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Review Article

Patient-centered pharmacovigilance: A review

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Abstract

Purpose: *To determine through a literature review, the current status of patients' involvement in adverse drug reactions (ADRs) reporting.*
Methods: *Eighteen (18) studies which were published within the period from 2010 to 2016 were reviewed. The studies were extracted from seven databases, viz, Google Scholars, Medline, Academic Search Complete "EBSCO", Health and Medical Complete ProQuest, Science Direct- Elsevier, SCOPUS and Wiley Online Library.*
Results: *The review revealed that although the reports by patients were of good quality, the patients' awareness of, and attitude towards, ADR reporting were generally poor.*
Conclusion: *The results of this review suggest the need for patients' enlightenment on ADRs reporting. Information on how to improve ADRs reporting is provided.*

Keywords: *Adverse drug reaction, Patients' reporting; Systematic review, Patient-centered pharmacovigilance*

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INTRODUCTION

Patient-centeredness is defined as "health care that establishes a partnership among practitioners, patients, and their families (when appropriate) to ensure that decisions respect patients' wants, needs, and preferences, and that patients have the education and support they need to make decisions and participate in their own care" [1].

Recently, patients' perspectives were incorporated into pharmacovigilance (PV) activities such as ADR reporting, signal detection and evaluation, risk management, medication error assessment, benefit–risk assessment and risk communication [2]. This review focuses on the participation of patients in reporting ADRs.

Adverse drug reactions (ADRs) are global problems in both developing and developed countries, where they contribute to significant morbidity and mortality [3-6]. A meta- analysis published in 1998 ranked ADRs between the fourth and the sixth leading causes of death in the US [7]. The main aim of documenting ADRs

is to prevent future injuries to patients [8].

The importance of patients ADRs reporting: New, unexpected and rare ADRs are often discovered when drugs are used in larger or in a different population than studied during initial clinical trials which are conducted in a controlled environment in a limited number of patients and with specific, notably short duration. Since the early 1960s, spontaneous reporting has been the main method of information on adverse reactions while healthcare professionals (HCPs) provide the information. However, underreporting has been a major drawback in this information. Therefore, reports from patients/consumers will be an extra source of information which may help in reducing the limitation imposed by underreporting [3,8-11]. A study conducted in the UK, which evaluated the effect of patients' reporting on signal generation, demonstrated that combining patients' reports with HCPs reports resulted in generation of 47 new signals for serious ADRs [12].

Furthermore, consumer reporting provides first-hand information about their experience with drugs which helps in early detection of ADRs, resulting in identification of more and unknown ADRs, especially with over-the-counter (OTC) and herbal drugs [13,14]. Some studies showed that patients identify and report ADRs quicker and earlier than HCPs do, and also provide more information related to their quality of life [15,16]. In addition, direct patients' reporting promotes patients' rights and improves their involvement in their health management [10].

Avenues for patients reporting

The World Health Organization (WHO) stated that reporting routes should be made readily accessible and cheap. Patients/ consumers may submit their reports by telephone, or through fax, e-mail, e-forms and paper forms which can be submitted in a pre-paid post. Paper forms should be available at local pharmacies, healthcare facilities or offices or in magazines produced by patients' organizations [9].

How to improve patients' engagement in ADRs reporting

Article 102, directive 2010/84/EU of the European Parliament, and of the Council of 15 December 2010 as amended regarding pharmacovigilance in Directive 2001/83/EC on the Community code relating to medicinal products for human use, stated "The member states shall take all appropriate measures to encourage patients, doctors, pharmacists and other healthcare professionals to report suspected adverse reactions to the national competent authority; for these tasks, organizations representing consumers, patients and healthcare professionals may be involved as appropriate" [17]. Therefore, patients reporting can be encouraged by:

1- Helping patients to share their experiences. It is important to increase their knowledge and awareness, and educate them about the importance of their participation through leaflets, posters, advertising through radio or television, and the use of the internet through websites or social media [9].
2- Involving HCPs to increase their patients' awareness [13].
3- Sending electronic reminders via emails or telephone call to patients/customers to encourage them to report [13].
4- Ensuring that the means of reporting are well known and easily accessible [9].
5- Ensuring that reporting forms contain clear instructions [9].
6- Acknowledging the receipt of reports by phone calls, letters or emails [9].
7- Providing the public a feedback by statistics published on public websites or in public newsletters [9].

