). The reason for refusal was not provided in 75 % of cases; when reasons were given, the most frequent were that the ADR had previously been reported to a GP (8.5 %), lack of time (3.4 %) or that the patient had forgotten the name of the drug (3.0 %).

In the period April 2010 to March 2011, the Pharmacovigilance Centre of the Veneto region received citizen's ADR reporting forms from 2,311 individuals, 46.7 % of all patients interviewed who had experienced suspected ADRs. The number of forms received corresponds to 66 %

Table 1 Patients interviewed, patients with ADRs, ADR forms accepted and sent by patients: distribution by sex and age groups

	Total	Men	Women	18–65 years	>65 years
Patients interviewed (*n*)	52,495	20,117	32,378	32,308	20,187
Patients with ADRs (*n*)	4,949	1,491	3,458	3,076	1,873
% (95 % CI) versus patients interviewed	9.4 (9.2–9.7)	7.4 (7.0–7.8)	10.7 (10.3–11.0)	9.5 (9.2–9.8)	9.3 (8.9–9.7)
ADR forms accepted (*n*)	3,509	975	2,534	2,310	1,199
% (95 % CI) versus patients with ADRs	70.9 (69.6–72.2)	65.4 (63.0–67.8)	73.3 (71.8–74.8)	75.1 (73.6–76.6)	64.0 (61.8–66.2)
ADR forms sent[a] (*n*)	2,311	623	1,612	1,429	757
% (95 % CI) versus ADR forms accepted	65.9 (64.3–67.4)	63.9 (60.9–66.9)	63.6 (61.7–65.5)	61.9 (59.9–63.8)	63.1 (60.4–65.9)
% (95 % CI) versus patients with ADRs	46.7 (45.3–48.1)	41.8 (39.3–44.3)	46.6 (45.0–48.3)	46.5 (44.7–48.2)	40.4 (38.2–42.6)

[a] 76 reports without sex and 125 reports without age

ADR adverse drug reaction

Table 2 Causality assessment of patient and general practitioner reports according to Naranjo algorithm score

Causality (score)	Patient reports ($n = 1,794$)		GP reports ($n = 226$)	
	Reports (n)	% (95 % CI)	Reports (n)	% (95 % CI)
Definite (≥9 points)	0		9	4.0 (1.4–6.5)
Probable (5–8 points)	145	8.1 (6.8–9.3)	198 (87.6)	87.6 (83.3–91.9)
Possible (1–4 points)	1,563	87.1 (85.6–88.7)	19 (8.4)	8.4 (4.8–12.0)
Doubtful (≤0 points)	86	4.8 (3.8–5.8)	0	

GP general practitioner

of all the forms accepted, with no significant differences between sex or age groups. In almost all cases (97.8 %), patients preferred to return the completed ADR form to the pharmacy. Very few used the internet (2.1 %) and even fewer used fax or mail (0.1 %). No patient reports unrelated to this study were received in the period under examination.

After quality control 1,794 forms (77.6 %) were entered into the Italian Pharmacovigilance Database (the remaining 517 reports were not used, because they lacked some basic information required for inclusion in the database). These patient reports substantially increased the spontaneous reporting rate in the Veneto region in 2010 compared with 2009, from 268 to 549 reports per million inhabitants (+122 %). In 2010, patient reports from the Veneto region made up 51 % of all reports received from patients and health professionals.

3.2 Comparison Between Patient and General Practitioner Reports

In the period from April 2010 to March 2011, 226 reports were sent by GPs in the Veneto region. Table 2 shows the causality assessment of patient and GP reports. The majority of patient reports were classified as possible, while most of those by GPs were classified probable, with a statistically different distribution in the two groups. Reports with doubtful causality assessment were excluded from the subsequent analyses.

Table 3 shows that in both groups more reports were made by women than men, and by those aged 18–65 years compared with older people; this difference was greater in patient than in GP reports.

As shown in Table 4, both patients and GPs reported mainly expected and non-serious reactions. However, serious and unexpected ADRs were significantly more frequently reported by GPs than patients. The majority of serious reports related to hospitalization or clinically significant conditions. No case reported by a GP was also reported by the patient concerned.