An Italian study has presented the impact of a regional program in promoting patients reporting where 211 pharmacists working in 118 community pharmacies were involved [14]. Each pharmacist was asked to select, during the study period, about 250 customers who had received at least one drug, and to present the spontaneous reporting form to those who had experienced a suspected ADR.

In a 4-month period, 52,495 customers were interviewed by the pharmacists and 4,949 of them made reference to a suspected ADR. The PV Centre of the Veneto region received 2,311 ADR reporting forms related to the study from customers. This study reinforces the need for creation of a partnership between practitioners and patients, and the impact of encouragement on patients' reporting [14].

The general aim of this review was to determine the status of patient's engagement in ADR reporting. The specific objectives were to identify patients' knowledge, attitude, and experience with ADRs reporting, as well as methods of patients' reporting, quality of patients' reports, factors that encourage patients to report, barriers

to patients' reporting and factors that can help patients to report.

METHODS

Data sources

Google Scholar, Medline, Academic Search Complete "EBSCO", Health and Medical Complete ProQuest, Science Direct- Elsevier, SCOPUS and Wiley Online Library were used to identify relevant publications related to patients' participation in ADRs reporting. The keywords and keyword combinations used were "patients and patient participation"; "ADR reporting", and "drug-related side effects and adverse reactions"'. The MeSH terms for Medline search were: "Patients"[Mesh] or "Consumer participation"[Mesh]) and "Drug-related side effects and adverse reactions" [Mesh] or "Adverse drug reaction reporting systems" [Mesh]) and "2010/01/01"(PDAT): "2016/12/31"[PDAT]) and "humans" [MeSH Terms]) and ("2010/01/01"[PDAT]: "2016/12/31"[PDAT]).

Review of the selected articles

All the articles found were reviewed in the different bibliography databases, first according to title, then according to the information provided by the abstracts, and then according to the full text. At each step, articles were either retained for analysis, or excluded (**Error! Reference source not found.**). For each selected full paper, the inclusion criteria were: English studies published from 2010 to 2016, and papers with clear objectives, for example studies aimed at assessing patients' experiences, analysis of patients' reports, and any objective compatible with the stated objectives of this review.

RESULTS

Description of articles included

A total of 18 articles met the inclusion criteria. Three studies investigated the situation of patients reporting in multiple countries (17, 50 and 11 countries). The highest number of studies (8 studies) were carried out in the UK, followed by the Netherland (4 studies, Figure 2).

Summary of results according to study technique

Majority of articles (11) were descriptive studies using self-administered questionnaires, interviews, and telephone interviews. Six (6) studies were retrospective analysis of patients' reports, while one investigation was a prospective observational study.

Descriptive studies

Subjects: Patients, consumers, and the general population

A study published in 2015 was conducted in Portugal to investigate knowledge and attitude of 948 consumers from community pharmacy about ADRs reporting. It revealed that 44.1 % of the consumers never heard about the national PV system, while about 13.3 % were not aware of

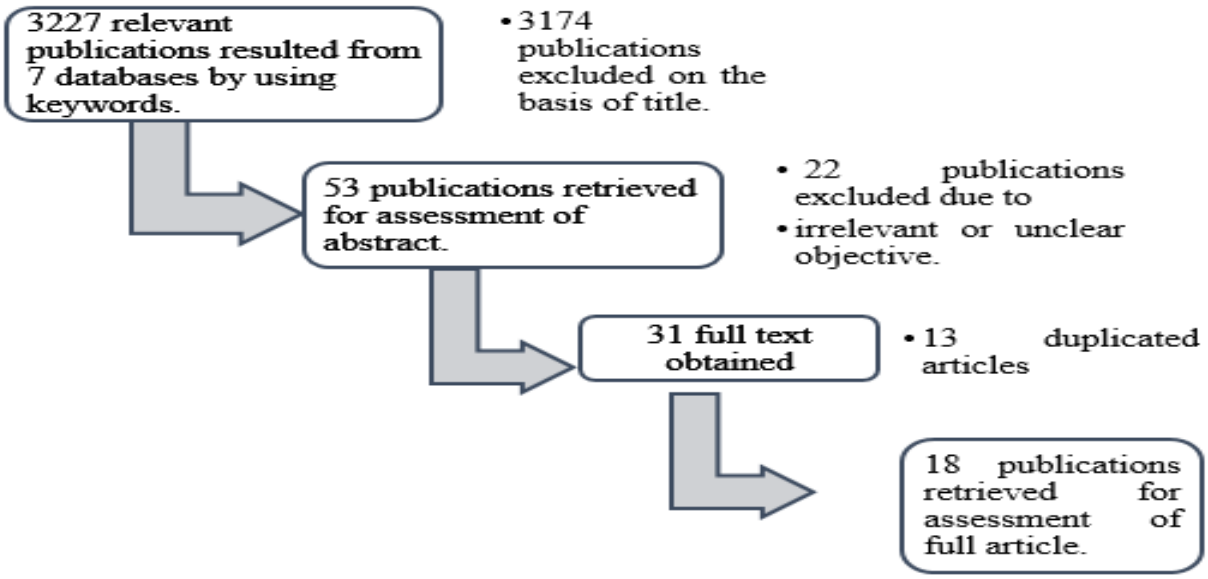

Figure 1: Publication selection process

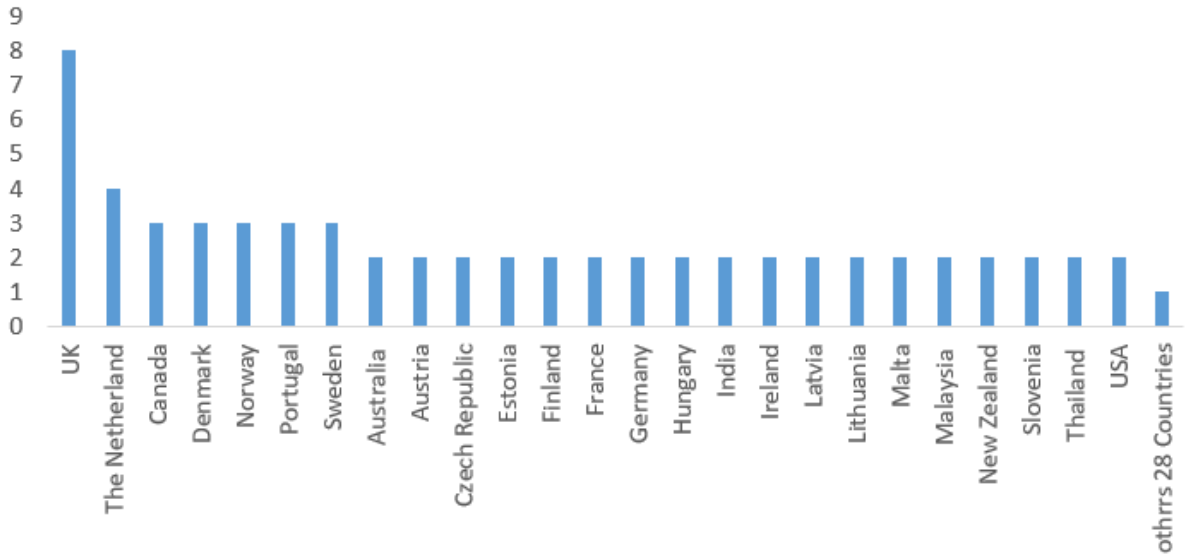

Figure 2: *Distribution of reviewed articles according to countries*

the possibility of reporting to HCPs. More than half (57.6 %) believed that they had already suffered from an ADR although only one consumer previously reported directly to the national PV system. Although 51 % of the consumers believed that they would benefit from reporting ADRs, only 27.8 % of them believed they should be responsible for reporting. When asked what they would do when they have ADRs, the percentages that stated that they would visit their GP, talk to their pharmacy, and report spontaneously were 39.9, 33.7 %, and 32.2 %, respectively) [18].

Two studies conducted in Thailand, published in 2015 and 2014 investigated Thai patients' experience with ADRs reporting [22]. The first study indicated that out of 257 patients who experienced suspected ADRs, more than half (59.1%) reported only one symptom as ADR, while 40.9% reported more than one symptom.

After stopping the medicine, 60.1 % reported that the symptoms disappeared, and 36.9 % reported that the symptoms were reduced. More than 56 % of the respondents felt high certainty about the suspected ADR [22]. The second study interviewed 100 patients whereby 51 % of them reported between one and five symptoms suspected as ADRs, while the rest reported more than 5 symptoms. About 56% of the reported symptoms were assessed to be accurate. A significant portion of the respondents (74%) claimed a relationship between duration of drug usage and ADRs, while 25% of them said that the symptoms disappeared or decreased on dechallenge [23].