The great majority of reports from both patients (95.6 %) and GPs (94.2 %) involved only one suspected drug. About half of the patient reports (52.6 %), compared with 43.4 % of those by GPs, reported no concomitant drug, a statistically significant difference.

Table 3 Sex and age distribution of patient and general practitioner reports

	Patient reports ($n = 1,708$)		GP reports ($n = 226$)	
	No.	% (95 % CI)	No.	% (95 % CI)
Sex				
Women	1,231	72.1 (69.9–74.2)	145	64.2 (57.9–70.0)
Men	477	27.9 (25.8–30.1)	81	35.8 (29.6–42.1)
Age				
18–65 years	1,152	67.4 (65.2–69.7)	121	53.5 (47.0–60.0)
>65 years	556	32.6 (30.3–34.8)	105	46.5 (40.0–53.0)

GP general practitioner

Table 4 Distribution of adverse drug reaction reports by reporter type, notoriety and seriousness, according to WHO criteria

	Patient reports		GP reports	
	Reports (*n*)	% (95 % CI)	Reports (*n*)	% (95 % CI)
Notoriety				
Expected	1,424	83.4 (81.6–85.1)	170	75.2 (69.6–80.8)
Unexpected	284	16.6 (14.9–18.4)	56	24.8 (19.2–30.4)
Seriousness				
Not reported	10	0.6 (0.2–0.9)	7	3.1 (0.8–5.4)
Non-serious	1,611	94.3 (93.2–95.4)	172	76.1 (70.5–81.7)
Serious	87	5.1 (4.1–6.1)	47	20.8 (15.5–26.1)
Death	0		1	
Hospitalization and prolonged hospitalization	53		22	
Persistent or significant disability or incapacity	4		4	
Life-threatening conditions	0		6	
Other clinically relevant conditions	30		14	

GP general practitioner

Patients more frequently reported gastrointestinal reactions (particularly abdominal pain, nausea and diarrhoea), whereas GPs more frequently reported systemic problems (headache, fever) and skin reactions (urticaria, pruritus and erythematous rash). The most evident differences between the two groups of reports were observed for reports of gastrointestinal, skin, application site, haematological and liver reactions (Table 5).

Another difference between patients and GPs involved the type of suspected drugs they reported (Table 6). Drugs belonging to ATC groups M (musculoskeletal system) and N (nervous system) were more frequently reported by patients than by GPs, whereas those belonging to groups J (anti-infective drugs for systemic use), L (antineoplastic and immunomodulating agents) and V (various) were more frequently reported by GPs than patients.

The 20 most frequently suspected drugs reported by patients and GPs are shown in Table 7. Some drugs that are widely used in Italy (i.e. ramipril, lansoprazole, amoxicillin/clavulanic acid and atorvastatin) are present in both lists. On the other hand, no vaccines, fluoroquinolones or antineoplastic agents are found among the drugs most commonly reported by patients, and no NSAIDs or corticosteroids among those reported by GPs.

4 Discussion

The main objective of this study was to assess the potential impact of an intervention to promote patient reporting. The importance of direct patient reporting has been highlighted by new European legislation on pharmacovigilance. The legislation directs member states to take all appropriate measures to encourage patients to report suspected ADRs to the relevant national authorities. Member states should also facilitate patient reporting through the provision of alternative reporting formats in addition to web-based formats [14]. The aim of the legislation is to improve the participation of patients in the decision-making process and to resolve the lack of a clear legal basis for patient reporting across the EU. As stated in a recent paper in this journal, the new legislation is designed to strengthen spontaneous reporting systems in Europe [29].

The methodology applied led us to calculate the incidence of adverse reactions in a cohort of adult citizens who use community pharmacies, bearing in mind that the true incidence in the population could be different, partly because of potential selection bias. The incidence of ADRs in our study (9.4 %) is in line with that in other published studies [21]. A recent review of the prevalence of adverse drug events in ambulatory care showed a median prevalence rate, in prospective studies, of 9.65 % (interquartile range [IQR] 3.3–17.35 %) [30].