A study conducted in Sweden to estimate one-month prevalence of self-reported ADRs among 7,099 adults from the general population revealed that 19.4% reported at least one ADE. About 32.9% of the 2,578 reported ADEs were ADRs; 0.8% were drug intoxications, 6.7 were drug dependencies, while 30.7% were morbidities due to drug-related untreated indications [24].

In one UK-based study to investigate how reporters to YSC identified ADRs, 16.7% of 1,362 respondents indicated that the symptoms were not present before the drug was administered, while 27.4% said that the symptoms manifested soon after starting the drug. Regarding their source of information, HCPs, patient information leaflet, and the internet constituted 15.9%, 8.4%, and 4.9%, respectively [25,26].

Subjects: National regulatory authorities/ organizations

Three studies [27-29] assessed the situation of patients reporting in different countries through self-administered questionnaires, interviews or phone calls to the national regulatory authorities in different countries. Table 1 shows the distribution of countries covered in these studies according to the year of country's acceptance of patients' reporting, and the methods of reporting. The results show that 44 countries allowed patients, relatives, and patients' associations to directly report ADRs to their National Health Competent Authorities (NCA). The first country to allow patients' reporting was Australia in 1964, followed one year later by New Zealand and Canada, and then USA in 1969. In the 1990s, three countries (Colombia, Hungary, and

Table 1: Year of acceptance of patients' reports, and methods of reporting in 52 countries