A higher incidence of ADRs in women compared with men has been reported previously. Women were also more prone than men to accept the spontaneous reporting form, confirming the greater propensity of women to report health problems [31, 32].

It is known that the incidence of ADRs in elderly patients is higher than in the overall adult population [30]. However, in our study, we found no differences in relation to age. This could be due to the different characteristics of patients who go to pharmacies compared with patients with ADRs in ambulatory or in hospital settings: frail and very elderly patients do not usually go to pharmacies [42].

Data on the incidence of ADRs in our study were collected from a cohort of adult citizens accessing community pharmacies and actively selected by the pharmacists. For

Table 5 Type of adverse drug reactions in patient and general practitioner reports according to the WHO-ART system organ classes

	Patient reports		GP reports	
	Reports (*n*)	% (95 % CI)	Reports (*n*)	% (95 % CI)
Gastrointestinal reactions	623	36.5 (34.2–38.8)	41	18.1 (13.1–23.2)
General disorders	393	23.0 (21.0–25.0)	65	28.8 (22.9–34.7)
Skin reactions	331	19.4 (17.5–21.3)	61	27.0 (21.2–32.8)
CNS and PNS reactions	270	15.8 (14.1–17.5)	37	16.4 (11.5–21.2)
Psychiatric disorders	191	11.2 (9.7–12.7)	19	8.4 (4.8–12.0)
Cardiovascular reactions	143	8.4 (7.1–9.7)	18	8.0 (4.4–11.5)
Respiratory system disorders	123	7.2 (6.0–8.4)	23	10.2 (6.2–14.1)
Genito-urinary disorders	85	5.0 (3.9–6.0)	5	2.2 (0.3–4.1)
Vision, hearing and vestibular disorders	79	4.6 (3.6–5.6)	15	6.6 (3.4–9.9)
Muscolo-skeletal reactions	78	4.6 (3.6–5.6)	21	9.3 (5.5–13.1)
Metabolic and endocrine disorders	46	2.7 (1.9–3.5)	10	4.4 (1.7–7.1)
Application site disorders	14	0.8 (0.4–1.2)	24	10.6 (6.6–14.6)
Haematological reactions	13	0.8 (0.3–1.2)	12	5.3 (2.4–8.2)
Liver and biliary system disorders	6	0.4 (0.1–0.6)	7	3.1 (0.8–5.4)

CNS central nervous system, *GP* general practitioner, *PNS* peripheral nervous system, *WHO-ART* WHO Adverse Reaction Terminology

this reason, caution is needed before extrapolating these data to the general population.

The most important result of the study is the high percentage of reports (46.7 %) delivered by patients referring an ADR to pharmacists. This is ten times higher than the published mean reporting rate (5 %) [10], and it is particularly important considering that in Italy the number of reports sent by patients was virtually nil before this study [17]. In Italy, almost all reports are sent by physicians (either hospital doctors or GPs) and no published data are available on the rate of under-reporting. However, the small number of reports sent by GPs in the Veneto region during the study period suggests a high rate of under-reporting and the need for interventions to improve their participation in pharmacovigilance. Thanks to the involvement of pharmacists in this study, the percentage of reports submitted by patients in the Veneto region in 2010 is similar to that reported in the USA (46 %), and much higher than in the UK (20 %), the Netherlands (19 %), Canada (11 %) or Denmark (9 %), which shows the potential impact of patient involvement in spontaneous reporting systems [33].

Certainly this high percentage could be explained by the active and important role played by pharmacists in promoting reporting by patients and by the good relationship between these two groups. This positive relationship is confirmed by the very large number of reports hand-delivered to pharmacists. It might also explain the small number of reports sent via the web, although published data show that use of the internet in Italy is very low compared with mean use in Europe, particularly among elderly women [34]. However, it should be remembered that the active role played by pharmacists related to the study setting, and that the situation might well be different in a normal context. The positive response by patients nevertheless proves their willingness to play an active role in the surveillance of drug-related problems, and more generally to be involved in the improvement of the health system [35, 36].

Patient and GP reports showed a different distribution by sex and age groups. This probably relates to the difference between our sample and patients in an ambulatory setting. For example, as stated above, we found the same incidence of ADRs in adult as in elderly patients. Moreover, a higher percentage of men and elderly patients refused the reporting form.

As for the quality of reports in a spontaneous reporting system, two different issues should be considered. First, the completeness of data provided in the form is extremely important for an efficient causality assessment of the report. From this point of view, the quality of patient reports was good, since about 80 % of reports contained all the information needed for their evaluation. This result could be further improved through better education of patients in pharmacovigilance.

Secondly, the quality of a spontaneous reporting system relates to its capacity to identify signals, e.g. drug-reaction pairs that were unknown or incompletely documented previously, or else an increased risk for known serious reactions.

Patients reported a higher percentage of known and non-serious reactions than did GPs. However, it must be noted that, despite guidelines suggesting that only serious and/or unknown reactions should be reported, three quarters of GP reports also involved expected and non-serious reactions, and the total number of reports of serious and unexpected reactions by patients was in any case higher than that by GPs. A possible explanation for the lower proportion of

Table 6 Suspected drugs reported by patients and general practitioners, grouped according to first-level Anatomical Therapeutic Chemical classification

ATC classification	Patient reports		GP reports	
	Reports (*n*)	% (95 % CI)	Reports (*n*)	% (95 % CI)
Cardiovascular system	359	21.0 (19.1–23.0)	38	16.8 (11.9–21.7)
Nervous system	288	16.9 (15.1–18.6)	23	10.2 (6.2–14.1)
Musculoskeletal system	271	15.9 (14.1–17.6)	18	8.0 (4.4–11.5)
Anti-infective for systemic use	262	15.3 (13.6–17.0)	69	30.5 (24.5–36.5)
Alimentary tract and metabolism	181	10.6 (9.1–12.1)	21	9.3 (5.5–13.1)
Genito-urinary system and sex hormones	96	5.6 (4.5–6.7)	8	3.5 (1.1–5.9)
Respiratory system	64	3.7 (2.8–4.6)	5	2.2 (0.3–4.1)
Blood and blood forming organs	58	3.4 (2.5–4.3)	6	2.7 (0.6–4.8)
Systemic hormonal preparations	56	3.3 (2.4–4.1)	3	1.3 (0.0–2.8)
Antineoplastic and immunomodulating agents	48	2.8 (2.0–3.6)	20	8.8 (5.1–12.6)
Sensory organs	29	1.7 (1.1–2.3)	3	1.3 (0.0–2.8)
Dermatological	15	0.9 (0.4–1.3)	3	1.3 (0.0–2.8)
Antiparasitic products	13	0.8 (0.3–1.2)	3	1.3 (0.0–2.8)
Various	2	0.1 (0.0–0.3)	10	4.4 (1.7–7.1)

ATC Anatomical Therapeutic Chemical, *GP* general practitioner

expected reactions reported by GPs compared with those reported by patients could be that, because these effects are described in the SPC, health professionals might be inclined not to report them but rather to focus on other 'unknown' ADRs. Alternatively, it could be that patients perceive some adverse reactions as serious problems that require reporting, whereas healthcare professionals consider them too trivial to report [37].

Even though the patient reports in our study were evaluated together with other reports in the signal detection activity by the Italian Medicines Agency, no patient report contributed to the signals identified during the study period. This could have been due to the low percentage of patient reports in the Italian database (8 %): it has been found that patient reports can contribute to generating signals in proportion to their relative presence in spontaneous reporting databases [4].

Many published studies highlight differences between patients and health professionals in the type of ADRs and suspected drugs reported, including a recent systematic review in this journal [38, 39, 43]. In our study, patients seemed to be more prone to report adverse events that are easily identified, particularly if they knew that the event could occur in association with drug therapy, e.g. gastrointestinal disorders with NSAIDs or diarrhoea with antibacterial drugs. On the other hand, adverse events like haematological reactions were identified mainly by physicians. Our results are in line with previous studies that found that patient reports often had richer narratives than those of healthcare professionals, and often contained detailed information about the impact of the suspected ADR on the patient's life [13, 33].