S/no.	Country	Year patient reporting started	Method of patients' reporting		
			Paper forms	***Electronic forms***	***Phone***
1	Algeria	2012 or 2013	Yes	Yes	NI
2	Argentina	2012 or 2013	Yes	Yes	NI
3	Australia	1964	Yes	Yes	Yes
4	Austria	2012 or 2013	Yes	Yes	NI
5	Belgium	2012 or 2013	Yes	Yes	NI
6	Brazil	2000s	Yes	Yes	NI
7	Bulgaria	2012 or 2013	Yes	No	NI
8	Canada	1965	Yes	Yes	Yes
9	China	2012 or 2013	Yes	Yes	NI
10	Colombia	1990s	Yes	No	NI
11	Croatia	2000s	Yes	Yes	NI
12	Cuba	No patient reporting	NA	NA	NA
13	Cyprus	No patient reporting	NA	NA	NA
14	Czech Republic	2000s	Yes	Yes	NI
15	Denmark	2000s	No	Yes	No
16	Estonia	2012 or 2013	Yes	Yes	NI
17	Finland	2012 or 2013	Yes	No	NI
18	France	2012 or 2013	Yes	No	NI
19	Germany	2012 or 2013	Yes	Yes	NI
20	Greece	2012 or 2013	Yes	Yes	NI
21	Hungary	1990s	Yes	Yes	NI
22	India	2012 or 2013	Yes	No	Yes
23	Ireland	2012 or 2013	Yes	Yes	NI
24	Israel	2012 or 2013	NI	NI	NI
25	Italy	2012 or 2013	Yes	No	NI
26	Japan	2012 or 2013	Yes	Yes	NI
27	Kenya	2012 or 2013	Yes	Yes	NI
28	Latvia	2012 or 2013	Yes	Yes	NI
29	Lithuania	2012 or 2013	Yes	Yes	NI
30	Luxembourg	2012 or 2013	Yes	Yes	NI
31	Malta	2000s	Yes	Yes	NI
32	Malaysia	NI	Yes	No	Yes
33	Mexico	2012 or 2013	Yes	Yes	NI
34	Morocco	2000s	Yes	Yes	NI
35	The Netherland	2000s	No	Yes	No
36	New Zealand	1965	Yes	Yes	Yes
37	Nigeria	2000s	No	No	Text message
38	Norway	2012 or 2013	No	Yes	No
39	Peru	No patient reporting	NA	NA	NA
40	Philippines	NI	Yes	No	Yes
41	Poland	2012 or 2013	Yes	Yes	NI
42	Portugal	2012	Yes	Yes	NI
43	Romania	No patient reporting	NA	NA	NA
44	Russia	No patient reporting	NA	NA	NA
45	Slovakia	2012 or 2013	Yes	Yes	NI
46	Slovenia	1990s	Yes	Yes	NI
47	South Africa	No patient reporting	NA	NA	NA
48	Spain	2012 or 2013	Yes	Yes	NI
49	Sweden	2000s	Yes	Yes	NI
50	Switzerland	2000s	Yes	Yes	No
51	UK	2000s	Yes	Yes	Yes
52	USA	1969	Yes	Yes	Yes

Key: NA = none applicable; NI = could not be identified from the three studies

Slovenia), and in the 2000s, twelve countries (Brazil, Croatia, Czech Republic, Denmark, Italy, Malta, Morocco, the Netherlands, Nigeria, Sweden Switzerland, and the UK) started establishing patient reporting, while the remaining countries started in 2012 or 2013. Regarding the reporting methods, 33 countries used online and paper reporting, 5 countries used paper forms only, 3 countries used online forms only, and one country used text messages. Furthermore, three countries (Germany, New Zealand, and Kenya) currently offer patients the opportunity to report through downloaded application for mobile devices.

Retrospective analysis of patients' reports

A study in India which evaluated 200 patients' reports revealed that more than half of the patients (54.3%) provided their contact information, and 80% of them described the ADRs, but details about concomitant drugs were missing [30]. The study suggested that in order to avoid missing out information, the required field should be highlighted or described as mandatory, and that the public should be educated to improve the quality of their reports [30]. In a UK-based study published in two articles, the first article dwelt on the relative contribution of patients in ADRs reporting by analysis of 5,180 patients' ADRs reports and 20,949 reports from HCPs which were submitted to YSC [31]. It revealed that 10.6% of ADRs were reported by both patients and HCPs. Furthermore, the combination of data from patients and HCPs reports identified an extra 508 signal of disproportionate reports (SDRs) that were not identified by analysis of the patient or HCPs datasets alone [31]. The second article which compared the characteristics of patients' and HCPs' reports, revealed that the most frequent method used to report an ADR was the paper YC for both reporter groups (61.1% and 62 %, respectively). The Internet was the next most frequently used method (13.6% and 8.7%, respectively), followed by the telephone (2.7% and 0.02%, respectively). Furthermore, patients tended to report a significantly higher number of suspected ADRs per YC report than HCPs, with median values of 3 (2–5) and 2 (1–3), respectively [32]. In another study in the UK, in which 230 reports were analyzed in order to understand how reporters to YSC identified the ADRs, it was shown that 74.8% of the reports included at least one aspect of association of the drug and the symptom, 61.3% stated that symptoms began after starting the drug, while 26.1% indicated that the symptoms reduced on dose reduction or complete withdrawal [25]. A study was conducted in France to investigate the quality of 1,006 patients' reports submitted to the French PV system [33]. These reports were classified as serious, medically serious, and non-serious ADRs (2.3%, 6.2%, and 91.5%, respectively). Moreover, 91.3% of the serious ADRs were ranked as possible but none of the patients' reports were classified as likely.No differences were found in unlabeled, serious ADRs between the patients' reports and HCPs reports (56.5% and 56.7%, respectively) [33]. A study in Sweden analyzed 442 consumers' reports regarding antidepressant drugs. It revealed that 878 out of 2,392 reported ADRs were psychiatric in nature [34]. Approximately, one-third of psychiatric ADRs were reported by patients within the age group of 30-39 years, while 23.9% were reported by patients in the 15-29 years age group [34].