Almost all the reports from both patients and GPs indicated only one suspected drug. This might suggest that patients can distinguish suspect drugs in a similar way to GPs, even if a lower causality assessment was observed in patient reports in this study. However, a recent qualitative study on patient reporting showed that patients identify suspected ADRs adequately and describe processes for assessing causality that mirror those in standard algorithms designed for use by health professionals [40]. The higher incidence of reports involving concomitant drugs from GPs compared with patients may have been due to the higher percentage of elderly patients, who are more often treated with many different drugs, in the GP reports.

The use of a drug and the type of dispensing influenced whether it was frequently suspected by patients of causing an ADR. Drugs widely used in the community setting, and over-the-counter products (e.g. amoxicillin and clavulanic acid, ketoprofen, ibuprofen, acetaminophen), were the drugs most frequently reported by patients. In contrast, few reports involving reactions to antineoplastic agents or contrast media—drugs mostly used in a hospital setting—were sent by patients.

No ADR reported by a patient was also reported by a GP. This is not surprising in the light of the very large extent of under-reporting by physicians, including serious, fatal or life-threatening reactions, and reinforces the need to improve patient reporting in the Italian pharmacovigilance system.

Table 7 The 20 drugs most frequently suspected of causing adverse drug reactions by patients and general practitioners

Patient reports		GP reports	
Drugs	Reports [*n* (%)]	Drugs	Reports [*n* (%)]
Amoxicillin/clavulanic acid	81 (4.7)	Flu vaccine	16 (7.1)
Ketoprofen	56 (3.3)	Pneumococcal vaccine	8 (3.5)
Ibuprofen	55 (3.2)	Bicalutamide	8 (3.5)
Simvastatin	45 (2.6)	Tetanus vaccine	7 (3.1)
Diclofenac	41 (2.4)	Amoxicillin/clavulanic acid	7 (3.1)
Lansoprazole	40 (2.3)	Lansoprazole	6 (2.7)
Aspirin	38 (2.2)	Ramipril	5 (2.2)
Ramipril	34 (2.0)	Levofloxacin	5 (2.2)
Amoxicillin	33 (1.9)	Ioexolo	4 (1.8)
Nimesulide	33 (1.9)	Clarithromycin	3 (1.3)
Acetaminophen	28 (1.6)	Drospirenone + ethinylestradiol	3 (1.3)
Amlodipine	28 (1.6)	Oxaliplatin	3 (1.3)
Drospirenone + ethinylestradiol	23 (1.3)	Simvastatin	3 (1.3)
Atorvastatin	22 (1.3)	Ciprofloxacin	3 (1.3)
Gestodene + ethinylestradiol	20 (1.2)	Ticlopidine	3 (1.3)
Metformin	20 (1.2)	Atorvastatin	3 (1.3)
Prednisone	19 (1.1)	Alendronic acid	3 (1.3)
Betamethasone	19 (1.1)	Furosemide	3 (1.3)
Calcium carbonate + cholecalciferol	19 (1.1)	Acetaminophen + codeine	2 (0.9)
Clarithromycin	18 (1.1)	Duloxetine	2 (0.9)

GP general practitioner

The role of community pharmacists is worth considering. In Italy, about 12 % of spontaneous reports come from pharmacists, but more than 80 % of these reports are sent by hospital pharmacists [41]. In the year in which our study was conducted, only 15 reports were sent by community pharmacists in the Veneto region, none of them involved in the study. Despite the many efforts made in recent years to increase the participation of community pharmacists in Italy in spontaneous reporting, their contribution is still small. This low participation is probably due to organizational problems rather than lack of interest in ADRs. Our study suggests that community pharmacists could play an important part in the Italian spontaneous reporting system by acting as facilitators of patient reporting. This role would not only include delivery of the reporting form, but would also involve different aspects of the patient-pharmacist relationship. On the basis of the results of our study, the Italian Medicines Agency is likely to modify the spontaneous reporting system so as to give patients the option of delivering their report directly to community pharmacies.