Prospective observational study

A Canada-based study aimed at assessing patients' contributions in ADRs reporting through telephone follow-up entailed prospective observation of 258 patients who were discharged from the emergency department (ED) [35]. It showed that one-quarter (25.2%) of the patients reported symptoms they believed were ADRs from ED discharge medications; 20.9% reported symptoms that met the researchers' definition of a patient-reported ADRs, while 24% of the patients had unplanned visits to ED, 5% of which were felt to be related to an ADRs [35].

Why patients did report or failed to report

In three studies [18,19,21], patients stated factors that can encourage or discourage them from reporting. Most of the patients stated they would report if the ADRs were serious, and that they liked to share their experiences. However, they said they would not report if the drug effect was not serious, expected or known (Table 2).

Patients' suggestions for improvement

In one study, patients gave some suggestions for improving their contributions to reporting [19]. Most of them agreed on the importance of publicity and promotion of the reporting scheme by HCPs (Table 3).

DISCUSSION

The involvement of patients in their health care management is one of their basis rights. Patients' rights should be the prime concern of any health care system, and one of patient-centered pharmacovigilance activities is the engagement of patients in reporting of ADRs.

Table 2: Factors that motivate or discourage patients to report

Study	Why did patients report?	Why did patients not report?
Matos *et al* [18] & van Hunsel [21]	- The ADRs were serious (n*= 1660)[1]. - They wanted to share their experience (n*= 1408). - They were worried about their situation (n*= 1328). - The possibility of reporting ADR (n*= 1266). - They want to be heard (n*= 1138). -They wanted actions to be taken (n*= 1134). - They wanted extra information (n*= 941). - The ADR was not mentioned in the leaflet. (n*= 894). - Someone told them about the possibility of reporting. (n*= 695)	- The side effect was not serious. (n=145) - The side effect was expected or known. (n=106)
McLernon *et al* [19]	- The pharmacist told them to report. (n=190). - A family member assisted them to report (n=56).	- They were discouraged by someone. (n=43) - They were discouraged by their GP (n=26). - An HCP refused to make a report on their behalf (n= 56). -Their GP was unaware of direct patient reporting (n=23). -The lack of personal feedback and time taken to report (n =25).

n is the sum of subjects in both studies*

Table 3: Patients' suggestions for improvement

Study	Suggestions
McLernon *et al* [19]	-Greater publicity and promotion of the scheme by HCPs, and wider availability and accessibility of the reporting forms. (n=143). -Suggestions for improvement to the forms: ✓ More space. (n=31). ✓ Simplifying questions. (n =15). ✓ Simpler language. (n= 3).

The known problem of underreporting of ADRs from HCPs emphasizes the importance of consumers' reporting as new and extra source of information. Thus, suspected ADRs can be detected and identified early, thereby decreasing their cost and burden on public health. Based on the various articles reviewed, it is clear that patients have inadequate knowledge and attitude regarding ADRs reporting and drug safety.