Our study has some limitations. First, the sample of citizens and GPs was limited to one Italian region. However, it should be noted that the characteristics of GP reports in our results are similar to those of other Italian GPs. Secondly, proper randomization was not possible in selecting patients, even though the pharmacists were asked to select people at different times of day. Thirdly, the number and the type of ADRs reported by patients may have been influenced by pharmacists, even though they were asked only to facilitate the reporting and not to interfere with the content of the report. Fourthly, the stimulation of patient reporting could have led to a different distribution of issues like seriousness or unexpectedness, as well as to potential bias in the comparison with passive GP reporting. Finally, the importance of patient reports in signal detection activity should be evaluated at a national level, with a greater number of reports.

One strength of our study is the large number of citizens interviewed; they were representative of the Veneto region population and this would suggest similar findings for the whole Italian population. Another strength is the involvement of community pharmacists, who up to now have not been involved in the spontaneous reporting system in Italy.

There are many issues that we intend to further investigate in the future. First of all, we want to verify our results in a larger study, which will include four other regions. As mentioned above, it is likely that the National Agency will ask pharmacists to participate in the Italian pharmacovigilance system as collectors of patients' reports, and the patient reporting form used in this study will probably be utilized all over Italy. Finally, a greater

number of patient reports in the Italian database over a longer period will make it possible to assess the effects of patient reporting on signal detection activity.

In this context, the lower causality assessment score for patient reports found in this study could be a limiting factor. It has been reported that patients use mainly temporal associations to link symptoms with medicines used [40]. However, this is also true for health professionals, and temporality is a key issue in all the standard algorithms designed for assessing causality. In our study, patients and GPs used different reporting forms. Unlike GPs, patients used a form that did not include a specific field relating to concomitant/predisposing factors for adverse reactions. The lack of this information leads to a lower causality assessment category using the Naranjo algorithm. However, reports with low causality assessment (apart from the 'doubtful' category) should not be considered less important in the context of spontaneous reporting, where the main goal is to identify unknown reactions and where health professionals too are generally asked to report ADRs even if they merely suspect a relation between a drug and an adverse event.

In spontaneous reporting systems, the causality assessment is an important task carried out by national and regional pharmacovigilance centres. Causality assessment of individual reports or clusters of reports depends on the completeness of the information provided, and from this point of view the reports sent by patients were mostly adequate. Moreover, it would be possible to select reports with high priority, e.g. reports relating to children or pregnant women, or reports of serious or unknown reactions, with a type of follow-up that will include not only the reporter but also the GP or hospital physician involved.

5 Conclusions

Our study shows that, in Italy, patient reporting has the potential to add value to the pharmacovigilance system. Overall, the quality of the information provided by patients' reports was good. The differences between reports by patients and GPs indicate a different point of view that can enrich spontaneous reporting.

Pharmacists in Italy could play an important part in encouraging reporting by consumers. On the basis of the positive results of our study, the Italian Medicines Agency is planning to launch a national campaign to promote the reporting of ADRs by patients, which is also in line with recent European legislation.

Acknowledgments The authors thank all participating pharmacists of the Veneto region for their significant work during the study and for their continuing cooperation. In addition, we thank Federfarma Veneto and the Professional Associations of Pharmacists of the Veneto region for their support in the research. We also thank Elena Arzenton, Davide Costantini, Monia Donati and Sibilla Opri (Department of Medicine and Public Health, Section of Pharmacology, University of Verona) for their important collaboration during the study. We thank Fernanda Ferrazin, Carmela Santuccio and Laura Sottosanti of the Italian Medicines Agency for their support. Finally, we thank Christine Harris for the English revision of the manuscript.

Conflict of interest The authors declare no potential conflicts of interest. This project was self-financed by the Pharmacovigilance Centre of the Veneto region. Roberto Leone is a member of the AIFA Commission on Pharmacovigilance.