Where they were unaware of the existence of PV system, 44.1% of patients believed that drugs prescribed physicians were completely safe, and that physicians were responsible for any side effects that occurred. Patients believed that they would benefit from reporting (51%- 93.7%) and stated that they felt responsible for reporting (27.8 - 92.5%). Regarding their experiences, some patients (19.4% - 59%) stated that they reported between 1 to 5 symptom, and most of them (93.6%) said the report form was easy to complete. Patients (16.7- 74%) identified the ADRs by setting a relationship between time of starting the drug and the reported symptoms, and 77% stopped the treatment. In addition, 32.2 – 92.5 % stated that if they experienced an ADR in future, they would report again; 39.9 % said they would visit their GP, while 33.7% stated that they would talk to their pharmacists. Most patients stated that they expected to have feedback and they would like to have feedback. Most of countries (33 countries) used papers and an online form to receive patients' reports; 5 countries used paper forms only, while 3 countries used electronic forms only. Notwithstanding the current era of technology, only one country used text messages, while 3 countries used application for mobile devices. The quality of patients' reports was relatively good, and there were no major qualitative differences between patients' reports and HCPs' reports. Patients described the ADRs and they indicated at least one aspect associated with the drug and the symptoms. Furthermore, patients reported a significantly higher number of suspected ADRs when compared to HCPs' reports; most of reported serious events were ranked as possible (91.3%), and their reports helped in identifying extra signals. However, there were some missing details e.g. information on concomitant drugs. The reviewed articles indicated that some patients did not report either because they were discouraged by their GP, or HCPs refused to make a report on their behalf, or their GP was unaware of direct patients reporting [19]. Since HCPs are considered the prime source of information for patients, it is necessary to improve their awareness and attitude regarding direct patients reporting, and to develop a culture of partnership with their patients. In addition, HCPs should be encouraged to involve their patients through

incentives and enlightenment, so as to decrease their workload. One of the reviewed articles indicated that patients reported ADRs because their pharmacist told them to do that [19]. Therefore, HCPs should encourage their patients to report, and educate their patients on how to report and how to identify the ADRs. This review has established that patients'/ consumers' knowledge of ADRs, and their attitude towards them are inadequate. Therefore, there is need to increase their awareness through educational campaign, posters and television advertisements to ensure that patients have enough time during their visits to get enough information from their HCPs. The current advancements in information technology should be exploited by way of sending text messages, phone calls, and reminder emails to patients to encourage them to speak up, and also by establishing mobile applications as means of reporting. Furthermore, PV centers may establish their own Twitter and Facebook accounts to spread the culture of reporting to the community. There is also the need to establish projects for data mining of safety information published by the community through the social media. The means of reporting should be well known, easily accessible, have enough space and be presented in a simple language. Lastly, information from patients' reports should be made available to them through PV centers' websites or newsletters

CONCLUSION

This review has provided data on patients' KAP, quality of patients' ADRs reporting, and direct patients reporting status in many countries. It showed poor knowledge and inadequate attitude of patients about ADRs reporting, and provided information about how to improve ADRs reporting by patients. In addition, it has emphasized the need for patients' education and training of health care professionals on the need for building partnership with patients.

Strengths and limitations of this review

The strength of this review lies in the fact that it has gathered information about patients' KAP, direct patients' reporting status in many countries, and the quality of patients' reports in one review, through accessing full text of all articles involving relevant studies in the last six years. The limitations are that the reviewed descriptive studies used self-administered questionnaire, which often is fraught with low response rates and information bias, especially if respondents misunderstood the questions.

DECLARATIONS

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Conflict of interest

No conflict of interest is associated with this work

Contribution of authors

The authors declare that this work was done by the authors named in this article and all liabilities pertaining to claims relating to the content of this article will be borne by them.

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