References

1. McLernon DJ, Bond CM, Lee AJ, et al. Patient views and experiences of making adverse drug reaction reports to the Yellow Card Scheme in the UK. Pharmacoepidemiol Drug Saf. 2011;20:523–31.
2. McLernon DJ, Bond CM, Hannaford PC, et al. Yellow card collaboration: adverse drug reaction reporting in the UK. A retrospective observational comparison of yellow card reports submitted by patients and healthcare professionals. Drug Saf. 2010;33(9):775–88.
3. van Hunsel F, van der Welle C, Passier A, et al. Motives for reporting adverse drug reactions by patient-reporters in the Netherlands. Eur J Clin Pharmacol. 2010;66:1143–50.
4. van Hunsel F, Talsma A, van Puijenbroek E, et al. The proportion of patient reports of suspected ADRs to signal detection in the Netherlands: case-control study. Pharmacoepidemiol Drug Saf. 2011;20:286–91.
5. Aagaard L, Nielsen LH, Hansen EH. Consumer reporting of adverse drug reactions: a retrospective analysis of the Danish adverse drug reaction database from 2004 to 2006. Drug Saf. 2009;32:1067–74.
6. Aagaard L, Hansen EH. Consumers' reports of suspected adverse drug reactions volunteered to a consumer magazine. Br J Clin Pharmacol. 2010;69:317–8.
7. Basch E. The missing voice of patients in drug-safety reporting. N Engl J Med. 2010;362:865–9.
8. Blenkinsopp A, Wilkie P, Wang M, et al. Patient reporting of suspected adverse drug reactions: a review of published literature and international experience. Br J Clin Pharmacol. 2007;63:148–56.
9. de Langen J, van Hunsel F, Passier A, et al. Adverse drug reaction reporting by patients in the Netherlands: three years of experience. Drug Saf. 2008;31:515–24.
10. Hazell L, Shakir SAW. Under-reporting of adverse drug reactions: a systematic review. Drug Saf. 2006;29:385–96.
11. Lopez-Gonzalez E, Herdeiro MT, Figueiras A. Determinants of under-reporting of adverse drug reactions: a systematic review. Drug Saf. 2009;32(1):19–31.
12. van Grootheest K, de Graaf L, de Jong-van den Berg LT. Consumer adverse drug reaction reporting: a new step in pharmacovigilance? Drug Saf 2003; 26(4): 211–7.
13. Herxheimer A, Crombag R, Alves TL. Direct patient reporting of adverse drug reactions: a fifteen-country survey and literature review. Health Action International (HAI) Europe. 2010. http://www.haiweb.org/10052010/10_May_2010_Report_Direct_Patient_Reporting_of_ADRs.pdf. Accessed 20 Jun 2011.
14. The European Parliament and the Council of the European Union. Directive 2010/84/EU of the European Parliament and of the

Council of 15 December 2010 amending, as regards pharmacovigilance, Directive 2001/83/EC on the Community code relating to medicinal products for human use [online]. http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2010:348:0074:0099:EN:PDF. Accessed 24 May 2012.
15. van Hunsel F, Härmark L, Pal S, et al. Experiences with adverse drug reaction reporting by patients: an 11-country survey. Drug Saf. 2012;35(1):45–60.
16. Italian Legislative Decree 20 April 1991. Document Information Ministry (Gazzetta Ufficiale) No. 133/1991.
17. The Italian Medicines Agency. Segnalazioni di sospette reazioni avverse dai pazienti. Reazioni 2009; 3(14):8. http://www.agenziafarmaco.gov.it/it/content/reazioni. Accessed 18 Jan 2012.
18. Stefini M. Ascoltare i pazienti arricchisce la farmacovigilanza l'esperienza di un'associazione di consumatori. Dialogo sui Farmaci 2010; 2:62–5. http://www.dialogosuifarmaci.it. Accessed 20 Jan 2012.
19. Planas LG, Kimberlin CL, Segal R, et al. A pharmacist model of perceived responsibility for drug therapy outcomes. Soc Sci Med. 2005;60:2393–403.
20. Bell JS, Whitehead P, Aslani P, et al. Design and implementation of an educational partnership between community pharmacists and consumer educators in mental health care. Am J Pharm Educ. 2006;70(2):28.
21. Thomsen LA, Winterstein AG, Søndergaard B, et al. Systematic review of the incidence and characteristics of preventable adverse drug events in ambulatory care. Ann Pharmacother. 2007;41(9):1411–26.
22. Italian Legislative Decree 12 December 2003. Document Information Ministry (Gazzetta Ufficiale) No.36/2004.
23. The Medicines and Healthcare products Regulatory Agency. Yellow Card Patient Reporting form. Available from URL: http://www.mhra.gov.uk/home/groups/pl-p/documents/websiteresources/con013935.pdf. Accessed 10 Feb 2010.
24. Naranjo CA, Busto U, Sellers EM, et al. A method for estimating the probability of adverse drug reactions. Clin Pharmacol Ther. 1981;30:239–45.
25. World Health Organisation. The Anatomical Therapeutic Chemical Classification System with Defined Daily Doses (ATC/DDD). http://www.who.int/classifications/atcddd/en. Accessed 20 Sept 2011.
26. Brown EG, Wood L, Wood S. The medical dictionary for regulatory activities (MedDRA). Drug Saf. 1999;20(2):109–17.
27. The Uppsala Monitoring Centre. WHO-ART: WHO Adverse Reaction Terminology. http://www.umc-products.com/DynPage.aspx?id=73589&mn1=1107&mn2=1664. Accessed 20 Sept 2011.
28. Italian National Institute of Statistics (ISTAT). Demography in figures. http://demo.istat.it/index_e.html. Accessed 28 May 2012.
29. Borg J-J, Aislaitner G, Pirozynski M, et al. Strengthening and rationalizing pharmacovigilance in the EU: where is Europe heading to? A review of the new EU legislation on pharmacovigilance. Drug Saf. 2011;34(3):187–97.
30. Taché SV, Sönnichsen A, Ashcroft DM. Prevalence of adverse drug events in ambulatory care: a systematic review. Ann Pharmacother. 2011;45:977–89.
31. Franconi F, Brunelleschi S, Steardo L, et al. Gender differences in drug responses. Pharmacol Res. 2007;55:81–95.
32. Zopf Y, Rabe C, Neubert A, et al. Women encounter ADRs more often than do men. Eur J Clin Pharmacol. 2008;64:999–1004.
33. Avery AJ, Anderson C, Bond CM, 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; 15:1–234, iii–iv.
34. Smihily M. Internet usage in 2007: households and individuals. http://epp.eurostat.ec.europa.eu/cache/ITY_OFFPUB/KS-QA-07-023/EN/KS-QA-07-023-EN.PDF. Accessed 30 May 2012.
35. Fortnum H, Lee AJ, Rupnik B, et al. Survey to assess public awareness of patient reporting of adverse drug reactions in Great Britain. J Clin Pharm Ther. 2012;37:161–5.
36. Lorimer S, Cox A, Langford NJ. A patient's perspective: the impact of adverse drug reactions on patients and their views on reporting. J Clin Pharm Ther. 2012;37:148–52.
37. Mitchell AS, Henry DA, Sanson-Fisher R, et al. Patients as a direct source of information on adverse drug reactions. BMJ. 1988;297:891–3.
38. Jarernsiripornkul N, Kakaew W, Loalukkana W, et al. Adverse drug reaction monitoring: comparing doctor and patient reporting for new drugs. Pharmacoepidemiol Drug Saf. 2009;18:240–5.
39. van Hunsel F, Passier A, van Grootheest K. Comparing patients' and healthcare professionals' ADR reports after media attention: the broadcast of a Dutch television programme about the benefits and risks of statins as an example. Br J Clin Pharmacol. 2009;67:558–64.
40. Krska J, Anderson C, Murphy E, et al. How patient reporters identify adverse drug reactions: a qualitative study of reporting via the UK Yellow Card Scheme. Drug Saf. 2011;34:429–36.
41. Moretti U. I farmacisti e la segnalazione spontanea. Reazioni. 2010;4(17):8. http://www.agenziafarmaco.gov.it/it/content/reazioni. Accessed 15 Feb 2012.
42. Italian National Institute of Statistics (ISTAT). The disability in Italy. http://www3.istat.it/dati/catalogo/20100513_00/arg_09_37_la_disabilita_in_Italia.pdf. Accessed 21 Feb 2013.
43. Inch J, Watson MC, Anakwe-Umeh S. Patient versus healthcare professional spontaneous adverse drug reaction reporting: a systematic review. Drug Saf. 2012;35:807–18.